Neuro-ophthalmic, Radiographic, and Pathologic Manifestations of Adult-Onset Alexander Disease

Adam Martidis, MD; Robert D. Yee, MD; Biagio Azzarelli, MD; Jose Biller, MD

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.

Alexander disease is a rare degenerative neurologic disorder characterized by diffuse demyelination in the presence of Rosenthal fibers.1 Initial reports described infants and young children with psychomotor retardation and enlargement of the head whose postmortem examinations revealed a diffuse distribution of refractile bodies throughout the central nervous system. These bodies were later found to be identical to Rosenthal fibers.2,3 Other reported features of infantile Alexander disease include hydrocephalus, spasticity, and seizures.3-5 Subsequently, a juvenile and adult form of the disease have been described. The juvenile form frequently exhibits bulbar palsy and hyperreflexia, but lacks megalencephaly and mental retardation. The adult form usually is seen with intermittent neurologic dysfunction, but may have no neurologic manifestations. All forms share the histopathological hallmark of a diffuse distribution of Rosenthal fibers throughout the central nervous system with variable demyelination.1-5 We report the neuro-ophthalmic, radiographic, and histopathological manifestations in a case of adult-onset Alexander disease.

REPORT OF A CASE

A 61-year-old white woman was evaluated who complained of loss of balance that was slowly progressive over 3 years. On examination, corrected visual acuity was 20/20 OU. Pupils were equal and briskly reactive with no afferent pupillary defect. Confrontation visual fields were full bilaterally and color vision was minimally depressed. Ocular motility showed a small, intermittent esotropia of 6 prism diopters at distance and an exophoria of 6 prism diopters at near. In center gaze, there were frequent, small amplitude, horizontal square-wave jerks. Vestibular nystagmus was not normally suppressed by fixation. In 40° of right gaze, there was a right-beating gaze paretic nystagmus with several beats of rebound nystagmus on return to center gaze. In 30° of left gaze, there was also a gaze paretic nystagmus with an associated rebound nystagmus. Results of slitlamp examination were normal except visually insignificant nuclear sclerotic cataracts. Results of the ophthalmoscopic examination were also normal.

Clinical eye movement studies were performed using electro-oculography. Re-
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 cerebral hemispheres with some deep white matter hyperintensities (Figure 3, right). The craniocervical 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. 

Rosenthal fibers are histopathological bodies consisting mainly of glial fibrils, ubiquitin, and some unidentified lipid material. They are seen in conditions in which chronic gliosis is present, including syringomyelia, chronic ependymitis, lipid granulomatosis, gliomas (including juvenile pilocytic astrocytomas), paraneoplastic gliosis, astrocytic scars, and delayed radiation necrosis. They can also occasionally be seen in multiple sclerosis, central pontine myelinolysis, and tuberous sclerosis. In Alexander disease, Rosenthal fibers are concentrated in subpial, perivascular, and subependymal areas, as well as the deep cerebral white matter and the ventral and lateral regions of the brainstem and spinal cord. 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.

Accepted for publication September 16, 1998.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, NY.

Reprints: Robert D. Yee, MD, Department of Ophthalmology, Indiana University School of Medicine, 702 Rotary Cir, Indianapolis, IN 46202 (e-mail: ryee@iupui.edu).

REFERENCES