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COGNITIVE DYSFUNCTION IN *FMR1* PREMUTATION CARRIERS

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Abstract

Premutation carriers of the fragile X mental retardation gene (especially men) older than 50 may develop a neurodegenerative disease, the fragile X-associated tremor/ataxia syndrome (FXTAS). Carriers may present with varied cognitive impairments. Attention, working memory, declarative and procedural learning, information processing speed, and recall are among the cognitive domains affected. Executive dysfunction is a prominent deficit, which has been demonstrated mostly in men with FXTAS. In more advanced stages of FXTAS, both men and women may develop a mixed cortical-subcortical dementia, manifested by psychomotor slowing and deficits in attention, retrieval, recall, visuospatial skills, occasional apraxia, as well as overt personality changes. Studies have shown dementia rates as high as 37-42% in older men with FXTAS, although more research is needed to understand the prevalence and risk factors of dementia in women with FXTAS. Neuropsychiatric symptoms are common and reflect the dysfunction of underlying frontal-subcortical neural circuits, along with components of the cerebellar cognitive affective syndrome. These include labile or depressed mood, anxiety, disinhibition, impulsivity, and (rarely) psychotic symptoms. In this paper we review the information available to date regarding the prevalence and clinical picture of FXTAS dementia. Differential diagnosis may be difficult, given overlapping motor and non-motor signs with several other neurodegenerative diseases. Anecdotal response to cholinesterase inhibitors and memantine has been reported, while symptomatic treatments can address the neuropsychiatric manifestations of FXTAS dementia.

Keywords

cognition; dementia; executive function; *FMR1* premutation; FXTAS; memory

BACKGROUND

Approximately a decade ago, a previously unrecognized neurodegenerative disease, fragile X-associated tremor/ataxia syndrome (FXTAS), was first described in carriers of the fragile X mental retardation (*FMR1*) gene premutation [1, 2]. The premutation is found in

1/130-260 women and 1/250-810 men in the general population, and consists of an expansion of 55-200 CGG trinucleotide repeats [3]. The normal gene has less than 45 repeats, and the 45-54 CGG repeat interval is called intermediate or gray zone. Full mutation alleles have over 200 CGG repeats, leading to gene silencing and absence or severe deficiency of the fragile X mental retardation protein (FMRP). Clinically, full mutations develop the fragile X syndrome (FXS). By contrast, individuals with the premutation have normal or slightly decreased FMRP levels but excessive mRNA, which leads to formation of intranuclear inclusions and cell toxicity [4, 5].

Among carriers of the premutation, about 45% of men in their 50s, and up to 16% of women, develop FXTAS [6-9]. FXTAS may also occur occasionally in individuals with gray zone alleles. Intention tremor, gait ataxia, parkinsonism, peripheral neuropathy, autonomic dysfunction, psychiatric symptoms, and cognitive changes are among FXTAS clinical manifestations [10]. Tremor and ataxia typically start between 50 and 70 years of age and progress in successive stages, as follows: 1) subtle or questionable tremor and/or balance problems; 2) minor tremor and/or balance problems, with minimal interference in activities of daily living (ADLs); 3) moderate tremor and/or balance problems with significant interference in ADLs; 4) severe tremor and/or balance problems, with need to use a cane or walker; 5) daily use of a wheelchair; and 6) patients are bedridden [2, 11, 12]. Cognitive deficits manifest about four years after the onset of tremor and ataxia, although, rarely, they may precede the movement disorder [13]. Affected individuals are likely to experience falls beginning about six years following the onset of the initial motor signs; by 16 years into the course of the illness, half the patients have significant difficulty with ADLs. Median survival is 21 years from the onset of the first signs of FXTAS [11, 14].

The purpose of this paper is to review the existing literature to date regarding cognitive deficits in premutation carriers, describe what is currently known about FXTAS dementia, and to present unique features of this movement disorder-associated dementia in the context of other neurodegenerative dementias.

COGNITIVE DEFICITS IN PREMUTATION CARRIERS

Premutation carriers have been extensively studied with the help of neuropsychological tests [15-24]. Male carriers have been scrutinized more closely, since women have a significantly lower prevalence and neurologic expression of FXTAS. Specific cognitive impairments involve attention, working memory, declarative and procedural learning, information processing speed, and capacity for response inhibition. Visuospatial skills and language are typically intact, with the exception of mild dysnomia [16, 19]. Occasionally, ideomotor apraxia has been noted [16].

One of the earliest neuropsychological studies of men with the premutation has revealed significant impairments in executive function and memory (both verbal and nonverbal) [15]. In a study comparing 33 men with FXTAS and 27 controls, those with FXTAS scored significantly lower than controls on measures of executive functioning and information processing speed [18]. Additionally, capacity for response inhibition was affected in men with FXTAS [17]. Grigsby et al. [19] performed the most comprehensive study of cognitive

functioning in premutation carriers to date. In that study, 109 men were examined who fell into three groups: asymptomatic carriers, carriers with FXTAS, and normal controls. Men with FXTAS performed worse than controls on Mini-Mental State Examination (MMSE) and on measures of intelligence, executive function, working memory, remote recall, declarative learning and memory, information processing speed, and temporal sequencing, as well as one visuospatial functioning measure [19]. In another study, male premutation carriers displayed statistically significant deficits in their ability to inhibit prepotent responses, compared to controls; these deficits progressively worsened with age and were strongly associated with presence of FXTAS symptoms [20]. Selective attention was also impaired in men with the premutation but did not show an aging effect [20]. The same group investigated working memory and its subcomponents (verbal, spatial, and central executive memory) across a broad sample of male premutation carriers aged 18-69 years [21]. This study highlighted a specific vulnerability on tasks that require simultaneous manipulation and storage of new information (executive control of memory); carriers with FXTAS symptoms also had impairments in verbal working memory, in addition to central executive memory [21]. Kogan et al. [22] found that men with the premutation had significant deficits in utilizing working memory, compared to family and non-family controls without the premutation.

All the above studies underscore executive dysfunction as a prominent cognitive deficit in men with FXTAS. Brega and colleagues suggested that executive dysfunction might mediate impaired performance on tests in other cognitive domains [25]. The appearance of executive dysfunction in male carriers prior to developing FXTAS remains unclear. Allen et al. [23] found a significant decrease in scores of general intelligence and a marginally significant decrease in logical memory scores in men with the premutation and motor symptoms, compared to their noncarrier male siblings, but no executive deficits. A full neurological exam was not performed in this study, so it is possible that participants had milder neurological impairments. The authors hypothesized that executive dysfunction is a marker of disease duration [23]. A very recent study identified more specific executive function deficits, such as the capacity for response inhibition, as opposed to global impairment [24]. In this multicenter collaboration, 100 asymptomatic male carriers from three independent cohorts were examined. Male carriers older than 50 years with over 100 CGG repeats scored significantly worse than noncarriers on the Stroop Word and Color Test, a measure of response inhibition [24]. The authors concluded that a subset of otherwise asymptomatic carriers is likely to have a deficit in inhibitory cognitive control.

The correlation of specific cognitive deficits with the CGG repeat length is an intriguing area of research that deserves further exploration. Recent studies revealed subtle, yet significant age- and CGG repeat size-related cognitive impairments in young female carriers aged 21-42 [26] and male carriers aged 18-69 without FXTAS [27]. Female carriers had a shorter reaction time on a quantitative magnitude comparison (distance effect) task compared with age-matched neurotypical women. However, the female carriers' performance was significantly poorer with increasing repeat size from 67 to 150 CGG repeats [26]. Also, carriers' performance deteriorated as their age increased from 20 to 42 years, although this change was not significant. In men with CGG repeat sizes over 100, increasing age was associated with decreased performance on executive function measures

involving inhibition ($p < 0.05$) and working memory ($p < 0.01$) [27]. Men with less than 100 CCG repeats were relatively risk-free from cognitive aging effects [27]. This is similar to the aging effect noted earlier by the same authors on capacity for response inhibition [20] and working memory [21], with the added effect of CCG repeat length. A combination of high CCG repeat size and low FMRP expression may further enhance vulnerability. In female carriers with over 100 CCG repeats and FMRP expression in hair roots below 60%, a 10% decrement of FMRP expression corresponded to a significant decrease in IQ scores by about six points [28].

As noted above, female premutation carriers have been studied in less detail. However, attention deficits have been both objectively measured and subjectively reported in this group [29]. Among 39 women with the premutation, only nine scored at or above the 50th percentile on the arithmetic portion of a standardized achievement test, but half scored at or above the 50th percentile in reading and spelling, suggesting that mathematics is an area of relative weakness in female carriers [30].

FXTAS DEMENTIA

Epidemiology and diagnosis

There is currently a paucity of data indicating which subset of premutation carriers may develop cognitive impairment, which ones among these might progress to dementia, and what the prevalence of FXTAS dementia is. The penetrance of marked cognitive impairment in male premutation carriers with over 70 CCG repeats is six times higher than in controls (33.3% vs. 5.1%) [31]. Dementia may occur in advanced stages of FXTAS (3-5), affecting 37-42% of men in the older cohorts described in the literature [13, 32]. Few studies of patients with FXTAS and dementia have been published to date [12, 13, 33-41]. Most of these were case reports or small case series and only two [13, 38] used rigorous criteria in diagnosing dementia. In our previous work, we used the National Alzheimer's Coordinating Center guidelines: impairment in two or more cognitive domains, progression of deficits, and functional decline secondary to the cognitive dysfunction [42]. DSM IV-TR criteria [43] are less ideal since they require presence of memory impairment, which, albeit common, does not always occur in FXTAS. Also, MMSE is not a reliable screening test in FXTAS, in our view, since it is heavily weighted towards cortical functions and FXTAS dementia involves both cortical and subcortical processes.

FXTAS dementia is a mixed cortical-subcortical dementia, characterized by psychomotor slowing and impairments in multiple cognitive domains, including executive function, memory (retrieval and recall), attention, language, and visuospatial skills [13]. Personality changes may occur, representing an accentuation of the premorbid personality (e.g., a man who has always been jovial starts making inappropriate jokes and flirts aggressively) or new aspects, such as apathy in a previously highly driven individual.

The striking gender difference in FXTAS dementia is worth mentioning, with many more cases having been reported in men than women. Only a few women with FXTAS and dementia have been reported to date in the international literature, and in some cases, the etiology of their cognitive impairment was multifactorial [36, 39-41]. Interestingly, Tassone

and colleagues found both AD lesions and FXTAS intranuclear inclusions on neuropathological exam in three women carriers with cognitive loss, while a fourth had Lewy bodies in addition to inclusions [44]. Of these four women, only three had received a clinical diagnosis of FXTAS. These results suggest that dementia is more common in female carriers than previously reported, and call into question the contribution of other neurodegenerative processes to the cognitive decline of premutation carriers [44]. Since the majority of studies have focused on male carriers as described in detail above, the sample of older women with FXTAS studied so far has been small. Therefore, more research is needed to elucidate the prevalence and clinical picture of dementia in women carriers, as well as comorbidity of with other neurodegenerative diseases.

Neuropsychiatric symptoms

Neuropsychiatric symptoms are common in FXTAS and reflect the dysfunction of underlying frontal-subcortical neural circuits, along with components of the cerebellar cognitive affective syndrome (CCAS) [45-47]. Neuropsychiatric manifestations include anxiety, depression, disinhibition, impulsivity, mood lability, irritability, apathy, and agitation [12]. In a small series of patients with FXTAS dementia, 20% had depressive symptoms, and 15% reported anxiety symptoms [13]. Frank psychotic symptoms are rare but paranoid ideation may occur, due to misinterpretation of others' intentions or behavior. We have also seen visual hallucinations in a minority of patients.

The FXTAS disease process involves multiple areas including the cerebellum, middle cerebellar peduncles (MCP), the cerebral and cerebellar white matter, and various cortical regions. Neuroimaging studies show cerebellar and cerebral atrophy, white matter disease, and increased MRI T₂ signal in the MCP, called the MCP sign [48]. The MCP conveys all cerebral cortical input to the cerebellum, so MCP lesions result in deafferentation of the cerebellum [49]. The cerebellum contributes not only to motor control, but also to the modulation of emotion and cognition. Lesions of the sensorimotor cerebellum (medial part of the posterior lobe) result in the cerebellar motor syndrome (ataxia, intentional tremor, dysmetria, and dysarthria) [47]. CCAS develops when lateral hemispheres of the posterior cerebellum (involved in cognitive processing) and/or the vermis (limbic cerebellum) are implicated, and includes impairments in executive function, visuospatial skills, linguistic processing, and affective dysregulation [47, 50]. FXTAS exemplifies many of the CCAS features, in addition to symptoms resulting from dysfunction of the cerebral white matter and of the limbic system.

Diffusion tensor imaging studies in men with FXTAS showed white matter abnormalities in the cerebellar-brainstem and limbic systems, in particular the middle and superior cerebellar peduncles, cerebral peduncle, as well as the fornix and stria terminalis [51]. The limbic system (particularly amygdala) plays a major role in the panic response [52]. Structural and functional imaging studies in premutation carriers support this thesis. Notable amygdala abnormalities in male carriers include an impaired response to fearful faces, a significant negative correlation of amygdala volume with CGG size for the 55-85 repeat range, and grey matter volume loss in men with FXTAS [53-55]. Additionally, female carriers

displayed a significant negative correlation between the hippocampal volume and severity of anxiety symptoms [56].

Differential diagnosis

Table 1 presents a comparison of FXTAS dementia with other dementias: AD, dementia with Lewy bodies (DLB), behavioral variant of frontotemporal dementia (bv-FTD), Huntington's disease, and Parkinson's disease dementia (PDD) [57-59]. These dementias were selected because they share several features with FXTAS dementia.

The only study to date comparing FXTAS dementia with another dementia included 68 patients with FXTAS (50 men and 18 women). Of those, 20 men had dementia and they were compared with 70 age- and education-matched men with mild Alzheimer's disease (AD). No significant differences were found between the two groups regarding scores of verbal fluency, working memory, and language, although the digit span forward, measuring simple attention, was better in patients with FXTAS than in those with AD [13]. Cognitive deficits in FXTAS dementia may be of similar severity as those in AD, although the two disorders have different profiles. Short-term memory loss is a diagnostic criterion [7], but recall problems are not always part of the FXTAS picture, as opposed to AD, where amnesic difficulties are prominent early.

Parkinsonism affects a subset of individuals with FXTAS; hence some premutation carriers have been misdiagnosed with (usually atypical) Parkinson's disease (PD). The presence of resting tremor, levodopa responsiveness, and the absence of nonparkinsonian neurological features suggest PD [57]. Executive function, retrieval and temporal ordering of information and procedural memory, along with visuospatial abilities and visual integration are impaired in PDD [57]. No carriers were identified among 137 men with PD screened for the *FMRI* premutation, showing that clinicians are very accurate in their diagnosis. However two men had gray zone alleles, one of whom developed marked cognitive decline and visual hallucinations by six-year follow-up [60]. This finding highlights an interesting question, whether the premutation or gray zone alleles contribute to an accelerated decline in patients with co-occurring neurodegenerative processes. This hypothesis is supported by neuropathological findings consistent with FXTAS inclusions and AD lesions (neurofibrillary tangles and neuritic plaques) in a 65 year-old man with rapidly progressive dementia, suggesting that both AD and FXTAS were present, and may have contributed to a faster decline [33]. Greco et al. [61] presented a woman with FXTAS and multiple sclerosis who developed progressive memory loss and died at age 52 with complex neurological impairments; in this case, co-occurrence of MS and FXTAS could have accelerated the clinical deterioration.

Other cortical-subcortical dementias with parkinsonism include corticobasal degeneration (CBD) and DLB [57]. CBD is rare (1.3% of dementia cases in an autopsy series), although it may be underdiagnosed [62]. Patients with CBD usually present with unilateral ideomotor apraxia, parkinsonism unresponsive to dopaminergic treatment, and/or other lateralized cortical features (i.e., cortic sensory neglect, visuospatial neglect, nonfluent aphasia), as well as the alien hand sign [63, 64]. Psychomotor slowing, dysexecutive syndrome, and impaired memory retrieval may also occur [57]. Depression may be present in up to 70% of

patients [65]. DLB is the second most common cause of neurodegenerative dementia, after AD, accounting for 15-25% of patients [57, 63, 66]. The DLB diagnosis is based on the clinical triad of fluctuating cognition, parkinsonism, and vivid visual hallucinations; patients are exquisitely sensitive to extrapyramidal side effects of antipsychotic medications [66]. Progressive supranuclear palsy (PSP) is the most common form of neurodegenerative parkinsonism after DLB and PD. With onset in the sixth decade, PSP is manifested by early postural instability, dysarthria, dysphagia, vertical gaze palsy, axial levodopa-unresponsive akinetic-rigid syndrome, and frontal-subcortical dementia [57, 63].

Upon review of 286 charts of men with ataxia, 55% had one clinical manifestation of FXTAS (progressive intention tremor, ataxia, and cognitive decline), 20% had two of the three features, and 4% had all three [67]. Thus, the differential diagnosis between FXTAS and other ataxias may be complicated by overlapping clinical signs, as well as the unfamiliarity of FXTAS. For example, spinocerebellar ataxias (SCA) are autosomal dominant, adult-onset disorders, of which SCA1 is the most common [57]. Patients with SCA can develop a mild dementia with difficulties in attention, executive function, motivation, impulse control, and in performing complex sequential tasks. Frank dementia occurs late in the course of the disease and may be present in up to 33% of patients with SCA2 and 25% of those with SCA1 [57]. Neuropsychiatric aspects include depression, aggression and psychosis, which may precede the cognitive and motor impairment [68, 69]. Similar to findings in PD, less than 2% of males tested for adult-onset ataxia had *FMR1* premutations [67, 70].

Bv-FTD may resemble FXTAS dementia, due to the prominent executive dysfunction, loss of social decorum, and disinhibited behavior in some patients, or apathy in others [58]. However the older onset age, presence of *FMR1* premutation, and characteristic movement disorder and MRI changes are consistent with FXTAS. Similar to bv-FTD, some patients with FXTAS may appear unempathic, making hurtful remarks to their loved ones, with little regard for how those could affect others [58]. In contrast to bv-FTD, we have seen less hyperorality and carbohydrate craving in patients with FXTAS. This is an illustration of the complex neuropsychiatric picture in FXTAS, which can pose significant diagnostic and therapeutic challenges to clinicians.

Treatment

Bench research studies and clinical trials exploring pharmacological agents that can more directly target disease mechanisms are under way. To date, only anecdotal reports of response to cholinesterase inhibitors and memantine exist in FXTAS; as in other neurodegenerative diseases, these agents do not reverse but may mitigate the progression of cognitive deficits [34, 71, 72]. Specific neurotransmitter abnormalities have not yet been studied but there is evidence of mitochondrial dysfunction and defective iron and zinc homeostasis in FXTAS [73, 74]; this could provide new directions for treatment. Symptomatic treatments have been used to address neuropsychiatric manifestations [75]. For a review of current psychopharmacological approaches used in FXTAS, please see *FXTAS and related psychiatric disorders*, in this issue.

CONCLUSION

In summary, multiple cognitive deficits have been demonstrated in premutation carriers of both genders, some being age- and CGG repeat size-related. Executive deficits, in particular working memory and capacity for response inhibition, have been shown in men with FXTAS, and may mediate impairments in other cognitive domains. In later stages of FXTAS, a mixed cortical-subcortical dementia may occur, with psychomotor slowing, dysexecutive syndrome, retrieval and recall deficits, personality changes, and varied neurobehavioral manifestations. FXTAS dementia is a newly described dementia in older premutation carriers, which shares some features with other neurodegenerative diseases, making the clinical diagnosis challenging. Further research studies are needed to characterize the FXTAS dementia prevalence, gender differences, clinical picture, and targeted therapies.

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