Case Report

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Psychosis and catatonia in fragile X: Case report and literature review

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Summary **Fragile X mental retardation 1 (*FMR1*) premutation associated phenotypes have been explored extensively since the molecular mechanism emerged involving elevated *FMR1* messenger ribonucleic acid (mRNA) levels. Lowered fragile X mental retardation protein (FMRP) can also occur which may have an additive effect to the high levels of mRNA leading to neurodevelopmental problems and psychopathology. This paper was aimed to review psychosis and catatonia in premutation carriers, express the role of elevated *FMR1* mRNA and lowered FMRP in the phenotype of carriers and present a case of psychosis and catatonia in a carrier. This case also demonstrates additional genetic and environmental factors which may also affect the phenotype. We review the literature and report an exemplary case of a 25 year old male premutation carrier with elevated *FMR1* mRNA, low FMRP, a cytochrome P450 family 2 subfamily D polypeptide 6 (*CYP2D6*)**2xN* mutation and a perinatal insult. This patient developed an autism spectrum disorder, psychosis, catatonia with subsequent cognitive decline after electro-convulsive therapy (ECT) for his catatonia. He had a premutation of 72 CGG repeat in *FMR1*, *FMR1* mRNA level that was over 2.4 times normal and FMRP level at 18% of normal, and additionally, a CYP2D6 allelic variant which leads to ultrarapid metabolism (UM) of medication. There is an overlapping pathophysiological mechanism of catatonia and fragile X-associated premutation phenotypes including autism and psychosis. This case demonstrates the shared phenotype and the overlap of the pathophysiological mechanisms that can influence the intervention. Multiple genetic and environmental hits can lead to more significant involvement in premutation carriers.**

Keywords: Catatonia, fragile X syndrome, premutation, psychosis

1. Introduction

Fragile X-associated premutation disorders represent a wide spectrum of clinical manifestations including neurodevelopmental disorder, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD); a neurodegenerative disorder, fragile X-associated tremor ataxia syndrome (FXTAS); neuropsychiatric disorders (depression, anxiety); and reproductive disorders (fragile X-associated premature ovarian insufficiency (FXPOI)) (*1-5*). The prevalence of the premutation is high in the general population and estimated approximately at 1:200 in females and 1:450 in males (*6,7*). In premutation carriers, in whom the expansion of CGG repeats in the promoter region of *FMR1* gene is 55-200, the *FMR1* gene remains active and demonstrates an increase in transcriptional activity, thus leading to increased *FMR1* mRNA levels up to 8-fold higher than in the normal range with 5-44 CGG repeats (*8-10*). The elevated *FMR1* mRNA causes toxicity because the hairpin formation in the CGG

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expansion sequesters important proteins needed for normal cellular function (*11*). In those with FXTAS there is inclusion formation in both neurons and astroglial cells in the brain and in the peripheral nervous system and these inclusions have the excess *FMR1* mRNA, fragile X mental retardation protein (FMRP) and many other proteins and neurofilaments (*11-13*).

Decreased levels of FMRP are observed in some premutation carriers due to reduced translational efficiency of *FMR1* mRNA containing the expanded CGG repeat (*14-16*). Lowered FMRP in the premutation range will often lead to neurodevelopmental problems including intellectual disability (ID), ASD and ADHD (*1*), although additional environmental or medical problems such as seizures, trauma, toxins or additional genetic mutations may also cause further developmental problems in these carriers (*17-19*).

FMRP is a mRNA-binding protein that regulates hundreds of mRNA targets at the synapse and it inhibits protein translation that is stimulated by metabotropic glutamate receptors (mGluRs) (*20,21*). The lack of FMRP will cause down-regulation of the gamma-amino butyric acid (GABA) A and B receptors and up-regulation of metabotropic glutamate receptor 5 (mGluR5) throughout the brain (*22-24*). FMRP is highly expressed in neurons and FMRP is critical for synaptic plasticity (*25,26*). Accordingly, the absence of this key protein in the synapse irreversibly alters neuronal connectivity to produce significant behavioral disorders including ID, ASD schizophrenia, bipolar disorder, and major depression (*27-29*). Therefore, the role of FMRP in the synapse affects not only fragile X-associated disorders but other neuropsychiatric disorders such as schizophrenia in those without an *FMR1* mutation (*30,31*). Moreover, Aziz *et al*. (*32*) reported that *FMR1* expanded CGG repeat of premutation and gray zone alleles (45-54 repeats), may demonstrate some clinical features of fragile X syndrome (FXS) in those who presented clinically. It is uncertain if the gray zone allele has FMRP deficits but the premutation demonstrates FMRP deficits that increase according to the CGG repeat number increases (*33*).

Catatonia is a neuropsychiatric syndrome characterized by abnormalities of movement, speech, functional skills and behavior and most commonly associated with mood disorders, psychotic disorders, ASD or other medical conditions, in the absence of psychiatric illness (*34-37*). Its historical association with schizophrenia is now widely regarded as an erroneous tradition, and has been revised in the most recent version of the Diagnostic and Statistical Manual (DSM) for psychiatric disorders, 5th edition (*38*). The central symptom of catatonia is disturbance of motor activity (overall increased activity, reduced activity or mixed) and a variety of other abnormal movements (*e.g*. reduced eye blink rate, grimacing, sudden cessation of movements or immobility) (*39*). Clinical diagnosis of catatonia requires at least 3 of the following symptoms: stupor (no psychomotor activity), catalepsy (maintaining a passively induced posture), waxy flexibility (slight, even resistance to positioning by the examiner), mutism, negativism (opposition or no response to instructions or external stimuli), posturing (spontaneous and active maintenance of a posture against gravity), mannerisms, stereotypies, agitation, grimacing, echolalia or echopraxia (*38*).

There are three neurochemical alterations that basically underlie the mechanism of catatonia *i.e*. dopamine hypoactivity, GABA hypoactivity, and glutamate hyperactivity (*40,41*). The second and the third alteration are similar to the FMRP deficient phenotype that is seen in the majority of FXS and the minority of fragile X-associated disorders individuals. However, dopamine dysfunction also occurs in those with FXS leading to ADHD in childhood (*42*). Aging individuals with FXS and those with FXTAS often have Parkinsonian symptoms related to dopamine dysfunction (*43,44*). Catatonia is a heterogeneous condition with discriminate subtypes of pathophysiological mechanisms, consequently, multiple agents may be required to treat acute catatonia, maintain or prevent the reoccurrence of chronic catatonia (*41*). However, at this stage benzodiazepines and electroconvulsive therapy (ECT) remain the most effective treatments of catatonia (*45*).

Psychiatric spectrum disorders have been discovered associated with fragile X-associated disorders include FXS and fragile X premutation (FXPM) since the 1990s ranging from mild to severe, such as hypersensitivity to stimuli, hyperarousal, inattention, hyperactivity, explosive and aggressive behavior, ASD, social anxiety, depression, mood/bipolar disorders, and psychosis (*46-49*). The neurobiology of fragile X syndrome is relatively well defined, while scientists have struggled to understand the consistent neurobiology of ASD, the most common neurodevelopmental psychiatric disorder. In FXS, decreased levels of FMRP will result in the FXS phenotype due to impaired synaptic plasticity leading to the cognitive impairment, relatively constant behavioral abnormalities and ASD in the majority of patients (*50,51*). Psychosis is seen in less than 10% of those with FXS (*49*) and some cases suggest that those with mosaicism or a lack of methylation so that there is both lowered FMRP and elevated mRNA, often called a double hit, have a higher rate of psychosis (*52-57*). Psychosis combined with catatonia has not previously been described in those with FXS or in those with the premutation. Below is a case of a premutation male with both psychosis and catatonia.

2. Case Report

2.1. *Subject and setting*

A 25-year old male with the fragile X premutation,

who had been diagnosed with ADHD, ASD, bipolar disorder, obsessive compulsive disorder (OCD) and Tourette syndrome presented initially at age 20 years old to the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at UC Davis Medical Center. His CGG repeat size was 72, *FMR1* mRNA was 2.4 (± 0.23) times normal and his FMRP level was 18.3 (± 0.2) which is severely deficient. He was born at 32.5 weeks gestation (premature) and delivered by C-section. He was a second twin born; he weighed 4lb 8oz whereas his fraternal twin sister (fragile X negative) weighed 4lbs 2oz. He had respiratory distress, was intubated and was in the intensive care unit for 40 days. He suffered an intraventricular hemorrhage (IVH) that affected his frontal lobes, although subsequent MRIs in childhood were read as normal.

Although he was a good eater, he was developmentally delayed with sitting at 13.5 months, crawling at 14 months, walking at 16 months, saying words at 12 months and phrases at about 30 months. He received speech and language therapy at age 2 because of language delay. He had a variety of autistic features such as memorizing names, phone numbers, neighborhood license plate numbers, poor eye contact, stereotypies and was diagnosed with a pervasive developmental disorder not other specified (PDD NOS). His psychiatrist diagnosed Tourette syndrome and obsessive compulsive disorder (OCD) because verbal and motor tics and obsessive symptoms developed when he was approximately 6 years old. He was also diagnosed with Bipolar Disorder when he was 10 years old. He had staring spells from 19 months through the ninth grade that were initially thought to be seizures. His electroencephalography (EEG) showed mild abnormalities and he was treated with valproate for both possible seizures and mood stabilization. His EEG was normal at age 18. Because of mood instability he was treated with lithium beginning in mid-adolescence, although he had an episode of lithium toxicity related to dehydration. He was also tried on multiple antipsychotics, risperidone, olanzapine, ziprasidone, asenapine, and eventually clozapine with very little benefit and many side-effects so they were all discontinued.

He had multiple psychiatric hospitalizations during his teenage and young adult life mainly related to behavior and emotional problems including mood instability, aggression, agitation and subsequently catatonia diagnosed at age 21 years old. At the time of his presentation with catatonia, some symptoms had been present for the past one year and included markedly increased motor activity with incessant pacing up to 5 or 6 hours each day , other abnormal movements (stereotyped finger movements, change in posture, episodic cessation of motor activity/freezing and grimacing), reduced speech, sudden and relatively unprovoked physical aggression, increased anxiety and obsessional preoccupations, diminished awareness of surroundings for personal safety, decline in skill level including inability to perform previously attained skills, and a delusional belief that his "father was John Lennon". There were no hallucinations noted and the delusion was reported to be associated with starting an antipsychotic agent. There was progressive weight loss with his catatonia with a total loss of 50 lbs over a one year period.

Pharmacogenetics examination found that he had a *CYP2D6*2xN* (duplication) indicating he was an ultrarapid metabolizer (UM) of medications, and developed akathisia (inner restlessness secondary to antipsychotics) and then he became mute. He received high doses of benzodiazepines (lorazepam) with partial improvement, followed by weekly ECT beginning at age 20, leading to gradual improvement of his catatonic symptoms. He received 21 bilateral treatments using the Monitored Electro Convulsive Therapy (MECTA) device (MECTA Corporation, Tualatin, Ore). After this treatment and improvement of his catatonia his ECT was gradually decreased and stopped for a year and restarted when his catatonic symptoms gradually reoccurred.

2.2. *Assessments, follow-up, and interventions*

He was examined at the MIND Institute, UC Davis Medical Center at age 20 and then subsequently at age 25 years old. He is a tall young man with a long face but his ears are not prominent, although his palate is high arched and his jaw is mildly prominent. He also has large testicles (40 to 45 ml bilaterally). He does not have tremor nor ataxia but he appears mildly sedated on his medications. He demonstrates poor eye contact and he speaks in a slow monotone voice. The Autism Diagnostic Observation Scale (ADOS) module 4 score falls in the autism range at age 25 with a significant worsening of his autism score since age 20. The patient's mother provided previous cognitive test results from outside assessments, which are included in Figure 1. Figure 1 gives an overview of the trajectory of his cognitive results.

The patient shows a significant decline in both

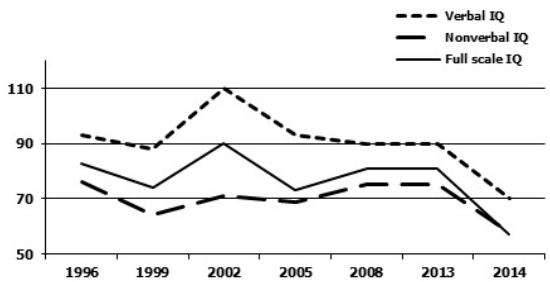

Figure 1. Overview of cognitive testing results. Trajectory of IQ testing 1996-2014, X-Axis shows the year the testing was done, the Y-axis shows the IQ score range (IQ scale: mean 100 and SD 15).

Table 1. Comparison of cognitive assessment sub-domains from 2005 and 2014

Items	2005 WISC-IV	2014 WAIS-IV
Verbal Comprehension[a]	93	70
Vocabulary	10	6
Similarities	9	3
Arithmetic	5	4[b]
Information	6	5
Comprehension	11	6
Perceptual Organization[a]	69	58
Picture completion	8	4
Block Design	6	6
Matrix Reasoning	7	1
Picture Arrangement	5	N/A
Visual Puzzles	N/A	2
Working Memory[a]	99	66
Digit span	9	4
Letter-Number Sequencing	Not reported	2
Processing Speed[a]	50	59
Digit Symbol Coding	4	1
Symbol search	Not reported	4

[a] Results given in Standard Score (Mean 100, SD 15), all other scores given in Scaled Scores (Mean 10, SD 3), [b] part of working memory in Wechsler Intelligence Scale for Children-IV (WAIS-IV).

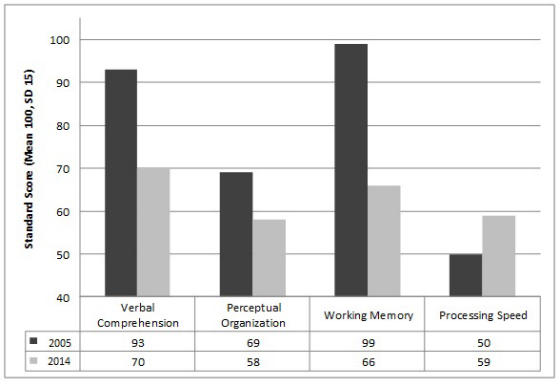

Figure 2. Comparison of IQ sub-domains from 2005 and 2014. The decreasing of three IQ sub-domains (verbal comprehension, perceptual organization, working memory) trajectory in 9 years.

verbal and nonverbal intellectual quotient (IQ) domains since age 20 (full scale IQ 81) compared to his current testing (full scale IQ 57) at age 25 (Figure 1). There is a recent significant drop in the full scale IQ score that is related to a decline in working memory capacity. From the literature, generally a decline in processing speed is reported during ECT (*58*), which could not be seen in our patient. The cognitive decline may or may not be directly related to the ECT, but his high level of benzodiazepine medication and sedation are likely contributing factors. Table 1 and Figure 2 give a more detailed overview of the different sub domains in the cognitive assessments. The patient was assessed with the Wechsler Intelligence Scale for Children-IV (WISC-IV) at age 15, and the WAIS-IV at age 25, both age-appropriate cognitive assessments with similar test-structure.

The psychiatric evaluation was based on the Structured Clinical Interview (SCI) for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) (SCID) (*59*) and conducted with the patient and his mother. The SCID confirmed the previously established diagnoses of Bipolar Disorder type II (age of onset 10 years old), psychotic symptoms and OCD. Per mother, the patient's obsessions and compulsions started at age 2 (as previously described), with an exacerbation around age 14, when he exhibited contamination fears, excessive hand washing, and watching favorite movies over and over. His psychotic symptoms became apparent around age 14 and consisted of misidentification delusions (believing that familiar people are famous persons), grandiose delusions (believing he will win a large amount of money or that he will become famous), and nihilistic delusions (thinking that everybody in the world will die, with him being the sole survivor). His magnetic resonance imaging (MRI) is normal except that his corpus callosum is somewhat narrowed.

He is currently receiving maintenance ECT treatment at age 25, with the goal of decreasing frequency as tolerated. Lorazepam was switched to clonazepam (1 mg three times a day and 0.5 mg at 8 pm). He is currently also taking lithium 300 mg three times daily and thioridazine 42.5 mg three times a day (because of his psychotic thinking and he has not tolerated all other antipsychotics), in addition to melatonin 3 mg at bedtime.

3. Discussion

The patient presented here is an individual with the fragile X premutation with both elevated *FMR1* mRNA levels and a significant deficit of FMRP, termed a double hit. He has features of FXS including a long face, high narrow palate and macroorchidism which are seen with more significant developmental problems or cognitive deficits in carriers (*60*). He had a history of questionable seizures which is also associated with ASD in our previous studies of carriers (*17*). His birth history included hypoxia which lowers FMRP levels and an IVH with damage to the frontal lobes that could add additional problems including executive dysfunction to the premutation condition. In addition, he has significant psychosis which is occasionally seen in those with low FMRP and high mRNA, a double hit FMRP (*52*).

FMRP deficits are not only associated with the severity of ID in FXS (*29,61-64*), but are also seen in other neuropsychiatric disorders without an *FMR1* mutation including schizophrenia, ASD, OCD, mood disorders, major depressive disorder and bipolar disorder (*27,30,31*). There may be many proteins/micro

RNAs (miRNAs) that regulate the expression of FMRP in those without an *FMR1* mutation. Kovacs *et al*. (31) found that the age of onset of schizophrenia and the IQ correlates with the level of FMRP in blood in psychotic patients that do not have an *FMR1* mutation. It is likely that those with the premutation may be even more vulnerable to the effects of lowered FMRP since their neurons already die earlier in culture related to the RNA toxicity of elevated *FMR1* mRNA (*65*). Further studies of psychotic thinking in those with the premutation and in those with the full mutation are warranted especially when it is associated with catatonia.

Individuals with autism are at an increased risk to develop catatonia, which occurs in 17% of adolescents and young adults with ASD (*36,66*). Age appears to be the risk factor of catatonia in addition to stressful events, passivity in social situations, and impairment of expressive language skills (*66*). Catatonia is a severe neuropsychiatric syndrome with a 2.5% risk of developing malignant catatonia (label used when no documented exposure to antipsychotic agents) and Neuroleptic Malignant Syndrome (NMS; label used when known exposure to antipsychotics). There is a considerable risk of mortality in individuals who develop malignant catatonia/NMS which is known to present with severe functional impairment, autonomic and cardiovascular instability, reduced food and fluid intake resulting in dehydration, weight loss, multi-organ failure and other medical complications (*41*). The neurochemical pathology of catatonia includes decreased GABA activity and up-regulation of the glutamate system, both of which occur in those with a premutation and a full mutation (*22,67,68*).

His treatment history was complicated by the pharmacogenetic result of *CYP2D6*2P/2P* variant which cause UM of *CYP2D6* metabolized drugs. Prevalence rates of the UM phenotype in American Caucasians is reported to be low at 4.3% compared to those in Ethiopians (30%) and in Saudi Arabian (20%) (*69-71*). Acknowledged UM allelic variants are *CYP2D6*1,*2,*35*, and **41* duplicated and multiduplicated, among those, *CYP2D6*2* and **41* are the most frequent variants of *CYP2D6* gene that cause extremely increased enzyme activity, wherein the lack of drug response/treatment failure is the most common clinical consequences (*72*). He has homozygous *CYP2D6*2P/2P* (*CYP2D*2xN*) promoter polymorphism (two copies of the gene), which may explain why he had failed multiple drug treatments. The failure of treatment may also be associated with various behavioral and psychiatric problems including catatonia, Bipolar Disorder type II with severe mood lability, aggression and psychotic thinking.

The patient's catatonia did not respond completely to benzodiazepines alone but he had a robust response to ECT. ECT is a well-established treatment for catatonia across the age span including children and adolescents (*73,74*). This is the first report of catatonia and ECT therapy in a premutation carrier, although the neurochemical changes that occur in both FXS and in premutation carriers (lower GABA and elevated glutamate, specifically mGluR5 up-regulation because of an FMRP deficit) is likely to predispose to catatonia (*40*). We would suggest testing for the *FMR1* mutation or at least checking FMRP levels when they become clinically available for those who experience catatonia.

Although this patient responded well to ECT therapy it is of great concern that his IQ declined over time. The etiology of his cognitive decline is unclear. Generally a decline in processing speed reported during ECT (*58*), but not decline in IQ. Cognitive functions are known to recover once ECT is completed and the recovery appears to be irrespective of the age of the patient (*75*). A recent review by the Food Drug Administration (FDA) found that cognitive function recovery following ECT may take up to six months after the completion of ECT (*76*). Therefore, measuring cognitive functions during ongoing ECT is likely to identify deficits, which are expected to recover upon completion of the treatment while a global score such as intellectual functioning will likely be influenced by deficits in language, fluency, spatial orientation and memory. However, other causes of cognitive decline, such as chronic catatonia should also be considered as contributing factors (*77*). We know that seizures can worsen cognitive and behavioral aspects of FXS and seizures are associated with ASD in premutation carriers (*17*). In addition his relatively high dose of benzodiazepines and thioridazine may have deleterious cognitive effects and could lead to intermittent sedation and a lack of stimulation in his environment especially since he is not in school currently. We have recommended cognitive stimulation with digital programs and vocational rehabilitation. His history of IVH might contribute to his cognitive deficits, although it would not explain the recent decline.

Recent work by the Benke laboratory at the University of Colorado has demonstrated that seizures in early life in rats without an *FMR1* mutation will disrupt the FMRP/Akt complex causing FMRP to pull away from the dendrites and move to the cell body, thereby disrupting the development of synaptic plasticity (*78*). Of concern is what ECT therapy will do to FMRP levels in those at risk for lowered FMRP levels particularly those with an *FMR1* mutation, such as the patient presented here (*77*). Studies of animal models that undergo ECT will help to evaluate this concern. In addition further work is needed to understand the relationship between premutation involvement, psychosis, ASD and catatonia and the most optimal treatments for these problems.

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