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Fragile X-associated tremor/ataxia syndrome

CLINICAL REVIEW

GRY HOEM

E-mail: gry.hoem@uit.no
Department of Medical Biology
University of Tromsø – The Arctic University of Norway
She contributed to the concept, design, literature search, drafting/revision of the manuscript and approved the submitted version.
Gry Hoem (born 1987), MD and PhD candidate.
The author has completed the ICMJE form and reports no conflicts of interests.

JEANETTE KOHT

Department of Neurology
Drammen Hospital
and
Institute of Clinical Medicine University of Oslo
She contributed to the design and drafting/revision of the manuscript, and approved the submitted version.
Jeanette Koht (born 1969), senior consultant and associate professor. She has a PhD in hereditary ataxias.
The author has completed the ICMJE form and reports no conflicts of interests.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a hereditary neurodegenerative disorder caused by a mutation on the X chromosome. The major signs and symptoms are tremor, ataxia and parkinsonism. Up to one in 2 000 persons over 50 years of age will develop the syndrome. There is reason to believe that too few individuals in Norway undergo testing for this condition.

The purpose of this paper is to provide readers with information about fragile X-associated tremor/ataxia syndrome, when this syndrome could/should be suspected, and how to arrive at a diagnosis. It is based on a discretionary selection of articles from the PubMed database and the authors' own experiences in clinical practice and research.

Pathogenesis and inheritance

Fragile X-associated tremor/ataxia syndrome is caused by a mutation in the *FMR1* gene (Fragile X Mental Retardation 1) on the X chromosome. This gene is best known for its association with the developmental disorder fragile X syndrome, which is the most common cause of hereditary developmental disability (1).

Fragile X syndrome affects more than 1 in 7 000 boys and 1 in 11 000 girls (1). It is one of three *FMR1*-associated disorders, the other two being fragile X-associated tremor/ataxia syndrome, and fragile X-associated primary ovarian insufficiency. All three are caused, with very few exceptions, by an expansion of CGG triplet repeats in a noncoding region of the *FMR1* gene on the X chromosome.

Non-affected individuals usually have around 30 CGG triplet repeats. If the number of triplets is ≥ 45, the repeat expansion can increase from one generation to the next. Such triplet repeat expansions are unstable and are often called dynamic mutations. If the number of CGG triplets exceeds 200 – a so-called full mutation – the gene is inactivated and the key FMR1 protein is no longer produced. This leads to fragile X syndrome (1).

Shorter expansions of 55–200 CGG triplets are called 'premutations' and can give rise to both fragile X-associated tremor/ataxia syndrome and *FMR1*-associated primary ovarian insufficiency. The gene is not inactivated in these cases; on the contrary it becomes more active, leading to the production of large amounts of expanded mRNA containing the CGG triplets (2). The problem here is not a lack of FMR1 protein, but a toxic mechanism initiated by the expanded mRNA (3). This explains why full mutations and premutations can give rise to completely different phenotypes.

In individuals with fragile X-associated tremor/ataxia syndrome, intranuclear inclusions form in both the central nervous system and peripheral tissues (3). Neurons and astrocytes in the cerebellum, basal ganglia, hippocampus and frontal cortex are particularly affected (4). For reasons that remain unclear, however, less than half of all premutation carriers develop fragile X-associated tremor/ataxia syndrome.

FMR1-associated conditions show X-linked inheritance. However, when triplet repeat expansions are inherited paternally, they are largely prevented from expanding further by unexplained mechanisms that occur during spermatogenesis (5). Further expansion of triplet repeats usually occurs in female germ cells, and therefore fragile X syndrome almost exclusively affects children of female premutation carriers.

Because of this pattern of inheritance, diagnosing an individual with one of these disorders could reveal an entire family's risk of all three conditions (6). Family medical history is therefore central to the diagnostic workup. It is important to ask whether an individual's first- or second-degree relatives include women with early menopause; persons over the age of 50 with ataxia, tremor and/or parkinsonism, or children with developmental disorders.

Epidemiology

According to a systematic review and meta-analysis, 1 in 855 men and 1 in 291 women are carriers of an *FMR1* premutation (1). About one in five women with a premutation will develop primary ovarian insufficiency (menopause before the age of 40) versus one in 100 women in the general population (7). In addition, about 40 % of men (8) and 16 % of women with premutations will develop fragile X-associated tremor/ataxia syndrome (9). This corresponds to an estimated prevalence of this syndrome in the general population of about 1 in 2 000 for both women and men over the age of 50 (1, 10).

The probability of developing fragile X-associated tremor/ataxia syndrome is not the same across the entire spectrum of premutations, but increases with the number of triplet repeats (11). Many studies have recruited participants from families with known fragile X syndrome, in which longer premutations are overrepresented. The prevalence of fragile X-

associated tremor/ataxia syndrome in premutation carriers may therefore have been overestimated (12). No population-based studies have investigated the prevalence of the syndrome in the general population.

Clinical features

Fragile X-associated tremor/ataxia syndrome is characterised by both motor and cognitive signs and symptoms. Patients often show disease onset in their early sixties, but the probability of developing the disorder increases with age. Around 40 % of male premutation carriers will have developed the syndrome by the time they reach 70, while the figure is 75 % after the age of 80 (8). Diagnosis of the syndrome is complicated by highly variable clinical signs and disease course.

The syndrome should be suspected in particular in men over the age of 50 with tremor, ataxia and parkinsonian traits, especially when multiple signs and symptoms are present, and/or the individual also has executive dysfunction. Women often have milder symptoms, and far fewer women than men with the syndrome have been described in the literature.

The first sign may be intention tremor, cerebellar ataxia, parkinsonism or cognitive impairment. Tremor is the most frequent symptom and is seen in 80 % of patients, cerebellar ataxia in 50 % and parkinsonism in 30 % (13). Most patients have mixed tremor, with tremors both at rest and during movement. Resting tremor alone is unusual, and can be an important clinical feature for differentiating fragile X-associated tremor/ataxia syndrome from Parkinson's disease.

Cerebellar ataxia manifests predominantly as a gait ataxia with unsteady, wide-based gait, difficulties with tandem gait, and increased tendency to fall. Cerebellar involvement also gives rise to slurred speech (dysarthria) and imprecise movements of the upper extremities (ataxia and dysmetria) in the majority of patients (13).

The classic cognitive symptom profile in fragile X-associated tremor/ataxia syndrome is a progressive loss of executive functions. Dementia is also seen at advanced stages of the disease, and it is reported that as many as 50 % of male patients over the age of 55 fulfil criteria for dementia (13). Patients with fragile X-associated tremor/ataxia syndrome also have increased rates of anxiety and depression, with a lifetime prevalence of severe depression of 44 %, and of anxiety disorders of 52 % (14).

In addition to cognitive and motor symptoms, patients show an increased incidence of neuropathy, sleep disorders, autonomic dysfunction, thyroid diseases, fibromyalgia, migraine and hypertension. These ailments are also seen more frequently in premutation carriers without the syndrome than in the rest of the population (3).

Clinical differential diagnoses

The movement abnormalities seen in fragile X-associated tremor/ataxia syndrome overlap with those of several more well-known disorders. In 2016, Robertson et al. published a systematic review in which they compared the phenotype of fragile X-associated tremor/ataxia syndrome to that of essential tremor, Parkinson's disease, autosomal dominant hereditary ataxias, multiple system atrophy, and progressive supranuclear palsy (13).

Although patients with fragile X-associated tremor/ataxia syndrome show complex clinical phenotypes, features such as parkinsonism, for example, can make it difficult to distinguish them from persons with Parkinson's disease (15). Symptoms early in the disease course may be mild and difficult to categorise. Individuals with minor unsteadiness and tremor may be diagnosed with essential tremor.

It is important to be aware that for persons with essential tremor who develop unsteadiness and/or executive dysfunction, alternative diagnoses, including fragile X-associated tremor/ataxia syndrome, should be considered. This also applies to cases with atypical development of other movement disorders. Table 1 provides a brief summary of the clinical similarities and differences between fragile X-associated tremor/ataxia syndrome and the movement disorders listed above (13).

Table 1

Differential diagnoses of fragile X-associated tremor/ataxia syndrome (13). MSA-P = multiple system atrophy (parkinsonian subtype), MSA-C = multiple system atrophy (cerebellar subtype), SCA = autosomal dominant spinocerebellar ataxia

Movement disorder	Tremor	Cerebellar ataxia	Parkinsonism	Other symptoms/signs
Fragile X-associated tremor/ataxia syndrome	Action tremor alone or together with resting tremor	Half of all patients	Around one-third of patients	Cognitive impairment with executive dysfunction, neuropathy, sleep disturbances
Essential tremor	Action tremor hands >> head > voice	No, but minor cerebellar abnormalities later in the disease course have been reported	No	No
Parkinson's disease	+/- tremor Resting tremor, most often in hands. Asymmetry	No	Rigidity, bradykinesia and/or postural instability +/- tremor	Non-motor symptoms, including sleep disorders, depression, reduced olfactory sense
Spinocerebellar ataxias	Intention tremor	Slowly progressive ataxia. Unsteady gait is typically the first symptom	May be seen in some SCA-types	Examination of eye movements often reveals fragmented, jerky tracking movements and slow saccades
Multiple system atrophy	Yes, seen frequently	Yes, in the cerebellar form (MSA-C)	Yes, in the parkinsonian form (MSA-P)	Autonomic dysfunction Dystonia REM-sleep disturbance
Progressive supranuclear palsy	Yes, but usually no tremor	Rarely	Axial rigidity most pronounced	Vertical gaze palsy and slow saccades Executive dysfunction

Robertson et al. recommend *FMR1* premutation testing of all individuals over the age of 50 who present with cerebellar ataxia and/or intention tremor with mild parkinsonism (13).

Diagnosis and treatment

Clinical examination, brain MRI and genetic testing are all required to diagnose fragile X-associated tremor/ataxia syndrome (Table 2) (3). MRI typically reveals generalised brain atrophy; in addition, T2-weighted images may show hyperintensity in the middle cerebellar peduncles (often referred to as the MCP sign) and the posterior region of the corpus callosum (16). The diagnosis should be made by a specialist in neurology and the follow-up include an offer of genetic counselling for the patient and her/his family.

Table 2

Diagnostic criteria for fragile X-associated tremor/ataxia syndrome, based on the updated diagnostic criteria outlined by Hagerman & Hagerman in 2016 (3)

Definite fragile X-associated tremor/ataxia syndrome		
One clinical and one radiological major criterion, or one clinical major criterion and intranuclear inclusions + premutation		
Probable fragile X-associated tremor/ataxia syndrome		
Two clinical major criteria, or one clinical minor criterion and one radiological major criterion + premutation		
Possible fragile X-associated tremor/ataxia syndrome		
One clinical major criterion and one radiological minor criterion + premutation		
	Major criteria	**Minor criteria**
Clinical signs	Intention tremor and gait ataxia	Parkinsonism, moderately to severely impaired short-term memory, loss of executive functions, or neuropathy
Radiology (brain MRI)	White matter lesions in the middle cerebellar peduncles or posterior regions of the corpus callosum	White matter lesions in the cerebrum. Moderate to severe generalised atrophy
Neuropathology	Intranuclear inclusions in neurons and astrocytes in the central nervous system	

At present, there are no medical treatments that can slow or halt the development of fragile X-associated tremor/ataxia syndrome. Only one clinical drug trial has been conducted in the disorder, with the NMDA receptor antagonist memantine; however, no improvement in tremor, ataxia or executive dysfunction was seen after one year of treatment (17). The main emphasis is therefore on symptomatic treatment.

Some patients have experienced a reduction in tremor with the use of beta-blockers and levetiracetam (3). Levodopa can produce improvements in parkinsonian symptoms, and should be tried in patients who experience these (3). Deep brain stimulation has also been

attempted; however, in several cases it exacerbated the ataxia despite improving the tremor (3). Balance and strength training under the guidance of a physiotherapist familiar with ataxia is the most effective intervention for gait abnormalities and unsteadiness (3).

Comorbidities such as neuropathic pain, muscle and skeletal pain, and depression may be treated with analgesics/antidepressants where indicated. Prolonged use of opioids should be avoided because this class of drugs may lead to exacerbation of neurological symptoms (3).

Fragile X-associated tremor/ataxia syndrome in Norway

Few persons in Norway undergo assessment for fragile X-associated tremor/ataxia syndrome. Throughout the whole of 2015, the university hospitals of Oslo, Bergen and Tromsø received a total of 11 requisitions for genetic testing with this indication (unofficial figures from Oslo University Hospital, Haukeland University Hospital, University Hospital of North Norway).

The prevalence of the *FMR1* premutation and of fragile X-associated tremor/ataxia syndrome are unknown in the Norwegian population. Based on international figures, it is estimated that up to 850 persons over the age of 50 in Norway have the syndrome, and that 8 900 women and 3 000 men are premutation carriers (all age groups). In light of these figures, it may be worth reconsidering current practices with respect to testing and diagnosis.

Based on the literature, it would also be reasonable in Norway to follow Robertson et al.'s recommendation to test all those over the age of 50 who present with cerebellar ataxia and/or intention tremor with mild parkinsonism, for the *FMR1* premutation. Genetic testing for the *FMR1* premutation is now performed at Oslo University Hospital, University Hospital of North Norway, and Haukeland University Hospital (18). In Norway, this analysis is inexpensive and requires only a standard EDTA blood sample. Sanger sequencing and exome-based gene panel tests (deep sequencing) are not suitable for detecting triplet repeat expansions such as CGG expansions.

Genetic testing for *FMR1* premutation should be performed more often as part of the workup for movement disorders in patients over the age of 50. If general practitioners or other clinicians suspect fragile X-associated tremor/ataxia syndrome, they can contact their nearest neurological department to discuss potential further diagnostic workup. Regional neurological departments should be consulted if necessary. First, however, someone needs to think of the diagnosis – and that requires increased awareness of fragile X-associated tremor/ataxia syndrome.

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