An Overview of Fragile X Associated Tremor/Ataxia Syndrome

Fragile X syndrome is traditionally identified in childhood. Here's what to know when encountering the associated tremor/ataxia in adult patients.

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Fragile X associated tremor/ataxia syndrome (FXTAS) is a recently-described progressive neurodegenerative disorder.[1] It is seen in carriers of permutation alleles of the fragile X mental retardation gene (FMR1 gene) on the X chromosome. Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. FXS is caused by the full mutation form of FMR1 gene leading to over 200 repeats of CGG trinucleotide. The number of repeats in permutation is between 55 to 200 CGG. Normal individuals have less than 39 repeats.

Full mutation as seen in FXS results in partial or complete silencing of the FMR1 gene, with partial or complete lack of FMR1 protein. In contrast, pre-mutations seen in FXTAS cause increases in FMR1 mRNA levels, which in turn lead to intranuclear inclusion formation and dysregulation of the nuclear lamin A/C architecture.

Clinical Features

FXTAS is mostly seen in male carriers, typically with a history of FXS in their grandchildren. Onset is typically in the sixth or seventh decade.

FXTAS is characterized by ataxia and intention tremor. Other features include parkinsonism, dementia, peripheral neuropathy and autonomic dysfunction. Most patients are usually misdiagnosed with either idiopathic Parkinson's disease, parkinsonism-plus syndromes, cerebellar ataxias or dementia.[2]

Women carrying pre-mutations usually present with premature ovarian failure. Few cases have been reported where women presented with neurological disease, one after chemotherapy use.[3]

Imaging Studies

MCP sign is described as high signal T2 changes in middle cerebellar peduncle and deep white matter of cerebellar hemisphere sparing the dentate nuclei. MCP sign is characteristic of FXTAS. It is not seen in permutations of the FMR1 gene without symptoms. Other MRI features include cerebellar atrophy and cerebral atrophy with deep white matter hyperintensities disproportionate to the patient's age.

Table 1. Diagnostic Criteria for FXTAS

Clinical criteria:
Major: Intention Tremor
Major: Gait ataxia
Minor: Parkinsonism
Minor: Moderate to severe short- term memory deficiency
Minor: Executive function deficit

Radiological Criteria:
Major: Middle cerebellar peduncle lesions
Minor: Cerebral white matter increased signal (T2/FLAIR)
Minor: Moderate to severe generalized atrophy

Neuropathological Criteria:
Major: Presence of ubiquitin—positive intranuclear inclusions

Source: Jacquemont S, Hagerman RJ, Leehey M, et al. Fragile X premutation Tremor/ Ataxia Syndrome: Molecular, Clinical, and Neuroimaging Correlates. American J. Human Genetics 2003;72: 869-878.

Diagnostic Criteria

The diagnostic criteria listed in Table 1 have been created in 2003.[4] All patients must have FMR1 gene testing with CGG repeat expansion between 55 and 200 repeats. *Definitive* FXTAS diagnosis is made if one major clinical criteria and one Major radiological or pathological criteria are met. *Probable* FXTAS diagnosis is made if two major clinical criteria or one major radiological plus one minor clinical criteria are met. *Possible* FXTAS diagnosis is made if one major clinical criteria and one minor radiological criteria are met.

DNA Testing

The fragile X mutation follows the traditional rules of X-linked inheritance in that all daughters but no sons of carrier fathers will get the mutation. However, there is a risk of unstable transmission between generations such that the number of repeats from premutation to full mutation also exists.

Full mutation of the FMR1 gene consists of CGG repeats of greater than 200, located in the 5' untranslated region of the gene. These repeats cause hypermethylation of the gene product, and leads to gene silencing. The subsequent absence of mRNA

leads to the Fragile X syndrome.[5]

The premutation allele, on the other hand, consists of 50-200 CGG repeats and is associated with an increase in FMR1 mRNA, as these tracks are not methylated. The resulting gain in function and over expression of the gene.[6]

Two types of DNA studies can be done: PCR and southern blotting. PCR studies take advantage of the flanking primers to amplify the DNA fragments that span the repeat segment. The size of the PCR products therefore reflects the number of repeats, thereby distinguishing between full mutation to premutation, and even an allele state of the "intermediate zone" with repeats in the range of 41-60. Another advantage offered is that the assay is unaffected by X inactivation in female carriers. However, a significant disadvantage of the PCR test is that the reaction itself is inversely related to the number of CGG repeats such that a large number of mutations are often difficult to amplify.

On the other hand, southern blotting analysis offers a more crude measurement of the size of repeats, but a more accurate assessment of the methylation status. Unlike PCR testing, the assay can be affected by X inactivation and skew the results.[5]

Sherman et al. proposed guidelines for genetic testing, offering that for those patients that present with late onset intention tremor and ataxia of unknown organ should get tested by both methods. Testing is especially recommended in those with a family history of movement disorder, fragile X syndrome, or mental retardation of unknown origin.

Treatment

There is no treatment for FXTAS, although there are reports of symptomatic management. There have been reported improvements of the cognitive decline with acetylcholinesterase inhibitors, and successful treatment of anxiety with venlafaxine or selective serotonin reuptake inhibitors. Primidone, beta blockers and carbidopa/levodopa have been reported as anecdotally improving symptoms of tremor. **PN**

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