

The Fragile X-Associated Tremor/Ataxia Syndrome

Relatively recently described, FXTAS is a progressive genetic disorder for which there is no cure, but symptomatic therapy is indicated.

The fragile X-associated tremor/ataxia syndrome (FXTAS) is a genetic disorder that typically affects males with tremor, ataxia, and cognitive deficits. The slowly progressive neurodegenerative disorder caused by a repeat expansion in the 'premutation' range (55-200 CGG repeats) in the fragile X mental retardation 1 gene (FMR1) manifests over the age of 55. FXTAS was originally described in 2001 when a developmental pediatrician noticed that the grandfathers of children with fragile X syndrome had a variable neurological disorder with tremor, ataxia, and parkinsonism.¹ Fragile X syndrome (FXS) is a developmental disorder associated with autism and intellectual disability (more severe in boys) and is caused by more than 200 CGG repeats in the FMR1 gene (for review see Hagerman et al. 2009).²

There are characteristic neuroimaging and pathological changes in individuals with FXTAS and neurological signs may respond to medications used for other disorders. Due to the genetic nature of the disease, clinicians who diagnose the disorder will need to counsel families regarding risk to children and grandchildren of related disorders.

Clinical Features

The clinical features of FXTAS are kinetic tremor and gait ataxia, but a variety of other signs have been associated, to include: parkinsonism, peripheral neuropathy, executive dysfunction, and autonomic abnormalities.¹ Neurological signs typically manifest in males over the age of 55, but females may be affected as well. The movement disorder symptoms tend to instigate referral from the primary care physician to neurologists for diagnosis.³ Initial symptoms and their severity are variable. Patients usually report tremor when doing tasks, such as handwriting. On examination, the tremor may be evident with posture, intention, handwriting or water pouring. The tremor may also be present in the legs or to a milder degree in the head and neck. Gait ataxia starts with difficulty with tandem steps but progresses to wide-based, unsteady

ambulation, with some instability with turning. In cohort studies, motor dysfunction is more severe with larger CGG repeat expansion sizes, and kinetic tremor and gait ataxia are frequently disabling in patients with higher repeat sizes.⁴ The movement disorder symptoms do progress over time, with patients having an average of six years prior to the onset of falls, 15 years until need of a walking aid, and 13 years until the tremor is disabling enough to interfere with activities of daily living.⁴

Cognitive difficulties in FXTAS include executive dysfunction, poor verbal fluency, and slowed processing speed.⁵ There is a direct correlation between repeat size and cognitive deficits. The cognitive changes usually progress at a variable rate, and a frontal subcortical dementia develops in at least 50 percent of individuals with FXTAS.⁶ In addition, psychiatric signs are common in FXTAS, to include apathy (93 percent), irritability (86 percent), depression (79 percent), disinhibition (64 percent), anxiety (50 percent), and delusions (29 percent).⁷ Anxiety is associated with the premutation,⁸ even without the presence of FXTAS and may be seen in daughters of individuals with FXTAS. The constellation of cognitive changes and behavioral problems can place a strain on caregivers, even if motor symptoms are relatively mild.

Neuropathic symptoms in FXTAS include vibratory sensation loss and diminished reflexes compared to normal controls.⁹ Nerve conduction studies in males with FXTAS show lower tibial nerve conduction velocities, prolonged F-wave latencies, smaller compound muscle action potential amplitudes, and reduced sural sensory nerve action potential amplitudes.¹⁰ The presence of neuropathy can worsen the underlying gait ataxia.

Although not neurological in nature, the premutation is also associated with premature ovarian failure or primary ovarian insufficiency, manifesting as menopause occurring prior to age 40 and variable problems with infertility.¹¹ This problem is frequently seen in daughters of individuals with FXTAS.

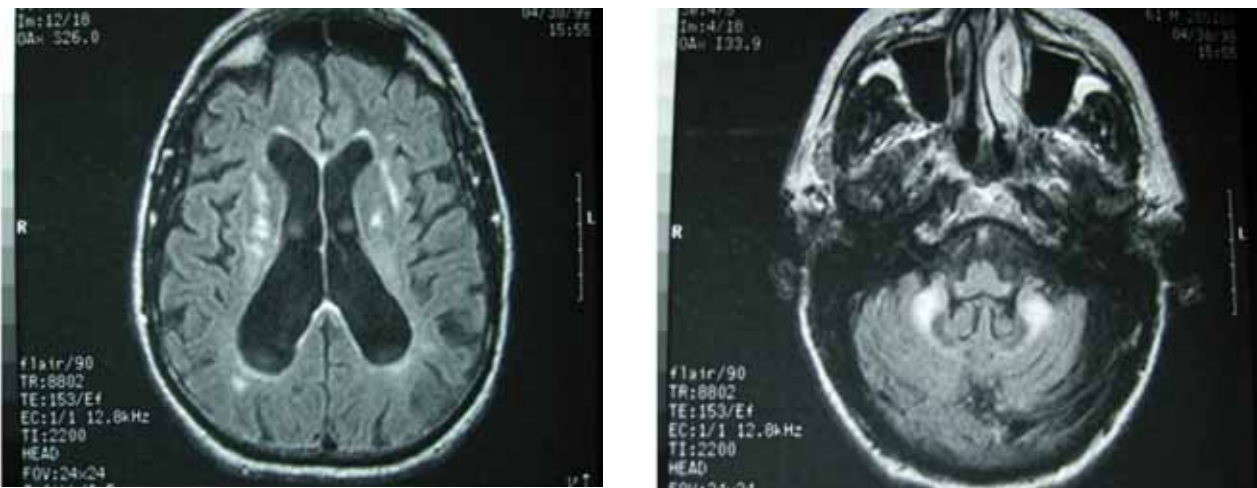


Figure 1. Magnetic resonance imaging in a patient with FXTAS. Left: Axial FLAIR shows white matter hyperintensities and global atrophy. Right: Axial FLAIR shows a hyperintense signal in the middle cerebellar peduncle or the 'MCP' sign.

Imaging

Brain imaging shows generalized atrophy in all patients after adjusting for age and mild to moderate cerebellar volume loss in 85 percent of patients^{12,13} (Fig. 1). Symmetric hyperintense lesions of the middle cerebellar peduncles sparing the dentate nuclei, termed the 'MCP' sign, are observed on T2 or FLAIR MRI images in 60 percent of cases.^{12,14} Abnormal signal is seen in the frontal and parietal subcortical and periventricular white matter in 75 percent of patients with FXTAS. Nigrostriatal dopaminergic function in FXTAS patients with parkinsonism (not responsive to dopaminergic therapy) has been investigated with [123I]FP-CIT SPECT and shown conflicting results, with normal uptake in some patients and a reduction in uptake in others.¹⁵⁻¹⁶

Neuropathology

Eosinophilic inclusions, similar to those seen in polyglutamine repeat disorders, are present in neuronal and astrocytic nuclei throughout the brain, especially in the cortex. The inclusions react to anti-ubiquitin antibodies and are distinct from previously described pathological intranuclear inclusions in other neurodegenerative disorders. The cerebellum displays marked dropout of Purkinje cells, Purkinje axonal torpedoes, and Bergmann gliosis.¹⁷

Genetics

FXTAS is inherited as an X-linked disorder and is more frequently seen in males due to presence of an additional normal

X chromosome in females. Expansion of a premutation range CGG repeat to a full mutation usually occurs over at least two generations, but only when passed on by a female to her offspring. Thus, individuals with FXTAS may have grandchildren with developmental delay (FXS) or daughters with premature ovarian insufficiency. The penetrance of FXTAS is age-dependent, with 17 percent of male premutation carriers aged 50-59, 38 percent of male carriers aged 60-69, 47 percent of male carriers aged 70-75, and 75 percent of males >80 meeting criteria for the disorder.¹³ FXTAS is seen in about eight percent of all females with a premutation over age 50 years,¹⁸ although females usually have later onset, less severe symptoms, and less progression. Manifestation of disease in females relates to not only CGG repeat length, but also activation ratio (the percentage of cells with the premutation X as the active X chromosome). Individuals with FXTAS were initially ascertained through FXS families, however, many affected patients are now diagnosed by neurologists or movement disorder specialists. This makes knowledge of the clinical features seen in various generations especially important for genetic counseling purposes. (Fig. 2)

Epidemiology

The prevalence of the FMR1 premutation in males in the general population is approximately one in 813.¹⁹ The prevalence of the FMR1 premutation in females is one in 259 in the general population.²⁰ On the basis of the carrier frequency, the prevalence of the disorder is estimated to be at least one in

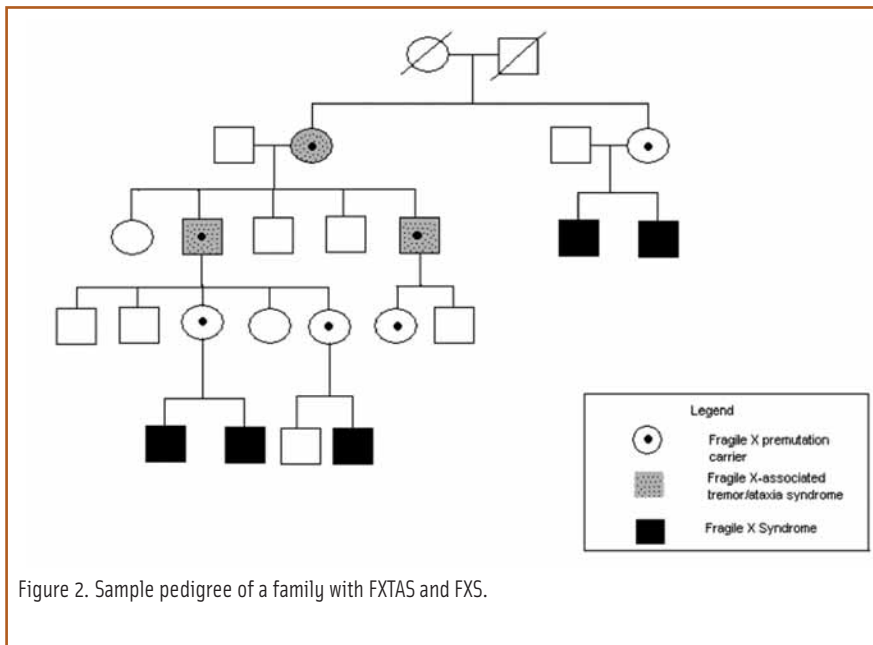


Figure 2. Sample pedigree of a family with FXTAS and FXS.

3,000 males over the age of 50 years in the general population. However, screening studies in movement disorder populations have yielded few cases overall, with the exception of cohorts of older males with negative spinocerebellar ataxia (SCA) genetic screening and multiple system atrophy cerebellar type.²¹

Diagnosis and Differential Diagnosis

Definitive diagnosis of FXTAS is made when PCR shows an expansion in the FMR1 gene in an individual with kinetic tremor or gait ataxia.¹³ The DNA test performed is the same for identification of either FXTAS or FXS, and may be termed fragile X DNA test, FMR1 DNA test, or FXTAS DNA test, depending on the laboratory. The fragile X DNA test is readily available at numerous university and commercial laboratories in the USA and through health services laboratories in many countries. There are few disorders that present with the constellation of symptoms and signs seen in FXTAS. Patients with FXTAS are most frequently initially diagnosed with a movement disorder: tremor, ataxia, or parkinsonism.³ However, initial diagnoses of dementia, stroke, normal pressure hydrocephalus, and multiple sclerosis have also been reported. SCA 12 is the SCA most similar to FXTAS clinically, with gait ataxia and kinetic tremor.²²

Pathophysiology

Molecular studies have shown that males with 55 to 200 CGG repeats have higher than normal levels of FMR1 mRNA and, at higher repeat sizes, mildly reduced fragile X

mental retardation 1 protein levels (FMRP).²³ Elevated mRNA levels may reflect a defect in the translation of the mRNA into FMRP.²³ In larger expansions (>200 CGG repeats), hypermethylation of the FMR1 promoter occurs, with transcriptional silencing of FMR1 and absence or reduction of expression of FMRP. FMRP is an RNA-binding protein that regulates translation at dendrites in response to neural activation, thereby modulating synaptic plasticity and dendritic morphology (for reviews see Ogren and Lombroso 2008).²⁴

Although FXS results from lack of FMRP, an alternative molecular mechanism has been proposed for FXTAS based on the finding of the elevated FMR1 mRNA levels in cells from premutation carriers, particularly at larger CGG repeat sizes. Accumulated FMR1

mRNA containing the CGG repeat is thought to exert a neurotoxic effect by sequestering and perturbing function of nuclear proteins. This mechanism is consistent with the findings of nuclear inclusions in mice expressing an FMR1 gene with a premutation expansion allele (~100 CGG repeats),²⁵ neurodegeneration in *Drosophila* expressing expanded CGG repeat,²⁶ and the correlation of numerous measures of disease severity in humans with the CGG repeat length.⁹ As predicted by the FMR1 mRNA toxicity mechanism for FXTAS, individuals with the FMR1 full mutation and FXS do not develop FXTAS, because the FMR1 gene silencing results in absent or reduced FMR1 mRNA and FMRP.

Treatment

No medications are consistently effective for FXTAS.²⁷ Patients are treated symptomatically, and clinicians may have success by targeting the most bothersome symptoms. Of the subjects receiving therapy for intention tremor, three of six reported mild to moderate improvement on primidone; three of eight had moderate improvement in tremor on beta-blockers, two of eight had moderate improvement on benzodiazepines, and one had mild improvement on memantine.²⁷ Parkinsonism (rest tremor, slowness, or stiffness) improved on carbidopa/levodopa in two of eight and on pramipexole in one of two subjects.²⁷ A recent case report did show improvement of the gait ataxia in a FXTAS subject on varenicline,²⁸ but anecdotal evidence with other patients suggests this medication may worsen tremor. Physical therapy for gait training

may be useful for patients with ataxia or parkinsonism. Slowing of cognitive decline was reported in two of six subjects on venlafaxine and three of nine subjects on acetylcholinesterase inhibitors.²⁷ Anxiety improved in two of six subjects on venlafaxine and five of eight subjects on benzodiazepines.²⁷ Gabapentin may be helpful for neuropathic pain in FXTAS.

Research

There are several lines of ongoing clinical research in FXTAS. Large population studies are being conducted to ascertain neurological patients with FMR1 repeat expansions. Two neurological phenotype studies to better characterize the executive dysfunction, neuroimaging, and cognitive markers in the disorder are being conducted. The first clinical trial in the disorder has started and is testing memantine, an NMDA receptor antagonist, to slow down the progression of disease. There is also ongoing work to characterize biomarkers of nuclear CGG-repeat toxicity and identify predictors of disease in presymptomatic carriers. It is hoped that in the future, mechanism-specific treatments that can reverse the course of the disease will become available through molecular and translational research. Specifically small molecules including siRNAs that disrupt the FMR1 RNA CGG repeat interactions are being investigated. PN

Deborah Hall, MD, PhD, Department of Neurological Sciences, Rush University Medical Center, Chicago, IL.

Elizabeth Berry-Kravis, MD, PhD, Departments of Neurological Sciences, Pediatrics, and Biochemistry, Rush University Medical Center, Chicago, IL.

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