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Parkinsonism in fragile X-associated tremor/ataxia syndrome (FXTAS): Revisited

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Abstract

Background—Parkinsonian features have been used as a minor diagnostic criterion for fragile X-associated tremor/ataxia syndrome (FXTAS). However, prior studies have examined parkinsonism (defined as having bradykinesia with at least rest tremor or postural instability) mostly in premutation carriers without a diagnosis of FXTAS. The current study was intended to elaborate this important aspect of the FXTAS spectrum, and to quantify the relationships between parkinsonism, FXTAS clinical staging and genetic/molecular measures.

Methods—Thirty eight (38) FXTAS patients and 10 age-matched normal controls underwent a detailed neurological examination that included all but one item (i.e. rigidity) of the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS).

Results—The FXTAS patient group displayed substantially higher prevalence of parkinsonian features including body bradykinesia (57%) and rest tremor (26%), compared to the control group. Furthermore, parkinsonism was identified in 29% of FXTAS patients. Across all patients, body bradykinesia scores significantly correlated with FXTAS clinical stage, *FMR1* mRNA level, and ataxic gait of cerebellar origin, while postural instability was associated with intention tremor.

Interpretation—Parkinsonian features in FXTAS appear to be characterized as bradykinesia concurrent with cerebellar gait ataxia, postural instability accompanied by intention tremor, and

frequent rest tremor, representing distinctive patterns that highlight the need for further clinical studies including genetic testing for the *FMRI* premutation. The association between *FMRI* mRNA level and bradykinesia implicates pathophysiological mechanisms which may link *FMRI* mRNA toxicity, dopamine deficiency and parkinsonism in FXTAS.

Keywords

Fragile X premutation; Parkinsonism; Bradykinesia; *FMRI* mRNA

1. Introduction

FXTAS is a neurodegenerative disorder affecting carriers of premutation CGG repeat expansions (range: 55–200) in the fragile X mental retardation 1 (*FMRI*) gene. FXTAS is most typically characterized by cerebellar ataxia and intention tremor [1]. Other common clinical presentations of FXTAS include parkinsonism, polyneuropathy, executive function deficits and cognitive impairment progressing to dementia in up to 50% of males patients over 65 years old. Neuropathological studies show that FXTAS patients have eosinophilic intranuclear *FMRI* mRNA-containing inclusions in neurons and astrocytes in diffuse regions, including the cortex, basal ganglia, thalamus, hippocampus, amygdala and substantia nigra. Radiological anomalies include white matter hyperintensities in the periventricular regions, splenium of the corpus callosum, pons and middle cerebellar peduncles (the ‘MCP sign’), and gray matter volume loss [2]. Individuals with the fragile X premutation have elevated *FMRI* mRNA levels, and in the upper range of the premutation (>120 repeats) there is reduced fragile X mental retardation protein (FMRP) levels.

Parkinsonian features have been included as a minor diagnostic criterion for FXTAS. The first study in patients with a clinical diagnosis of FXTAS documented a 57% prevalence of mild bradykinesia and 10% of rest tremor in 20 male patients, but these authors did not report the percentage of cases having both bradykinesia and rest tremor [1]. In a videotape study [3], seven male fragile X pre-mutation carriers showed higher tremor (rest and action) and rigidity scores on the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS), but their scores of bradykinesia and balance were not significantly different from those in a combined group of normal controls and female premutation carriers. Leehey et al. [4] evaluated motor symptoms (tremor, ataxia and parkinsonism) in a larger premutation carrier sample and found overall motor impairment that was significantly correlated with CGG repeat length. In a case series, Hall et al. [5] described 4 non-FXTAS fragile X premutation carriers with motor features very similar to idiopathic Parkinson’s disease (PD). Dopaminergic transporter SPECT imaging studies have shown evidence of nigrostriatal degeneration (e.g. Ref. [6]) in FXTAS cases with parkinsonism.

Since prior studies examining parkinsonism in fragile X pre-mutation carriers were predominantly performed either in those without a diagnosis of FXTAS, or in a small sample size ($n = 5$, except for 1 study [1] with a $n = 20$), the relationships between parkinsonism, FXTAS clinical staging and genetic/molecular measures have not been well characterized. The current study was intended to elaborate this important aspect of the FXTAS spectrum.

2. Subjects and methods

2.1. Participants

Retrospective videotape review was performed in a cohort of FXTAS participants ($n = 38$, 8 females) and 10 normal controls (Table 1) recruited from the University of California Davis. There were no differences in age ($t_{46} = 0.82$, $p = 0.42$) or sex ($\chi^2 = 0.64$, $p = 0.43$) between the two groups. Study procedures were conducted following protocols approved by the UC Davis institutional review board and all subjects have provided informed consent. All patients had received a FXTAS diagnosis according to published criteria for probable or possible FXTAS [1]. FXTAS clinical staging was also made for each patient to score functional impairment as follows: 0 = normal functioning; 1 = subtle or questionable tremor and/or balance problems; 2 = minor, but clear tremor and/or balance problems producing no significant interference with activities of daily living (ADLs); 3 = moderate tremor and/or balance problems with at least occasional falls and significant interference in ADLs; 4 = severe tremor and/or balance problems requiring the use of a cane or walker; 5 = use of a wheelchair on a daily basis; 6 = bedridden. The FXTAS clinical stage for all patients included in the present study was 2 (mean = 3.1 ± 0.9).

2.2. Structured videotape procedure

Subjects underwent a structured videotaped examination, using three standardized scales: the Clinical Rating Scale for Tremors (CRST), the motor section of the UPDRS, and the International Cooperative Ataxia Rating Scale (ICARS), to capture aspects of tremor, parkinsonism, and cerebellar dysfunction (see Berry-Kravis et al. [3] for more details). One item from the Unified Huntington Disease Rating Scale (UHDRS) (i.e. tandem walking) was also included. Participating movement disorders neurologists (D.A.H., M.A.L. and L.Z.) blinded to the premutation status scored the videotapes of the participants, including controls. Data analyses for the current study focused on the UPDRS measures except for rigidity, since rigidity could not be reliably rated from the videotape.

The UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria was applied to our study cohort in order to characterize the prevalence of parkinsonism. Participants needed to have bradykinesia with at least one of rest tremor or postural instability to qualify as having motor parkinsonism.

2.3. Genetic and molecular testing

FMRI CGG repeat lengths and *FMRI* mRNA levels (in normal population, mean = ~ 1.4) were quantified following procedures described previously [7].

2.4. Statistical analyses

Prevalence of individual parkinsonian features and of "parkinsonism" were computed. Comparisons between FXTAS patients with and without parkinsonism were performed using *t*-tests except for the UPDRS score and FXTAS stage which were tested with the non-parametric Mann-Whitney *U* test. Spearman's rank-order correlation was employed to evaluate the associations between UPDRS score, FXTAS clinical stage, and genetic/molecular measures.

3. Results

3.1. Prevalence of parkinsonian features and parkinsonism

Analyses of the UPDRS scores revealed that 56.8% of FXTAS patients had body bradykinesia, 26.3% had rest tremor, and 41.7% had postural instability (using a cut-off 1 for all 3 features). Chi-square test showed that the prevalence of bradykinesia in the 38 FXTAS patients was significantly higher than in the age-matched normal control group (Table 2), with a borderline significance in the same direction suggesting more frequent rest tremor in the FXTAS group. No significant group difference was found for the prevalence of postural instability, although this sign was also more often observed in FXTAS (41.7% vs. 20%, Table 2).

There were 11 cases who met our criteria for parkinsonism, yielding a 28.9% prevalence which is more than 20-fold higher than the commonly reported ~1% of parkinsonism in people 65–74 years of age. Four of our 8 females were regarded as having parkinsonism, suggesting a very high prevalence of parkinsonism in female FXTAS patients, even though Chi-square test did not find a significant gender difference ($\chi^2 = 2.18, p = 0.14$).

t-Tests showed no significant differences between the FXTAS subgroups with and without parkinsonism in age, CGG repeat length, or *FMRI* mRNA levels (*p*'s 0.80). Non-parametric Mann–Whitney *U* test revealed no subgroup differences in FXTAS clinical stage, postural tremor, intention tremor, or gait (*p*'s 0.29).

3.2. Correlational analyses

Across all patients, body bradykinesia scores were significantly correlated with the UPDRS gait (Spearman rho = 0.62, $p < 0.0001$), cerebellar ataxia as measured by the UHDRS tandem walking test (rho = 0.59, $p = 0.0003$), FXTAS clinical stage (rho = 0.36, $p = 0.028$), and mRNA level (rho = 0.52, $p = 0.006$). Postural instability displayed a marginally significant association with intention tremor (rho = 0.34, $p = 0.049$). No significant correlations were observed with rest tremor.

CGG repeat length was positively correlated with FXTAS clinical stage (rho = 0.63, $p = 0.0004$), and mRNA levels (rho = 0.74, $p < 0.0001$). *FMRI* mRNA level was also associated with FXTAS clinical stage (rho = 0.48, $p = 0.012$). CGG repeat length correlated with only one of the motor measures analyzed, namely tandem walking on the UHDRS (rho = 0.46, $p = 0.028$).

4. Discussion

In this retrospective videotape study in fragile X premutation carriers with FXTAS, analyses on the UPDRS scores revealed higher prevalence of body bradykinesia (57%) and rest tremor (26%) in the patient group compared to age-matched normal controls. Postural instability is also very common (42%) in our FXTAS patients, but the prevalence was not significantly higher compared to that in normal controls, likely due to the small sample size of the control group. The frequency of bradykinesia found in the present study is similar to that in 20 FXTAS males of Jacquemont et al. [1], but the rest tremor prevalence was twice

as high as reported previously. The parkinsonian features in our FXTAS patients were also much more frequent than in the general older population. For example, in an older community-dwelling population (> 65 years of age, mean age = 76.6), Louis and colleagues [8] found prevalences of 20% for bradykinesia, 2% for rest tremor and 27% for postural instability. Furthermore, parkinsonism (defined as having bradykinesia with at least rest tremor or postural instability) was identified in 29% of patients. The prevalence (50%) of parkinsonism in females with FXTAS found in the current study is also worth noting, which is somewhat inconsistent with a previous study in female patients with movement disorders [9] that suggested an association between Parkinson's disease and fragile X gray-zone expansions (CGG range = 40–54), but not premutation range expansions. Thus, it remains to be elucidated whether this high rate of parkinsonism in our female FXTAS patients represents a true biological difference or a chance finding due to the relatively limited sample size.

This is the first study examining the association between parkinsonian signs and both CGG repeat length and *FMRI* mRNA level in FXTAS. Our results obtained significant correlations for CGG repeat length with cerebellar ataxia as measured by the UHDRS tandem walking test, but not with other motor symptoms. *FMRI* mRNA levels were correlated with body bradykinesia and gait measures on the UPDRS, but were not significantly associated with rest tremor or postural instability. The Parkinson's disease related pathophysiology underlying bradykinesia is distinguishable from rest tremor and has been related to perturbed activation or inhibition of the basal ganglia-thalamocortical pathway [10], likely involving the dorsal premotor cortex (dPMC) and dorsolateral prefrontal cortex (dLPFC). MRI studies of FXTAS patients have demonstrated gray matter volume reduction in brain regions including (but not limited to) midbrain, striatum, thalamus, supplementary motor area (SMA), and dLPFC [6, 10]. The *FMRI* mRNA toxicity which causes the sequestration and functional perturbation of CGG binding proteins has been suggested to be the pathogenesis of FXTAS [2]. The correlation found between *FMRI* mRNA and bradykinesia, the cardinal PD feature with robust association with dopamine deficiency, may implicate pathophysiological mechanisms, which link *FMRI* mRNA toxicity, the dopamine pathway and parkinsonism in FXTAS. Mitochondrial dysfunction may be another aspect shared by PD and FXTAS, as one study [11] suggested that toxic *FMRI* mRNA transcription involving mitochondrial dysfunction plays a role in the pathogenesis of parkinsonism in fragile X premutation carriers with small CGG expansions (4085 repeats).

Investigations have been conducted to assess the frequency of fragile X premutations in persons with parkinsonism and PD. Results converge on the notion that the presence of the premutation is not significantly higher in patients with PD. Thus, fragile X pre-mutation screening in clinical populations with parkinsonism is likely to be unproductive (e.g. Ref. [12]). However, because of the fairly frequent occurrence of the *FMRI* premutation (1:209 in females and 1:430 in males) [13] and the established association between FXTAS and parkinsonism, constrained patterns of parkinsonian features which are more closely related to fragile X premutations could still be useful in clinical practice. Here, we propose that parkinsonism persons having bradykinesia associated with cerebellar gait ataxia, or postural

instability concurrent with intention tremor, are more likely to have the *FMR1* premutation than those who do not show such patterns of motor symptoms. These specific patterns may increase the yield of *FMR1* premutation screening. Note that although the FXTAS group appeared to have a higher prevalence of rest tremor than normal controls, no correlations were found between rest tremor and FXTAS features, suggesting that rest tremor is a somewhat non-specific parkinsonian feature for the *FMR1* premutation.

We recognize limitations in the present study including the modest sample size and the lack of rigidity measures. Further investigations integrating complete measurement of parkinsonian features, brain MRI, and dopamine transporter imaging in larger groups of FXTAS patients are recommended in order to better understand the mechanisms underlying parkinsonism in this late-life neurogenetic disorder.

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Table 1

Demographic and genetic profiles (mean (SD)).

	Controls (N = 10)	All FXTAS (N = 38)	Parkinsonism (N = 11)	Non-Parkinsonism (N = 27)
Age	64.3 (7.3)	66.6 (8.2)	67.1 (7.9)	66.4 (8.4)
Female (%)	1 (10.0%)	8 (21.0%)	4 (36.4%)	4 (14.8%)
FXTAS stage	–	3.05 (0.87)	3.09 (0.70)	3.04 (0.94)
CGG repeats	–	92.6 (19.6)	93.2 (15.1)	92.2 (21.9)
CGG range	–	57–141	74–119	57–141
mRNA	–	3.13 (1.20)	3.19 (0.98)	3.10 (1.26)

Table 2

Prevalence of parkinsonian features in FXTAS and normal controls (NC).

	FXTAS (N = 38)	NC (N = 10)	χ^2	p
Bradykinesia (%)	56.8	0	10.26	0.001
Rest tremor (%)	26.3	0	3.32	0.068
Postural instability (%)	41.7	20	1.58	0.210