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Ages of Onset of Mood and Anxiety Disorders in Fragile X Premutation Carriers

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Abstract

Objective—*FMRI* premutation carriers of both genders have a high lifetime prevalence of anxiety and depressive disorders, however little is known regarding the onset ages of these conditions. This study compared onset ages of mood and anxiety disorders in premutation carriers with typical onset ages of the same disorders in the general population.

Methods—Eighty-one premutation carriers (42% men; average age 62, SD 10) with and without FXTAS completed the Structured Clinical Interview for DSM-IV-TR. Onset ages of mood and anxiety disorders were compared to the corresponding typical population onset ages using the signed rank test.

Results—Overall median onset ages of MDD (46 years old, $p < 0.0001$), panic disorder (40 years old, $p = 0.0067$), and specific phobia (11.5 years old, $p = 0.0003$) were significantly higher in premutation carriers compared to the general population. Median MDD onset ages in male carriers (52 years old) and those with FXTAS (49.5 years old) were significantly higher relative to the general population (median 32, both $p < 0.0001$). Tremor and ataxia emerged significantly later than MDD and the anxiety disorders studied.

Conclusion—Depressive and anxiety disorders in premutation carriers have a later onset compared to the general population, but precede the onset of motor symptoms. This may be due to progressive mRNA toxicity in the limbic system, white matter changes leading to neuronal dysconnectivity, and interaction with environmental factors. Psychosocial factors may be protective. Further research is needed to understand the full spectrum of psychiatric phenotypes in *FMRI* premutation carriers.

Keywords

FMRI premutation; fragile X tremor/ataxia syndrome (FXTAS); onset age; MDD; depression; anxiety

BACKGROUND

Premutation expansions (55-200 CGG repeats) of the fragile X mental retardation 1 (*FMRI*) gene occur in the general population with an estimated prevalence of 1 per 130-260 women and 1 per 250-810 men [1]. When premutation alleles are maternally transmitted, they may expand into the full mutation range, to over 200 repeats. The full mutation results in partial or complete silencing of the gene and thus deficiency or absence of the *FMRI* protein (FMRP), clinically manifesting as the fragile X syndrome (FXS). The premutation is associated with normal or slightly reduced FMRP levels although *FMRI* mRNA is increased [2]. The excess mRNA leads to sequestration of proteins, forming intranuclear inclusions found in neurons and astrocytes throughout the brain, peripheral nervous system, and various organs [3-5].

Fragile X-associated tremor/ataxia syndrome (FXTAS) is the neurodegenerative disorder described in premutation carriers [6, 7]. FXTAS affects up to 45% of older male carriers and up to 16% of female carriers [8-10]. Clinical manifestations of FXTAS include intention tremor, ataxia, parkinsonism, peripheral neuropathy, autonomic dysfunction, psychiatric symptoms, and cognitive deficits [11]. Tremor and ataxia typically start between 50 and 70 years of age, preceding cognitive impairment by a decade [8, 11, 12]. Women who are carriers may also develop primary ovarian insufficiency, fibromyalgia, hypertension, migraines, and thyroid disease, and have more neuropsychiatric symptoms (anxiety and sleep disturbances), compared to non-carrier women [9, 10, 13-15].

Psychiatric features in premutation carriers of both genders include anxiety, depression, irritability, personality change, disinhibition, and cognitive impairment [16-19]. Hessel et al. [16] found higher obsessive-compulsive symptoms in premutation carriers of both genders, compared to published norms. Almost two thirds of premutation carriers with FXTAS may develop mood disorders in their lifetime, and 52% have anxiety disorders [20]. Carriers without FXTAS had a significantly higher lifetime prevalence of social phobia than the general population, whereas the prevalence of major depressive disorder (MDD), panic disorder, posttraumatic stress disorder, and specific phobia was significantly higher in those with FXTAS, compared to the general population [20]. The FXTAS dementia has been described [12, 21, 22], with deficits involving multiple cognitive domains, including notable executive dysfunction [23-25]. Dementia may occur later in the illness course, more commonly in men, although it has also been reported in women [26-29]. Up to 42% of men in advanced stages of FXTAS had dementia [12; 30].

The prevalence of mood and anxiety disorders in carriers has been recently described and compared to the general population [18, 20]. However, little is known to date about the onset of psychiatric disorders in premutation carriers and whether the premutation predisposes individuals to earlier manifestations of psychopathology. Roberts et al. [18]

studied 93 women carriers and reported a median age of onset of 27 years for MDD and of 15.5 years for anxiety disorders. In this study we investigated the onset ages of selected psychiatric disorders in carriers relative to the general population.

METHODS

Participant recruitment

The study protocol was approved by the Institutional Review Board at the University of California, Davis. Participants were selected from a cohort of 120 premutation carriers enrolled in a large research study at the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute between September 2007 and October 2010. All participants gave informed consent. Most carriers were identified through cascade testing from families with a member with FXS. There was a partial overlap with participants described by Bourgeois et al. [20] however only those with MDD, generalized anxiety disorder (GAD), panic disorder, social phobia, and specific phobia were included in the present study, in order to yield an adequate sample size for analytic purposes.

Evaluation protocol

The evaluation protocol consisted of genetic testing, a detailed history and physical (including neurological) examination, a comprehensive neuropsychological test battery, and a psychiatric assessment based on the Structured Clinical Interview for DSM-IV-TR (SCID) [31]. The SCID was customized prior to initiating this study, as informed by literature review and our previous research experience with premutation carriers [17-19] and included the mood, anxiety, substance use, somatoform, and adjustment disorders modules, as well as the psychotic symptom screening questions. Diagnoses were established based on the DSM-IV-TR diagnostic criteria [32], for both current and lifetime conditions. Onset of psychiatric and neurological symptoms was ascertained based on the participants' report; collateral history was collected if participants had memory difficulties. Multiple psychiatric diagnoses in the same patient were recorded as separate cases, thus one individual could account for multiple cases. The FXTAS diagnosis was established by expert clinicians, based on previously published diagnostic criteria [33].

Measures of cognitive ability included the intelligence quotient (IQ) determined using the Wechsler Adult Scale of Intelligence-Third Edition [34] and the Mini-Mental State Examination [35], although this test is geared more towards exploring cortical functions and thus suboptimal in the presence of subcortical processes, such as in FXTAS. Molecular studies, including CGG repeat size and *FMRI* mRNA, were performed as described below. Genomic DNA was isolated from peripheral blood leucocytes (5 ml of whole blood) using standard methods (Puregene Kit; Gentra Systems, Inc., Minneapolis, MN). Southern blot analysis, PCR analysis and calculation of the repeat size for both methods were performed as described by Tassone et al. [36]. Total RNA was isolated from peripheral blood leukocytes using Tempus tubes (Applied Biosystems, Foster City, CA). Reverse transcriptase reactions and quantifications of *FMRI* mRNA were performed as described by Tassone et al. [2].

Typical ages of onset of psychiatric disorders

Ages of onset of psychiatric disorders in the general population were established through a thorough literature review, taking into consideration the median (50% percentile band) age. References included prospective follow-up studies of up to 50 years [37-40] and large U.S. population-based studies: the Epidemiologic Catchment Area Study (ECA) [41], the National Comorbidity Survey Replication (NCS-R) [42], and the National Epidemiologic Survey on Alcohol and Related Conditions [43, 44]. If any discrepancy was noted in ages of onset across different studies, ages resulting from the larger epidemiologic study were used in the analysis. Typical onset ages were determined to be: 32 years old for MDD [37-39, 45] and GAD [39, 44, 45], 24 years old for panic disorder [45, 46], 13 years old for social phobia [45, 47, 48], and 7 years old for specific phobia [40, 43, 45, 47].

Statistical Analysis

Our primary analysis examined the ages of onset of psychiatric disorders in premutation carriers, relative to typical ages of onset for these specific disorders in the general population. Most study participants were able to remember the exact ages when they first experienced the symptoms, especially if these were associated with traumatic incidents. However, some could only recall experiencing mood and/or anxiety symptoms for the first time during certain decades (e.g., in their 20s). In these cases, decades were approximated by median ages, for example 0-9 years, by 4.5 years old; 10-19 years, by 14.5 years old; and so on. The observed onset ages of each psychiatric disorder were then compared to the corresponding onset ages in the general population, using the signed rank test. P-values were adjusted for multiple testing in the primary analysis using the Hochberg method to control the family-wise type I error rate [49]. Gender and marital status effects, as well as correlations of onset ages with molecular data, were explored. Onset ages of motor symptoms (ataxia and tremor) relative to onset ages of the psychiatric disorders were also examined descriptively, using the signed rank test.

RESULTS

Participant characteristics including age, gender, education level, IQ, MMSE score, *FMRI* mRNA, and CGG repeat size are summarized in Table 1, stratified by FXTAS status. Thirty-four premutation carriers did not have FXTAS, 45 had FXTAS, and the diagnosis was unclear in two cases. Cognitive and molecular characteristics of the study cohort were consistent with characteristics of premutation carriers. The final sample of 81 participants included 34 (42%) men. Average age was 62 years (range, 39-87; SD 10), with 14 years of education on average (range, 5-23; SD 3). Among the 47 carriers diagnosed with MDD, 23 (49%) also had a history of one or more anxiety disorders. Among the remaining 34 participants, 20 (59%) had one type of anxiety disorder, 8 (23%) had two, and 6 (18%) had three lifetime anxiety disorders.

The observed onset ages of psychiatric disorders in premutation carriers compared to the typical onset ages in the general population in the referenced studies are presented in Table 2. Table 2 also shows how many carriers in each category provided exact ages of onset on SCIDs. The observed MDD median onset age in premutation carriers was 46 years,

significantly higher than the onset age in the general population ($p < 0.0001$). This higher MDD onset age was due to individuals with FXTAS (median 49.5 years old, $p < 0.0001$); onset age among carriers without FXTAS was not different from the typical MDD onset age (median 34 years old, $p = 0.4293$).

With regard to the anxiety disorders investigated, median ages of onset in premutation carriers were significantly higher than in the general population for panic disorder (40 years old, $p = 0.0067$) and specific phobia (11.5 years old, $p = 0.0003$). When stratified by FXTAS status, median age of specific phobia onset in those without FXTAS (12.5 years old) was significantly higher relative to the general population (7 years old, $p = 0.0026$). Although for panic disorder, median onset age in carriers with FXTAS (37 years old) was higher compared to the general population (24 years old), there was insufficient data for hypothesis testing. Median onset ages of GAD (19 years old) and social phobia (7 years old) in premutation carriers were not significantly different than in the general population. Analyses stratified by FXTAS status for GAD and social phobia were similar to analyses on all carriers.

Next, gender differences in onset ages were explored. With the exception of MDD, where the sample size allowed for a preliminary analysis (17 men, 26 women), there was insufficient data to conduct a statistical analysis stratified by gender. Among premutation carriers, MDD onset age in men (median 52) was significantly higher than in women (median 34, $p = 0.023$). When compared with the mean onset age in the general population (32 years old), male carriers had a significantly higher age of onset (median 52, $p < 0.0001$) but there were no significant differences for female premutation carriers (median 34, $p = 0.1917$).

Among the 81 carriers in the study, except for one participant whose marital status was unknown, 64 (79%) were either married or partnered and 16 (20%) were widowed or divorced. There was no significant difference between the two marital status groups for MDD onset age. There was insufficient data to explore marital status effects for the other psychiatric disorders.

The correlation of onset ages with *FMRI* mRNA and CGG repeat sizes was tested based on the available molecular data, in 35 carriers. There was a significant positive correlation of MDD onset age with *FMRI* mRNA ($p = 0.0149$), but not with CGG repeat size. No significant correlation was detected for the other psychiatric disorders.

A descriptive analysis was performed to determine the onset ages of motor symptoms, specifically ataxia and tremor, relative to onset ages of mood and anxiety disorders in carriers. The median onset age of ataxia was 55 years old, significantly higher than onset ages of the psychiatric disorders studied (MDD, $p < 0.0001$; GAD, $p = 0.0039$; panic disorder, $p = 0.0117$; social phobia, $p < 0.0001$; specific phobia, $p < 0.0001$). Results were similarly significant with respect to tremor (median onset age, 54) for each psychiatric disorder, except for panic disorder. This is not surprising, since FXTAS onset is around age 50, while MDD and anxiety disorders usually present earlier.

DISCUSSION

This is the first investigation of onset ages of mood and anxiety disorders in *FMRI* premutation carriers of both genders, with and without FXTAS, as well as an exploration of the time course of psychiatric manifestations relative to tremor and ataxia (in carriers with FXTAS). Interestingly, and contrary to our hypothesis, the median onset ages of MDD, panic disorder, and specific phobia in premutation carriers were significantly higher than in the general population. In carriers with FXTAS, only the median onset age of MDD was significantly higher compared to the general population. A limitation of our study derived from approximating some onset ages by decades (see Table 2). We will thus focus the discussion on the carriers with MDD who constituted the largest group (N = 43), with almost 100% exact onset ages (N = 41) collected.

The later onset of MDD in premutation carriers relative to the general population may be due to several reasons. Etiology of psychiatric illness is multifactorial, determined by biological and psychosocial contributors. We hypothesized that mRNA toxicity building over time in the limbic system may play a role. Premutation carriers may become more vulnerable to stressors later in life, in the context of complex neurodegenerative changes. Psychiatric illness may thus manifest for the first time in late life, once the disease burden in certain cortical and subcortical areas has reached a critical level. Huntington's disease (HD) is the prototype trinucleotide repeat illness and has served as a model for the study of other neurodegenerative diseases such as Alzheimer's and Parkinson's disease. All these disorders share features including: delayed onset; selective neuronal vulnerability; widespread expression of disease-related proteins throughout life; abnormal protein processing and aggregation; and cellular toxic effects [50]. FXTAS shares some of these aspects, although not all: FMRP is normal or slightly decreased, while the excess mRNA becomes toxic. In a recent study of 1766 European HD Network's Registry patients, 48% presented with motor symptoms, 20% had a psychiatric onset, 8% had cognitive signs first, and 13% had a mixed onset [51]. Also, 40% of patients had a lifetime history of severe psychiatric disturbances (psychosis, aggression and suicidal ideation) [51]. Higher CAG repeat size predicts an earlier HD onset, accounting for up to 50-70% of variance in onset age; the remainder is likely due to modifying genes and the environment [50]. In our study, later MDD onset ages were associated with higher mRNA levels but not with CGG repeat size, although this needs to be interpreted cautiously in light of the limited molecular data available. No clear correlation of CGG repeats with psychiatric symptoms has been shown so far [16, 20]; Hessler et al. [16] found elevated *FMRI* mRNA levels to be associated with obsessive-compulsive symptoms in male carriers. Future research could also investigate any correlation of onset ages with FMRP levels.

Diffusion tensor imaging studies revealed abnormalities in the cerebellar-brainstem and limbic systems of men with FXTAS [52]. White matter changes, leading to neuronal dysconnectivity, may also contribute to pathology associated with the premutation and have been postulated as a mechanism in conversion and other psychiatric disorders [53]. In multiple sclerosis (MS), which may be erroneously diagnosed or co-occur with FXTAS in premutation carriers [54], depression, psychosis, and cognitive deficits may be present and are believed to be caused by demyelinating lesions in frontal-subcortical circuits [55].

However, psychiatric symptoms are only associated with MS onset in 2% of cases [56], which is different than the FXTAS progression we observed.

Premutation carriers are typically emotionally strong individuals, with high educational and professional attainment and marked obsessive-compulsive traits [16, 23]. When facing life stressors, they may use coping strategies such as intellectualization and problem solving [30]. These coping skills can mitigate the development of psychiatric symptoms, serving as protective factors. Most of our participants were married, although we found no differences in MDD onset ages across marital status groups. Having never been married or being divorced, separated, or widowed increases the MDD risk in the general population and specifically in women with the premutation [18, 57].

We also observed a gender difference, with MDD onset age in male (but not female) carriers being significantly higher than in the general population. Female carriers may have children with FXS, and the intense stress of raising children with developmental delays may contribute to an earlier onset of MDD than in male carriers, whose daughters may have the premutation but often are asymptomatic and only get diagnosed as carriers in adulthood. Child behavioral problems are strongly associated with maternal stress, anger, anxiety, and depressive symptoms, and inversely correlated with mothers' quality of life [58].

Our findings strongly suggest that psychiatric symptoms precede motor disturbances in FXTAS. It has been previously shown that neurological symptoms may be followed by cognitive dysfunction, especially in men, about a decade later [11, 12], but this is the first study to explore the time course of psychiatric symptoms relative to the other clinical manifestations of FXTAS. Patients with FXTAS face physical limitations, even severe disability, in advanced illness stages. It is nevertheless unlikely that the late onset of MDD we observed was due to the adjustment to having a severe neurodegenerative disease, for two reasons. First, mood and anxiety disorders secondary to medical conditions (including FXTAS) and adjustment disorders were recorded as separate diagnoses and not included in the analysis. Second, ataxia and tremor emerged later than MDD and the anxiety disorders studied (many participants did not even know they had the premutation until years after developing psychiatric symptoms). This finding is salient for psychiatrists, important to keep in mind when evaluating individuals with later onset of MDD and panic disorder than expected in the general population. Genetic testing should be considered in patients with a family history of FXS, mental retardation, developmental delays, or autism spectrum disorders.

A possible confounder might be related to the face-to-face interviews. Respondents prefer to disclose sensitive health matters in anonymous or computer-administered questionnaires rather than through personal interviews [59, 60]. Furthermore, lifetime histories of phobias established through interviews may not be reliable, both due to subject recall of unreasonable fears and to interviewer assessment of which fears constitute phobias [61]. Another limitation is that onset ages of psychiatric disorders were established through SCID, which could introduce a recall bias. Our participants were older (average age, 62) and may not have remembered precisely the onset of symptoms many years prior to the interview.

However most had intact cognitive functioning (mean MMSE, 29) and similar approaches were used in the referenced epidemiologic studies.

The sample size in this study was moderate; a larger sample would help improve the precision of the estimation of onset ages and enhance the analytic power for some psychiatric disorders when stratified by FXTAS status. Other psychiatric disorders could be explored (e.g., bipolar disorder, other anxiety disorders, or substance use disorders) as well. Larger studies will allow for further stratification on potential confounders, including age, race, gender, education, and socioeconomic factors, which we were unable to address in this study. Also, future studies could explore the sequence of anxiety and mood disorders in those individuals with co-occurring conditions, since half of our carriers diagnosed with MDD had comorbid anxiety disorders.

In conclusion, premutation carriers of both genders with and without FXTAS often develop anxiety and mood disorders. Overall, MDD, panic disorder, and specific phobia had later onset than in the general population, but preceded the onset of motor symptoms. MDD in male carriers and in those with FXTAS also had onset significantly later compared to the general population. Putative explanatory mechanisms include progressive mRNA toxicity in the limbic system, white matter abnormalities leading to neuronal dysconnectivity, and interaction with environmental factors, as well as the presence of protective factors (high psychological strength and social support). Further research is needed to understand the full spectrum of psychiatric phenotypes in premutation carriers and the related risk factors and protective strategies.

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Table 1

Participant characteristics.

	N	Min	Mean	Max	SD
All premutation carriers					
Age (years)	81	39	62	87	10
Education (years)	70	5	14	23	3
CGG repeats	74	58	89	190	23
FMRI mRNA	70	1.26	2.60	5.53	0.77
Full Scale IQ	68	76	108	139	15
MMSE	75	20	29	30	2
Male gender, n (%)	34 (42%)				
Married/Partner, n (%)	64 (79%)				
Carriers without FXTAS					
Age (years)	34	39	57	85	10
Education (years)	28	12	15	20	2
CGG repeats	30	58	88	190	29
FMRI mRNA	28	1.26	2.28	3.22	0.45
Full Scale IQ	28	78	109	139	16
MMSE	30	27	30	30	1
Male gender, n (%)	8 (23%)				
Married/Partner, n (%)	24 (71%)				
Carriers with FXTAS					
Age (years)	45	40	66	87	9
Education (years)	40	5	14	23	3
CGG repeats	43	58	90	133	17
FMRI mRNA	42	1.59	2.81	5.53	0.86
Full scale IQ	40	76	107	134	15
MMSE	43	20	28	30	3
Male gender, n (%)	26 (58%)				
Married/Partner, n (%)	38 (84%)				

Min = minimum, Max = maximum, SD = standard deviation

IQ = Intelligence Quotient, MMSE = Mini-Mental State Examination.

Table 2

Onset ages of psychiatric disorders in premutation carriers, compared to the general population.

	N	Exact ages	Min	Median	Max	General population	p-value ^a
All premutation carriers							
Major depressive disorder	43	41	13	46	70	32	< 0.0001*
Generalized anxiety disorder	12	9	4.5	19	61	32	0.1079
Panic disorder	16	15	8	40	63	24	0.0067*
Social phobia	25	16	4.5	7	66	13	0.4155
Specific phobia	34	25	4	11.5	45	7	0.0003*
Carriers without FXTAS^b							
Major depressive disorder	15	14	13	34	63	32	0.4293
Generalized anxiety disorder	4	3	4.5	20	61	32	--
Panic disorder ^c	9	9	8	43	63	24	0.0742
Social phobia	12	6	4.5	4.75	50	13	0.3423
Specific phobia	18	13	4.5	12.5	45	7	0.0026*
Carriers with FXTAS							
Major depressive disorder	26	25	16	49.5	70	32	< 0.0001*
Generalized anxiety disorder	8	6	4.5	15.5	50	32	0.0547
Panic disorder	5	5	21	37	60	24	--
Social phobia	13	10	4.5	13	66	13	0.9844
Specific phobia	15	11	4	13	40	7	0.0698

N = number of carriers with the psychiatric disorder; Exact ages = number of carriers with exact ages of onset available; Min = minimum; Max = maximum age

^a p-value not provided for sample size < 5

^b FXTAS diagnosis was unclear for 2 premutation carriers

^c One male outlier with onset age 50 was removed

* Significant after using the Hochberg method to control the family-wise type I error rate.