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New clinical findings in the fragile X-associated tremor ataxia syndrome (FXTAS)

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Abstract

The objective of this paper was to assess the phenotypic variance in patients with the Fragile X-associated Tremor Ataxia Syndrome (FXTAS) and to further elucidate genotype–phenotype correlations in the illness. A second goal was to generate hypotheses regarding symptom progression based on careful histories in our sample that can now be tested in ongoing longitudinal studies. The variability of clinical signs and symptom progression in FXTAS complicates our understanding of its phenotype and presents a series of problems in clinical trial design. Similarly, pre-motor and non-motor symptoms have not been adequately explored to answer outstanding questions regarding genotype–phenotype associations in FXTAS. This was a cross-sectional study of *FMR1* premutation carriers from known fragile X syndrome pedigrees. We report on the first 50 subjects who have completed a full neurologic evaluation and a brain MRI. Subjects were selected on the basis of motor symptoms or abnormal results (>1 SD) on a quantitative instrument designed to detect mild tremor and ataxia (CATSYS 1994). A neuropsychological battery included the WAIS-III, COWA, and WCST. Statistical analysis used ANOVA and Fisher's exact test with $p<0.05$. All *FMR1* premutation carriers were men of mean age 65±7 years. According to the

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diagnostic criteria of Jacquemont et al. (Am J Hum Genet 72(4):869–878, 2003), 21 subjects met criteria for definite FXTAS, 10 for probable, 9 for possible, and 10 were indeterminate. Duration of motor symptoms was significantly longer in the definitive group (8.6±6) compared to the other groups ($p<0.01$). The presentations in 40 subjects, excluding the indeterminate group, included: tremor 24, ataxia 5, memory symptoms 3, parkinsonism 2, and torticollis 1. The data suggest at least two dominant phenotypic presentations: (a) a tremor-dominant subtype in which the onset of ataxia is delayed; (b) a second in which ataxia is the dominant presentation from the outset. In both subtypes, once ataxia emerges it tends to track frontal cognitive changes ($p<0.01$). The data support the view that FXTAS is a late-life neurodegenerative disorder with involvement of motor, non-motor, and cognitive systems. The results suggest at least two presentations with tremor-and ataxia-predominant phenotypes. In both, global cognitive decline appears to track ataxia. Prospective longitudinal studies are needed to validate this proposed evolution of FXTAS and its relevance to future clinical trials design.

Keywords

Fragile X tremor ataxia syndrome; FMR1 premutation; Neurodegeneration; Ataxia; Tremor; Parasomnias; Sensorineural hearing loss

Background and introduction

Carriers of the *FMR1* premutation allele (55–199 repeats as defined by the American College of Medical Genetics [1]) are at significant risk for a late-onset neurodegenerative disorder, FXTAS [2, 3]. This disorder is distinct from that manifested in carriers of the full mutation (>200 repeats), or fragile X syndrome (FXS), with respect to the molecular etiology and clinical phenotype. The primary features of FXTAS are action tremor and gait ataxia. Associated features include parkinsonism, autonomic dysfunction, peripheral neuropathy, and cognitive dysfunction [3]. Cognitive changes are highly variable and include global impairments as well as specific executive cognitive dysfunction [4, 5]. Preliminary reports suggest that psychiatric symptoms include anxiety, agitation, disinhibition, and depression. This characteristic pattern of cognitive and behavioral deficits resembles that in other forms of frontal–subcortical dementia [6].

Neuro-imaging features of FXTAS on T2-weighted brain MRI include white matter changes in the periventricular, subcortical white matter, and in middle cerebellar peduncles (MCP) [7]. The increased signal intensity of the MCP has been incorporated in the diagnostic criteria for “definite” FXTAS [3]. Though distinctive, it is found in only about 64% of individuals with FXTAS [8]. The most prominent neuropathologic features of FXTAS are: (1) cerebral and cerebellar white matter disease that is pathologically distinct from that found in cerebrovascular and demyelinating disorders, (2) astrocytic pathology in white matter, and (3) eosinophilic, ubiquitin-positive intranuclear inclusions in brain and spinal cord [9, 10].

In order to further define the range and variability of symptoms associated with FXTAS, we report the detailed neurologic findings in the first 50 subjects who were evaluated for possible FXTAS. Subjects were selected on the basis of their *FMR1* carrier status and a positive screening that indicated the presence of tremor and/or ataxia. A comprehensive neurologic exam was then performed to further characterize motor and cognitive symptoms using standardized assessment tools. In addition, subjects were screened for non-motor symptoms that often accompany other degenerative disorders of movement and cognition. These included sleep dysfunction [11, 12], restless legs syndrome (RLS) [13], and

autonomic and sensory dysfunction previously reported in some patients with FXTAS [14, 15].

Finally, using carefully obtained historical cross-sectional data, we attempt to track the course of the various possible clinical presentations of FXTAS.

Experimental design and methods

Subject evaluation

The evaluation for FXTAS among premutation carriers was conducted in three stages. Stage 1 was a screening process in which all identified premutation carriers were interviewed by telephone to determine eligibility to participate in each assessment or task required in the study based on their medical history (see exclusion criteria in Methods). In Stage 2, subjects were visited in person and completed a computerized neuro-motor test battery and, when eligible, a neuropsychological test battery. A positive finding of tremor or ataxia in Stage 1 or Stage 2 qualified the subject for further neurologic evaluation in Stage 3. Stage 3 evaluations took place an average of 11 months after Stage 2. In 92% of cases, a family member intimately familiar with the subject's medical history was present to corroborate all responses. The work presented here is thus the summary of evaluations conducted in the first 50 symptomatic and/or CATSYS-positive subjects selected for the Stage 3 evaluation.

Stage 1: eligibility and screening by medical history—Initially, we contacted families known to have a relative diagnosed with fragile X syndrome. We then surveyed all family members to identify premutation carriers and non-carriers over age 50. If a premutation carrier male was identified in a sibship, he and his entire carrier and non-carrier siblings were recruited regardless of symptoms. Asymptomatic, CATSYS-negative, and unaffected carriers are currently being evaluated. Stage 1 consisted of a medical history by a project coordinator who was familiar with the subject's carrier status. During the medical history, subjects were asked if they were aware of any problems with tremor or ataxia, and if so, for how long. If the subject endorsed either of these symptoms, they were selected for the full neurologic evaluation (Stage 3), regardless of the result of Stage 2. Medical records related to symptoms of FXTAS were also obtained where possible.

Stage 2: testing for tremor, ataxia and cognitive defects—A trained psychologist who was blind to the subject's carrier status performed all testing in Stage 2. The objective neuro-motor tests used in this stage are explained in detail in Allen et al. [16]. Briefly, all subjects were screened for motor symptoms of FXTAS using the Coordination Ability and Tremor System 2000 (CATSYS 2000; www.catsys.dk) and the Grooved Pegboard. Using these instruments, we identified signs of ataxia, tremor (postural or intention), and decreased manual coordination. Subjects who scored greater than one standard deviation above the mean for a normative, age matched population were scored as positive for that symptom.

Subjects were also asked to complete a neuropsychological test battery if eligible. Subjects were deemed ineligible if they reported medical conditions that could have contaminated the interpretation of results, mainly, a history of stroke, head injury with loss of consciousness, active substance abuse, or a primary language other than English.

The neuropsychological test battery evaluated: (1) general cognition using the Wechsler Adult Intelligence Scale—III (WAIS-III) and the Montreal Cognitive Assessment (MOCA), (2) executive function using the Controlled Oral Word Association Test, subtests of the Wisconsin Card Sorting Test (total errors and perseverative responses), and the Delis–Kaplan Executive Function System (letter number switching score), and (3) memory using the Wechsler Memory Scale (WMS). Pre-morbid intelligence was estimated using the North

American Adult Reading Test (NAART). Self-report questionnaires were administered to measure symptoms of depression and anxiety (Center for Epidemiological Studies Depression Scale, Social Phobia and Anxiety Inventory, and the State-Trait Anxiety Inventory).

Stage 3: full neurologic evaluation—Subjects who endorsed tremor and/or ataxia (Stage 1), tested positive for these signs in the CATSYS (Stage 2) moved on to Stage 3. If the CATSYS results were missing, the subject was invited to be examined for symptoms of FXTAS by our movement disorders specialist who confirmed and interpreted the sign in question. The following broad areas of neurologic symptoms were assessed:

Motor symptoms Tremor was assessed by type (rest, postural or intention) and body region. Ataxia was assessed via examination of gait, limb coordination, speech, and eye movements. Ataxia brought out only during a tandem walking was coded as a special case with the designation “tandem only” (to) in Table 1.

We also used validated severity scales. For tremor, we used the Clinical Rating Scale for Tremor (CRST); for ataxia the International Cooperative Ataxia Rating Scale (ICARS); and for parkinsonism the United Parkinson's Disease Rating Scale (UPDRS). The criteria for positive tremor or ataxia was a score of >1 in any of the relevant items, or a positive score on the CATSYS. The criteria for parkinsonism were: (a) a pill rolling rest tremor of unilateral onset; or (b) global bradykinesia (≥1/4 using UPDRS item # 40) with abnormal posture (e.g., stooping or dropped shoulder), and/or asymmetric arm swing not explained by orthopedic/arthritic problems.

Non-motor symptoms Subjects eligible for the full neuropsychological cognitive battery received evaluations of three principal domains: cognition, memory and executive functioning. Impairment was defined of a difference in VIQ or PIQ scores on the WAIS-III and NAART of at least 15. The NAART is commonly used to estimate pre-morbid intelligence (NAART VIQ-WAIS-III VIQ>15; NAART PIQWAIS-III PIQ>15). Memory problems were considered significant if scores for at least two of the three WMS subtests fell below two standard deviations of the published mean. Executive dysfunction was defined as a score of two standard deviations below mean on two of four executive function tests outlined above.

Subjects ineligible for the full neuropsychological battery received an abbreviated battery. This included the MOCA, a test more sensitive to frontal lobe dysfunction than the Mini Mental Status Exam [18] and the NAART. Cognitive impairment on this battery was defined as a MOCA score of <26. These test results were supplemented with the neurologic exam, which included a detailed history of change in functional capacity.

Subjects were also questioned for symptoms suggestive of sleep dysfunction. They completed a standardized questionnaire for snoring (a symptom of possible sleep apnea) and RLS [19–21]. We recorded as “presumptive rapid eye movement behavioral disorder” (REM-BD) any subject whose spouse reported periodic nightmare-like episodes with frantic motor or vocal activity during which the subject appeared to be reenacting a (bad) dream.

We assessed sensory disturbances eliciting symptoms suggestive of peripheral neuropathy and hearing loss, or other signs including distal skin changes, abnormalities of deep tendon reflexes, weakness, and fasciculations. For hearing loss, we relied on the history, the bedside exam, or an extensive review of available medical records. To assess autonomic dysfunction, we administered the SCOPA-AUT questionnaire which consists of 25 items assessing autonomic dysfunction in six physiologic domains [22]. Orthostatic intolerance

was defined as a tendency to become lightheaded and/or dizzy, as “if ready to pass out” when standing suddenly. This symptom had to respond to quickly sitting or lying down.

a. Clinical assessments: Using this cross-sectional sample, we obtained historical information on the onset and order of symptom presentation. To improve symptom awareness asymptomatic CATSYS-positive subjects were made aware of the specific sign in question (tremor, ataxia, bradykinesia, etc.) by demonstrating it during the exam and making sure that the clinical history included this new information. This was critical to obtaining the best possible recall of chronology. Accordingly, during the clinical history, all CATYS-positive subjects and their significant others became reporters of their (sometimes newly recognized) physical findings. Overall severity of disability was measured using the modified Rankin scale which ranges from 0=no symptoms [or signs] to 5=severe disability, bedridden [17].

b. Neuro-Imaging: Brain MRI images were obtained using a 2.0-T unit in 45/50 subjects. The images were interpreted by one of two neuroradiologists knowledgeable about imaging findings in FXTAS, and by one of us (JLJ) who made sure that obvious findings like the MCP sign were not missed. The neuroradiologists were blind to subjects' symptoms, exam findings, and carrier status.

c. Adjudication of FXTAS diagnosis: Adjudication of the final FXTAS diagnostic category was based on a final review of the all results including, the available medical records and MRI findings. We used the standardized criteria for FXTAS diagnosis as outlined in Jacquemont [3] and Table 1.

Laboratory methods

DNA was extracted from buccal samples or blood using the Qiagen QiAmp DNA Blood Mini Kit. *FMR1* CGG repeat sizes were determined by a fluorescent-sequencer method, as described elsewhere [23], the ABI Prism 377 DNA Sequencer or ABI 3100 Genetic Analyzer. For male samples that did not amplify, a second PCR-based, hybridization technique was used to identify a possible high repeat size band. If a ladder of bands was seen in the PCR result for a subject, indicating mosaicism, a Southern blot was also done to assure there were no full mutation sized bands [23]. Any subject with full mutation alleles was not included in the analysis.

Statistical analysis

As appropriate, all values are expressed as mean±SD. Fisher's goodness of fit test for proportions was used to calculate ratios for individual symptoms (e.g., the concordance between ataxia and cognitive impairment). Scores for the quantitative rating scales were analyzed separately since there is redundancy across the scales and pooled scores. *T* tests were used to evaluate differences in these scores between groups. In the case of non-motor symptoms, we compared the proportion of patients with a particular symptom or sign, to the estimated prevalence of the finding in an age matched population. Analysis of variance (ANOVA) was used to test for differences between groups. A Tukey's Studentized range test was used as a post hoc test to determine which groups were significantly different from each other. All calculations were done using SAS V9.

Results

Using Jacquemont's criteria, which are anchored on the presence of MRI changes [3], 21 subjects met diagnostic criteria for definite FXTAS, 10 for probable, 9 for possible, and 10 for indeterminate FXTAS (see Table 1). We will first provide the general descriptive

overview of the 50 subjects by symptoms associated with FXTAS. Subsequently, we will describe progression and duration of these symptoms and how they affect function. Lastly, we will examine the genotype–phenotype correlation in this select study sample.

Motor symptoms

Tremor Only 24 of the 50 subjects complained of tremor. Of the 45 subjects who had CATSYS results, 35 had evidence of tremor. Of the 35, 15 (43%) were not aware of having tremor. When intention tremor was present, it was more prominent and functionally disabling than the postural tremor. Intention tremor affected the arms more than any other part of the body. Titubation and/or voice tremor were present in five cases. Rest tremor was present in seven individuals but never in isolation, nor was it as prominent as the other tremor types.

Using the CRST, the mean tremor severity score for the group was 12.9±15 with most of the severity stemming from the intention tremor. The scores reflect a broad, cross-sectional representation of severity raging from 0 to 61.

Ataxia Gait ataxia was less common as a presenting symptom than tremor, yet nine patients presented with ataxia. Of those nine, seven went on to develop tremor and two developed parkinsonism. Of the 50 subjects, 43 displayed ataxia on CATSYS or the neurologic exam. Of the 41 subjects tested using CATSYS, 66% (27/41) had abnormal balance scores. Of those with abnormal scores, only 30% (8/27) had reported imbalance. On neurologic exam 12 subjects had difficulty with tandem walking only and none was aware of having balance problems. Of the ten tested with the CATSYS only five had imbalance detected by this instrument. Eight of these subjects exhibited additional coordination difficulties in the heel to shin task or with rapid alternating foot tapping. Using the ICARS, the mean ataxia severity score for all subjects was 14.1± 15 with a range of 0–52.

Parkinsonism Sixteen of the subjects (32%) had parkinsonism, but it was the presenting symptom in only two (Table 1, Presentation Order). Parkinsonian signs tended to be subtle compared to the more common tremor/ataxic presentations. The most common findings were bradykinesia and mixed tremor with postural/kinetic being more common and prominent than rest tremor. Rigidity and dystonic symptoms were uncommon. Only one subject met the diagnostic criteria for Parkinson's disease (PD) [24], whereas the other 15 met criteria established for this study (see “Experimental design and methods”). The one patient who presented with PD, had typical idiopathic PD for >10 years complicated in the last two with dementia, more prominent intention tremor and ataxia primarily due to motor blocks and impaired visuo-spatial function. Using the UPDRS, there was a wide range of scores (range 0–55), again, showing the variability of presentation. The mean score was 12.3±12.

Non-motor symptoms

Cognitive impairment Forty-five of the 50 subjects were tested for cognitive impairment either using the full (36 items) or shortened battery (9 items; see Methods and Table 1). Of the five subjects who were excluded from testing, two had recent vascular events, one had active substance abuse, and two received recent private neuropsychological testing. These two were reported to have cognitive impairment by outside specialists who had initiated treatment with donepezil and/or memantine. Among the 36 subjects who completed the full neuropsychological battery, 16 showed global cognitive decline and two of those showed significant executive impairment. Among the nine subjects who were evaluated using the shortened battery, cognitive impairment was detected in five. Thus, about half the subjects

presented with some evidence of cognitive impairment (23/50). Two of eleven subjects between ages 50–60 and 21/39 over age 60 had cognitive impairment.

Autonomic dysfunction Erectile dysfunction was by far the most common autonomic symptom and was reported by 56% of our subjects, a rate that is statistically higher than that reported in the general population (56% vs. 34% in men above age 60, $p<0.001$) [25] (Table 2). Bladder symptoms were present in 24% of our subjects and 16% had symptoms of orthostatic intolerance. The prevalence of these symptoms was no different from that reported in adult populations (see Table 2) [25].

Peripheral nervous system Symptoms and signs of peripheral neuropathy were present in 10/50 subjects. In some the neuropathy had been documented in medical records by EMG/NCS. Six of these ten had diabetes or a history of alcohol abuse. In the other four, the clinical picture was consistent with the neuropathy described in FXTAS, mainly diminished distal reflexes and vibratory sensation [14]. In only one of these four subjects was the loss of proprioception severe enough to account for the ataxia. The onset of neuropathic signs and symptoms in relation to motor symptoms was difficult to assess. There was no association between autonomic dysfunction and peripheral neuropathy as 26/33 cases exhibited autonomic dysfunction in the absence of clinically apparent peripheral neuropathy. In this cohort, the incidence of peripheral neuropathy signs and symptoms was no different from that reported in the general population (see Table 2) [26].

Fifty percent of subjects reported hearing loss. Although hearing was not tested in this study, 98% of those with hearing loss had previously documented sensorineural hearing loss. In most cases, this was verified through medical records. This incidence of hearing loss was statistically higher than that reported in the general elderly population (50 vs. 30%, $p<0.002$) [27] (Table 2).

Sleep dysfunction Recognizing that we were unable to verify REM-BD using polysomnography, “presumptive” REM-BD appears to be more frequent in our sample compared with to reports in the general population (16% vs. 2%, $p<0.0001$, Table 2) [27]. Snoring, a presumptive marker of sleep apnea, was no different in our sample compared to historical control obtained from similar questionnaires of snoring in the general adult population [29]. The same was true for RLS symptoms (Table 2).

Neuro-imaging

MRI results were available in 45/50 subjects. All but three subjects exhibited general volume loss. On T2-weighted MRI imaging, all but eight exhibited white matter changes deemed by the independent radiologist to be excessive for age. Increased signal intensities in the MCP were detected in 42% of subjects who were thus classified as definite FXTAS [3]. The clinically probable cases had generalized volume loss with mild cerebellar vermial atrophy (in the absence of generalized cerebellar atrophy), white matter changes and no other brainstem abnormalities. Specifically, 5/8 subjects with possible, 9/11 with probable and 21/21 with definite FXTAS had white matter changes and mild vermial atrophy.

Disease progression

Presentation—Based on the self-report obtained during Stage 1 screening; only 31/50 endorsed motor symptoms. Of the 15 subjects who reported no motor symptoms, 7 turned out to have tremor and ataxia, 5 had tremor only, and 2 had ataxia and parkinsonism on neurologic exam. After being made aware of these signs during the exam (see “Experimental design and methods”), 46/50 were then able to recognize the finding(s) and report on its chronology with the help of the significant other. The chronology reported here

is based on this history obtained after all signs were properly demonstrated and recognized by the subject.

Intention and/or postural tremor were the presenting motor signs in 28 of the 46 subjects with symptoms, ataxia in nine, tremor plus ataxia in six and parkinsonism in three. Nine subjects who reported no tremor at screening (Stage I) or during the initial history were able to recognize the tremor at the end of the neurologic exam. Similarly, nine subjects who did not report ataxia were able to recognize it after the exam. In these cases, the clinical signs were mild and insidious and thus not functionally impairing. Overall, the mean age of onset of motor symptoms was 59±11 years based on the clinical history, which is consistent with that reported by Leehey et al. [30].

In this sample, there were two major presentations of FXTAS. First, 16/50 presented with *tremor only* and of these, 38% (6/16) had evidence of cognitive impairment at the time of screening (Table 2). In the second major group who presented with both ataxia plus tremor (n=21), motor symptoms tended to present 5 to 7 years later than those who presented with tremor only. In this second group, 69% (15/21) had evidence of cognitive impairment (Table 2).

Duration and severity—In eight out of 20 subjects who presented with tremor and later developed other motor symptoms, tremor preceded the onset of the additional motor symptoms by more than 10 years. In fact, one definite FXTAS subject had postural tremor for 20 years, two probable FXTAS subjects had postural tremor for 47 and 20 years, and one indeterminate FXTAS subject had postural tremor for 45 years. These four individuals were excluded from symptom duration analyses because, historically and clinically, they appeared to have had essential tremor (ET) before the onset of FXTAS-associated symptoms. Similar cases have been reported in the literature [30].

Duration of motors symptoms was significantly longer in subjects with definite FXTAS (7.9±5 years) compared to subjects in the probable (2.6±2 years) or possible (4.7± 5 years) FXTAS groups (p<0.01). Average duration of symptoms for all subjects was 5.1±5.2 years, ranging from 0 to 18 years. Subjects with a longer duration of symptoms had more severe symptoms on the Rankin scale (r=0.42, p<0.01).

Examination of each of the motor symptom scales indicates that the higher scores on each scale are significantly positively correlated with diagnostic certainty, duration of symptoms and severity as measured by the Rankin scale (Table 1). There was a difference in the range of duration of symptoms between tremor (0–20 years, mean duration 10.5±11) and ataxia (0–7, mean duration 4.3±4.6).

Twenty-five subjects had no significant disability or symptoms despite detectable motor signs (Rankin score=1, Table 1). Seven subjects had a Rankin score of 2, 11 subjects had a score of 3, and 7 subjects had a score of 4. Thus, over one-third of participants had at least moderate disability.

With respect to cognitive impairment, those with definite FXTAS had a higher incidence of cognitive impairment (67%) than subjects in other diagnostic categories (31%, p=0.01, Table 3). However, there was no association between the *presence* of any motor symptom and cognitive impairment (Table 3). *Duration* of ataxia was significantly longer in subjects with cognitive impairment compared to cognitively intact subjects (Table 3). The duration of tremor was not associated with cognitive impairment (Table 3).

The MCP sign is used to determine disease certainty. Examination of subjects with this one MRI feature indicates that they were older (68±1.2 vs. 64±1.2, p= 0.01), more likely to be

cognitive impaired (Fisher's exact test p=0.04), and to have a longer duration of symptoms (8±1 vs. 3±1 years, p<0.01) than subjects without the MCP sign.

Genotype–phenotype correlations

Individual CGG repeats are detailed in Table 1. The mean repeat length for all 50 subjects was 93.2±26 with a range from 52 to 160. There was no correlation between repeat size and age of onset (r=−0.08, p=0.61). There was no difference in the CGG repeat size among the definite (95.4± 15), probable (104.6±36), possible (84.7±25), and indeterminate groups (85.0±32; ANOVA p=0.25). Similarly, CGG repeat sizes did not correlate with disease severity as measured by the CRST (r=0.12, p=0.40), ICARS (r=0.03, p=0.81), or UPDRS (r=0.01, p=0.97). CGG repeat size did not correlate with the level of disability as measured by the Rankin Score (r=0.07, p=0.6)

Discussion

This cross-sectional study of 50 *FMR1* premutation carriers is the first step in the examination of a larger group of subjects who harbor the mutation and may or may not be symptomatic. The first 50 subjects reported here had either reported symptoms (Stage 1, 31/50) or had a positive CATSYS screen (Stage 2, 45/47). Other subjects with the *FMR1* premutation who had negative results in the first two assessment stages are currently undergoing full neurologic exams and are not part of this report.

We identified subjects from a systematic survey of carrier status from families with a diagnosis of FXS to avoid inflating estimates of penetrance that would have resulted from symptom-based recruitment. Given the lowincidence of this X-linked disorder, a more accurate estimate of penetrance will require a larger number of subjects [31, 32].

Diagnosis of FXTAS

We compared three methods of FXTAS ascertainment: (a) self-report of tremor or ataxia; (b) objective CATSYS measures of tremor or ataxia; (c) a detailed neurologic exam by a movement disorders expert. The latter, along with all available data, was used as the gold standard to adjudicate a diagnosis with a corresponding level of diagnostic certainty.

Almost all subjects screened using CATSYS were shown to have tremor and/or ataxia (45/47), but only about two-thirds were aware of symptoms (Table 1). The neurologic history and exam detected tremor and/or ataxia in all but one of the CATSYS-positive subjects. The reported symptoms of the two CATSYS-negative subjects were undetected during the exam. The one CATSYS-positive subject missed during the neurologic exam was asymptomatic, and historically, had intermittent tremor. These results corroborate the high sensitivity of CATSYS at detecting motor manifestations of FXTAS [16] and suggests that the neurologic exam is a highly sensitive tool for detection of even asymptomatic subjects

Clinical findings

Motor symptoms—From a motor standpoint, tremor was the first recognizable symptom of FXTAS in the majority (28/50) of our subjects. From the history obtained in this cross-sectional sample, tremor appeared to progress slowly, similar to the mild cognitive defects noted between ages 50–60. Historically, ataxia tended to develop later, or 5–7 years from the onset of the first motor symptom. Based on these observations, we agree with published reports that interpret long-standing tremor in FXTAS as evidence of “comorbid incidental ET” [30]; indeed, some patients may well carry both diagnoses. This probably diagnostic coincidence has also been noted in other neurologic illnesses like ET where 19% of patients eventually meet criteria for PD [33].

Ataxia of gait was the second most common presenting symptom. Gait ataxia was more common and disabling than appendicular ataxia. Speech dysarthria was distinctly uncommon and nystagmus was not found. Patients whose initial symptom was ataxia presented 5 years later than those who presented with tremor.

Difficulty with tandem gait in the absence of ataxia was less common than gait ataxia. This level of imbalance is within the realm of what can be seen in many patients with ET who are not considered ataxic [34, 35]. Many of our subjects were surprised at their difficulty with this simple task when demonstrated during the exam. This form of “tandem ataxia” may be linked to the intention component of the FXTAS tremor. It suggests a higher degree of cerebellar involvement than that associated with isolated postural tremor. Although not generally referred to as ataxia, tandem difficulty may be the first stage of FXTAS ataxias; all subjects with gait ataxia had severe difficulties with tandem walking.

In PD, motor scores track cognitive decline [36]. Our data suggest that ataxia may also track cognitive impairment because the duration of ataxia was longer in cognitively impaired compared to cognitively intact carriers ($p<0.01$). This was of note because it was only true for ataxia and not for tremor or parkinsonism in our sample. Further clarification of this possible correlation between cognition and ataxia would require longitudinal studies and a better understanding on how cerebellar dysfunction may have an independent effect on cognition [37, 38].

Parkinsonism was generally mild with UPDRS scores in the range of patients with early PD. The most common findings were bradykinesia and mixed tremor with postural/kinetic being more common and prominent than rest tremor. Rigidity and dystonic symptoms were uncommon. In the context of FXTAS, we view parkinsonian signs as non-specific accompaniments of neurodegeneration in the elderly. For example, it has been well documented that 20% of Alzheimer's disease patients have non-specific parkinsonian signs on physical exam. It seems these signs are not a useful therapeutic target in FXTAS unless the patient has comorbid PD, as in two of our patients. Any potential relation between the two disorders, such as synergism between their neuropathologies, remains speculative.

It should be clear that the above “progression of symptoms” narrative is limited by the cross-sectional nature of the sampling, and the inevitable shortcomings of having to rely on patient recall. This limitation notwithstanding, we obtained valuable information to generate hypothesis for prospective and longitudinal studies by having our expert in movement disorders carefully interview each subject and their significant other. This type of retrospective information is often used in clinical studies as part of the inclusion/exclusion criteria.

Non-motor symptoms

With respect to cognition, global cognitive dysfunction was a significant finding in our study sample both in early cases with less than definite FXTAS (31%), and in most with definite FXTAS (67%). This strengthens the impression that cognitive impairment is an early and progressive clinical feature of FXTAS. Interestingly, our results identified only two subjects with executive dysfunction despite other studies in which executive dysfunction was a consistent finding [5]. In our sample, deficits in non-executive cognitive domains were more common and independent of executive dysfunction. This finding extends to our larger study sample of men >50 with the premutation [39].

Erectile dysfunction (ED) and urinary symptoms appear to be the most common autonomic symptoms. Apart from the high prevalence of ED in our sample, early autonomic dysfunction appears to be of less clinical significance than in other forms of

neurodegeneration. In PD, for instance, the estimated frequency of ED is as high as 70%, and the incidence of urinary symptoms is 40–68% [40].

The detection of peripheral neuropathy in our investigation relied heavily on symptom reporting and non-quantitative assessment of sensory finding which could have underestimated the incidence of this symptom. Most of these unselected patients in our sample had diabetes mellitus. In the opinion of our neurologic specialist, only one subject had neuropathic symptoms severe enough to account for their balance problems. Accordingly, we would find it difficult to justify routine electrophysiologic screening for peripheral neuropathy in asymptomatic premutation carriers or patients with FXTAS.

By relying on the history and available medical records alone, we could have underestimated the incidence of hearing loss in our sample. Nonetheless, we found it to be significantly higher than that found in the general population. This suggests a possible pathophysiologic link making the auditory nerve more sensitive than other peripheral nerves to the injurious effects of FXTAS. This is the first time this association is reported in FXTAS. Sensory neural hearing loss is a common finding in a number of other neurodegenerative conditions, particularly in those linked to mitochondrial defects, or to age-related decline in oxidative phosphorylation [41–43].

Sleep disorders, particularly RLS and REM-BD are common in other neurodegenerative disorders like the alpha synucleopathies [11, 44]. Symptoms consistent with REM-BD were a significant finding in our sample. However, interpretation of our results is tempered by the fact that we were unable to obtain polysomnographic confirmation of this. Our findings suggest that further investigation of parasomnic phenomena in FXTAS is indicated.

Overall, our data suggest that FXTAS may have two principal presentations. In the first, patients present with tremor as their most prominent symptom. In the second group, patients present with early imbalance with or without tremor. In this subset, the incidence of cognitive impairment appears to be higher than those presenting with tremor. In patients presenting with tremor who later develop ataxia, the emergence of ataxia seems to herald a second and more accelerated stage during which cognitive and non-motor symptoms begin to track the progression of motor symptoms. Of the non-motor symptoms, erectile dysfunction, sensorineural hearing loss and sleep disorders appear to be closely associated with FXTAS. Peripheral neuropathy is also of interest but appeared to be less important in our cohort than has been previously reported [14, 15].

Neuro-imaging

The MCP sign is neither sensitive nor specific to FXTAS. It is present in only 60% of pathologically confirmed cases [7]. Although rare, similar findings have been noted in patients with other entities like multiple sclerosis and multisystem atrophy (MSA) [45]. Rather than a diagnostic marker, the results presented here suggest that the MCP sign is the strongest radiographic marker of disease progression and disability. Other non-specific radiographic signs in FXTAS like generalized volume loss and white matter changes were present in all subjects with the MCP sign and with probable FXTAS. Most but not all subjects with possible FXTAS also exhibited these findings. Cerebellar vermial atrophy is another finding periodically mentioned in the literature but not sufficiently emphasized. When co-existing with generalized volume loss, it may offer a more specific radiographic marker of early FXTAS.

Taken together, the radiographic findings suggest that generalized volume loss and white matter changes are early, albeit non-specific neuro-imaging sign of FXTAS. It remains to be

determined whether quantitative volumetric assessment of absolute relative cerebral volume loss of can serve as a early radiographic marker of FXTAS compared to the MCP sign.

Genotype–phenotype correlations

We did not observe a correlation of CGG repeat length with age of onset or severity of motor symptoms in contrast to other reports (reviewed in [46]. Instead, we found that symptom severity was mainly a function of duration of illness (r= 0.47; p<0.01) rather than repeat size (r=0.07; p<0.6). There are several possible explanations for these conflicting results. First, the correlation observed in some study samples may be due to the inclusion of non-carriers (or those with lower repeats and very few symptoms of FXTAS, if any) in an analysis, not just carriers. For instance, non-carriers were included in correlations of repeat length with severity of motor symptoms, [47] the presence of neuropathy [48], but in a separate study, not in the a correlation with age of onset [49]. Second, differing results could be a result of sample size. For comparison, our sample of premutation males was 50 while that of Tassone et al. [49] was 93. Third, the phenotype distribution may differ among studies due to selection biases. In our sample analyzed here, only men who were able to come to our site were included. This may bias against those with severe ambulation problems. Fourth, and perhaps most interestingly, the repeat size distribution may differ among studies. If the repeat size range is narrow, a correlation may be observed. However, this does not seem to be a property in our series (range is 52–160 repeats) nor in the others [47–49]. Although the range is wide, each study may vary in the premutation allele frequencies. If there is a non-linear relationship between repeat size and the trait, an analysis that assumes linearity may obscure the relationship. The other premutation-associated trait, FXPOI, clearly show this non-linear effect: those with midrange premutation repeats (70–99) have the highest risk for ovarian insufficiency compared with the lower and higher premutation ranges [23, 50]. Thus, it may be that some study samples may include more individuals who fall into the linear range of the association while other samples may have higher frequencies of those at the lower and higher ends of the repeat distribution.

Implications for future research

From a diagnostic standpoint, our data bring to question the utility of the current definite, probable, and possible diagnostic categories of FXTAS [3]. Once the premutation status is known, our data suggest these categories are simply a function of symptom duration, and add little more to the specificity or certainty of the diagnosis. The intent at the time of the publication of Jacquemont et al. was to reduce the number of false positive FXTAS cases that may be misdiagnosed in the world of patients with tremor and ataxia. Since then, it has become clear that the number of FXTAS patients found among phenotypically similar patients with ET, MSA, spinocerebellar ataxia (SCA), and PD is so small as to not warrant the routine screening for FXTAS in these populations. [51, 52] Kamm et al., for instance, found no premutation carriers among 81 pathologically proven cases of MSA. In patients with ET, MSA, and SCA, categories such as definitive, probable and possible have not proved useful in the clinical management or in conducting clinical research in these patients. Of note is that patients with the gray zone (intermediate) CGG expansions (40–55) allele may behave differently from patients with the *FMR1* premutation. In these cases, recent evidence suggests that this allele may be over represented among patients with familial MSA-C [51].

In conditions without readily available genetic markers, the diagnostic categories like the one currently used in FXTAS may still play a role in the clinic or in research. Once genetic screening is available, these diagnostic categories become far less helpful. From a practical standpoint, we are concerned that an overemphasis on the Jacquemont diagnostic categories may unnecessarily exclude patients with probably or possible FXTAS who may otherwise

be good candidates for future clinical trials. Finally, the Jacquemont criteria are heavily weighted on the presence of the MCP sign, which our data suggests is simply a function of symptom duration.

In summary, our data suggests FXTAS has at least two phenotypic presentations, a tremor-predominant one and one dominated by ataxia from the outset. Analysis of historical data indicates that the time course for each may be different. These conclusions need to be replicated in larger multicenter, longitudinal studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Genotype, phenotype and clinical presentations

CGG repeats	Stage 1		Stage 2			Stage 3: Neurologic evaluations							
	Self-reported motor symptoms		CATSYS/Neuropsychological tests			History and exams				Severity of MRI findings			Global disability
	T	A	T	A	CI	Age at exam	Duration of 1st motor symptom	Presentation order of motor symptoms	Cognitive impairment (Test administered)	MCP sign	White matter changes	Volume loss (cerebral/cerebellum)	Modified rankin score
Definite FXTAS													
93	√	–	√	√		65	2	T/A	N(S)	√	√	√	3
99	√	–	√	√	–	56	8	P→T	N(FB)	√	√	√	1
99	–	√	√	√		68	7	A→T→P	Y[a]	√	√	√	4
98	√	√	√			66	15	T→A	Y(FB)	√	√	√	3
91	√	–	√		–	62	12	T→A	N(FB)	√	√	√	2
90	√	√				65	6	T→A→P	N[a]	√	√	√	3
125	√	–	√	√	√	67	15	T→A(d)	Y(FB)	√	√	√	3
115	√	√	–	√		71	18	T→A	Y(S)	√	√	√	2
97	–	–	√	√	–	61	11	T→tan	N(FB)	√	√	√	1
125	–	√	–	√	√	61	3	A→T→P	Y(FB)	√	√	√	3
86	√	√				75	20	T (et)→A→P	Y(S)	√	√	√	4
63	–	–	√	√	–	70	12	T→A	N(FB)	√	√	√	1
100	–	–	√	√	√	72	1.5	A→T→P	Y(FB)	√	√	√	3
90	√	√	√	√	–	63	9	T (ti)→A	N(FB)	√	√	√	4
89	√	–	√	–	√	71	3	T→P	Y(FB)	√	–	√	1
75	√	–	√	–	√	75	2	T	Y(FB)	√	√	√	1
97	√	√	√	√	√	76	7	T/A→P	Y(SB)	√	√	√	4
80	√	√	√			75	10	A→T→P	Y[a]	√	√	√	4
95	–	√	√	√		72	13	A→T	Y(SB)	√	√	√	4
92	√	–	√	√	√	65	4	T→A→P	Y(FB)	√	√	√	2
105	–	–	–	–	√	74	1	T	Y(SB)	√	√	√	1
Probable FXTAS													

CGG repeats	Stage 1		Stage 2			Stage 3: Neurologic evaluations							
	Self-reported motor symptoms		CATSYS/Neuropsychological tests			History and exams				Severity of MRI findings			Global disability
	T	A	T	A	CI	Age at exam	Duration of 1st motor symptom	Presentation order of motor symptoms	Cognitive impairment (Test administered)	MCP sign	White matter changes	Volume loss (cerebral/cerebellum)	Modified rankin score
100	√	–	√	√	√	55	5	T→tan	Y(FB)	–	√	√	1
160	√	–	√	–	√	72	5	T→tan→P	Y(FB)	–	√	√	3
78	–	–	√	√	–	68	47	T (et)→A (e)→P	N(FB)	–	–	√	1
80	–	√	–	–	–	61	2	A (e)→T	N(FB)	–	√	√	2
125	√	–	√	–	√	66	2	T→tan	Y(FB)	–	√	√	3
125	√	–	√	–	–	65	5	T	N(FB)	–	√	√	2
80	–	–	√	√		73	0	T/tan	Y(FB)	–	√	√	2
71	√	–	√	–	–	59	2	T→tan	N(SB)	–	–	–	1
67	√	√	√			74	20	T (et)→A (e)	N(SB)	–	√	√	3
160	–	–	√	√	–	60	0	None	N(FB)	–	√	√	1
78	–	√	√	√	√	68	12	A→T	Y(FB)	–	√	–/√	2
Possible FXTAS													
85	–	–	√	√		53	5	A (e)→P	N(SB)	–	√	√/–	3
60	–	–	–	√	–	73	0	T/A	Y(FB)	–	–	–	
55	√	–	√	–	–	60	10	T→A	N(FB)	–	–	–/√	
125	–	–	–	√	–	62	0	P	N(FB)	–	√	√	
78	√	√	√		–	62	10	T→tan	N(FB)	–	√	√	
72	√	–	√	–	–	70	5	T→tan	N(FB)	–	√	√	
125	–	–	–		–	65	0	T/tan	N(FB)	–	√	√	
84	–	–	√	–	–	57	0	T	N(FB)	–	–	√	
Indeterminate FXTAS													
85	√	√	√	√	–	54	1	T→A (CIDP)	N[a]	NA	NA	NA	3
75	–	–	√	√	–	65	0	None	N(FB)	–	–	–	
54	–	–	√	√		77	0	None	N[a]	NA	NA	NA	
52	–	√	√	–	–	70	13	P→T→A	Y(FB)	NA	NA	NA	4
68	–	√	–	–	–	60	0	T	N(FB)	–	√	√	

CGG repeats	Stage 1		Stage 2			Stage 3: Neurologic evaluations							
	Self-reported motor symptoms		CATSYS/Neuropsychological tests			History and exams				Severity of MRI findings			Global disability
	T	A	T	A	CI	Age at exam	Duration of 1st motor symptom	Presentation order of motor symptoms	Cognitive impairment (Test administered)	MCP sign	White matter changes	Volume loss (cerebral/cerebellum)	Modified rankin score
72	–	–		√	–	68	0	tan	N(FB)	NA	NA	NA	
68	–	–	√	–	√	64	45	T (et)→tan	Y(FB)	–	–	√	
101	–	–	–	√	–	66	0	T/tan	N(FB)	NA	NA	NA	
125	–	–	–		–	56	0	T	N(FB)	–	√	√	
150	–	–		√	√	59	0	T	Y(FB)	–	√	–/√	

Age at the time of the neurologic exam (Stage 3), which was conducted an average of 11 months after Stage 2. Duration of 1 st motor symptom and order of presentation are based on the consensus of the subject, family and/or caregiver who was present at the time of exam. Whenever possible this information was corroborated by reviewing outside medical records. Cognitive and non-motor symptoms are not considered here. Radiologic imaging criteria are also per Jacquemont et al. [3] Major criteria=MRI white matter lesions in middle cerebellar peduncles (MCP) and or brain stem; Minor criteria=MRI white matter lesions in cerebral white matter or moderate-to-severe generalized atrophy using visual inspection. “Definite” FXTAS=a premutation carrier with the MCP sign or neuropathologic confirmation along with intention tremor or gait ataxia; “probable” FXTAS=a carrier with the MCP sign and either Parkinsonism, at least moderate short-term memory dysfunction, or an executive dysfunction deficit or has both tremor and ataxia in the absence of the MCP sign; “possible” FXTAS=a carrier with either tremor or ataxia and either white matter lesions in the cerebrum or at least moderate generalized cerebral atrophy; and “indeterminate” FXTAS=one major or minor clinical feature suggestive of FXTAS in the absence of radiographic findings or with no available radiographic studies. Checkmark=finding is present; horizontal line=absent

Blank Data missing due to exclusions, equipment malfunction, or testing not administered, *T* tremor, *ti* titubation, *et* essential tremor, *A* ataxia, *tan* tandem only, *d* dysarthria, *e* ethanol, *CIDP* chronic inflammatory demyelinating polyneuropathy, *CI* cognitive impairment, *FB* full neuropsychological battery administered, *SB* short neuropsychological battery administered, *T/A* same onset of tremor and ataxia, *P* parkinsonism, *NA* not available

[a] Neuropsychological tests not administered

Table 2
Prevalence of non-motor symptoms in subjects compared to age-adjusted estimates

Symptom	Subjects (*N*=50; %)	Men>60 years (%)	Chi-square test/*p* value
Sleep disorders			
Symptoms suggestive of rapid eye movement behavioral disorder (REM-BD)	10	2	16.3/<0.0001
Heavy snoring (possible sleep apnea)	24	25	0.03/0.87
Restless leg syndrome (RLS)	16	10	2.00/0.16
Autonomic dysfunction			
Erectile dysfunction (ED)	56	34	10.8/0.001
Orthostatic intolerance	16	16	0.0/1.00
Bladder dysfunction	24	30	0.86/0.35
Sensory disturbances			
Hearing loss	50	30	9.52/0.002
Peripheral neuropathy	20	26	0.94/0.33

The references used in the comparisons between the age-adjusted incidence of non-motor symptoms in our sample and that in the general population is cited in the Results and summarized here. For REM-BD reference [28]; for OSA, [29]; for hearing loss [27]; for RLS [19]; for peripheral neuropathy [26]

Table 3

Correlates of cognitive impairment

		Cognitive impairment		Statistical significance
		No	Yes	
Diagnostic certainty category	Definite	7/21	14/21 (67%)	Chi-square, p=0.01
	Not definite[a]	20/29	9/29 (31%)	
Presentation of motor symptoms	Tremor	10/16	6/16 (37.5%)	Chi-square, p=0.039
	Ataxia or ataxia/tremor	6/21	15/21 (69%)	
Duration of motor symptoms (years)	Tremor	3.3±4	3 1.67±1.86	t test, p=0.32
	Ataxia	1.5±2	4.1±5	t test, p=0.03

[a]Includes all other diagnostic categories