

Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices

Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)



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Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that was discovered in 2001 after clinicians noted a pattern of neurological symptoms present in older (primarily male) grandparents and parents of those individuals with the diagnosis of fragile X syndrome (FXS) and fragile X-associated primary ovarian insufficiency (FXPOI).

FXTAS is caused by a trinucleotide CGG repeat expansion in the premutation range (55-200) in the fragile X mental retardation 1 (*FMR1*) gene. It is an inherited neurodegenerative disorder that affects adults over 50 years old and is associated with a spectrum of neurological and medical symptoms. FXTAS affects men with the premutation more frequently than women because of the protective effect of the second X chromosome in females.

The prevalence of *FMR1* premutation carriers is approximately 1 in 260 females and 1 in 813 males in the general population. Among the premutation carriers, approximately 40% of males older than 50 years and 8% of female carriers older than 40 years develop FXTAS. Therefore, the prevalence of FXTAS is estimated to be ~ 1 in 8000, which indicates that it is less common than essential tremor and Parkinson's disease in older adults.

Diagnosis/Recognition

Onset of FXTAS is typically in the early fifth decade, with mean age of onset of tremor and/or ataxia in males at approximately 61 years. Symptoms of FXTAS vary among individuals. Typically they include progressive cerebellar ataxia, tremor, parkinsonism, and cognitive decline, specifically executive functioning. Additionally, psychiatric disturbances and autonomic and peripheral neuropathies may be present.

Tremor usually presents first. Action tremor is most common, although many affected individuals may not be aware of its impact on their daily living activities. Mild, intermittent tremors may be present for years before the diagnosis. Resting tremor is uncommon. Almost all affected patients develop cerebellar gait as the disease progresses. Unexplained falls and tandem gait is abnormal in ~50% of male carriers older than 50 years of age. Other impairment includes parkinsonism, sensory neuropathy, and weakness contributing to poor balance.

As the condition progresses, cognitive dysfunction such as executive impairment and dementia may become present. These symptoms may influence intelligence, working memory, remote recall, information-processing speed, and temporal sequencing. Impaired executive function may lead to psychiatric and behavioral disorders as noted by increased anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression.

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Individuals with FXTAS usually have abnormal MRI findings, such as increased T2 sign, in the middle cerebellar peduncles (MCP sign), white matter lesions (“inclusions”) or generalized brain atrophy.

Of note, approximately 20% of women with the *FMR1* premutation develop FXPOI. These individuals do not seem to have an increased risk of FXTAS compared with women who carry the premutation but have normal ovarian function.

Testing for FXTAS is performed by confirming *FMR1* premutation carrier status (by the *FMR1* DNA test) and by brain MRI findings.

| Guidelines for Whom to Test for FXTAS | |
|--|---|
| Cerebellar ataxia | 50 years or older and unknown cause |
| Action tremor | Presence of cerebellar ataxia, parkinsonism, or dementia (50 years or older and unknown cause) |
| Dementia | Presence of cerebellar ataxia, Parkinsonism, or action tremor (50 years or older and unknown cause) |
| Some FXTAS signs | Middle cerebellar peduncle sign; or patient or family history of infertility, ovarian insufficiency; or family history of <i>FMR1</i> carriers, fragile X syndrome or fragile X-associated disorders. |
| Multiple system atrophy cerebellar subtype | |

| FXTAS Diagnostic Criteria in <i>FMR1</i> Premutation Carriers | |
|--|--|
| Definite | Presence of 1 major radiological sign plus 1 major clinical symptom |
| Probable | Presence of either 1 major radiological sign plus 1 minor clinical symptom or has the 2 major clinical symptoms. |
| Possible | Presence of 1 minor radiological sign plus 1 major clinical symptom |
| Symptom types | |
| • Radiologic | |
| Major | MRI white matter lesions in MCPs and/or brain stem |
| Minor | MRI white matter lesions in cerebral white matter |
| Minor | Moderate to severe generalized atrophy |

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|------------|---|
| | |
| • Clinical | |
| Major | Intentional tremor |
| Major | Gait ataxia |
| Minor | Parkinsonism |
| Minor | Moderate to severe short-term memory deficiency |
| Minor | Executive function deficit |

Current Treatment Guidelines

The goal of therapy for FXTAS is to reduce symptoms and slow the progression of disease. Management of FXTAS is complex and involves appropriate follow-up by an adult neurologist. It is also important to evaluate other potential causes of dementia such as vitamin B12 deficiency, folate deficiency, and depression. Additionally, individualized care regarding the possible adverse events from the medications is essential. Referrals to urology, rehabilitative medicine, genetic counseling, and social work should be considered.

Currently, intervention is limited to symptomatic therapy as there have been no controlled clinical trials. Treatment recommendations are based on anecdotal reports and knowledge of other disorders that are similar to FXTAS. For example, action tremor and parkinsonism in FXTAS may respond to medications used for essential tremor and Parkinson's disease, respectively. Action tremors may respond to B-blockers, primidone, and topiramate. Treatment of psychiatric symptoms with selective serotonin inhibitors may be effective. It is important to note that treatments for FXTAS should be individualized as symptoms vary in every individual. Treatments should also be approached globally utilizing medications, psychological counseling, rehabilitative interventions such as speech, occupational and physical therapy, and gait training. Consideration should also be given to supportive services and counseling for the family. Specialty fields helpful in the care of individuals with FXTAS include neurology, psychiatry, psychology, rehabilitation, urology, cardiology, and movement disorders neurology.

Genetic counseling for family members is recommended as all daughters of male patients with FXTAS will be *FMR1* premutation carriers. Female patients with FXTAS will pass on their *FMR1* mutation to 50% of their offspring, with the potential of their premutation expanding to a full mutation. The full mutation leads to fragile X syndrome, an inherited form of intellectual and developmental disabilities.

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Additional Resources

<http://www.fragilex.org/fragile-x-associated-disorders/fxtas/>

<http://www.fxtas.org>

<http://www.wemove.org/ASO/default.asp?dis=1>

Leehey M, Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *Journal of Investigative Medicine* 57(8), 2009.

Author note: This guideline was authored by Jeannie Visootsak, MD, and was reviewed and edited by consortium members both within and external to its Clinical Practices Committee. It has been approved by and represents the current consensus of the members of the Fragile X Clinical & Research Consortium.

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*The Fragile X Clinical & Research Consortium was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any Fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the **National Fragile X Foundation** for more information. (800-688-8765 or www.fragilex.org)*