A 61-year-old woman had a 3-year history of imbalance. Eye movement studies revealed square-wave jerks, gaze paretic nystagmus, rebound nystagmus, impaired smooth pursuit, impaired optokinetic nystagmus, and abnormal fixation suppression of vestibular nystagmus. A brain magnetic resonance imaging study showed extensive areas of increased signal from the middle cerebellar peduncles and dentate nuclei, which enhanced with gadolinium. Histopathological analysis of a needle biopsy specimen of the left cerebellar peduncle revealed diffuse gliosis in the presence of symmetrically distributed areas of demyelination. There were associated Rosenthal fibers. Clinicopathologic correlation supported a diagnosis of Alexander disease. An adult patient with a history of progressive imbalance, ocular motility abnormalities consistent with cerebellar and/or brainstem dysfunction, and diffuse, symmetric hyperintense magnetic resonance imaging signals in brainstem and cerebellar white matter should suggest a diagnosis of adult-onset Alexander disease.
Results confirmed the presence of square-wave jerks, gaze paretic nystagmus, rebound nystagmus, impaired smooth pursuit (Figure 1), impaired optokinetic nystagmus, and abnormal fixation suppression of vestibular nystagmus (Figure 2). These findings were consistent with abnormalities localized to the pons and/or cerebellum.

A brain magnetic resonance imaging study with and without gadolinium was obtained showed extensive areas of increased signal from the middle cerebellar peduncles and dentate nuclei, left greater than right (Figure 3, left). There was diffuse confluent increased signal in the brachium pontis bilaterally extending into the lateral aspect of the pons, the midbrain, and the medulla. Focal periventricular hyperintensities were scattered in the cerebrum with some deep white matter hyperintensities (Figure 3, right). The craniocebral junction and midcervical spinal cord also showed lesions. Areas of abnormal signal demonstrated enhancement with gadolinium. There was no midline shift or mass effect, nor was there abnormal enlargement of any structures. A differential diagnosis was established that included demyelinating, neoplastic, and infectious diseases.

A needle biopsy of the left cerebellar peduncle was performed. Histopathological studies revealed hypocellular white matter with astrogliosis and deposition of numerous Rosenthal fibers (Figure 4, top). Immunostaining for myelin basic protein showed a moderate reduction in myelinated axons, and staining for neurofilament protein showed a slight reduction in the number of axonal elements. Tissue examined under the electron microscope showed extensive loss of myelinated axons that were replaced by strongly fibrillar astrocytic processes and Rosenthal fibers (Figure 4, bottom). Clinicopathologic correlation supported a diagnosis of adult-onset Alexander disease.

COMMENT

The adult form of Alexander disease has an early stuttering course followed by steady progression with increasing disability. Cases may clinically resemble multiple sclerosis.1-3 Clinical features include cerebellar dysfunction with ataxia, disorders of extraocular motility, and spasticity.2 Previously reported eye movement abnormalities include impaired smooth pursuit, gaze-evoked horizontal nystagmus, slowed saccades, and ocular myoclonus. Other reported neurologic manifestations include palatal myoclonus, spastic paresis, hyperreflexia, tremor, and gait disturbance.1 Previous neuroradiologic findings include increased cerebel-
lar white matter hyperintensity and diffuse periventricular signal hyperintensities, as well as atrophy of the lower brainstem, cervical spinal cord, and cerebellum on magnetic resonance imaging. There have been reports of Alexander disease with Rosenthal fiber deposition in the molecular layer of the cerebellum.

The present case seems most consistent with a diagnosis of adult-onset Alexander disease. Histopathological studies show diffuse deposition of Rosenthal fibers in the presence of mild gliosis and demyelination. The demyelination is not of a degree that would be exhibited by multiple sclerosis, another clinical entity in the differential diagnosis. Histopathological analysis failed to demonstrate the presence of neoplastic elements. Radiographically, there is diffuse central nervous system infiltration with no mass effect or enlargement of intracranial structures. There is also no histopathological evidence of an infectious cause. In conclusion, an adult patient with a history of imbalance, ocular motility abnormalities consistent with cerebellar and/or brainstem dysfunction, and diffuse, symmetric hyperintense magnetic resonance imaging signals in brainstem and cerebellar white matter should suggest a diagnosis of adult-onset Alexander disease.

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