Abstract.

Fragile X-Associated Tremor / Ataxia Syndrome (FXTAS), is a progressive neurodegenerative disease, with motor disorders, cognitive deficits and dementia, neuropathy, and dysautonomia.

In this article, there is an overview of the main clinical features and radiological findings, as well as a short reference on the molecular mechanisms responsible for the disease, in order to facilitate non-specialist doctors or nurses to early recognize FXTAS.

1. Introduction.

This is the most common form of inherited mental retardation recognized in the late 1990s. It is caused by a permutation in the FMR1 gene on the X chromosome.

The FMR1 gene contains a 5’ untranslated CGG repeats region [1], from 6 to 55 triplets in length. In gene permutation, there is an expansion of the CGG repeats between 55
to 200 triplets. With a length of more than 200 triplets (full mutation), the gene becomes non-functional [2]. In individuals with a full mutation of the *FMR1* gene, FXTAS has never been observed.

The syndrome is characterized by tremor, ataxia, parkinsonism, cognitive decline, dementia and neuropathy. It occurs at ages greater than 50 years and it is estimated that one of the 259 females [3] and one of the 813 men [4], are carriers of an *FMR1* premutation. This may suggest that the syndrome is probably one of the most common late-onset neurodegenerative diseases.

2. Molecular basis of FXTAS.

The *FMR1* gene produces mRNA FMR1 which is transcribed into FMRP protein. This protein is an RNA-binding protein which regulates translation at the dendrites, and modulates synaptic plasticity and dendritic morphology [5]. In gene premutation, the reduced FMRP production causes a 2 to 10 fold increase in the mRNA FMR1 levels. This imbalance which presumably compensates a transcriptional deficit of FMRP [6], is believed to cause neurotoxic effects due to the excessive interaction of the trinucleotides’ binding proteins and the transcription factors with the excess of mRNA FMR1 and / or its extended CGGn contained in its molecule. This disorder could be addressed through the ubiquitin /proteasome pathway. In case of this pathway failure, inclusions are generated, which may be function protectively, but may also trigger the apoptosis pathway and the neuronal death [7,8]. The presence of intranuclear inclusions in both neurons and astrocytes but not in oligodendrocytes throughout the brain consist the pathological hallmark of FXTAS. The inclusions are ubiquitin-positive but negative in both TAU protein and synuclein. In this sense, it seems that FXTAS does not belong to any known group of neurodegenerative diseases which is
characterized by the presence of intracellular inclusions (Pick, Parkinson, MSA disease) [9] (Figure 1).

![Figure 1.](image)

**Figure 1.**

Micrograph of cortical neuronal and astroglial cells bearing intranuclear inclusions (brown, ubiquitin immunostaining). A nucleolus (blue) in the neuronal nucleus is shown (magnification x1000).

Source: [http://archneur.ama-assn.org/cgi/content/full/65/1/19](http://archneur.ama-assn.org/cgi/content/full/65/1/19)

The nuclear inclusions, which are numerous in the hippocampus, was found to contain mRNA FMR1 and many proteins associated with numerous neuronal functions. This means that a reduction of these factors from the cell pool, will significantly burden the cellular processes [10].

3. **Clinical features.**

Tremor and ataxia are the first movement disorders, and the patients often report incidents of falls. The tremor initially occurs during intentional movements in performing daily tasks and in the course of the disease, postural tremor may also occur. It usually affects the upper limbs, starting with the dominant hand and then extended to the other [11].

Ataxia is consistent with a cerebellar subtype, having difficulty with tandem gait and stance, whereas parkinsonian type rigidity is less obvious [12, 13].
Peripheral neuropathy occurs in the lower extremities, with reduced deep tendon reflexes, reduction of touch, pain, muscular weakness and abnormalities in the proprioceptive response [14].

The cognitive deficits are initially subtle. They are related to a reduction of the executive cognitive functions and working memory, and they are not usually assessed [15,16]. A little impairment of the primary declarative memory and episodic recall seem to coexist. Characteristic executive cognitive deficits are the impairment in the initiation of purposeful, and the goal-directed activity.

The psychiatric features of FXTAS appear as anxiety, depression, irritability, disinhibition or inappropriate behavior [17]. Psychiatric disorders such as cognitive deficits often appear early, before motor deficits [18]. Dementia in some cases occurs simultaneously with anxiety or mood disorders [17], with characteristics of frontal subcortical-type dementia and leads to a complete loss of the patient’s autonomy [19].

4. Radiological features.

In brain MRI, a generalized atrophy, a decrease in brain volume (mainly parietally and frontally), pons and cerebellum is observed [20, 21]. There are confluent areas of increased signal intensity on T₂ weighted or FLAIR acquisitions, periventricular and in the deep white matter of the cerebral hemispheres [22]. Spongiform intercellular edema in the middle cerebellar peduncle (MCP), is illustrated as an increased T₂ signal intensity of the MCP, but it is found in only 60% of the patients [23].

The radiological findings have been confirmed by neuropathological analyses in post-mortem brains of patients and they fully justify the clinical features of the syndrome.
5. Conclusion.

The FXTAS appears to be a common progressive neurodegenerative disorder of late age, with early symptoms which are not usually recognized but are attributed to aging or other neurologic diseases. Since there is no effective treatment, it is important to identify the syndrome early with a DNA research of the Fragile X (FMR1), in order to genetically determine the premutated carriers of the gene, to provide them with genetic counseling recommendations.

References.


5. Bear MF, Huber KM, Warren ST. The mGluR theory of fragile X mental retardation. Trends


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