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MR Imaging of Leukoencephalopathy Associated with Navajo Neuropathy

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Navajo neuropathy is a hereditary sensorimotor disease that occurs in members of the Navajo Indian tribe. It appears to be recessively inherited and becomes clinically evident in early childhood. Although initially described as a peripheral neuropathy with predominant involvement of myelinated axons [1], we have encountered two patients with CNS abnormalities on MR imaging, indicating that this disorder may also involve central white matter.

Case Reports

Case 1

A 15-year-old Navajo girl presented with a primary complaint of increasing difficulty with ambulation and clawlike deformity of the left-hand fingers. The diagnosis of Navajo neuropathy had been made in childhood on the basis of failure to thrive, corneal scarring, sensorimotor deficits, and sural nerve biopsy. A current neurologic examination revealed generalized muscle atrophy with weakness of the lower extremities. Deep tendon and corneal reflexes were absent. Pain and light touch sensations were absent distal to the ankle and diminished proximally. Proprioception was absent below the knees. The patient displayed a high-steppage gait with footdrop and had poor balance with a positive Romberg sign. Cerebrospinal fluid IgG was increased (12.6%) but myelin basic protein was within normal limits. An EMG revealed slowed nerve conduction and suggested neurogenic atrophy. Brainstem auditory evoked responses were normal.

MR imaging at 1.5 T demonstrated bilateral comma-shaped areas of diminished signal intensity in the cerebellar white matter on a short TR/short TE (T1-weighted) pulse sequence (Fig. 1A). Subcortical white matter in the frontal and parietal lobes bilaterally also had foci of decreased signal intensity with T1 weighting. All of these regions were hyperintense on long TR/long TE (T2-weighted) images (Figs. 1B and 1C). No periventricular white matter lesions were present.

Case 2

A 17-year-old Navajo boy was admitted for treatment of an ulcer of the left foot. Navajo neuropathy had been diagnosed at 4 years of age on the basis of typical motor and sensory deficits. The patient was of short statute (<3rd percentile height and weight) and had delayed sexual maturation. Neurologic examination revealed absence of deep tendon and corneal reflexes. Responses to pain, light touch, and vibration were markedly diminished distal to the elbows and knees. Position sense was poor and the patient ambulated with a foot-slapping gait. An EMG revealed nerve conduction velocities slowed to 30% of normal and absent evoked responses from the lower extremities. A sural nerve biopsy showed severe loss of large and small myelinated fibers with endoneurial and perineural fibrosis and scarring.

The long TR/long TE pulse sequence from the MR study delineated subtle increased signal intensity in the cerebellar white matter in a pattern similar to that seen in case 1 (Fig. 2). The cerebral white matter had a normal appearance.

Discussion

The Navajo are the largest tribe of native Americans in the United States, with reservations in northeastern Arizona, northwestern New Mexico, and southeastern Utah [2]. They are of the Athapaskan linguistic stock and refer to themselves as the Diné (the People) [2]. Although tribal custom requires that one marry outside one's clan, Navajo neuropathy is believed to be recessively inherited. The disorder is classically characterized by severe acral mutilation, corneal ulceration, and marked weakness, although patients without acromutilation or corneal scarring and with only mild weakness have been described [1, 3]. Autonomic dysfunction, failure to thrive, short stature, and scoliosis are also encountered in certain patients [1, 3]. Sural nerve biopsy reveals almost total loss of myelinated fibers with no evidence of regeneration, while unmyelinated axons show both degeneration and regeneration [1]. No "onion bulb" formation is seen. A few biopsies have also displayed extensive perineural and endoneurial fibrosis. Nerve conduction velocities are markedly slowed [1].

The above findings are found in patients with Navajo neuropathy, Type A, as in the two patients in this report. A Type

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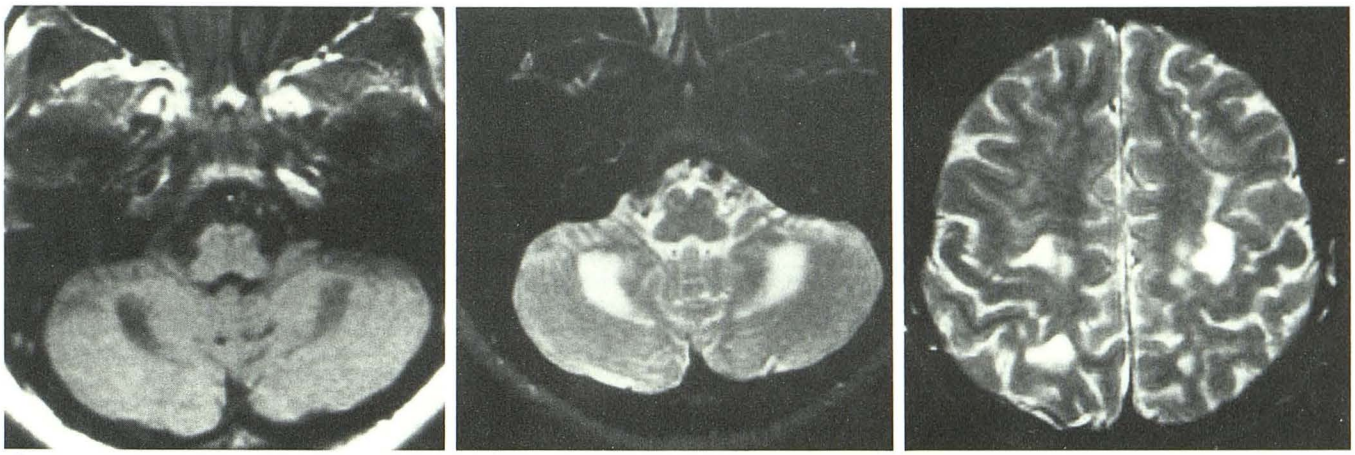

Fig. 1.—Case 1.
***A*, Axial spin-echo 600/20/1 (TR/TE/excitations) MR image reveals bilateral, comma-shaped areas of decreased signal intensity involving the cerebellar white matter.**
***B* and *C*, Axial spin-echo 2500/80/1 MR images reveal corresponding areas of increased signal intensity within the central cerebellar white matter (*B*) and subcortical white matter of the frontal and parietal lobes bilaterally (*C*).**

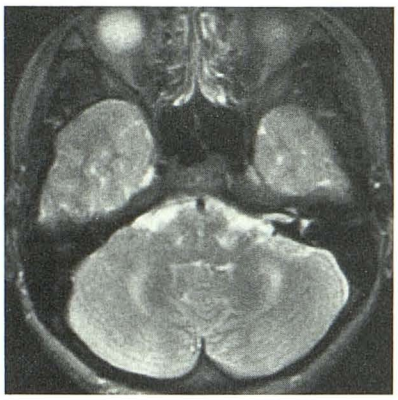

Fig. 2.—Case 2. Axial spin-echo 2800/90/1 MR image through cerebellum reveals subtle signal hyperintensity in the cerebellar white matter in a pattern similar to that in case 1.

B disease has been described, in which neurologic examinations and nerve conduction studies are normal but there are autonomic disturbances and severe neuropathic arthropathies [3, 4]. Nerve biopsies in Type B Navajo neuropathy reveal diminution of unmyelinated and small myelinated fibers with preservation of large myelinated fibers [4].

The reason for the increased signal seen with MR is unknown, as we had no pathologic material available for study. Obtaining such specimens may be difficult because postmortem examinations are against tribal practices (R. Amos, personal communication, 1988), and brain biopsy is difficult to justify given the relative ease, safety, and diagnostic yield of sural nerve biopsy. Although gliosis or axonal degeneration could be responsible, we believe that demyelination is the most likely explanation given the devastation of peripheral myelin seen on peripheral nerve biopsies. The involvement of CNS white matter suggests this disorder might be called "Navajo leukoencephalopathy."

Peripheral neuropathy occurs with several leukodystropies: metachromatic leukodystrophy (MLD), Krabbe disease, and adrenoleukodystrophy variants (adrenomyeloneuropathy and adrenoleukomyeloneuropathy) [5]. Although the late infantile form of MLD has a similar age of onset as Navajo neuropathy, patients with MLD are intellectually impaired and display characteristic ultrastructural inclusions on nerve biopsies [5]. Neither of these features is seen in Navajo neuropathy, although lipid inclusions are often seen within the perineurium and Schwann cells (PC Johnson, unpublished observations). Patients with Krabbe disease have an onset in infancy and die within 2 years. Mental retardation also is a feature of Krabbe disease; however, the neuropathy tends to be milder than with MLD [5]. In both leukodystrophies the neuropathy appears to be predominantly motor-related. Spinocerebellar degenerations of either the Menzel type (olivopontocerebellar atrophy) or Holmes type (cerebelloolivary atrophy) may have an associated neuropathy [6, 7]. Biopsies of sural nerve in certain patients have shown reductions in the number of myelinated fibers with sparing of nonmyelinated fibers [6]. Sensation is generally spared with the spinocerebellar degenerations as opposed to Navajo neuropathy. No supratentorial white matter changes have been described in olivopontocerebellar degeneration [8, 9].

Cree leukoencephalopathy is a fatal white matter disorder recognized in infants of that northern tribe [10]. Although the Cree are also of the Athapaskan linguistic stock, this disease is clinically separable from Navajo neuropathy and has not been encountered in the southwestern tribe.

In summary, Navajo neuropathy Type A is a hereditary sensorimotor neuropathy that severely affects peripheral myelinated and unmyelinated axons. CNS white matter signal abnormalities may be seen with MR imaging, especially in the cerebellum, and probably reflect demyelination. The disorder is clinically distinct from leukodystrophies and spinocerebellar degenerations, which may have associated peripheral neuropathies. Neuroradiologists performing MR imaging in this pop-

ulation should be alert for these findings and obtain imaging studies at initial patient presentation to ascertain if this CNS abnormality occurs early in the clinical course of the disease or is a subsequent development. Definitive diagnosis, however, will continue to be based on clinical findings and peripheral nerve biopsy.

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