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FXTAS: Pathophysiology and Management

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Abstract

Purpose of Review: The purpose of this paper is to review the prevalence, pathophysiology, and management of FXTAS.

Recent findings: The pathophysiology of FXTAS involves RNA toxicity due to elevated levels of the premutation-expanded CGG-repeat *FMR1* mRNA, which can sequester a variety of proteins important for neuronal function. A recent analysis of the inclusions in FXTAS demonstrates elevated levels of several proteins, including SUMO1/2, that target molecules for the proteasome, suggesting that some aspect(s) of proteasomal function may be altered in FXTAS. Recent neuropathological studies show that Parkinson disease and Alzheimer disease can sometimes co-occur with FXTAS. Lewy bodies can be found in 10% of the brains of patients with FXTAS. Microbleeds and iron deposition are also common in the neuropathology, in addition to white matter disease and atrophy.

Summary: The premutation occurs in 1:200 females and 1:400 males. Penetrance for FXTAS increases with age, though lower in females (16%) compared to over 60% of males by age 70. To diagnose FXTAS, an MRI is essential to document the presence of white matter disease, a primary component of the diagnostic criteria. Pain can be a significant feature of FXTAS and is seen in approximately 50% of patients.

Keywords

FXTAS; premutation; inclusions; treatment; Lewy bodies

Introduction:

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder characterized by intention tremor and cerebellar ataxia, in addition to cognitive decline [1,2]. However, FXTAS is often confused with fragile X syndrome (FXS), which is caused by alleles with much larger expansions (full mutation; >200 CGG repeats). Full mutation alleles generally become hypermethylated, resulting in gene silencing and the absence of the

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FMR1 protein (FMRP) – a totally distinct mechanism from the *increased* gene activity for premutation alleles. The loss of FMRP typically causes intellectual impairment and autism.

For the premutation (55 to 200 CGG repeats), the excess mRNA leads to toxicity by a variety of mechanisms, including the sequestration of proteins important for neuronal function such as DROSHA and DGCR8 [3]; dysregulation of calcium and subsequent mitochondrial dysfunction, leading to oxidative stress and the production of reactive oxygen species [4,5,6,7,8,9]; and a possible role of out-of-frame, non-AUG translation through the CGG repeat, producing a polyglycine-containing peptide, FMRpolyG [3,10,11,12,13,14]. Although the precise mechanism(s) by which the expanded CGG repeat RNA triggers FXTAS pathogenesis is unclear – and is the subject of current study – the result is white matter disease (WMD) that is seen as hyperintensities on the T2 FLAIR MRI. In approximately 60% of males [15] and in 10% of females [16], the middle cerebellar peduncles (MCP) are affected by WMD; the MCP finding is a major diagnostic criterion on MRI [17,18]. Other MRI findings include WMD in the splenium of the corpus callosum and in the periventricular areas in females [16*]. Recent studies have shown that the lateral ventricles can become dramatically dilated in the late stages of FXTAS, causing distortion of brain structure that includes thinning of the corpus callosum [19*]. Some patients even reach radiological criteria for normal pressure hydrocephalus, although there is no evidence that surgery for this condition in those with FXTAS results in any patient improvement.

Additional symptoms of FXTAS include neuropathy, executive function deficits, short-term memory deficits, and autonomic dysfunction, including hypertension, hypotension, erectile dysfunction, and incontinence; eventually, approximately 50% of males with FXTAS develop dementia. Many individuals with FXTAS can develop Parkinsonian symptoms, such as a resting tremor, masked facies, difficulty initiating movement, and shuffling gait. A recent neuropathological study demonstrated depletion of dopamine in the substantia nigra for those with Parkinsonian symptoms and the presence of Lewy bodies in 10% of the brains with FXTAS that were analyzed *postmortem* [20].

Neuropathological studies

The primary neuropathological feature of FXTAS is the presence of solitary, eosinophilic intranuclear inclusions (negative for tau and alpha-synuclein). The inclusions have both the *FMR1* mRNA and are enriched for over 200 proteins [21]. Although there is no dominant protein species, conjugated small ubiquitin-related modifier 2 (SUMO 2) protein and p62/sequestosome-1 (p62/SQSTM1) proteins were found to be highly enriched within the inclusions. Other proteins involved with RNA binding, protein turnover, and DNA damage repair were also enriched within the inclusions. The ubiquitin- and SUMO-based modifiers suggest that inclusion formation is the result of increased protein loads and elevated oxidative stress, leading to maladaptive autophagy. FXTAS inclusions occur throughout the central nervous system (CNS), with the highest numbers in the hippocampus [22]. The inclusions are found in both neurons and astrocytes but are not observed in oligodendrocytes [23]. The inclusions of FXTAS can also be seen in the peripheral nervous system, the esophagus or lower GI tract, the Leydig cells of the testicles, the thyroid, and the adrenal or cardiac conduction system [24]. These areas can be associated with other symptoms

associated with FXTAS such as cardiac arrythmias [25], swallowing problems, erectile dysfunction and low testosterone levels, hypothyroidism, and constipation. Some of these problems can occur before the onset of tremor and ataxia, which is usually in the early 60s [26].

More recent proteomics analysis of *postmortem* FXTAS cerebral cortex tissue from groups of FXTAS cases and controls generally showed only minor differences in the overall proteomes, with significant differences generally involving decreased abundance of proteins [27]. The largest decreases were observed for tenascin-C (TNC), cluster of differentiation 38 (CD38), and phosphoserine aminotransferase 1 (PSAT1) – proteins generally associated with other neurodegenerative disorders; their roles, if any, in the pathogenesis of FXTAS remain to be determined. Interestingly, one of the proteins with greatest increase in abundance was SUMO1/2, which provides further evidence for a process of dysregulated protein degradation. The FMRpolyG peptide, proposed as a driver of FXTAS pathology based on cell and animal models, was not detected among nearly 6,000 proteins identified in the Holm et al. [27] study. Often in those who have had significant cognitive decline, changes typical of Alzheimer disease (AD), tau aggregates and neurofibrillary tangles, are observed in FXTAS brains [28].

Psychiatric and Neuropsychological Studies

Psychiatric problems are common in those with FXTAS and include depression or anxiety and, eventually, apathy or agitation [29]. However, psychiatric problems are seen earlier in the lives of premutation carriers, with anxiety often appearing in childhood [30]. Approximately 50% of carriers may have anxiety, depression, panic attacks, or obsessive-compulsive behavior [31] during adulthood; the term fragile X-associated neuropsychiatric disorder (FXAND) has been coined to collectively recognize these symptoms to facilitate treatment and counseling [32].

In a 2020 study by Schneider et al. [16] of 53 females across all stages of FXTAS (mean age 66.9 years), compared with 63 age-matched controls without the premutation, demonstrated less cognitive decline than has been reported in males [33,34,35]. Only 10.7% of females with FXTAS had the MCP sign, but 61.5% demonstrated WMD in the splenium of the corpus callosum; this sign was added to the diagnostic criteria of FXTAS after the international premutation conference in 2014 [18,36]. Deep cerebral white matter changes were seen in 35% of females, and white matter hyperintensities were seen in the pons in 30.8% of the same group. The age of onset of FXTAS was negatively correlated with CGG-repeat size ($R = -0.37$; $p = 0.02$). Psychiatric problems included significant differences compared with controls and to population data generated by previous studies, with elevated rates for depression, panic disorder, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder [35]. The most surprising finding was the stable neurocognitive abilities of these females. Across the stages of FXTAS, the full scale IQ and the verbal IQ stayed relatively stable, as did the Mini-Mental State Exam (MMSE); although, as expected, the measures of executive function, including working memory, declined, as did the performance IQ and the Purdue

Pegboard, most likely related to the interference of the tremor. We did not see dementia in these females.

Loesch et al. [37**] demonstrated significant differences in the progression of FXTAS features in males versus females with FXTAS. Males progressed at least twice as fast in longitudinal studies in both tremor and ataxia measures, whereas parkinsonian symptoms progressed equally in both sexes. However, females progressed faster than males in the Symptom Checklist-90-R (SCL-90-R) items related to the overall psychiatric pathology score (Global Severity Index), as well as the anxiety and obsessive-compulsive domain scores on the SCL-90-R [37].

Additional features of premutation carriers that can begin before the onset of FXTAS but continue into FXTAS include insomnia, sleep apnea, migraines, autoimmune problems, fibromyalgia, and hypothyroidism. These problems require treatment because they can subsequently interfere with optimal brain function, particularly as FXTAS progresses. Many of these conditions lead to pain symptoms, and at least 50% of those with FXTAS have chronic pain, typically from neuropathy or muscle pain, migraines, or fibromyalgia. For many individuals, a central pain syndrome is established and is difficult to treat. Patients are often started on opioids from a pain clinic, increasing the risk of opioid addiction and further progression of FXTAS.

Recent studies of the gait in individuals with FXTAS demonstrate significant balance problems that are worse when the patient is walking fast or turning, or when given a dual task of walking with problem solving [38**,39]. In addition, when walking and performing a mental task, the patient will prioritize gait over the cognitive task so a better cognitive performance may occur more often when seated than with walking [38].

A recent study utilized the Kinesia system for tremorography to quantify upper extremity tremor and bradykinesia in patients with FXTAS compared to those with PD and essential tremor [40**]. That study demonstrated that patients with FXTAS had significantly reduced finger-tap speed compared to those with essential tremor and had significantly higher kinetic tremor compared to PD. The authors also found that males had significantly greater postural and kinetic tremor and slower finger-tap speed compared to females with FXTAS, consistent with the sex differences in FXTAS severity previously reported [40]. The tremorography measures of the Kinesia system correlated significantly with tremor and bradycardia ratings on the FXTAS rating scale (FXTAS-RS). These precise quantitative tremor and bradykinesia measures demonstrate that the Kinesia system would be a beneficial outcome measures for future treatment trials in FXTAS.

Management of FXTAS

There is, at present, no specific targeted treatment for FXTAS that will reverse the neuropathology, with the focus of current treatment directed toward symptoms. Medication for tremor includes primidone, beta blockers, or topiramate [41]. If parkinsonian symptoms are present, then Sinemet® (carbidopa and levodopa) may be beneficial, particularly for tremor. Ataxia is more difficult to treat but options include amantadine, riluzole, or varenicline; however, those medications have not been studied specifically for FXTAS.

Psychiatric symptoms such as anxiety or depression can worsen cognitive decline and should be treated. Usually an SSRI, such as sertraline or escitalopram, along with counseling can be helpful; anecdotally, these medications can also improve irritability. FXTAS can cause significant marital problems, particularly if the spouse with FXTAS is irritable or disinhibited. Often, the non-affected spouse is depressed, so medication and counseling can be very helpful for the couple or individually. The stress of FXTAS on caretakers is enormous, and they often need additional help such as a visiting nurse. The general recommendations for lifestyle changes can be beneficial both emotionally and physically for those with FXTAS, including avoiding toxins such as smoking, varathane inhalants, illicit drugs, pesticides, or general anesthesia, specifically isofluranes, since they have been associated with FXTAS onset or exacerbation of symptoms in case studies [15,42]. Daily exercise can help with mitochondrial dysfunction, inflammation, and depression or anxiety and should be encouraged [15,43]. Referral to a physical therapist can be helpful for ataxia and muscle strengthening, especially if the PT is from a movement disorder clinic with extra training in ataxia. Weight loss can also help with pain symptoms, particularly in those with back pain and especially if they have had back surgery, which is very common in those with FXTAS. Treating vitamin deficiencies and hypothyroidism is likely to help CNS function. For instance, vitamin D deficiency is common in the general population, and such deficiency is associated with inflammatory responses [44] and neurocognitive abilities [45]. A diet high in antioxidants (e.g., green tea, berries, turmeric, omega 3, and even mitochondrial supplements such as ubiquinone (CoQ10) have been found to be helpful by many patients; however, controlled trials of such supplements have not been carried out in those with FXTAS yet. Notably, these lifestyle recommendations have not been studied in controlled trials in those with FXTAS.

The treatment of pain symptoms is important because pain is a common symptom. If the pain is neuropathic, then gabapentin or pregabalin can be helpful. In addition, topical lidocaine patches or even topical cannabidiol (CBD) can be helpful. Those with fibromyalgia or a chronic pain syndrome can sometimes find benefit from duloxetine (Cymbalta) or another SNRI such as venlafaxine. Oral CBD can also help with pain, and over-the-counter hemp websites usually have preparations of CBD with very little THC. It is important to avoid THC because psychotic symptoms or paranoia can occur in carriers of the premutation. CBD has multiple effects in the CNS and is currently being studied for Parkinsonian symptoms, including tremor and levodopa-induced dyskinesias. CBD exerts its neuroprotective effects through reducing oxidative stress; stimulating peroxisome proliferator-activated receptor gamma (PPAR-ϒ), which blocks proinflammatory effects; stimulating anti-inflammatory effects; and improving the function of mitochondrial complexes I, II, III and IV [see review 46*]. Controlled trials of CBD in FXTAS are needed.

Only a handful of drug treatment studies have been carried out in those with FXTAS. A controlled, 12-month trial of memantine [47] did not show benefit for either tremor or ataxia. However, a follow-up analysis of the event-related potentials (ERPs), performed in 41 patients as part of the original controlled study, demonstrated improvement in cued memory recall as manifested by an increase in the amplitude in N400 on memantine versus placebo [48]. In addition, improvement in attention was also demonstrated in the ERP

measures, with many patients commenting on improvements in processing information [49]. Medications that can slow cognitive decline in AD such as donepezil, rivastigmine, and galantamine may be useful in FXTAS but have not been subjected to controlled trials.

An open-label trial of allopregnanolone, a neurosteroid that can stimulate neurogenesis, was given intravenously (2–6 mg infused over 30 minutes) weekly for 12 weeks in 6 patients with FXTAS [50]. One patient had alleviation of neuropathy and improvement of ataxia; there was also some improvement in cognitive function, including executive function, memory abilities, and improvement on the N400 ERPs. Although this study showed promise, further controlled trials are needed.

A third trial in FXTAS was an open label with 10 patients utilizing citicoline (5'diphospho-choline), an over-the-counter endogenous nucleotide and intermediate in the biosynthesis of structural membrane phospholipids. It is a phospholipase A2 inhibitor which has been used to treat neurodegenerative disorders including AD; it was helpful for the *Drosophila* premutation model [51]. Patients were given 1000 mg per day for one year. Although the primary outcome measure of improvement in the FXTAS-RS [26] was not met, there was stability over time and some mild improvements on the Stroop-Color Word test and in an anxiety measure. One patient developed thrombocytopenia; although other side effects were minimal.

Future trials

One promising future trial involves the use of ANAVEX2–73 (AV2–73), a sigma-1 receptor (S1R) agonist and the lead compound of Anavex Life Sciences Corp. It has demonstrated safety and tolerability in phase 1 and 2 human clinical trials in AD, Parkinson disease dementia, and in Rett syndrome [52,53,54,55]. AV2–73 improves mitochondrial function, oxidative stress, and calcium dysregulation in several disorders [56,57]. AV2–73 treatment improved P300 amplitude in AD [58]; this ERP component is abnormal even in pre-clinical stages of FXTAS [59] and reflects the carriers' characteristic impairments in attention and working memory that only worsens with FXTAS.

Conclusion:

There is no targeted treatment for FXTAS, but several medications can improve the tremor and psychiatric problems, including anxiety and depression. Studies regarding early cognitive and motor deficits prior to the onset of FXTAS, in addition to neuroimaging, demonstrate changes to the premutation brain with aging compared to controls. Neuropathological studies have shown the occasional co-occurrence of other aging problems such as PD and even AD in those with FXTAS. Females progress more slowly in motor symptoms, although more rapidly in psychiatric symptoms compared to males with FXTAS.

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Conflicts of interest

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Key Points:

- Lifestyle changes, such as weight loss, healthy eating, avoiding toxins, exercising daily, and treating hypertension, psychiatric problems, sleep apnea, or hypothyroidism, can help CNS function in FXTAS.
- Women with FXTAS progress more slowly in tremor and ataxia but more rapidly in psychiatric symptoms compared to males.
- Postmortem CNS studies in FXTAS have demonstrated that iron deposition and microbleeds are more severe than controls without the premutation.
- Parkinsonism is common in those with FXTAS, which is related to dopamine depletion in the substantia nigra, though Lewy bodies can be seen in 10% of brains with FXTAS.