

Fragile X Premutation in Adult Psychiatry: Four Cases and Overview of Clinical Presentation

ARTICLE IN PRESS

E. Cem ATBAŞOĞLU¹, Direnç SAKARYA², Güvem GÜMÜŞ AKAY³, Ayşegül SAKARYA⁴,
Aylan TÜKÜN⁵

SUMMARY

Fragile X carrier status, also named as Fragile X premutation (FraX-PM), is defined by trinucleotide repeat expansions of shorter length compared to those that cause the full syndrome. Its clinical significance has been limited to the risk of further expansion to a full mutation in the offspring of carriers, until it was recently recognized as a clinical syndrome on its own, manifested by unique symptom constellations, as well as a combination of neuropsychiatric signs and symptoms that may be indistinguishable from several commonly seen disorders. The complex heterogeneity of its neuropsychiatric manifestations may render the diagnosis challenging, unless the clinician is familiar with the clinical picture and transmission pattern. We present four cases of FraX-PM, diagnosed in an adult psychiatry setting and confirmed by genetic testing. The aim of this report is to increase familiarity among psychiatric practitioners, since this common condition is seldom included in the current diagnostic practice, which is based on atheoretical definitions.

Key words: carrier state, diagnosis, genetic testing, Fragile X syndrome, premutation

INTRODUCTION

Fragile X syndrome (FraX) is the most common inherited cause of mental retardation and also the most common single gene cause of autistic disorder. First cases reported by Martin and Bell (1943) were children with mental retardation. At present, autistic disorder and dysmorphic findings (especially long face, prominent jaw, and large ears) are the two other commonly known components. The name was coined upon Lubs' (1969) description, in cytogenetic analysis, of the distal region in the long arm of X chromosome as 'fragile.' Krawczun et. al. (1985) determined the exact locus (Xq27.3). The responsible gene, identified by Verkerk et. al. (1991), was named as the *Fragile X mental retardation 1* (FMR1) gene.

Findings of the syndrome are indirect results of an expansion of the CGC nucleotide repeats in the 5'-untranslated region (5'-UTR) region of FMR1 (Reiss and Dant 2003). The CGG repeat number in this region is polymorphic in the general population, with common (normal) alleles including

5-54 repeats. Numbers above 200 result in methylation of the promotor region, thereby inhibiting the expression of FMR1 and the synthesis of its product, which is called the *Fragile X Related Mental Retardation Protein* (FMRP). Patients with this condition (a full mutation) exhibit the characteristic signs and symptoms of the syndrome (Tassone et. al. 1999). Individuals with 55-200 repeats are carriers. Carrier status is also termed as a premutation (PM), since repeat numbers show a tendency to increase during meiosis, being transformed into full mutations in the offspring (Fu et al. 1991, Nolin et. al. 2003). Classical FraX is rare (1/2500 - 1/4000), however diagnostic prevalence may not be an accurate reflection of the prevalence of the mutation allele (Hagerman 2008). Fragile X premutation (FraX-PM) is not uncommon, and may be relatively higher in some geographic locations (e.g., 1/100 - 1/150 in Israel) (Pesso et. al. 2000, Toledano-Alhadeef et. al. 2001).

Recently it has been recognized that FraX-PM is also associated with a variety of clinical manifestations (Farzin et al. 2006), among which two are systematically defined phenotypes seen

Received: 03.12.2011 - Accepted: 06.04.2012

¹M.D., Prof., Ankara University Brain Research Center, Ankara; ²M.D., Specialist, Denizli Military Hospital Psychiatry Section, Denizli; ³Ph.D., Assoc Prof., Ankara University Brain Research Center, 'M.D., Resident, Ankara University Faculty of Medicine, Department of Psychiatry, ⁴M.D., Prof., Ankara University Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey.

E-mail: e.cem.atbasoglu@medicine.ankara.edu.tr

in FraX-PM carriers and not in patients with the full syndrome. One is Premature Ovarian Failure (POF), which is commonly diagnosed on the basis of early menopause, although intermittent and unpredictable ovarian function may be a more reliable definition (Kokcu 2010). This is a heterogeneous condition with many possible causes other than the FraX-PM. The second, Fragile X Tremor Ataxia Syndrome (FXTAS) is a late-onset degenerative disorder that consists of intention tremor, cerebellar symptoms and cognitive disturbances, and is more common in males above the age of 50 (Chonchaiya 2009).

Until recently, many other symptoms and comorbid diagnoses in PM carriers have been regarded as coincidental. However, some of them are more common in carriers compared to the general population, so that the FraX-PM phenotype includes anxiety disorders, mood disorders, attention deficit hyperactivity disorder, impulse control disorder, and disorders of the thyroid, breast, glucose and lipid metabolism, as well as fibromyalgia, multiple sclerosis (MS) and mild forms of the manifestations of a full mutation, e.g., autism spectrum disorders, mild intellectual disabilities, and learning difficulties (Bourgeois et al. 2009).

Establishment of the genetic (etiologic) diagnosis in PM carriers presenting with psychiatric symptoms may increase awareness about POF and FXTAS and help with their diagnoses. It may also initiate a process of genetic counseling, which is especially needed by families that do not include a diagnosed index case with a full mutation. In cases with multiple early-onset and complex psychiatric symptoms, recognition of the FraX-PM phenotype may save the patient and the psychiatrist many other diagnostic tests and therapeutic interventions.

We report on 4 cases diagnosed in an adult psychiatry setting with FraX-PM and confirmed with genetic testing. The aim of this article is to increase awareness among psychiatrists about the possibility of a FraX-PM diagnosis in cases with complex or vague neuropsychiatric presentations.

GENETIC DIAGNOSIS

The number of polymorphic CGG repeats and methylation status were studied with the Southern Blot technique. Total genomic DNA was isolated from 500 µl peripheral blood samples collected in EDTA tubes, by using a *PureGene Blood Core kit B* (Qiagen, 1042606) according to the manufacturer's instructions. Isolated DNA was digested with *EcoRI* and methylation-sensitive *EagI* restriction enzymes. After restriction enzyme digestion, Southern Blot analysis was performed by using the *Fragile X Gene Prober™ GLFX Dig1* probe (Gene Link, 40-2004-41) (Biancalana et al. 1996).

CASES

Case 1: A 32 year-old woman was referred by her gynecologist, who had been treating her for infertility and needed to consult the case upon observing her lack of determination about having a child despite the apparent commitment to treatment. She was a university graduate, unemployed at the time of assessment, and had been married for 7 years. She had a history of two spontaneous abortions and one failed attempt at in vitro fertilization. Her recent pelvic ultrasonogram had indicated a low ovarian follicle reserve, bringing the issue again to the couple's agenda. The main complaint she reported to the psychiatrist was difficulty falling into sleep, which had been present on and off since her childhood. She was concerned about the harm her sleep problem might inflict on the baby during pregnancy and after delivery. She had previously seen neurologists and used several medications on an irregular basis. Her husband and parents viewed the problem as "fear of inability to sleep". The first time she had sought medical help for the sleep problem was when she was a university student. Somnograms were reportedly normal and she was prescribed a medication with the diagnosis of depression. Her medical records indicated no previous neurologic diagnosis, normal electroencephalograms and cranial magnetic resonance imaging findings on several occasions. Previous medications included zopiclone, clonazepam and mirtazapine prescribed in optimal doses. Her most recent diagnosis was Primary Insomnia. She reported irregular use of zopiclone during the month before and expressed her need to be assured that her insomnia would be completely cured so that she would never experience insomnia and need any medication should she become pregnant. Her anxiety was judged to have been present for a long time, with no obsessive or phobic content. She also reported that she had been feeling for a long time that she had many physical imperfections, especially on her face, which made her deeply sad and anxious. She spent long periods of time examining her face in the mirror, trying to convince herself that the flaws were minor. Reliable and potentially relevant information in her family history was as follows: Father was a perverse and inpatient man, and he had recently been experiencing hand tremors. Her younger brother had frequent arguments with her parents and suffered from depressive episodes. Another young brother had died at the age of 18 months with no cause known to the patient. Her paternal uncle was single, known to dislike social relations, lived alone in a small hometown, and did not get along well with family. A paternal aunt was known to have waited for years to have a baby after she had been married. Her paternal grandmother suffered from memory loss for a short time before her death.

Case 2: A 69 year-old man, on lithium carbonate for bipolar disorder, was evaluated upon the request of his neurologist, who had assessed him for hand tremors and wanted to know whether the reported diagnosis was accurate and if so whether lithium was the only option. The patient was an academic,

divorced, had two children, and had been on lithium with almost full compliance for about 20 years. He reported having benefited also from psychotherapy and methylphenidate, which had been prescribed for a brief period with the diagnosis of attention deficit hyperactivity disorder. Reliable and potentially relevant information in his family history was as follows: One maternal aunt had a diagnosis of MS; one cousin (son of another maternal aunt) had died from suicide; one other cousin (son of a third maternal aunt) was known as shy and introverted and his academic achievement was low; his mother was known by many people to be somewhat naive (e.g., she would sometimes make inappropriate comments in social conversation or ask questions that sounded odd for her level of education), she also suffered from chronic muscle pain with no known cause. The patient's first episode of psychosis with auditory hallucinations, persecutory delusions and lack of sleep dated back to his college years and he was diagnosed as manic. He reported having had only one other manic episode since then, and could provide less detail of this second episode. Further detailed work on history revealed no major mood episode but chronic and mild to moderate symptoms of depression. After he reported in the following assessment a brief period of intense cannabis use prior to the first episode, the diagnosis of bipolar disorder was reviewed and neurologic examination was repeated. In addition to resting tremor and intention tremor, he had difficulty with tandem gait and complained of a word-finding difficulty and occasional urinary incontinence. Cranial MRI revealed moderate cerebral and cerebellar atrophy, atrophy of the corpus callosum, a large cisterna magna, and increased signal intensity in T2-weighted images in the middle cerebellar peduncles. These signs and symptoms fulfilled the diagnostic criteria for "Definite FXTAS" as defined by Bourgeois et al (2009).

Case 3: A 25 year-old man was assessed as an outpatient, accompanied by his parents, after leaving the hospital where he was being treated for agitation, self injury (wrist-slashing) and auditory and visual hallucinations. He was single and a student at a sports academy. For the last few years he had been treated for schizophrenia and alcohol and substance abuse. He had previously been treated for behavioral problems at home and at school with the diagnosis of attention deficit hyperactivity disorder. He had been on antipsychotics and psychostimulants for 10 years with poor compliance. He reported the use of cannabis, *ecstasy* and LSD. His parents reported that as a child he had been mostly considerate and respectful, however naughty at times. During high school he was a favored player on the basketball team, and he had spent most of his time practicing and traveling without major problems, until his academic achievement started to decline. At initial evaluation, in addition to the symptoms described above, he was found to have a markedly short attention span, several visual illusions and synesthetic experiences, and impairment in judgement and reality testing. He was also noted to

have dolichocephaly, large ears and flat feet. His mother had a history of frequent upper respiratory tract infections and menopause at the age of 45. She also had hearing loss and was treated for a long time for thyroid disease and dyslipidemia. Her mother and brothers also had dyslipidemia.

Case 4: A 31 year-old man had been assessed for the first time at the age of 20 with chief complaints of moodiness, overly meticulous behavior, tendency to procrastinate, irritability and inability to control his anger. At that time he was a university student. He had been treated before with the diagnoses of treatment-resistant depression and rapid-cycling bipolar disorder. Treatment had consisted of antidepressants, mood stabilizers and antipsychotics, all at sufficient doses and for sufficient durations. At initial assessment his speech was difficult to follow due mainly to what appeared to be loose associations. He was appropriately engaged with the interview and, judging by his academic achievement, did not have an intellectual disability. On closer examination during the following interviews, this finding was judged to reflect an overinclusive line of thought and a general difficulty in social communication, resulting from a low capacity of joint attention and abstraction, tendency of repetitive behavior, and restricted interests. Thus, an autistic spectrum disorder was included in the differential diagnosis. He and his parents reported hyperactive behavior and a lack of ability to protect himself from danger during his preschool and primary school years. This was replaced in his early teens by overly meticulous behavior, attention to irrelevant details, and procrastination, which markedly decreased his academic achievement. During high school he mostly avoided ordinary social contact, and he spent most of his time with his few apparently new areas of interest. Despite his depression and loneliness he managed to obtain a score on the university entrance exam that was good enough to be accepted to an average licence program. Nevertheless his symptoms continued and his level of social functioning decreased further. He attributed most of his problems to either the failure of his parents to understand him or his intolerance of other people's ignorance and moral weaknesses. His sexuality was mainly limited to fetishistic voyeurism, which, in the context of impaired social cognition and impulse control, led to problems with law and further decreased his self respect and social and occupational functioning. During his 10-year follow up, his quality of life decreased as the social requirements appropriate for his age have changed. His parents' unrealistic expectations of a full recovery and adjustment also had an unfavorable impact on treatment. During the family interviews addressing this issue, his mother was observed to have similar deficits in social cognition. Overall, his follow-up and treatment addressed the diagnoses of obsessive compulsive disorder, social anxiety disorder, major depressive disorder, cluster B personality disorders, attention deficit hyperactivity disorder and paraphilia. Treatment included several medications, psychotherapy,

Table 1. Multiaxial Assessment with the DSM-IV TR criteria

I	II	III	IV	V
1. Dyssomnia NOS				
2. Generalized Anxiety Disorder	-	FraX-PM, POF	Problems with primary support group	41
3. Body Dysmorphic Disorder				
1. Alcohol Abuse				
2. Psychotic Disorder NOS*	-	FraX-PM, FXTAS	Problems with primary support group	55
3. Cannabis Abuse*				
1. ADHD				
2. Cannabis Dependence				
3. Alcohol Abuse				
4. Hallucinogen Abuse	-	FraX-PM	Problems related to interaction with the legal system / crime	21
5. Amphetamin- like Substance Abuse				
6. Amphetamin-like Substance –Int.				
7. Hallucinogen –Persisting Perception Disorder				
1. Asperger Disorder			Problems with primary support group	
2. ADHD	-	FraX-PM	Problems related to interaction with the legal system	21
3. Impulse Control Disorder NOS**			/ crime	

ADHD: Attention Deficit Hyperactivity Disorder, NOS: Not Otherwise Specified, FraX-PM: Fragile X Premutation, FXTAS: Fragile X Tremor Ataxia Syndrome, Int.: Intoxication, POF: Premature Ovarian Failure

* Not current / complete remission

** Mentioned in text as Fetishistic Voyeurism: DSM-IV TR stipulates that unusual sexual activity patterns that do not fulfill the criteria for any of the Paraphilias but are characterized by impulsivity be diagnosed as Impulse Control Disorder NOS.

family interventions and psychoeducation, and was unsuccessful. His grandmother was reported to have been on lithium for a long period of time with severe symptoms of hoarding and a diagnosis of recurrent major depressive disorder.

Table 1 summarizes the DSM-IV TR (American Psychiatric Association 2000) diagnoses in 5 Axes. Axis I diagnoses were reviewed using the Turkish version of the Structured

Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Çorapçıoğlu et. al. 1999).

DISCUSSION

Details of the diagnostic process are outlined in Table 2.

Table 2. FraX-PM diagnostic process

Case no. Referring specialty	Reason for referral / seeking help	Chief complaint / major finding	Clinical characteristics that suggest the diagnosis of FraX-PM with simultaneous presence (apart from positive family history)	CGG Repeat Number	Methylation status
1 OB-GYN	Indecisiveness about pregnancy Low ovarian follicle reserve	Indecisiveness, inability to sleep	POF Early-onset anxiety disorders Atypical sleep disorder	150	Homozygous-normal methylation / selective inactivation
2 N	Resting tremor and intention tremor Lithium use	Tremor and desire to discontinue lithium	Atypical history of psychosis and mania Subclinical ADHD and PDD Fulfillment of the criteria for definite FXTAS (Clinical: intentional tremor, cerebellar ataxia; Radiologic: White matter lesions in the middle cerebellar peduncles at MRI)	66	Normal methylation
3 -	Inadequate response to previous treatment	No complaint Psychosis symptom present	Attribution of psychosis to substance abuse and review of the diagnosis of schizophrenia ADHD Dysmorphic features	80-90 Somatic mosaicism	Normal methylation
4 -	Inadequate response to previous treatment	Problems in social relationships, low level of achievement	Atypical features of mood disorder Asperger Disorder ADHD Subclinical PDD symptoms in mother	81	Normal methylation

ADHD: Attention Deficit Hyperactivity Disorder, FXTAS: Fragile X Tremor Ataxia Syndrome, MRI: Magnetic resonance imaging, N: Neurology, OB-GYN: Obstetrics and Gynecology, PDD: Pervasive Developmental Disorder

The notable feature of these cases is that some of their descriptive diagnoses were too common to prompt reassessment and all the peculiarities in their clinical picture, such as atypical symptoms or course, inadequate treatment response, or an unusual combination of diagnoses that are common individually, could have been ignored, if we had relied on formally defined concepts of comorbidity, subtypes, or course-specifiers as explanations. Similarly, diagnostic categories or attributes that are liable to the physician's subjective bias in a descriptive assessment but are nevertheless accepted as objective or valid simply because they have long been present in psychiatric nomenclature and are still defined in current formal classifications (e.g., personality attributes or disorders diagnosed on the basis of the data provided by standard questionnaires rather than clinical expertise) could have decreased the likelihood of reviewing the diagnosis.

Missing the etiologic diagnosis in cases with FraX-PM might have many negative consequences: (1) Carriers of the PM and their families will miss many of the interventions that are indicated only by the genetic diagnosis (e.g., family interventions, especially when several members are affected; treatment of commonly associated conditions that may be asymptomatic, e.g., dyslipidemia, or symptomatic with manifestations that might be misattributed to the established psychiatric diagnosis, e.g., hypothyroidism), (2) carriers of the PM will not receive the genetic counseling they need or information regarding their own health risks, (3) attempts at managing a misdiagnosed treatment resistance in the setting of psychiatry might expose patients to unnecessary interventions and their side-effects, or the "treatment-resistant" label might increase patients' likelihood of receiving too many comorbid and potentially more stigmatized diagnoses, which is a risk that cannot be overseen, if one should "first ... not harm".

Correct identification of individuals with probable FraX-PM requires a detailed past and family history, exclusion of all general medical conditions that might cause the recently detected psychiatric symptoms, and reliance in the diagnostic process more on clinical reasoning than patient reports alone.

Referral of the potential FraX-PM patient to the medical geneticist requires careful timing. One reason for caution is the relatively low level of information available to the public in Turkey and a higher likelihood of fearful or guarded responses to any genetic information or relevant suggestion (Karabulut et. al. 2000). Secondly, the information provided could have an impact on family dynamics, and the psychiatrist's experience and familiarity with the particular patient and significant family members should be adequate to predict possible reactions and the consequences that will unfold.

All symptoms findings and disorders commonly seen in FraX-PM carriers are also common in the general population, therefore the nature of their association with the PM

must be investigated with controlled studies. However, as the prevalence of FraX-PM is not lower than the prevalences of many of the associated descriptive diagnoses, inclusion of FraX-PM among the possible diagnoses is advised if the disorders known to be commonly associated with FraX-PM (1) are multiple in a patient, or (2) show an inadequate response to treatment, or (3) display atypical features, or (4) are also present in family members.

We are currently studying the sensitivity and specificity of a FraX-PM diagnostic algorithm that we developed for use in adult psychiatry.

REFERENCES

- American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV) Washington D.C.
- Biancalana V, Taine L, Bouix JC ve ark. (1996) Expansion and methylation status at FRAXE can be detected on EcoRI blots used for FRAXA diagnosis: analysis of four FRAXE families with mild mental retardation in males. *Am J Hum Genet*, 59:847-54.
- Bourgeois JA, Coffey SM, Rivera SM ve ark. (2009) A review of fragile X premutation disorders: expanding the psychiatric perspective. *J Clin Psychiatry*, 70:852-62.
- Chonchaiya W, Schneider A, Hagerman RJ (2009) Fragile X: A Family of Disorders. *Adv Pediatr*, 56:165-86.
- Çorapçıoğlu A, Aydemir A, Yıldız M ve ark. (1999) DSM-IV Eksen I Bozuklukları için Yapılandırılmış Klinik Görüşme. Hekimler Yayın Birliği.
- Farzin F, Perry H, Hessel D ve ark. (2006) Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *J Dev Behav Pediatr*, 27 (2 Suppl): S137-44.
- Fu YH, Kuhl DP, Pizzuti A ve ark. (1991) Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell*, 67: 1047-58.
- Hagerman PJ (2008) The fragile X prevalence paradox. *J Med Genet*, 45: 498-9.
- Karabulut HG, Atbaşoğlu C, Akbostancı C ve ark. (2000) Huntington hastalığında genetik yordama testi: nörolojik, genetik ve psikiyatrik değerlendirme. *Parkinson Hastalığı ve Hareket Bozuklukları Dergisi*, 3:7-12.
- Kokcu A (2010) Premature ovarian failure from current perspective. *Gynecol Endocrinol*, 26:555-62.
- Krawczun MS, Jenkins EC, Brown WT (1985) Analysis of the fragile-X chromosome: localization and detection of the fragile site in high resolution preparations. *Hum Genet*, 69:209-11.
- Lubs HA (1969) A marker X chromosome. *Am J Hum Genet*, 21: 231-44.
- Martin J ve Bell J (1943) A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry*, 6:154-7.
- Nolin SL, Brown WT, Glicksman A ve ark. (2003) Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. *Am J Hum Genet*, 72: 454-64.
- Pesso R, Berkenstadt M, Cuckle H ve ark. (2000) Screening for fragile X syndrome in women of reproductive age. *Prenat Diagn*, 20:611-14.
- Reiss AL ve Dant CC (2003) The behavioral neurogenetics of fragile X syndrome: analyzing gene brain behavior relationships in child developmental psychopathologies. *Dev Psychopathol*, 15:927-68.
- Tassone F, Hagerman RJ, Iklé DN ve ark. (1999) FMRP expression as a potential prognostic indicator in fragile X syndrome. *Am J Med Genet*, 84:250-61.
- Toledano-Alhade F, Basel-Vanagaite L, Magal N ve ark. (2001) Fragile-X carrier screening and the prevalence of premutation and full-mutation carriers in Israel. *Am J Hum Genet*, 69:351-60.
- Verkerk AJ, Pierretti M, Sutcliffe JS ve ark. (1991) Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, 65:905-14.