Acute Disseminating Encephalomyelitis in Neuromyelitis Optica

Closing the Floodgates

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Objective: To report the clinical and radiological features of 2 patients with neuromyelitis optica (NMO) associated with severe acute disseminating encephalomyelitis. The first patient had anti–aquaporin 4 antibodies (NMO-IgG) but no lesion enhancement, in contrast to the second patient who was seronegative for NMO-IgG but had clear lesion enhancement on magnetic resonance imaging.

Design: Clinical, laboratory, and radiological analysis of 10 patients presenting with features compatible with an NMO-spectrum disorder, 2 of whom developed acute disseminating encephalomyelitis.

Setting: Inpatient ward at the Department of Neurology, Hadassah University.

Patients: Patients admitted during a 1-year period with features compatible with an NMO-spectrum disorder.

Interventions: Medical histories and imaging data were reviewed and serum samples were analyzed for the presence of NMO-IgG.

Main Outcome Measures: Clinical and paraclinical evidence of brain involvement.

Results: Of 10 patients tested, 5 were positive for NMO-IgG. One seropositive and 1 seronegative patient had an acute disseminating encephalomyelitis–like episode. In both cases, the clinical, laboratory, and electroencephalographic findings supported a diagnosis of acute disseminating encephalomyelitis. Magnetic resonance imaging demonstrated extensive bilateral white matter lesions in both patients. Lesions in the seropositive patient were notably lacking in enhancement following gadolinium injection, whereas robust lesion enhancement was observed in the seronegative patient.

Conclusions: Acute disseminating encephalomyelitis without lesion enhancement on magnetic resonance imaging may represent a childhood manifestation of seropositive NMO. The lack of enhancement suggests an intact blood-brain barrier and supports a unique mechanism of edema induction due to dysfunction of water channels.

Arch Neurol. 2008;65(2):267-271

Neuromyelitis optica (NMO) encompasses a group of inflammatory diseases characterized by recurrent episodes of myelitis and optic neuritis. The discovery of antibodies directed against the water channel aquaporin 4 (AQP4), referred to as NMO-IgG, has allowed a broadening of the NMO spectrum, which recognizes that involvement of central nervous system structures other than the optic nerves and spinal cord is not uncommon, and has prompted a suggested revision of the diagnostic criteria for NMO. Indeed, a characteristic pattern of brain involvement has been delineated in which the hypothalamic and periventricular areas are affected.

Here we describe a patient with seropositive NMO whose clinical course included an episode closely resembling acute disseminating encephalomyelitis without lesion enhancement on magnetic resonance imaging (MRI). For comparison, we describe a seronegative patient with a similar presentation but with gadolinium enhancement (GDE) of white matter lesions. We propose that the unexpected lack of GDE reflects a distinct mechanism of edema generation in seropositive but not seronegative NMO.

METHODS

All of the patients admitted to our center during a 1-year period (September 1, 2005, to August 31, 2006) were assessed for the possible presence of an NMO-spectrum disorder according to the newly suggested diagnostic criteria. We included all of the patients with re-
current optic neuritis, those with acute myelitis that was recurrent or extensive (≥3 contiguous segments), and those with combined optic neuritis and acute myelitis. We did not include patients with nonextensive myelitis who had MRI results meeting the diagnostic criteria for multiple sclerosis by Paty et al. Serum from all of the included patients was tested for the presence of NMO-IgG (DBA Mayo Medical Laboratories, Rochester, Minnesota).

### RESULTS

#### FINAL DIAGNOSES AND EVIDENCE OF BRAIN INVolVEMENT

Ten patients were included for NMO-IgG testing, of whom 5 tested positive. Four patients ultimately satisfied revised NMO criteria, of whom 2 were seropositive for NMO-IgG (Table).

Two patients had an acute episode with an encephalopathic component and radiological evidence of extensive brain involvement.

### REPORT OF CASES

#### Case 1

A 13-year-old boy presented with rapidly progressive leg weakness and urinary retention. Clinical examination revealed a parapyramidal syndrome with sensory loss below the midthoracic region with no evidence of systemic disease. His cerebrospinal fluid was mildly lymphocytic (10 cells/mL) without oligoclonal bands. Spinal MRI demonstrated an intramedullary lesion extending from C7 to T8 with cord swelling (Figure 1A), at that time, visual-evoked potentials and MRI results of the brain were normal (Figure 2A). A 1-week course of intravenous methylprednisolone was followed by full resolution of all of the clinical features within 7 days of treatment cessation.

Four months later, he presented with acute motor dysphasia and right hemiparesis progressing to severe confusion and somnolence within 12 hours. T2-weighted and fluid-attenuated inversion recovery MRI images of the brain revealed extensive bilateral hyperintense lesions affecting the white matter of the subcortex, centrum semiovale, and brainstem without GDE (Figure 2B and C). His cerebrospinal fluid contained a grossly elevated protein level (419 mg/dL) and 5 lymphocytes per milliliter. Electroencephalography performed during confused wakefulness recorded a bilateral symmetrical 8 rhythm consistent with encephalopathy (Figure 3). A 5-day course of intravenous steroids was followed by complete clinical resolution within 2 weeks. Neither episode was preceded by clinical features of systemic infection or vaccination.

Despite bimonthly treatment with intravenous steroids, during the following 2 years he had 5 episodes compatible with acute relapsing myelitis and 3 episodes of optic neuritis. Monthly treatment with plasmapheresis and steroids was initiated, and during the subsequent 3 years the patient experienced a single episode suggestive of mild myelitis associated with a delay of the treatment protocol interim period from 4 to 6 weeks.

A brain MRI repeated at age 17 years revealed partial resolution of lesions. At age 19 years, his serum tested positive for NMO-IgG.

#### Case 2

A 21-year-old woman presented with acute bilateral visual loss progressing during 2 days to total blindness with minimally reactive pupils. Brain MRI results (Figure 2D) were initially normal. Cerebrospinal fluid analysis revealed 216 lymphocytes per milliliter and a very high protein content (527 mg/dL). A high-dose steroid regimen was initiated; however, 4 days later she developed acute spastic quadriparesis, urinary retention, and confusion. Electroencephalography showed generalized slowing, and
a repeat brain MRI revealed deep white matter foci with GDE (Figure 2E and F). Magnetic resonance imaging of the spine revealed an extensive patchy lesion with partial enhancement (Figure 1B). Her serum tested negative for the presence of NMO-IgG. Subsequent rehabilitation and treatment with plasmapheresis and steroids...
were followed by moderate improvement in motor function, although her vision remained unchanged.

**COMMENT**

Patient 1 satisfied the recently proposed diagnostic criteria for NMO and tested positive for NMO-IgG. Notably, he had a single episode of acute resolving encephalopathy with diffuse involvement of brain white matter occurring within 4 months of his initial myelitic presentation at age 13 years.

While this episode may be described as acute disseminating encephalomyelitis–like, the absence of GDE is not typical of acute disseminating encephalomyelitis. A similar radiological finding occurred in a 13-year-old girl with seropositive NMO and diffuse white matter lesions.

In contrast, brain MRI during the encephalopathic episode of patient 2, who was seronegative for NMO, revealed robust lesion enhancement. We propose that the unexpected lack of enhancement in seropositive but not seronegative patients with NMO reflects the unique mechanism of edema induction associated with NMO-IgG.

The NMO-IgG targets AQP4, and seropositivity is 76% sensitive and 94% specific for NMO. The recent finding of reduced immunoreactivity of AQP4 in NMO lesions suggests that the loss of AQP4 function may be pathogenetic in patients with an NMO-spectrum disorder.

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*Figure 3.* Electroencephalography results of patient 1 show a diffuse bilateral δ rhythm consistent with encephalopathy.
Whereas spinal and optic nerve NMO lesions are usually severe with demyelination and cavitation, brain lesions are often a transient consequence of inflammation without demyelination and may be due to temporary disruptions in water transport. Aquaporin 4 passively transports water molecules into and out of the brain via the perivascular membrane according to osmotic gradients and plays a role in both the generation and elimination of brain edema. Importantly, loss of perivascular AQP4 activity in the basal state results in cellular swelling, ostensibly due to a failure to eliminate water generated from cellular metabolism. Thus, brain edema developing as a result of functional impairment of AQP4 would be expected to occur in the context of an intact blood-brain barrier, which may explain the lack of enhancement of brain lesions in some seropositive patients.

Expression of AQP4 increases during brain maturation in rats. Although comparable human data are unavailable, we speculate that in contrast to adults, children may be more sensitive to a loss of AQP4 function owing to a relative lack of these water channels. We suggest that patients, particularly children presenting with an acute disseminating encephalomyelitis-like disease without enhancement of brain MRI lesions, should be examined for the presence of NMO-IgG.

Accepted for Publication: June 8, 2007.

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Financial Disclosure: None reported.

Funding/Support: This work was supported in part by the Agnes Ginges Fund for Research in Neurology.

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