Fragile X-associated tremor/ataxia syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that affects some older adult carriers of the premutation in the FMR1 gene, which is located on the X chromosome. It is part of the fragile X-associated disorders spectrum, alongside Fragile X syndrome (FXS) and other conditions. FXTAS typically manifests later in life, usually after the age of 50, and predominantly affects men, although women can also develop symptoms, albeit often less severely.

Etiology: FXTAS is caused by a premutation in the FMR1 gene. The premutation is characterized by an expansion of CGG nucleotide repeats (55-200 repeats) in the gene. This leads to increased levels of FMR1 mRNA, which is thought to have toxic effects on neurons, particularly in the cerebellum and other brain regions involved in motor coordination and cognitive function.

Clinical Features: FXTAS is characterized by a range of motor, cognitive, and psychiatric symptoms, including:

Intention tremor: Tremors that become more pronounced when trying to perform voluntary movements, such as reaching for an object. Cerebellar ataxia: Problems with balance and coordination, leading to unsteady walking and difficulty with fine motor tasks. Cognitive decline: Memory problems, executive dysfunction, and sometimes dementia. Parkinsonism: Slowness of movement, rigidity, and tremor (similar to Parkinson's disease). Neuropathy: Numbness or tingling in the extremities. Psychiatric symptoms: Depression, anxiety, and irritability can also be part of the syndrome. Diagnosis: FXTAS is diagnosed based on clinical symptoms, neuroimaging, and genetic testing. MRI findings often show white matter hyperintensities in the middle cerebellar peduncles, as well as generalized brain atrophy. Genetic testing confirms the presence of the FMR1 premutation.

Treatment: There is no cure for FXTAS, and treatment is primarily supportive and symptomatic:

Medications: To manage symptoms like tremor and ataxia, drugs used in Parkinson’s disease (e.g., levodopa) or anti-seizure medications may be prescribed. Antidepressants can help with mood disorders. Physical and occupational therapy: These can help manage motor symptoms and improve quality of life. Supportive care: Cognitive decline and other complications may require support in daily activities as the disease progresses. Prognosis: FXTAS is a progressive condition, and symptoms typically worsen over time. The rate of progression and severity vary, but the disorder can lead to significant disability. Life expectancy may be reduced, particularly if complications such as pneumonia, falls, or other conditions arise.

Early recognition of FXTAS and interventions to manage symptoms can help improve quality of life for patients. Additionally, genetic counseling is important for families, as the FMR1 premutation can be passed on to future generations.

Campins-Romeu M, Conde-Sardón R, León-Guijarro JL, Sastre-Bataller I. Unilateral MRIgFUS thalamotomy: Long-term follow-up in fragile X-associated tremor/ataxia syndrome. Neurologia (Engl Ed). 2024 Oct;39(8):710-712. doi: 10.1016/j.nrleng.2024.09.004. PMID: 39396267.