Clinical and Neuropathologic Findings in a Woman With the FMR1 Premutation and Multiple Sclerosis

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**Background:** Multiple sclerosis (MS) and fragile X–associated tremor/ataxia syndrome (FXTAS) have overlapping clinical signs and symptoms.

**Objectives:** To present a case with evidence of both MS and FXTAS and to discuss the relationship of both disorders.

**Design:** Case report.

**Setting:** Fragile X Research and Treatment Center at the University of California, Davis, Medical Center.

**Patient:** Woman with the FMR1 premutation who died of MS at the age of 52 years.

**Main Outcome Measures:** Magnetic resonance imaging, physical examination, and neuropathologic examination results.

**Results:** Magnetic resonance imaging, physical examination, and autopsy neuropathologic examination revealed diagnostic features of MS and FXTAS.

**Conclusion:** The molecular mechanism of RNA toxicity, including the elevation of αB-crystallin levels observed in FXTAS, may lead to enhanced predisposition to autoimmune diseases.

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**REPORT OF A CASE**

A 32-year-old woman presented with right arm numbness that persisted for 2 months, followed by an episode of optic neuritis; both resolved spontaneously. At 38 years of age, she presented with a left extensor plantar reflex, loss of dexterity in the right hand, appendicular ataxia that involved the right lower extremity, and mild gait ataxia. Brain magnetic resonance imaging (MRI) revealed mild diffuse atrophy and multiple foci of increased T2-weighted signal intensity in the periventricular white matter and cerebellum, consistent with a demyelinating disorder (Figure 1). She was diagnosed as having relapsing-remitting MS. Lumbar puncture was not performed. Despite treatment, her condition deteriorated during the next 3 months, with reducing bilateral lower extremity sensation and motor function, worsening ataxia, and frequent urinary incontinence.

At 43 years of age, progression involved bilateral hand and lower extremity numbness, upper extremity intention tremor, gait ataxia, spastic paraparesis, short-term memory deficits, progressive dysthria, disinhibition, and depression. During the next 9 years, additional medications, including...
weekly methotrexate, interferon beta-1b, and mitoxantrone, were used. Her family history includes parkinsonism in her maternal grandfather and ovarian dysfunction (mid-30s) in her daughter, with workup revealing a premutation FMR1 allele (84 repeats). No other family history of fragile X syndrome was found. Given her daughter’s carrier status and her own neurologic problems, the patient was tested and found to have a premutation allele (75 repeats). The activation ratio (fraction of normal active FMR1 alleles) was 0.44. The FMR1 RNA level was elevated (mean [SD], 2.80±0.12 times normal), consistent with premutation carrier status.2 She died at the age of 52 years after progressive memory impairment, loss of motor control, significant ataxia, and tremor.

Coronal sections of the brain (1133 g) showed moderate frontal gyral atrophy, with scattered, variably sized, discrete regions of gray discoloration in cerebral and cerebellar white matter, especially prominent in periventricular locations but also in the basal ganglia, brainstem, and left middle cerebellar peduncle. On microscopic examination, these abnormalities appeared as areas of demyelination in various stages of activity (Figure 2). Microfoci of perivascular parenchymal pallor with lymphocytic infiltrates were present in early lesions. Midstage plaques showed infiltrates of foamy macrophages and lymphocytes, reactive astrocytosis, and microglial activity at their margins; scant perivascular mononuclear inflammatory infiltrates were also seen (Figure 2A). Inactive plaques showed parenchymal collapse with microcystic change. Correspondingly, Bielschowsky (axon) stain and Luxol fast blue/periodic acid–Schiff (myelin) stain showed varying degrees of axonal and myelin loss, respectively. Patchy areas of demyelination were seen in the molecular layers of both the cerebrum and cerebellum. Immunocytochemical staining for CD4+ lymphocytes (helper T cells) was negative in subacute lesions and revealed scant positive cells in a burned-out plaque (Figure 2C); CD8+ lymphocytes (killer T cells) were common in subacute plaques and scant in chronic plaques (Figure 2D). CD20 (B-cell) immunostaining was negative in both. Glial fibrillary acidic protein immunostaining showed reactive astrocytes in and around plaques and in nearby gray matter.

Ubiquitin immunostaining identified few intranuclear inclusions in astrocytes throughout the brain and rare inclusions in cortical neurons, as described for FXTAS.3 Astrocytic inclusions were within regions of de-
In conclusion, additional studies regarding the association of MS and FXTAS are warranted. The screening of individuals with atypical MS for the FMR1 premutation is also recommended, particularly if there is a family history of primary ovarian insufficiency, developmental delay, autism, intention tremor, ataxia, or neuropathy.

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REFERENCES