Psychiatric Phenotype of the Fragile X–Associated Tremor/Ataxia Syndrome (FXTAS) in Males: Newly Described Fronto-Subcortical Dementia

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Objective: The authors describe and quantify the neuropsychiatric symptoms present in a cohort of males with the fragile X mental retardation 1 (*FMR1*) premutation allele who have developed fragile X–associated tremor/ataxia syndrome (FXTAS).

Method: Fourteen male carriers of the *FMR1* premutation who had clinical manifestations of the FXTAS syndrome and 14 age- and education-matched controls were assessed with the Neuropsychiatric Inventory (NPI), formal cognitive testing, and genetic analysis.

Results: Males with FXTAS had significantly higher total NPI scores ($p < .004$) and significantly higher scores on the agitation/aggression ($p < .004$), depression ($p < .004$), apathy ($p < .004$), disinhibition ($p < .004$), and irritability ($p < .004$) scales, compared with controls. Cognitive performances on the Mini-Mental State Examination did not correlate with severity of symptoms on the NPI.

Conclusions: The neuropsychiatric manifestations of FXTAS, based on this preliminary report, appear to cluster as a fronto-subcortical dementia. Clinicians encountering patients with clinical dementia with motor symptoms suggesting FXTAS should consider genetic testing to determine whether the patient's dementia syndrome is secondary to a fragile X premutation carrier status.

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Our understanding of the fragile X mental retardation 1 (*FMR1*) gene has changed recently because of evidence of clinical problems in carriers of the *FMR1* premutation. While the *FMR1* full mutation is known to cause fragile X syndrome, the most common inherited form of mental retardation, it has been discovered that a premutation can cause the fragile X–associated tremor/ataxia syndrome (FXTAS) in a subgroup of older carriers.[1–6] Premutation alleles are defined by a CGG trinucleotide expansion ranging from 55 to 200 repeats in the 5' untranslated region of the *FMR1* gene. The premutation occurs in approximately 1/800 men and 1/250 women in the general population.[7,8] In one study[1] of prevalence in a cohort of 123 families with fragile X in California, the number of older male carriers with the premutation who developed tremor and ataxia was significantly different from controls and included 17% in their 50s, 38% in their 60s, 47% in their 70s, and 75% in their 80s. This high prevalence rate has not yet been confirmed by other studies. However, recent screening studies of patients who present with ataxia have demonstrated that 4% to 5% of ataxia patients have the *FMR1* premutation.[9,10]

FXTAS is a neurologic syndrome characterized by a progressive intention tremor and ataxia. Patients may also

Table 1. Participant Demographics of Male Subjects With and Without FXTAS

Demographic	FXTAS, %[a] (N) (N = 14)	No FXTAS, %[a] (N) (N = 14)
Age, y		
50–54	0 (0)	7 (1)
55–59	7 (1)	14 (2)
60–64	21 (3)	29 (4)
65–69	50 (7)	21 (3)
70–74	7 (1)	7 (1)
75–79	14 (2)	21 (3)
Education		
High school	100 (14)	93 (13)
College	86 (12)	86 (12)
Advanced degree	43 (6)	57 (8)
Ethnicity		
White	79 (11)	79 (11)
American Indian	7 (1)	0 (0)
Unknown	14 (2)	21 (3)

[a]Percentages may not add up to 100% due to rounding.
Abbreviation: FXTAS = fragile X–associated tremor/ataxia syndrome.

Table 2. FXTAS Stages

FXTAS Stage	Clinical Description
1	Subtle or questionable signs
2	Minor, but clear, tremor and/or balance problems; minor interference with ADL
3	Moderate balance and/or tremor problems and at least occasional falls with significant interferences with ADL
4	Severe tremor and/or balance problems. Use of a cane or walker
5	Use of a wheelchair on a daily basis
6	Bedridden

Abbreviations: ADL = activities of daily living, FXTAS = fragile X–associated tremor/ataxia syndrome.

have features of parkinsonism, peripheral neuropathy, and autonomic dysfunction, including hypertension and impotence. Neuroradiological findings include global brain atrophy and white-matter disease, with an enhancement of T2 signal intensity in the middle cerebellar peduncles (MCPs) and in the periventricular area.[3]

These motor symptoms are often accompanied by a progressive cognitive decline, including memory loss and executive function deficits, with a gradual emergence of dementia in some individuals.[4–6] Additional psychiatric problems in patients with FXTAS include mood and anxiety symptoms and irritable behavior. However, the psychiatric comorbidity in FXTAS has not yet been studied specifically.[3,6] While the progression of cognitive decline in individuals with FXTAS is variable, the authors are beginning to observe a pattern of involvement emerge from neuropsychological assessments performed on individuals with the syndrome.

In addition to impaired executive functioning, cognitive deficits, such as decline in working memory and information processing, have been observed in later stages of the disorder. Many individuals appear to remain relatively stable for a decade or longer, whereas others experience a rapid downhill course (within 5 to 6 years), which also leads to clinical dementia.

In a recent study of 64 male carriers with FXTAS, 21% had a decline in IQ to below 85, in addition to adaptive problems that were consistent with dementia.[6] Deficits in cognitive functioning may be associated with and/or preceded by psychiatric symptoms such as depression, anxiety, irritability, and behavioral disinhibition, as are seen with other dementia syndromes.[11] Given the recent discovery of FXTAS, research into the diagnosis and a more comprehensive understanding of the cognitive decline and clinical features are emerging. Identifying the neuropsychiatric symptoms that accompany FXTAS will advance our understanding of the phenotypic characteristics of this disorder and help to direct treatment of affected individuals.

METHOD

Our study reports on the neuropsychiatric symptoms observed in carrier males clinically diagnosed with FXTAS compared with age- and education-matched males without the *FMR1* premutation.

Participants

Patient demographic information is summarized in Table 1. Participants with FXTAS in this study included 14 adult male patients (mean age = 66 years [SD = 8.1]) recruited from all regions of the United States to participate in ongoing research on FXTAS at the University of California, Davis, M.I.N.D. Institute. All affected males had at least completed their high school education, with the majority (86%) having a college degree and 43% having an advanced degree.

Affected males were diagnosed with either "definite" or "probable" FXTAS using criteria defined by Jacquemont et al.[3] These criteria are based on a clinical description of the degree of movement and gait problems, and a score is assigned to each FXTAS stage, as outlined in Table 2. Mean FXTAS score for the 14 patients (on a 6-point scale) was 3.86 (range 2–5). None of the patients in our sample had an FXTAS score of 1, which signifies subtle or questionable signs, and none had an FXTAS score of 6, which signifies a bedridden condition. One man had a score of 2, defined as a clear tremor or balance problem that does not interfere with functioning. There were 2 individuals with an FXTAS score of 3, a stage of the disorder characterized by moderate balance or tremor, at least occasional falls, and symptoms significantly interfering with activities of daily living. The majority of our affected patients, 9, had an FXTAS score of 4. During this stage, individuals exhibit severe tremor and/or balance problems and require a cane or walker. Two patients had an FXTAS score of 5, a stage of the disorder in which patients need a wheelchair.

Table 3. FXTAS, NPI, MMSE, and Molecular Scores for Each Participant With FXTAS

Case	FXTAS Score	NPI Score	MMSE Score	No. of CGG Repeats	*FMR1* mRNA Level (SE)
1	4	47	26	73, 87	2.64 (0.13)
2	4	24	26	90	3.61 (0.13)
3	4	44	27	89	2.82 (0.45)
4	4	48	30	90	3.69 (0.50)
5	3	40	16	130	3.46 (0.06)
6	4	8	30	103	4.42 (0.14)
7	3	48	30	94	3.30 (0.13)
8	5	17	25	115	3.76 (0.04)
9	2	21	26	125	NA[a]
10	4	26	30	108	4.15 (0.37)
11	4	34	29	116	4.02 (0.43)
12	4	40	27	84	2.21 (0.18)
13	4	29	22	89	3.42 (0.48)
14	5	38	21	62	3.35 (0.35)

[a]Insufficient sample size for RNA analysis.
Abbreviations: *FMR1* = fragile X mental retardation 1, FXTAS = fragile X–associated tremor/ataxia syndrome, MMSE = Mini-Mental State Examination, mRNA = messenger RNA, NA = not applicable, NPI = Neuropsychiatric Inventory, SE = standard error.

Table 4. Mean ± SD Values of Full-Scale IQ, Verbal IQ, Performance IQ, NPI Scores, and MMSE Scores for Males With FXTAS and Control Males

Measure	FXTAS Group (N = 14)	Control Group (N = 14)
Full-Scale IQ[a]	96.4 (11.1)	116.9 (19.9)
Verbal IQ[b]	102.3 (11.9)	116.0 (20.5)
Performance IQ[a]	87.3 (11.4)	111.1 (13.3)
NPI[a]	33.1 (12.6)	1.1 (2.4)
MMSE[b]	26.1 (4.1)	29.4 (1.6)

[a]Significant difference between groups at Bonferroni corrected $p < .004$.
[b]No significant difference between groups.
Abbreviations: FXTAS = fragile X–associated tremor/ataxia syndrome, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SD = standard deviation.

The criteria for "definite" FXTAS include tremor and/or ataxia in addition to the presence of the MCPs sign on MRI.[3] Five patients had "probable" FXTAS with tremor and/or ataxia but without the presence of the MCPs sign; in 3 patients the MCPs sign could not be ruled out. Magnetic resonance imaging revealed brain atrophy and white-matter disease in all 14 affected patients with the *FMR1* premutation. The molecular variables of each affected participant are outlined in Table 3, including the number of CGG repeats and the messenger RNA (mRNA) levels. Typical CGG repeat numbers[12] are 1–49, and the mean mRNA level[12] is 1.42 (0.25 SE). All affected participants had a neurologic examination that was consistent with FXTAS, and a clinical staging of FXTAS was completed. Two affected participants were being treated for diabetes, and 8 were being treated for hypertension.

The 14 control participants were age- and education-matched adult males who did not have the *FMR1* premutation (mean age = 67.6 years [SD = 5.7]), as confirmed by molecular genetic testing. One control had diabetes mellitus type 2, and 4 had hypertension. The controls were recruited from fragile X families (N = 11) or were volunteers from typical families (N = 3).

All participants signed informed consent releases for this study, which was approved by the Institutional Review Board at the University of California, Davis, Medical Center or the University of Colorado Health Sciences Center, Denver.

Neuropsychiatric Inventory

Description of affected participants' behaviors was obtained by clinical interviews using the Neuropsychiatric Inventory (NPI)[13] (administered by S.B. and J.C.) with spouses, who were asked to describe the onset of their husband's symptoms after they first noted tremor and/or ataxia. The NPI is a structured interview that measures observable behaviors and is widely used to identify neuropsychiatric symptoms that co-occur in dementing disorders.[14] This inventory measures psychiatric problems in 12 domains (delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and appetite). Symptom severity is ranked on a scale from 1 to 3 in increasing order of severity, and frequency of symptoms is ranked on a scale from 1 to 4 in increasing order of frequency. A total score is determined by multiplying the frequency of symptoms score by the severity score. Participants are considered symptomatic if they receive an NPI score > 0 in any behavioral domain. A single domain score ≥ 4 or total NPI score ≥ 4 is regarded as clinically significant and has been used as the threshold criterion for inclusion in treatment trials for dementia-associated neuropsychiatric symptoms.[14,15] The NPI has good reliability, and its validity is consistent with other measures that assess behavior disturbances.[16] Each group's mean ± SD score is listed in Table 4.

Cognitive Testing

All patients underwent cognitive testing utilizing the Wechsler Adult Intelligence Scale-Third Edition (WAIS III).[17] Since patients presented to the research clinic following the onset of FXTAS symptoms, none of them had undergone prior cognitive testing. Although we do not have data on premorbid IQ functioning, the vast majority of our sample had obtained a bachelor's degree or higher (43% had received a Ph.D.). The Mini-Mental State Examination (MMSE) was also completed to assess cognitive mental status.[18] Both measures were administered by J.C., a neuropsychological technician who received specialized training to administer these measures. The MMSE is divided into 2 sections: the first includes verbal responses and covers orientation, memory, and attention; the maximum score is 21. All participants were asked to do the

Table 5. Percentage of Participants With and Without FXTAS With Symptom Present in Each NPI Domain

NPI Domain	FXTAS, % (N) (N = 14)	No FXTAS, % (N) (N = 14)
Delusions	29 (4)	0 (0)
Hallucinations	7 (1)	0 (0)
Agitation/aggression*	57 (8)	0 (0)
Depression*	79 (11)	14 (2)
Anxiety	50 (7)	0 (0)
Elation/euphoria	0 (0)	0 (0)
Apathy*	93 (13)	0 (0)
Disinhibition*	64 (9)	0 (0)
Irritability*	86 (12)	7 (1)
Abnormal motor movements	21 (3)	0 (0)
Nighttime problems	43 (6)	14 (2)
Appetite changes	43 (6)	0 (0)

*Significant difference between groups at Bonferroni corrected $p < .004$.
Abbreviations: FXTAS = fragile X–associated tremor/ataxia syndrome, NPI = Neuropsychiatric Inventory.

serial 7s, and those who failed this task were then asked to spell *world* backwards for completion of the memory component. Having this second, relatively easier, task as an alternate to the serial 7s might account for the higher than expected MMSE scores found in the affected group. The second part tests the ability to name, follow verbal and written commands, write a sentence spontaneously, and copy 2 complex, overlapping polygons; the maximum score is 9. Maximum total MMSE score is 30. The test is not timed and has been proved valid and reliable.[19]

RESULTS

Statistical analysis with a Bonferroni adjustment for multiple comparisons yielded significant differences between the sample of affected males and the control males in several domains (see Table 4). Analysis of the cognitive assessment data suggested significant differences between the 2 groups on the Full-Scale IQ measure ($t = 3.23$, $df = 26$, corrected $p < .004$) as well as the Performance IQ ($t = 5.08$, $df = 26$, corrected $p < .004$) scales. The comparison on Verbal IQ level was in the same direction but not significant. As expected, males with FXTAS had significantly elevated scores on the NPI compared with controls ($t = 9.3$, $df = 26$, corrected $p < .004$). Average score for the 14 patients on the NPI scale was 33.14 (SD = 12.6) compared with the control group mean of 1.07 (SD = 2.4).

In terms of the profile on the NPI for the 14 patients, apathy was the most common symptom, reported as present in 93% of the sample (with an apathy score greater than 0). Table 5 lists symptoms associated with each NPI subscale, the percentage in each group presenting with the symptom, and the significant difference in symptoms between the 2 groups. Depression (79% of the sample) and irritability (86%) were frequently observed symptoms, which typically presented as increasing withdrawal and being less affectionate with others. Agitation/aggression was also endorsed often for the FXTAS patients (57%) by their spouses.

Disinhibition was another commonly described behavioral problem (64% of sample). Several respondents recounted their spouses' making inappropriate remarks or engaging in improper behavior in public settings. A number of the affected sample made sexually provocative or racist comments. One man was inappropriately hugging others who were not receptive, another urinated in public places, and 2 were making impulsive purchases. Disinhibited behavior caused marked distress among caregivers. Almost half the participants exhibited anxiety, with changes in routine and separation from their spouses as the most frequent precipitants.

The MMSE analysis with a Bonferroni adjustment suggested a trend for lower MMSE score in the affected sample ($t = 2.79$, $df = 26$, corrected NS). The correlation between the MMSE scores and NPI scores in the affected group was not significant ($r = –0.07$, NS). This nonsignificant correlation coefficient is due to 3 FXTAS participants who had exceptionally low scores (16, 21, 22, respectively) on the MMSE yet relatively high NPI scores (36, 38, 29, respectively). The majority of the affected sample (10/14 participants) had an MMSE score of 26 or higher, which is above the customary cutoff (23 or 24) associated with clinical dementia. All but 1 of the control males had a score of 28 or higher on the MMSE, as would be expected in an unaffected sample. (One control male had an MMSE score of 24.)

There was no association among the affected males between the IQ scores and the NPI score ($r = –0.20$, $df = 14$, NS to Verbal IQ; $r = –0.21$, $df = 14$, NS to Performance IQ; $r = –0.24$, $df = 14$, NS to Full-Scale IQ). All affected participants had a Verbal IQ in the average to above-average range (see Table 4), yet all participants, except 2, had an NPI score greater than 4, which is considered clinically significant. Therefore, psychiatric symptoms are seen before deficits in Verbal IQ develop. No other measures were significantly associated with the NPI score. There was no significant association between the affected males' CGG number and the NPI score ($r = –0.38$, NS).

The FXTAS score had a restricted range in this sample and did not exhibit significant associations with the other measures among the affected sample, with one exception. The exception was a nonsignificant correlation between the Performance IQ score and the FXTAS score ($r = 0.55$, $df = 14$, $p = .06$).

DISCUSSION

This study represents the first controlled evaluation of neuropsychiatric symptoms in patients with FXTAS. Since FXTAS is a newly described syndrome, we are just beginning to develop an understanding of the psychiatric

problems associated with this condition. Although the clinical reports have mentioned symptoms of anxiety, depression, and irritability,[1,6,20,21] these are relatively common symptoms in the general population, and even more common in the elderly who have cognitive decline. However, our study demonstrated that these neuropsychiatric symptoms, as assessed by the NPI, are significantly more common in men with FXTAS compared with controls of the same age.

Neuropsychiatric symptoms commonly occur in a range of neurodegenerative disorders, including dementia of the Alzheimer's type (DAT), Parkinson's disease, Huntington's disease, frontotemporal dementias, and dementia with Lewy bodies (DLB). Generally 50% to 80% of patients with dementia suffer neuropsychiatric symptoms at some time during the course of their illness.[11,14] In one U.S. study,[14] an estimated 61% of persons with dementia displayed 1 psychiatric symptom or more in the month prior to being seen. Apathy, delusions, hallucinations, and sleep impairment were the most common disturbances.

Dementia syndromes are clinically classified into the categories of *cortical* and *subcortical*. This phenomenological distinction is intended to correlate psychiatric symptoms with the putative anatomic location of neuropathology.[22–24] *Cortical* dementias, the prototype being DAT, present with more notable deficits in the "cortical" symptoms of apraxia, agnosia, aphasia, and amnesia not helped by memory cueing or prompting.[22,23,25–30]

Subcortical dementias are those associated with disorders such as Parkinson's disease, Huntington's disease, and multi-infarct dementia, a subtype of vascular dementia. These dementias feature more prominent apathy, slowness of psychomotor status and thought (bradyphrenia), and difficulties with memory retrieval that can be helped by cueing or prompting.[22,23,26–28] The psychiatric symptoms of depression and anxiety are more likely to occur in subcortical dementias; treatment of these symptoms can improve cognitive performance.[22,23,26–28]

Alongside the *cortical* versus *subcortical* dichotomy is the distinction within the group of cortical dementias, variably referred to as *frontal lobe dementia*, *frontotemporal dementia*, or *lobar dementia*. Patients with these dementias present with more dramatic impairments in impulse control, motivation, mood, and executive function than deficits in memory per se.[31–37] Further complicating the phenomenological classification of dementias are reports of some dementias with simultaneous features of both frontal lobe and subcortical dementia.[22] Dementia due to Parkinson's disease and dementia due to Huntington's disease are examples.[27,28,38,39]

A unifying explanation of how patients could have simultaneous subcortical and frontal lobe dementia symptoms (in addition to other cortical dementia symptoms) is that the subcortical dementing process (often understood as progressive neurodegeneration) also interrupts connections between the frontal lobes and subcortical structures, thus "disconnecting" the frontal lobes (functionally) from other neural structures.[40] This clinical phenomenon has led to the use of the term *fronto-subcortical dementia*.[40] Considering all of the complicating factors cited above, and mindful of the limitations of the distinctions between *cortical* versus *subcortical* and *fronto-subcortical* dementias, we propose this novel syndrome of FXTAS dementia as an example of fronto-subcortical dementia.

Based on the cognitive testing results and the results on the NPI in our case series, there are numerous items of support for this classification. The increased scores on the NPI on apathy, irritability, and depression/anxiety suggest a pattern of psychiatric symptoms consistent with the mood disturbance common in subcortical dementia. Additionally, the symptoms of behavioral disinhibition and aggression (which may reflect impaired frontal lobe inhibitory function) are consistent with a frontal lobe dementia. Inferentially, the lack of clinically dramatic agnosia, apraxia, aphasia, and memory defects unassisted by cueing in our cases suggests that FXTAS dementia is not primarily a *cortical* dementia. The less than dramatic deficits on MMSE scores in the majority of our cases, despite clinically significant decreased cognitive performance and low rates of psychotic symptoms, also suggest a subcortical rather than cortical dementing process.

As researchers begin to describe the behavioral phenotype of FXTAS, identifying the associated neuropsychiatric symptoms will be as important as distinguishing the associated cognitive and motor impairments. Recognizing the neuropsychiatric profile of FXTAS will contribute to our understanding of the underlying brain pathology and add to our knowledge of the effects of being a premutation carrier of the *FMR1* gene. Distinguishing the particular patterns of psychiatric symptoms that cooccur with FXTAS will be helpful in differentiating the diagnosis of FXTAS from other dementing conditions. Identifying the onset and progression of neuropsychiatric symptoms in FXTAS will help clarify the course of the disorder.

When fitting the FXTAS dementia into the clinical arena, it may be necessary to distinguish this newly described syndrome from some of the more common dementias that may present with cognitive, motor, and associated mood symptoms. Clinically, FXTAS patients may appear similar to patients with the overlapping conditions of DLB, Parkinson's disease with dementia (PDD), and frontotemporal dementia (FTD). DLB is characterized by a fluctuating cognitive status, attentional deficits, visuospatial dysfunction, complex visual hallucinations, delusions, and extrapyramidal symptoms.[41,42] The clinical appearance of PDD is similar to that of DLB.[42] One distinguishing feature is that patients with PDD initially present with motor symptoms, while those with DLB may

present with concurrent motor and cognitive symptoms, or with cognitive symptoms alone initially.[42] Depression and slowness of thought (bradyphrenia) are also commonly seen in patients with PDD.[43] Comorbid depression in patients with PDD is associated with more rapid cognitive decline.[44] In 1 study, DLB and PDD patients were found to have similar neuropsychological profiles; they performed better on memory tests but worse on attentional tasks than patients with DAT.[45]

Several uncommon dementia syndromes may present with concurrent dementia and neurologic findings that warrant distinction from FXTAS. Spinocerebellar ataxia type 17 is characterized by behavioral symptoms, fronto-subcortical dementia (with reduced verbal fluency, decreased executive function without apraxia and agnosia), ataxia, rigidity, and dystonia. Neuropathology reveals cortical, subcortical, and cerebellar atrophy.[46] Aceruloplasminemia, a disorder of iron metabolism, features retinal degeneration, diabetes mellitus, and neuropsychiatric illness. The neuropsychiatric symptoms include dementia, ataxia, and movement disorder.[47] Neurodegeneration with brain iron accumulation type 1 (formerly Hallervorden-Spatz syndrome) is an autosomal recessive neurodegenerative disorder that features dementia, dystonia, rigidity, choreoathetosis, and optic atrophy.[48] Progressive supranuclear palsy (PSP) is a degenerative disorder that features fronto-subcortical dementia, rigidity, akinesia, postural instability, and eye movement abnormalities.[49] Corticobasal degeneration features dementia, rigidity, akinesia, apraxia, tremor, and myoclonus.[49] Executive impairments (most likely due to basal ganglia and frontal lobe involvement) are common.

It appears that the items of the NPI have some clinical utility in distinguishing among dementia types. Lyketsos et al.[50] found that delusions were more common in DAT, while depression was more common in vascular dementia. The other NPI domains did not distinguish between the 2 types. Litvan et al.[51] compared patients with Huntington's disease (HD) with PSP patients and found that the HD patients had significantly more agitation, irritability, and anxiety on the NPI, while the PSP patients had significantly more apathy. Paulsen et al.[52] examined 52 patients with HD (there was no comparison group) and found neuropsychiatric symptoms in 98% of them. Dysphoria, agitation, irritability, apathy, or anxiety was present in over 50% of patients, incidences reported to be higher than in other dementias. Hirono et al.[53] used the NPI to compare behavioral features of FTD, DLB, and Alzheimer's disease (AD). The FTD patients had significantly more euphoria, aberrant motor behavior, and disinhibition compared with the AD and DLB patients but significantly fewer delusions. Among the 3 groups, DLB patients had significantly more hallucinations than the FTD and AD patients. Bozeat et al.[54] compared FTD patients with AD patients using the NPI and found that altered eating behavior and loss of social awareness were significantly more common in FTD patients. In a study on the NPI with FTD patients, Mourik et al.[55] found 2 clusters of co-occurring behavioral symptoms: psychosis (including agitation, irritability, delusions, and hallucinations) and mood (including anxiety and depression). Apathy, aberrant motor behavior, and disinhibition were each present in more than 50% of patients.

The pathophysiology of FXTAS is interesting in that an elevated *FMR1* mRNA level, compared with individuals without the premutation, is seen in all carriers,[12] and a toxic mRNA mechanism is hypothesized to be the cause of FXTAS.[56] The elevated mRNA levels lead to the formation of eosinophilic intranuclear inclusions in neurons and astrocytes throughout the brain but not in Purkinje cells in the cerebellum.[57] The area of the brain with the greatest frequency of inclusions is the hippocampus, which is part of the limbic system. Atrophy secondary to inclusion-mediated apoptosis in the hippocampus requires further study to understand its association with the symptom presentation of FXTAS.

Anxiety is a common problem, even in young carriers of the premutation,[58] so it may be part of the phenotype of the premutation before the development of FXTAS. However, anxiety and the additional neuropsychiatric problems dramatically increase as the neurologic problems of FXTAS develop. Some of the psychiatric problems may be related to the cognitive deficits of FXTAS, including executive function deficits.

The prognosis of the clinical dementia in FXTAS awaits prospective clarification. In DAT, the usual expected progression in MMSE points in the untreated condition is a loss of 2 to 4 MMSE points/year: cholinesterase inhibitors may mitigate this loss by slowing decline or may even stabilize cognition, at least in the short term.[31] For clinical intervention for FXTAS dementia, it appears prudent (as the authors have done with several cases to date) to intervene as if FXTAS were a frontotemporal dementia.

As in other neurodegenerative disorders, the spouses and caregivers of patients with FXTAS experience varying degrees of stress, depending on the extent of their partner's impairment and the resources available to them. In the early stages, the spouse has to cope with the behavioral and psychological changes that occur in patients with this disorder. Moreover, since this is a newly identified disease, there is uncertainty as to the typical progression and course of symptoms, an uncertainty that adds to caregiver anxiety.

In the middle stages of the condition, both patient and spouse may express concerns about the patient's declining self-care and fear of loss of intimacy. Often, at this stage, patients will be resistant to the introduction of balance aids such as canes or a walker. During the later stages of FXTAS, issues facing family members include the onset of dementia, loss of mobility, long-term care, and end of life planning.

The spouse and other family members of patients with FXTAS should be offered psychosocial support and have the opportunity to consult with a genetic counselor. The genetic counselor will be able to address the emotional as well as the ethical, legal, and social issues of FXTAS, as it is a progressive neurologic genetic condition related to a mental retardation syndrome diagnosed in children. Patient testing confidentiality, autonomy, the right to know, and risk-benefit ratio of *FMR1* testing in other family members should all be addressed.

FXTAS is a newly described neurologic syndrome that affects premutation carriers of the *FMR1* gene. Since little has been written about this disorder, patients and caregivers have expressed concern as to the natural progression of the disease and how they can plan for it. This concern has added significantly to family and patient distress.

The limitations of the current study include the use of only 1 psychiatric measure, the NPI, which is a list of symptoms that does not necessarily address the presence of psychiatric syndromes. None of the patients had a comprehensive psychiatric evaluation. Future studies to address the phenomenology of FXTAS dementia and its psychiatric comorbidity would be strengthened by the use of structured clinical interviews, such as the Structured Clinical Interview for DSM-IV-TR, as part of a comprehensive psychiatric evaluation.

CONCLUSION

Fourteen FXTAS patients were assessed for cognitive and other psychiatric function with the NPI, the MMSE, and formal neuropsychological testing. The constellation of cognitive and mood symptoms is consistent with classification of FXTAS dementia as a fronto-subcortical dementia. Further phenomenological description and prognosis implications of FXTAS dementia await prospective validation. Empirical treatment of the cognitive and emotional symptoms of FXTAS dementia may increase psychiatric functioning in affected patients.

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