Brain Abnormalities in Neuromyelitis Optica

Sean J. Pittock, MD; Vanda A. Lennon, MD, PhD; Karl Krecke, MD; Dean M. Wingerchuk, MD; Claudia F. Lucchinetti, MD; Brian G. Weinshenker, MD

Background: Neuromyelitis optica (NMO) is a severe demyelinating disease defined principally by its tendency to selectively affect optic nerves and the spinal cord causing recurrent attacks of blindness and paralysis. Contemporary diagnostic criteria require absence of clinical disease outside the optic nerve or spinal cord. We have, however, frequently encountered patients with a well-established diagnosis of NMO in whom either asymptomatic or symptomatic brain lesions develop suggesting that the diagnostic criteria for NMO should be revised.

Objective: To describe the magnetic resonance image (MRI) brain findings in NMO.

Design: Observational, retrospective case series.

Patients: We ascertained patients through a clinical biospecimens database of individuals with definite or suspected NMO. We included patients who (1) satisfied the 1999 criteria of Wingerchuk et al for NMO except for the absolute criterion of lacking symptoms beyond the optic nerve and spinal cord and the supportive criterion of having a normal brain MRI at onset; (2) had MRI evidence of a spinal cord lesion extending 3 vertebral segments or more (the most specific nonserological feature of having a normal brain MRI at onset; (2) had MRI evidence of a spinal cord lesion extending 3 vertebral segments or more (the most specific nonserological feature to differentiate NMO from MS); and (3) were evaluated neurologically and by brain MRI at the Mayo Clinic.

Main Outcome Measures: Magnetic resonance images were classified as normal or as abnormal with either nonspecific, multiple sclerosis–like or atypical abnormalities. We evaluated whether brain lesions were symptomatic and analyzed the neuropathologic features of a single brain biopsy specimen.

Results: Sixty patients (53 women [88%]) fulfilled these inclusion criteria. The mean±SD age at onset was 37.2±18.4 years and the mean±SD duration of follow-up was 6.0±5.6 years. Neuromyelitis optica–IgG was detected in 41 patients (68%). Brain MRI lesions were detected in 36 patients (60%). Most were nonspecific, but 6 patients (10%) had multiple sclerosis–like lesions, usually asymptomatic. Another 5 patients (8%), mostly children, had diencephalic, brainstem or cerebral lesions, atypical for multiple sclerosis. When present, symptoms of brain involvement were subtle, except in 1 patient who was comatose and had large cerebral lesions.

Conclusions: Asymptomatic brain lesions are common in NMO, and symptomatic brain lesions do not exclude the diagnosis of NMO. These observations justify revision of diagnostic criteria for NMO to allow for brain involvement.

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rologists are reluctant to diagnose NMO (and thus treat accordingly) when MRI abnormalities are detected in the brain. However, in validating the clinical utility of the autoantibody, NMO-IgG, which is 91% specific and 73% sensitive for the diagnosis of NMO, we have identified about 200 patients with definite or suspected NMO, of whom several have brain lesions by MRI despite otherwise satisfying diagnostic criteria that are characteristic of NMO, including a spinal cord lesion extending over 3 segments or more during an acute attack. Brain involvement in a subset of these patients is symptomatic. Despite having brain lesions that were atypical for MS and a clinical course suggesting NMO during extended follow-up visits, many of these patients had been classified as having MS rather than as having NMO because of their brain MRI findings. In this observational study, we describe the brain abnormalities we have encountered in patients with NMO.

Over the past 5 years we have ascertained 90 patients with definite NMO and 103 with suspected NMO through a clinical biopsies database established in the context of serological evaluation including patients from Mayo Clinic and outside institutions. For our study we included patients who (1) satisfied criteria for the diagnosis of NMO, other than the requirement for a normal brain MRI at onset and absence of symptoms outside of the optic nerves and spinal cord; (2) had MRI evidence of a spinal cord lesion extending 3 vertebral segments or more, the most common and specific feature to differentiate NMO from MS; and (3) had a neurological evaluation at the Mayo Clinic and a brain MRI analyzed by the study neuroradiologist (K.K.). The present study excludes any of the patient cohort used to generate the diagnostic criteria proposed by Wingerchuk et al.

By retrospective review of medical records for all patients, we recorded demographic data, dates of symptom onset and last follow-up visit, dates of brain MRIs, Expanded Disability Status Scale (EDSS) score at last follow-up, neurological symptoms outside of the optic nerves and spinal cord, and the results of NMO-IgG testing. Brain MRIs were classified by consensus of 3 observers—a neuroradiologist (K.K.) and 2 NMO-experienced MS subspecialist neurologists (S.J.P. and B.G.W.). All raters were blinded to age, sex, and other risk factors for white matter lesions, but were aware that the patients had a clinical diagnosis of NMO. Brain MRIs were classified into 1 of the 4 following subgroups: (1) normal, (2) nonspecific lesions, (3) MS-like lesions, and (4) atypical lesions. Only 1 of these 4 subgroups was assigned to a single scan. Patients could be categorized additionally as having an incidental, unrelated finding or as having an extension of cervical cord T2-weighted signal abnormality into the brainstem, alone or in addition to subgroups 2 through 4 described earlier. From the T2-weighted MRIs the lesions were scored by number, location (frontal, parietal, temporal, occipital, infratentorial, juxtaglottic, callosal, pericallosal, or periventricular), size, and configuration. Number and location of enhancing lesions were recorded from the postcontrast T1-weighted MRIs. A combination of lesion characteristics, including location, size, configuration, enhancement characteristics, and presence of mass effect, allowed scans to be classified as MS-like or as non–MS-like, in which case they were classified as nonspecific or atypical. Those with MS-like lesions were scored to determine whether they satisfied the Barkhof et al criteria for the diagnosis of MS.

Large confluent cerebral hemisphere lesions (>3 cm) and confluent diencephalic lesions (involving the thalamus and hypothalamus) were considered atypical. We classified as nonspecific any nonenhancing deep white matter lesions that were not ovoid, did not abut on, or were not perpendicular to the ventricles or were too few to satisfy the Barkhof et al criteria for MS.

To analyze the temporal profile of brain MRI findings, initial brain MRIs were divided into 2 temporal categories: onset MRIs performed within 6 months of symptom onset and late MRIs performed more than 6 months after symptom onset. This study was approved by the Mayo Foundation Institutional Review Board (IRB 1463-04). Data are given as the mean±SD unless otherwise indicated.

RESULTS

Sixty patients fulfilled the inclusion criteria; 53 (88%) were women. All had 1 attack or more of optic neuritis and longitudinally extensive myelitis (≥3 vertebral segments); 42 (70%) had recurrent unilateral or bilateral optic neuritis, and 45 (75%) had recurrent longitudinally extensive myelitis. Age at onset was 37.2±18.4 years and the interval from onset was 6.0±5.6 years. The median EDSS score at last follow-up was 6.0 (range, 0 [best]-10 [worst]). Forty-one patients (68%) were seropositive for NMO-IgG. The initial brain MRI for the total study population was performed at a median of 6.5 months (interquartile range [IQR], 0.5-48) after disease onset.

PATIENTS WITH NORMAL ONSET OR LATE FIRST BRAIN MRIs

Of these 30 patients (age 38.1±17.0 years), the first brain MRI (Table 1) was performed at onset in 14. Three of 9 having a subsequent MRI remained normal (median imaging interval, 15 months; IQR, 11.0-30.4); 2 developed nonspecific abnormalities (imaging intervals, 9.3 and 204 months); 2 developed atypical abnormalities (patients 4 and 5 with atypical lesions in Figure 1 and Table 2), and 2 developed cervical cord lesions extending into the lower brainstem (imaging intervals, 3.0 and 104 months).

The first brain MRI for the remaining 16 patients was late (Table 1). Five of 6 having a subsequent MRI remained normal (median imaging interval, 40.2 months; IQR, 25.3-93.1); 1 developed MS-like lesions and fulfilled the Barkhof et al criteria after an imaging interval of 70.0 months (patient 6 with MS-like lesions, Figure 1).

PATIENTS WITH NONSPECIFIC CHANGES ON ONSET OR LATE FIRST BRAIN MRI

Of these 24 patients (age 47.1±15.9 years), the first brain MRI (Table 1) was at onset in 10. Two of 6 having a subsequent MRI remained in the nonspecific category (imaging intervals, 2.8 and 14.1 months); 2 developed MS-like abnormalities and fulfilled the Barkhof et al criteria for MS (imaging intervals, 102.9 and 10.0 months; patients 4 and 5 with MS-like lesions in Figure 1); and 2 developed atypical changes (imaging intervals, 4.0 and 2.5 months; patients 2 and 3 with atypical lesions in Figure 1 and Table 2).
The first brain MRI for the remaining 14 patients with nonspecific changes was late (Table 1). Five of 6 having a subsequent MRI remained in the nonspecific category (median imaging interval, 16.4 months; IQR, 7.7-22.3) and 1 developed atypical findings (imaging interval, 7.3 months; patient 1 with atypical lesions in Figure 1 and Table 2).

The 24 patients whose initial brain MRI revealed nonspecific changes were older at the time of MRI than patients whose initial brain MRIs were normal (P = .06, Wilcoxon t test). Their lesions were typically located in the deep white matter of the cerebral hemisphere; 10 (40%) had 3 lesions or fewer, 8 (33%) had 4 to 6 lesions, 5 (20%) had 7 to 15 lesions, and 1 (5%) had more than 15 lesions. Two patients in this subgroup had additionally rostral extension of signal abnormality from the cervical cord into the lower brainstem.

PATIENTS WITH MS-LIKE INCIDENTAL AND BRAINSTEM LESIONS ON FIRST BRAIN MRI

Three patients had MS-like changes on the initial brain MRI (1 with onset MRI [patient 3] and 2 with late MRIs [patients 1 and 2], Figure 1 and Table 1). One patient had rostral extension of a cervical cord lesion into the lower brainstem only on the initial MRI. Two patients had incidental mild communicating hydrocephalus; 1 of these patients developed nonspecific changes on subsequent imaging.

SUMMARY OF PATIENTS WHO HAD MS-LIKE OR ATYPICAL CHANGES AT LAST FOLLOW-UP MRI

Six patients (10%) had lesions on the last available MRI that were classified as MS-like (Figure 1). Five (83%) of these patients were NMO-IgG positive, and 4 (66%) fulfilled the Barkhof et al9 criteria for MS within 3 years of onset.

Five patients (8%) were classified as having atypical brain lesions (Table 2 and Figure 1). Three had diencephalic involvement (thalamic or hypothalamic). Some had concomitant midbrain or cerebellar lesions (Figure 2). Two had extensive signal abnormality in cerebral white matter (Figure 2); 1 had extension of the cervical cord lesion into the lower brainstem. Three were children (aged 5-13 years at onset).

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Table 1. Magnetic Resonance Imaging (MRI) Timeline and Classification

<table>
<thead>
<tr>
<th>First Brain MRI</th>
<th>Subsequent Brain MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset MRI Within 6 mo of Initial Symptoms (n = 27)</strong></td>
<td><strong>Abnormal</strong></td>
</tr>
<tr>
<td>Total (Normal)</td>
<td>Normal</td>
</tr>
<tr>
<td>No. in Sample (Total No. (Median Time, mo) to MRI (IQR))</td>
<td>(Median Time, mo) to Follow-up MRI (IQR)</td>
</tr>
<tr>
<td>Normal</td>
<td>17 (24.0) [10.4-93.6]</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>10 (1.4) [0.8-2.4]</td>
</tr>
<tr>
<td>MS-like (Barkhof et al9 criteria)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Atypical</td>
<td>0</td>
</tr>
<tr>
<td>Extension into brainstem</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.5)†</td>
</tr>
</tbody>
</table>

| Late MRI >6 mo After Initial Symptoms (n = 32)‡ | |
| Total (Normal) | Normal | Nonspecific | MS-Like (Barkhof et al9 criteria) | Atypical | Extension into Brainstem |
| Total No. (Median Time, mo) to MRI (IQR) | (Median Time, mo) to MRI (IQR) | | |
| Normal | 16 (35.8) [13.2-80.4] | 12 (73.3) [25.2-136.8] | 0 | 5 | 1 (1) |
| Nonspecific | 14 (30.5) [13.2-99.2] | 6 (122) [40.8-147.6] | 0 | 0 | 1 (1) |
| MS-like (Barkhof et al9 criteria) | 2 (34.8) [20.4-51.0] | 0 | NA | NA | NA |
| Atypical | 0 | 0 | NA | NA | NA |
| Extension into brainstem | 2 (Also nonspecific) | 0 | NA | NA | NA |

Abbreviations: IQR, interquartile range; MS, multiple sclerosis; NA, not applicable.

*Single patient with extension of signal abnormality from cervical cord into the brainstem.
†Patient had incidental communicating hydrocephalus.
‡Date of onset was unavailable for 1 patient (with incidental hydrocephalus and nonspecific changes on MRI, not included in table).

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Figure 1. Timeline and brain magnetic resonance imaging (MRI) classification of patients with neuromyelitis optica whose MRIs at the last follow-up visit were classified as multiple sclerosis (MS)-like (n = 6) or atypical (n = 5). Patients not shown had a normal MRI at the last follow-up visit (n = 26) or nonspecific MRI abnormalities (n = 23).

The first brain MRI for the remaining 14 patients with nonspecific changes was late (Table 1). Five of 6 having a subsequent MRI remained in the nonspecific category (median imaging interval, 16.4 months; IQR, 7.7-22.3) and 1 developed atypical findings (imaging interval, 7.3 months; patient 1 with atypical lesions in Figure 1 and Table 2).

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Five patients (8%) were classified as having atypical brain lesions (Table 2 and Figure 1). All were positive for NMO-IgG. Three had diencephalic involvement (thalamic or hypothalamic). Some had concomitant midbrain or cerebellar lesions (Figure 2). Two had extensive signal abnormality in cerebral white matter (Figure 2); 1 had extension of the cervical cord lesion into the lower brainstem. Three were children (aged 5-13 years at onset).
Table 2. Clinical and Magnetic Resonance Imaging (MRI) Features of Patients With Neuromyelitis Optica (NMO) and Atypical Brain Lesions

<table>
<thead>
<tr>
<th>Patient No./Age at Onset, y/Race*</th>
<th>Duration of Optic Neuritis Follow-up, y</th>
<th>EDSS Score at Last Visit</th>
<th>No. of Optic Neuritis Attacks</th>
<th>No. of Myelitis Attacks</th>
<th>Extensive White Matter Lesions</th>
<th>Diencephalic Involvement</th>
<th>Brainsomm</th>
<th>Extension From Cervical Cord to Medulla</th>
<th>Other</th>
<th>Symptoms Outside the Optic Nerves and Spinal Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/13/W</td>
<td>1.4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Extension into L posterior limb internal capsule and deep white matter of R cerebellum</td>
</tr>
<tr>
<td>2/40/AA</td>
<td>9.6</td>
<td>2</td>
<td>1</td>
<td>8.5</td>
<td>+</td>
<td>−</td>
<td>L superior cerebral peduncle and L pyramid</td>
<td>−</td>
<td>Mild L facial droop and disconjugate eye movements</td>
<td></td>
</tr>
<tr>
<td>3/5/W</td>
<td>2.8</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Transient diplopia, upbeat and gaze evoked nystagmus</td>
</tr>
<tr>
<td>4/13/SA</td>
<td>6.8</td>
<td>3</td>
<td>6</td>
<td>6.5</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Nausea</td>
</tr>
<tr>
<td>5/38/AA</td>
<td>6.9</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: AA, African American; EDSS, Expanded Disability Status Scale; SA, South American; W, white; +, positive; −, negative.
*All patients were female, NMO-IgG positive, and without oligoclonal IgG bands in cerebrospinal fluid.
†See Figure 1 and Figure 2 for further details.

SUMMARY OF CLINICAL SYMPTOMS OR SIGNS OUTSIDE THE OPTIC NERVE AND SPINAL CORD, AND NEUROPATHOLOGY OF A SINGLE BRAIN BIOPSY SPECIMEN

Six (10%) of the 60 total study patients had symptoms or signs referable to structures outside the optic nerves and spinal cord. Three who had atypical brain MRI findings at last follow-up MRI are described in Table 2. The first patient, who had extensive white matter hemisphere spherical lesions, was a 13-year-old girl (patient 1, Table 2) who developed fulminant encephalopathy. Her brain biopsy specimen revealed active inflammatory demyelination, with prominent macrophage infiltration, relative preservation of axons, and gliosis (Figure 3). The tissue specimen was insufficient for immuno histochemical characterization of the lesion. The second and third patients had diencephalic lesions and symptoms of nausea, transient diplopia, and nystagmus.

A fourth patient whose initial MRI was normal, and whose subsequent MRIs fulfilled the Barkhof et al criteria, had 2 episodes of trigeminal neuralgia. A fifth patient with a normal onset brain MRI reported diplopia 5 months later; no subsequent MRI was performed. A sixth patient reported facial numbness 48 months after the initial symptom onset; MRI revealed nonspecific findings.

COMMENT

In this series of 60 patients who had NMO, 36 (60%) had MRI evidence of brain abnormalities. In 6 (17%) of these 36 patients, brain lesions were symptomatic. Despite not requiring a normal brain MRI at onset for inclusion in our study, 30 patients did have a normal initial brain MRI (ie, fulfilled all of the Wingerchuk et al criteria for diagnosis of NMO). Half of those developed brain abnormalities (nonspecific, atypical, or MS-like) on subsequent MRIs.

One might argue that patients who had nonspecific or MS-like lesions on the initial MRI did not have NMO. However, with the exception of having an abnormal brain MRI finding, the diagnosis of NMO for all patients in this study was made on the basis of clinical and radiological features that distinguish NMO from MS. No gold standard exists for the diagnosis, and all proposed diagnostic criteria, including those proposed by our group, are subject to modification based on studies such as this one. All patients in this study had at least one episode of optic neuritis and at least one episode of longitudinally extensive myelitis; 41 patients (68%) were seropositive for NMO-IgG, which is a highly sensitive and specific marker of NMO and is not detected in patients with classic MS. The high rate of seropositivity and the clinical inclusion criteria that we used for this study strongly support the diagnosis of NMO. Spinal cord lesions in MS are rarely longer than a single vertebral segment, whereas all of our patients had spinal cord lesions extending 3 vertebral segments or more, as is typical of NMO.

Brain MRI lesions encountered in most patients were nonspecific. Importantly, however, 6 patients (10%) had lesions that were highly suggestive of MS, 5 (83%) of whom were seropositive for NMO-IgG and 4 (66%) of whom fulfilled the Barkhof et al criteria. This further validated their clinical classification in the NMO spectrum.
of disease. The diencephalic, brainstem, or cerebral hemispheric lesions observed in 5 patients (8%), mostly children, were distinctly atypical for MS. The fact that children (defined as being ≤16 years) accounted for only 7 (11%) of the patients in this series suggests that children with NMO are more susceptible to atypical brain lesions.

The single patient (a child) who underwent brain biopsy for a large hemispheric lesion had an inflammatory demyelinating lesion. The small specimen size precluded immunopathological analysis. Future investigations are needed to determine whether brain lesions in NMO exhibit the vascular hyperplasia, vasculocentric deposition of immunoglobulin, and complement prod-

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Figure 2. Illustration of atypical brain lesions encountered in patients with neuromyelitis optica seen on magnetic resonance imaging (MRI). Time course is detailed in Table 1 and Figure 1; clinical details are summarized in Table 2. A Left, Patient 1 had extensive bitemporal subcortical nonenhancing white matter fluid-attenuated inversion recovery (FLAIR) signal abnormality. A Center, Patient 2 had a large confluent FLAIR signal abnormality in the right parietal area that demonstrates diffuse gadolinium enhancement (A, right). B, Patient 3 had FLAIR abnormality in hypothalamus (B, right, arrow) and right cerebral peduncle (C, center, arrow). B Center, Patient 4 had a FLAIR signal abnormality in the thalamus (arrow), hypothalamus, and optic chiasm extending into the superior cerebellar peduncle and the floor of the fourth ventricle. B Left, Patient 5 had a confluent nonenhancing signal abnormality from the anterosuperior thalamus-hypothalamus (arrow) to the optic tracts behind the chiasm to the superior surface of the mesencephalon extending to the periaqueductual area (right→left) to the superior cerebellar peduncles, and the pontine tegmentum (C, right, arrows). Additional patient; extension of T2-weighted MRI signal abnormality into the medulla (C, left, arrow) in a patient with an otherwise normal brain-MRI.
ucts and infiltration by eosinophils and granulocytes as are characteristic in NMO spinal cord lesions.\textsuperscript{13}

In the original cohort of patients used by Wingerchuk et al\textsuperscript{2} to formulate diagnostic criteria for NMO, non-specific brain MRI abnormalities were not an exclusion criterion. Furthermore, in that original cohort 3 (11%) of 28 patients had lesions that fulfilled the Paty criteria for MS,\textsuperscript{14} and 3 (11%) of 28 patients had T2-weighted signal abnormality in the medulla that was contiguous with a longitudinally extensive cervical cord lesion.\textsuperscript{2} Several clinicopathological series have reported a subset of cases with extension of lesions into the medulla or whole brainstem.\textsuperscript{12,15} O’Riordan et al\textsuperscript{16} described a variety of brain MRI abnormalities in patients having a diagnosis of NMO including involvement of the lower medulla in continuity with the cervical cord abnormalities, multiple deep white matter lesions (mostly supratentorial), a lesion in basal ganglia, and minor age-related changes.

Although no clinical trials have been conducted for NMO, clinical observations from several centers of excellence suggest that optimal treatments for MS and NMO differ. Immunosuppressive medications (eg, azathioprine, corticosteroids, and rituximab) seem to be effective treatments for NMO\textsuperscript{1,2,17,18} while immunomodulatory therapies such as interferon-beta and glatiramer acetate are promoted for early treatment of MS.\textsuperscript{19} Therefore, it is important to differentiate these 2 disorders. The observations we report and cite justify revising diagnostic criteria for NMO to allow inclusion of brain involvement.

The remarkable similarity of hypothalamic lesions observed in 3 of our patients to lesions described by Poppe et al\textsuperscript{20} suggests that these lesions are specific for NMO and, thus, a clue to its pathogenesis. Vernant et al\textsuperscript{21} described lesions in the hypophysis and inferior hypothalamus in 3 of 8 Antillean women with an illness that resembled NMO and was associated with clinical and laboratory evidence of hypothalamic endocrinopathies. We did not inquire or test for evidence of endocrine abnormalities in our patients.

The pathogenesis of NMO is incompletely understood, but immunopathological and serological observations, as well as beneficial responses to rituximab and plasmapheresis therapy, implicate a circulating autoantibody as the principal effector of the lesions of NMO. In sections of normal central nervous system tissues, NMO-IgG binds to the abluminal face of microvessels, pia, and Virchow-Robin sheath.\textsuperscript{7} The vasculocentric distribution of the antigen of NMO-IgG is similar to that described for sites of immunoglobulin and complement deposition seen in spinal cord lesions of patients with NMO in autopsy and biopsy specimens.\textsuperscript{13} The autoantigen of NMO-IgG has been identified as the water channel protein, aquaporin 4.\textsuperscript{22} This protein is located in astrocytic foot processes at the blood-brain barrier and is the most abundant water channel in the central nervous system. It is not restricted to optic nerve and spinal cord.\textsuperscript{23} If aquaporin 4 is, indeed, the target antigen of a pathogenic autoantibody in NMO, its expression in the brain, as well as in the optic nerves and spinal cord, may explain the occurrence of brain lesions in this study.

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Pittock, Lennon, Krecke, Wingerchuk, Lucchinetti, and Weinshenker. *Drafting of the manuscript: Pittock and Lennon. Critical revision of the manuscript for important intellectual content: Pittock, Lennon, Krecke, Wingerchuk, Lucchinetti, and Weinshenker. Statistical analysis: Pittock and Wingerchuk. Administrative, technical, and material support: Pittock, Krecke, and Wingerchuk. Study supervision: Pittock, Lennon, Lucchinetti, and Weinshenker.*

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