Fragile X-Associated Tremor/Ataxia Syndrome: Autopsy Brain MR Imaging Alterations Correlated with Histopathology

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Purpose
To correlate MR imaging findings with brain histopathology in autopsy material obtained from subjects with fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is a newly described late onset neurodegenerative disorder characterized by cerebellar ataxia, tremor, and dementia. It occurs in older individuals with premutation alleles for fragile X syndrome (55-200 CGG repeats). The clinical syndrome (1), MR imaging findings (2), and the results of histologic study of nonimaged brain autopsy material (3) have been described recently.

Materials & Methods
Postmortem T1- and T2-weighted MR images were obtained of the intact cerebral hemispheres, brain stem, and cerebellum of three individuals with known FXTAS. Brains were subsequently sectioned, and mapped sampling for histologic analysis was done to correspond to MR abnormalities. Special stains were done on histologic sections to elucidate the nature of the pathologic changes. Additionally, ubiquitin staining followed by optical analyzer counts were performed on all brains to quantitate the numbers and distribution of neuronal and intracytoplasmic intranuclear inclusions.

Results
Correlation of autopsy and postmortem MR findings in three FXTAS subjects revealed distinct volume loss involving brainstem and cerebellum. MR imaging demonstrated faintly increased T2 signal in the middle cerebellar peduncles, and prominently increased T2 signal in periventricular white matter of the cerebral hemispheres. Changes were most prominent in the frontal lobes, where periventricular white matter increased T2 signal intensity extended to involve subcortical arcuate fibers. Macroscopic sectioning showed corresponding white matter to be softened and slightly darker than expected. Grossly, the pons and cerebellar peduncles showed atrophy. Microscopically, the cerebral white matter abnormalities consisted of patchy to confluent areas of parenchymal pallor with loss of axons and myelin in varying degrees, without evidence of vascular hyalinopathy.
Eosinophilic intranuclear inclusions were present in neurons and astrocytes throughout the cerebrum and brainstem, with the greatest preponderance in hippocampal neurons. The cerebellum displayed dropout of Purkinje cells, swollen axons in the internal granular cell layer, and deep white matter spongiosis.

**Conclusion**

Abnormal white matter MR imaging findings in FXTAS were associated with spongiosis, and with loss of axons and myelin in cerebral, cerebellar, and brainstem white matter. Umbiquitin positive intranuclear inclusions were present in neurons and astrocytes of the cerebral and cerebellar cortex, in the dentate nuclei of the cerebellum, and in the hippocampus. The cerebellum also showed Purkinje cell loss, axonal swellings in the internal granular cell layer, and deep white matter spongiosis.

**References**