Fragile X Premutation With Atypical Symptoms at Onset

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Objective: To evaluate the presence of carriers of the fragile X premutation among male patients with sporadic ataxia without expansion into known spinocerebellar ataxia genes.

Design: Clinical and genetic examinations were performed on patients with sporadic pure ataxia and patients with ataxia associated with extracerebellar features such as pyramidal and extrapyramidal signs, dementia, or peripheral neuropathy.

Setting: University department of neurology.

Patients: One hundred forty-two Italian men with sporadic ataxia with onset at age 30 to 84 years.

Interventions: The CGG repeat size of the FMR1 gene was evaluated with fluorescent polymerase chain reaction. Premutated allele lengths were confirmed with Southern blot analysis.

Results: FMR1 premutation alleles with a repeat number greater than 55 were detected in 3 probands (2.1%) from a total of 142 male subjects initially referred to our university medical center for evaluation of sporadic ataxia. Two patients had typical fragile X syndrome with associated tremor or ataxia, and the third patient had spastic paraparesis without clear symptoms of cerebellar ataxia and without the common signs seen at magnetic resonance imaging.

Conclusions: Genetic analysis of the FMR1 gene could provide a reliable diagnostic tool for the definitive diagnosis of late-onset ataxias. Additional studies are needed to clarify the importance of premutation screening in patients with movement disorders or other associated atypical features at onset, such as paraparesis.

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Fragile X syndrome with associated tremor or ataxia (FXTAS) is a late-onset neurologic disorder caused by the presence of a premutation (55-200 CGG repeats) in the 5’ untranslated region of the FMR1 gene in affected individuals. Predominant signs in male subjects carrying the premutation include cerebellar ataxia, intention tremor, and cognitive decline, occasionally associated with other symptoms such as peripheral neuropathy, lower limb proximal muscle weakness, and autonomic dysfunction, with age at onset between 50 and 70 years. Magnetic resonance imaging (MRI) in patients with FXTAS reveals diffused brain atrophy with a characteristic peculiar feature consisting of a T2-hyperintense signal of the middle cerebellar peduncles or brainstem that is often associated with cerebral white matter lesions. A characteristic neuropathologic sign is the presence of ubiquitin-positive intranuclear inclusions in both neurons and astrocytes.

The wide and variable phenotype of this disorder overlaps the clinical features of some neurologic diseases, making FXTAS diagnosis difficult without molecular analysis. In addition, in female carriers, who rarely manifest the disease, the FXTAS phenotype is milder, with later onset than in male subjects. Premutated alleles are not frequently identified in other neurologic disorders or disturbances, including multiple system atrophy, Parkinson disease, and essential tremor, thus, genetic testing for FMR1 in these patients often is not recommended. In contrast, various screenings for FMR1 performed in patients with sporadic spinocerebellar ataxia suggest that expanded FMR1 alle-
les may be considered a possible genetic cause of late-onset ataxia.

We evaluated the presence of carriers of the fragile X premutation among male patients referred to our medical center with a clinical diagnosis of spinocerebellar ataxia and who were negative for expansion in known spinocerebellar ataxia genes (1, 2, 3, 6, 7, 8, 12, 17; dentatorubropallidoluysian atrophy; and Friedreich ataxia).

### METHODS

**PATIENTS**

We selected and clinically examined 142 Italian men with ataxia with age at onset between 30 and 84 years. Among these patients, 65 (46%) were 50 years or older at onset of the initial symptoms.

All patients provided a complete history and underwent physical and neurologic examinations and laboratory testing to exclude other diseases. The diagnosis of sporadic ataxia was based on a history of sporadically occurring progressive deterioration of the cerebellar function manifested by at least 2 signs, gait or limb ataxia along with ocular dysmetria and dysarthria, in the absence of other causes of ataxia such as medications, cerebellar neoplasia, and multiple sclerosis. Patients with progressive ataxia variably associated with extracerebellar features such as pyramidal signs, extrapyramidal signs, dementia, and peripheral neuropathy were also included.

The ethical committee at our institution approved the project. Written informed consent was obtained from the patients participating in the study.

**MOLECULAR ANALYSIS**

The CGG repeat size of the \textit{FMR1} gene was evaluated with fluorescent polymerase chain reaction and standard-sized markers using an automatic DNA sequencer (ALF Express; Pharmacia LKB, Uppsala, Sweden) and fragment analysis software (Fragment Manager; Pharmacia LKB). DNA samples from patients with fragile X syndrome and carriers of the fragile X premutation served as positive controls. Premutated allele lengths were confirmed with Southern blot analysis.

Among the 142 patients, \textit{FMR1} premutation alleles with a repeat number greater than 55 were detected in 3 probands (2.1%) with late-onset ataxia (Table). None of the patients had a family history of fragile X syndrome.

Proband 1 was a 62-year-old man who was initially examined because of mild paraparetotaxic gait who had diabetes mellitus and mild hypertension with no cognitive impairment. The proband is a moderate smoker (half a pack per day). The proband reported that gait symptoms worsened in the last few months, causing difficulties in daily life, with increased muscle tone in the lower limbs (Ashworth scale score, 2 bilaterally), diffuse hyperreflexia, no clonus, and a positive bilateral Babinski sign. The proband underwent brain and spinal MRI, with normal findings; brain spectroscopy, also with normal findings; and stimulation of motor and somatosensory evoked potentials, which indicated pyramidal tract alterations predominantly in the lower limbs and mild sensory impairment. A lumbar puncture was performed, and all chemical and microbiologic test results were normal. The International Cooperative Ataxia Rating scale score was 13/100. The patient now has a peculiar paraparetic-spastic gait and mild kinetic tremor of the right arm.

Proband 2 was a 70-year-old man who was referred for evaluation of left hand resting tremor that began at the age of 56 years. The symptoms had increased with time, with a mixed postural component progressively involving the contralateral limbs. At age 62 years, the patient experienced several falls caused by gait disequilibrium, lateral and retropropulsion; later, bradykinesia developed, and the patient became apathetic and was unable to stand without falling. He has been wheelchair bound since 2004. The International Cooperative Ataxia Rating scale score was 53/100. Brain MRIs showed marked cerebral atrophy, moderate subcortical and brainstem white matter lesions, and definite hyperintensity on T2-weighted images that was localized in the white matter of the middle cerebellar peduncles. Measurement of the repeat length showed that both probands 1 and 2 carried \textit{FMR1} alleles of 80 CCG triplets.

Proband 3 was a 69-year-old man. At the age of 55 years, he had isolated right hand intentional tremor. The neurologic examination did not indicate involvement of the extrapyramidal and pyramidal systems. Five years after disease onset, pancerebellar dysfunction developed, including gait ataxia, decreased muscle tone, dysmetria, and dysarthria. The International Cooperative Ataxia Rating scale score was 53/100. An MRI T2-weighted image of the brain obtained 2 years previously showed symmetrically increased signal intensity in the cerebral white matter and in the middle cerebellar peduncles. The proband carried an \textit{FMR1} premutation of 103 CCG repeats.

### RESULTS

![Table. Clinical, Neurologic, and Molecular Characteristics in Patients Carrying the \textit{FMR1} Premutation](https://jamanetwork.com/)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proband 1</th>
<th>Proband 2</th>
<th>Proband 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>Age at onset of initial symptoms, y</td>
<td>60</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait difficulties</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spastic paraparesis</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cerebellar ataxia (limbs)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cerebellar dysarthria</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensory impairment</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MRI findings, T2-weighted images</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperintense middle cerebellar peduncles</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperintense cerebral white matter</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>\textit{FMR1} premutation size, No. of triplets</td>
<td>80</td>
<td>80</td>
<td>103</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; +, present; -, absent.
FMRI premutations were not present in the group of patients with onset of symptoms before age 50 years. With the exception of the 3 patients with premutated alleles, the FMRI triplet repeat distribution in the group with late onset of symptoms was fewer than 42 triplets.

COMMENT

Genetic analysis of FMRI expansion in our cohort of patients reveals the presence of the premutation in 3 of 142 male subjects initially referred to our medical center for evaluation of sporadic ataxia without pathogenic expansions in the known spinocerebellar ataxia genes. Two patients had typical FXTAS, including common disease features such as ataxia and tremor and alterations seen on MRIs. One patient exhibited symptoms attributable to spastic paraparesis with mild ataxia.

Recently, Jacquemont et al16 described 3 carriers of the FMRI premutation (2 female, 1 male) with a severe form of FXTAS characterized by, in addition to the other typical symptoms, early onset of spastic paraparesis, which represents a new clinical feature not previously associated with the common manifestations of the disease. Our proband 1 had an atypical form, differing from the previously described cases16 in that it was characterized by spastic paraparesis with late onset of initial symptoms. The absence of a clear cerebellar ataxia syndrome, along with normal spinal and brain MRIs, creates doubt that this patient truly has an unusual form of FXTAS. However, we cannot exclude the possibility that the more common symptoms of this disease will develop later.16 Inasmuch as carriers of the FMRI1 premutation have been reported among patients initially seen because of other common neurologic diseases,17 such as spastic paraparesis16 and Alzheimer disease,1,18 we can assume that FXTAS may occasionally be misdiagnosed. These results, therefore, suggest that patients with atypical features at onset should also be examined for FXTAS until a definitive diagnosis is ascertained. We could speculate that paraparesis may be one of the various but less frequently expressed features in the wide clinical spectrum of FXTAS, occasionally an early clinical sign of the FMRI premutation.

Our results confirm that FXTAS could be a recurrent cause of sporadic ataxia in patients with adult onset of the disease. In addition, in men with older age at onset, we found that approximately 4.6% (3/65) of FXTAS cases with sporadic ataxia may be attributable to the effects of premutated alleles, confirming previous data in the Italian population.13

Findings in probands 1 and 2 in our study confirm the basic clinical and radiologic features of the disease and the similar premutated allele size in patients with sporadic ataxia and those in families with fragile X with an FXTAS phenotype. This suggests that the toxic effects of premutated FMRI RNA on the nervous system could lead to a clinical manifestation that is indistinguishable from spinocerebellar ataxia, possibly sharing common pathogenic mechanisms. That the preexpanded alleles of some genes could manifest as a not fully penetrant but clinically evident neurologic disease raises an important issue for other genetic risk factors possibly involved in spinocerebellar ataxias or other triplet expansion disorders.

CONCLUSION

Genetic analysis of the FMRI gene could prove to be a reliable diagnostic tool for the definitive diagnosis of late-onset ataxias in male patients even if more precise details of the FXTAS prevalence in the general population are needed before making definitive conclusions about the contribution of this premutation to movement disorders. We hypothesize that the molecular analysis of patients with movement disorders or other associated atypical features at onset, coexisting with later onset of ataxia, may yield expanded FMRI alleles. However, we confirm the notion that a careful neuroradiologic examination should be performed in all patients with spinocerebellar disorders because the hyperintense signal on T2-weighted images of the middle cerebellar peduncles is specific to FXTAS and can be considered an important indication for precise and cost-effective premutation screening.

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