Dementia in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Comparison With Alzheimer’s Disease

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Neurocognitive deficits in fragile X-associated tremor/ataxia syndrome (FXTAS) involve attentional control, working memory, executive functioning, and declarative and procedural learning. To date, no studies comparing FXTAS with other dementias have been done. We characterize the dementia in FXTAS, comparing it with Alzheimer’s disease. Retrospective chart review of 68 adults (50 men, 18 women) with FXTAS. 20 men with FXTAS dementia were matched by age, gender, and education to patients with mild Alzheimer’s dementia (AD). Neuropsychological measures were compared between the two groups: Boston Naming Test (BNT), phonemic fluency (Controlled Oral Word Association Test), digit span forward (DSF) and backward (DSB). Comparisons were based on analysis of covariance and t-tests to assess significant differences between groups. 50% of men with FXTAS and no women were cognitively impaired. On mean scores of verbal fluency (22.83 in FXTAS vs. 28.83 in AD, \( P = 0.112 \)), working memory (DSB, 4.80 in AD vs. 5.41 in FXTAS, \( P = 0.359 \)), and language (BNT, 48.54 in AD vs. 54.20 in FXTAS, \( P = 0.089 \)), there were no significant differences. Digit span forward, measuring attention, was significantly higher in subjects with FXTAS dementia (8.59, vs. 7.10 in AD, \( P = 0.010 \)). Individuals with FXTAS have significant cognitive deficits, on the order of those in AD although the cognitive profiles in these dementias are not similar. Further research is needed to outline the neuropsychiatric profile in FXTAS and the correlation of genetic markers with the progression and severity of cognitive loss.

KEY WORDS: cognitive impairment; neuropsychological; neuropsychiatric profile


INTRODUCTION

Carriers of fragile X mental retardation 1 (FMR1) premutation alleles (55–200 CGG repeats) are typically spared the more serious neurodevelopmental problems associated with the full-mutation (>200 CGG repeats) of fragile X syndrome. However, many adult male premutation carriers develop a neuropsychiatric syndrome characterized by intention tremor, ataxia, parkinsonism, cognitive-behavioral changes, and more variable features such as peripheral neuropathy, lower limb proximal muscle weakness, and autonomic dysfunction [Jacquemont et al., 2007]. FXTAS affects 17% of male premutation carriers in their fifties and up to 75% of males in their eighties [Jacquemont et al., 2004a]. The onset of the neurological syndrome is usually between 50 and 70 years of age [Jacquemont et al., 2004b; Leehey et al., 2007], and motor features often precede the cognitive changes by a variable time interval.

Neuropathologically, FXTAS represents an inclusion body disease, with eosinophilic ubiquitin-positive intranuclear inclusions found throughout the brain, in both neurons and astrocytes, especially in the hippocampus and frontal cortex, as well as in the deep cerebellar nuclei [Greco et al., 2002, 2006]. The presence on MRI of symmetrical regions of T2 hyperintensity in the middle cerebellar peduncles (MCP) and adjacent cerebellar white matter is a major radiologic diagnostic criterion for FXTAS [Brunberg et al., 2002; Hagerman and Hagerman, 2004a]. Cerebellar cortical atrophy, white matter disease, and cerebral atrophy have also been noted on neuroimaging studies [Brunberg et al., 2002; Jacquemont et al., 2003; Loesch et al., 2005].

In affected adult premutation carriers, disorders ranging from mild cognitive deficits to frank dementia may be present. Neuropsychiatric difficulties associated with FXTAS include impairments in: attention, working memory, executive functioning, and both declarative and procedural learning [Grigsby et al., 2006a]. Short-term memory deficits and executive dysfunction constitute minor clinical diagnostic criteria for FXTAS [Hagerman and Hagerman, 2004b]. Executive functioning and capacity for response inhibition were affected in 25...
men with FXTAS [Grigsby et al., 2006b]. Psychiatric symptoms also occur in FXTAS and include: depression, irritability, anxiety, and disinhibited, socially inappropriate, or reclusive behavior [Bacalman et al., 2006; Bourgeois et al., 2007]. This syndrome was described as a novel frontal-subcortical dementia [Bacalman et al., 2006; Bourgeois et al., 2006].

A great deal is known about frontal subcortical dementias, some of which present with clinical parkinsonian features and characteristic inclusions on neuropathological exam [Cumings, 2003]. Examples are Parkinson’s disease (PD), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA). Cognitive slowing, apathy, lack of initiative, retrieval deficit but preserved recall initially, dysexecutive functioning, and mood disturbances, along with movement disorders are typical of neurodegenerative processes involving subcortical structures [Mendez and Cummings, 2003]. Due to the presence of hippocampal inclusions [Greco et al., 2006], FXTAS also involves learning and recall deficits, which are not characteristic of subcortical dementias. In addition, inclusions have been found in the frontal cortex, correlating with the frontal cognitive dysfunction. This pattern of involvement points to a mixed cortical-subcortical dementia picture associated with FXTAS, albeit later in the course of illness. Corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB) are disease processes involving both subcortical and cortical structures and are classified as mixed cortical-subcortical dementias. Interestingly, parkinsonism is a hallmark of both these disorders, of which CBD is typically more difficult to diagnose clinically [Litvan et al., 1997].

To date, no studies have compared the cognitive functioning in FXTAS to other dementing disorders. Several case series describing the neuropsychiatric profile of FXTAS patients [Bacalman et al., 2006; Grigsby et al., 2006b; Bourgeois et al., 2007] have been published, as well as a study comparing 33 men with FXTAS and 27 healthy controls on neuropsychological variables [Grigsby et al., 2007]. FXTAS subjects scored significantly lower than controls on measures of executive functioning and information processing speed, displaying a pattern of cognitive performance somewhat similar to that observed in the frontal variant of frontotemporal dementia and several of spinocerebellar ataxias, but different than the deficits in Alzheimer’s disease (AD) [Grigsby et al., 2007].

The largest comprehensive study of cognitive impairment in FXTAS involved 109 men, grouped into asymptomatic pre-mutation carriers, premutation carriers with FXTAS, and normal controls [Grigsby et al., 2008]. Men with FXTAS performed worse than controls on Mini-Mental State Examination (MMSE, Folstein et al., 1975), intelligence, executive function, working memory, remote recall of information, declarative learning and memory, information processing speed, and temporal sequencing, as well as one measure of visuospatial functioning, whereas language and verbal comprehension were spared. These results further support the idea that FXTAS involves substantial executive impairment and diffuse deficits in other cognitive functions.

Based on previous findings describing the executive dysfunction in FXTAS and on the known pattern of neuropsychological impairment in AD, our hypothesis was that subjects with FXTAS and dementia will perform worse than patients with AD on measures of executive functioning, such as verbal fluency and working memory, and will have better performance on measures of language and visuospatial abilities.

METHODS

Subjects

The institutional review board at the University of California, Davis reviewed and approved the study protocol. The present study consisted of a retrospective chart review of 68 adult patients (50 men and 18 women) with FXTAS, performed by two independent reviewers. Detailed baseline and 18-month follow-up history and physical examinations, neurological, and in most cases psychiatric, consultations were available. Based on the information collected, a clinical diagnosis of dementia or cognitively impaired non-demented was determined, when applicable. The clinical diagnosis of dementia was established using the National Alzheimer’s Coordinating Center criteria [NACC, 2006] (impairment in two or more cognitive domains, progression of deficits, and functional decline secondary to the cognitive dysfunction). Affected cognitive domains noted in this review included executive function, memory, attention, language, visuospatial function, and personality. When cognitive deficits in one or more domains were present but functional impairment was absent or could not be differentiated from the disability secondary to motor symptoms, a diagnosis of cognitively impaired non-demented was given. Although a memory deficit was not necessary for diagnosis, all subjects included in the study had impairment in this domain. Twenty-five subjects showed cognitive impairment by history of whom 21 had dementia, and 4 individuals were cognitively impaired non-demented. Exclusion criteria were: other neurodegenerative dementias, history of cerebrovascular accidents, traumatic brain injury, and alcohol abuse or dependence. Subjects whose MMSE score had improved at 18-month follow-up were also excluded, since cognitive decline could not be supported. A total of 20 patients were included in the data analysis after matching for age and education. Information was collected as to the time of onset of the motor (tremor or ataxia) and cognitive symptoms, as well as presence of comorbid psychiatric conditions, such as depression, anxiety, and preexisting attention deficits. Although the initial sample consisted of subjects of both genders, only men presented with cognitive impairment meeting inclusion criteria. Table I summarizes the characteristics of the 20 subjects with FXTAS and dementia included in the study.

The comparison group consisted of adults with AD, matched by age, gender, education level, and mild dementia stage (MMSE score higher than 24). The demographic and neuropsychological data on patients with AD was collected from an existing database at the UC Davis Alzheimer’s Disease Center, a dementia specialty research clinic where most patients are referred by their primary care physician or other specialists for a diagnostic work-up.

We analyzed data for 90 subjects, including 20 individuals with FXTAS and 70 with mild AD. In addition to meeting inclusion criteria (impairment in two or more cognitive domains, progression of deficits, and functional decline secondary to the cognitive dysfunction), subjects with AD were selected to match subjects with FXTAS with respect to age and education: age within ± 4 years and education within ± 1 year.

Neuropsychological Variables

A battery of neuropsychological measures was administered to both groups. For the purposes of this study, we selected tests that had been administered to both groups, with the aim of sampling several major cognitive domains. Phonic fluency was measured by having patients generate words beginning with F, A, and S [Controlled Oral Word Association Test, COWAT, Spreen and Benton, 1977] or C, F, and L, as consistent with standard instructions. Previous studies have shown the two versions to be comparable [Lacy et al., 1996; TROYER, 2000]. Verbal phonemic fluency is considered a measure of executive functioning as it involves the ability to generate information actively [Grigsby et al., 2007]. Simple attention was measured by an individual’s longest digit span forward (DSF), and longest digit span backward (DSB) was used to assess working
memory [Wechsler, 1987, 1997]. The Boston Naming Test [BNT, Kaplan et al., 1983] was used to assess expressive language or confrontational naming.

**Statistical Analysis**

The statistical analysis involved the comparison between FXTAS and AD groups with respect to the primary neuropsychological outcome variables. Since neuropsychological measures were on a continuous scale, the \( t \)-test was used to assess significant differences between groups. Confounding due to disease severity was controlled through inclusion criteria and also supported by no difference in MMSE score. Potential confounding due to heterogeneity in age and education between groups was controlled by matching in the design. In addition, matching on age to within \( \pm 4 \) years of age resulted in AD subjects having a slightly higher average age, although the difference was not significant. Nonetheless, to control for age directly, comparisons between AD and FXTAS groups with respect to the primary neuropsychological outcome measures were also done using analysis of covariance and the results/conclusions remained the same. Thus, we report the results from the simpler analysis based on the \( t \)-test comparisons. All statistical tests were two-sided at level 0.05.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Education (years)</th>
<th>CGG repeats</th>
<th>MMSE</th>
<th>Motor sx onset (years)</th>
<th>Cognitive sx onset (years)</th>
<th>Cognitive domains affected( ^a )</th>
<th>Depression/ anxiety</th>
<th>Comorbid medical conditions</th>
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<tr>
<td>1</td>
<td>78</td>
<td>16</td>
<td>87</td>
<td>26</td>
<td>11</td>
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<td>CLL</td>
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<td>21</td>
<td>105</td>
<td>27</td>
<td>9</td>
<td>1</td>
<td>M, Ex, P</td>
<td>Depression</td>
<td>CAD</td>
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<td>3</td>
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<td>15</td>
<td>60</td>
<td>25</td>
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<td>Seizure d/o</td>
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<tr>
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<td>15</td>
<td>90</td>
<td>26</td>
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<td>10</td>
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<td>M, p, VS</td>
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<td>18</td>
<td>94</td>
<td>23</td>
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<td>M, p</td>
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<td>M, p</td>
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<td>14</td>
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<td>4</td>
<td>1</td>
<td>M, attn</td>
<td>Anxiety</td>
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</table>

**RESULTS**

**Patient Characteristics**

There was no difference between groups in age or education, as would be expected given that the groups were closely matched on these variables. Although AD subjects were marginally older (mean AD/FXTAS 70.9/68.1), the difference was not statistically significant (\( P = 0.083 \)). Table II summarizes the characteristics of the study subjects. Mean CGG repeat size in the group of 21 men with FXTAS dementia was 97 (range, 60–142; standard deviation 20), whereas mean CGG repeat size in the four cognitively impaired non-demented men was 82 (range, 71–94; standard deviation 11).

Overall we found that 25 (50%) of males with FXTAS but no women were cognitively impaired, as defined by our inclusion criteria. Twenty-one men (42%) met criteria for dementia and four (8%) were cognitively impaired but not demented. In our initial sample of 68 subjects with FXTAS, the age range was 42–89 years, with a mean of 64.8 years. The mean age in the group of men that met criteria for dementia or other cognitive impairment was 69.2 years, ranging from 55 to 89. Thus, men with FXTAS who developed cognitive impairment were significantly older (\( P = 0.038 \)) than the overall group of subjects with FXTAS, consistent with previous findings.

| TABLE II. Characteristics of Study Subjects in AD and FXTAS Groups |
|----------------|----------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Age            | 70.9           | 6.43              | 68.1              | 6.06              | 0.083             |
| Education      | 16.0           | 2.18              | 16.8              | 2.73              | 0.196             |
| MMSE           | 26.4           | 1.68              | 26.9              | 2.25              | 0.338             |

SD, standard deviation.
motor symptoms generally preceded the onset of cognitive difficulties by a variable interval, between 1 and 13 years (mean time interval of 3.7 years), as established based on history obtained from patients and their caregivers (see Table I). However, one subject presented with cognitive and behavioral problems by approximately 2 years before the onset of clinically significant tremor and ataxia. In regard to psychiatric comorbidity, patients with FXTAS and dementia included in this study (n = 20, Table I) had depression (20%) and anxiety symptoms (15%), as established by self- or caregiver report or through psychiatric evaluation.

**Neuropsychological Comparisons**

Mean performance on measures of verbal fluency, as shown by COWAT PAS and CFL test, was lower in subjects with FXTAS dementia (22.83) than patients with AD (28.83), although the difference was not statistically significant (P = 0.112). On working memory (DSB, 4.80 in AD vs. 5.41 in FXTAS, P = 0.359) and language (BNT, 48.54 in AD vs. 54.20 in FXTAS, P = 0.088), the differences were not significant. DSF score, measuring attention, was significantly higher in subjects with FXTAS dementia (8.59 vs. 7.10 in AD, P = 0.01). Table III summarizes the average performance on these tasks for AD and FXTAS dementia groups. These results remain valid after controlling for age in an analysis of covariance.

**DISCUSSION**

In this study, we directly compared the neurocognitive profile of patients with FXTAS dementia to patients with Alzheimer’s dementia. Due to multiple neuropsychological test versions used and the limited sample size, our findings need to be replicated before they can be generalized. There were several differences. Specifically, language performance was lower in AD than FXTAS, which is expected due to the biparietal involvement in AD, leading to significant language impairment. For most individuals with FXTAS, both speech and language are intact, although some individuals with advanced FXTAS may show a cerebellar type of dysarthria [Grigsby et al., 2006a]. Visuospatial functioning, as measured by tests such as the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Block Design (Wechsler, 1997), was not included in this comparison. Patients with AD typically have severe impairments in constructional abilities, although subjects with FXTAS also scored significantly worse than normal controls on Block Design in a recent study [Grigsby et al., 2008]. On the other hand, measures of executive function, such as verbal fluency, are expected to yield lower values in FXTAS, which is characterized by more frontal involvement, and our results confirmed this finding. Although attentional control was found to be impaired in other studies [Grigsby et al., 2006a], by comparison with patients with AD, FXTAS subjects performed significantly better on a measure of simple attention in our study. Other measures, including sustained attention or visual attention, should be further studied.

Significant impairments in declarative verbal learning and memory (both immediate and delayed recall) were found in men with FXTAS as well as in male premutation carriers without FXTAS, compared to normal controls [Grigsby et al., 2008]. Although all subjects with FXTAS included in our study reported subjective memory impairment, also confirmed by family caregivers, we did not examine differences in learning and recall performance between the two groups in our study.

Cognitively impaired patients with FXTAS showed moderate to severe deficits in working memory in a case report [Grigsby et al., 2006a] and when compared to normal controls [Grigsby et al., 2007]. In the present study, no significant difference was found between the working memory scores of patients with FXTAS dementia and AD, as quantified by DSB. This shows that the working memory impairment encountered in FXTAS dementia is not substantially different than the typical deficit found in patients with AD.

None of the females with FXTAS in our sample had dementia or other cognitive impairments. This is consistent with previous studies, showing that women with the premutation have less severe neurological involvement, develop FXTAS less often, and when they do develop FXTAS, they have less severe cognitive deficits and milder brain changes on MRI than males with FXTAS [Hagerman et al., 2004; Adams et al., 2007]. This is presumably related to the protective effect of the second X chromosome in women although it is possible that neuroprotective effects of estrogen are also a factor [Berry-Kravis et al., 2005]. Despite lower prevalence and milder forms of FXTAS in women, there has been a recent case report of cognitive impairment in a 72-year-old woman with 103 CGG repeats, tremor, premature ovarian failure, and radiologic signs [Al-Hinti et al., 2007]. While our study shows a significant gender difference, in that only men developed cognitive impairment, these results should be interpreted with caution due to the small number of women included.

FXTAS is a neurodegenerative disorder and although tremor typically begins at approximately 60 years with onset of ataxia 2 years later, dementia is a late clinical component [Leehey et al., 2007]. Our study supported this by finding that cognitively impaired men with FXTAS were significantly older than the overall sample of subjects with FXTAS. In a recent study, mean ages of onset were 62.6 ± 8.1 years (range, 39–78 years) for tremor and 63.6 ± 7.3 years (range, 47–78 years) for ataxia [Tassone et al., 2007]. We noted great variability in time intervals between the reported onset of motor and cognitive symptoms, with one subject whose cognitive decline preceded ataxia and tremor. Future prospective studies documenting clinicians’ longitudinal observations are needed to better ascertain this temporal relationship, since the patients’ and caregivers’ report is subjective.

CGG repeat size was found to be inversely correlated with age of onset of tremor and ataxia [Tassone et al., 2007] and with...
age of death [Greco et al., 2006]. In our study, men with FXTAS dementia had a mean CGG repeat size of 97, versus a mean of 82 in cognitively impaired non-demented subjects. Although our group of cognitively impaired non-demented patients was small, these values are similar to findings of a previous study [Greco et al., 2006]. Individuals with FXTAS and dementia (n = 5) had a mean CGG repeat size of 92, whereas non-demented cognitively impaired subjects (n = 6) had a mean CGG repeat size of 80, although neurocognitive diagnostic criteria were unclear.

In addition to observing differences between AD and FXTAS dementia, we learned more about the neurocognitive profile of individuals with FXTAS. Dementia associated with FXTAS fits a mixed cortical–subcortical pattern, due to involvement of both cortical (hippocampal, frontal) and subcortical (MCP, white matter) areas. The previously described picture of a frontal-subcortical dementia does not seem sufficient to explain all the deficits. Other mixed dementias with parkinsonism are CBD and DLB. Of course, cerebrovascular disease may lead to a combination of lacunar and large infarcts, causing a mixed cortical–subcortical dementia picture. The cognitive changes in CBD include a unique combination of focal parietal and frontal-subcortical deficits: ideomotor apraxia, perseveration (e.g., shyness, social phobia, and obsessive-compulsive symptoms) and depression have been described in both male and female premutation carriers [Sobesky et al., 1994; Hoss et al., 2005; Bacalman et al., 2006]. Men and women with FXTAS reported higher levels of somatization, interpersonal sensitivity, depression (especially in men), and psychoticism [Hess et al., 2005; Bourgeois et al., 2007]. In our study, patients with FXTAS and dementia (n = 20; Table I) had comorbid depression (20%) and anxiety (15%). This observation is doubly relevant: first, it confirms the high prevalence of mood and anxiety symptoms noted in previous studies, and depression can also predispose to dementia. Second, since anxiety and depression can influence a subject’s behavior during interview, leading to poor effort and suboptimal cooperation with neuropsychological testing, artificial lowering of test results due to psychiatric comorbidities cannot be ruled out. In cases where 18-month follow-up data were available, progression after treatment of depression was investigated. Generally, only subjects whose MMSE scores had lowered indicating cognitive decline were included in the sample. Subjects were automatically excluded if improvement in MMSE score was noted following antidepressant treatment. Further studies utilizing standardized psychiatric interviews (e.g., Structured Clinical Interview for DSM-IV for Axis I Disorders, SCID-I) [First et al., 2002] are under way, in order to collect more specific information on concurrent psychiatric diagnoses.

The other important implication of our findings is therapeutic. Cholinesterase inhibitors (ChEIs): donepezil, rivastigmine, and galantamine have proven beneficial for cognitive and behavioral disturbances in mild to moderate AD and DLB. Although a cholinergic deficit has not been established in FXTAS dementia, there are positive anecdotal effects of anticholinergic treatment in FXTAS [Bourgeois et al., 2006; Hall et al., 2006]. Future studies looking at response to cognitive enhancers in patients with FXTAS dementia, including the N-Methyl-D-aspartate (NMDA) antagonist memantine, will shed more light on possible medication management strategies. One cardinal aspect in geriatric pharmacology is paying close attention to drug–drug interactions and minimizing unnecessary use of medications, especially those with deleterious effects on cognition, for example, anticholinergics, antihistamines, benzodiazepines, and opioids. Many patients with FXTAS are on dopaminergic medications for their parkinsonian symptoms, and theoretically the interaction of antiparkinsonian medications with ChEIs may limit the efficacy of either drug by disrupting the acetylcholine/dopamine balance in the striatum [Bentue-Ferrer et al., 2003]. In practice however, clinical deterioration of parkinsonism has not been reported in patients taking concurrent ChEI medications [Schrag, 2004].

In conclusion, individuals with FXTAS dementia have significant cognitive deficits, on the order of those in AD, although the cognitive profiles in these dementias are not similar. The cognitive component is a major part of FXTAS, and may develop into a mixed cortical-subcortical dementia. Further research is needed to outline the neuropsychiatric profile in FXTAS and the correlation of genetic markers with the progression and severity of cognitive loss.

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