Brain Abnormalities in Neuromyelitis Optica

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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 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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Over the past 5 years we have ascertained 90 patients with definite NMO and 103 with suspected NMO through a clinical biospecimens 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,2 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 MS8; and (3) had a neurological evaluation at 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.

METHODS

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 ± 6.6 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.

RESULTS

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 2.3 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 al\textsuperscript{9} 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).

| Table 1. Magnetic Resonance Imaging (MRI) Timeline and Classification |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                            |                  |                  |                  | Abnormal        |                  |
|                            | Total No.        | No. in Sample    | Abnormal         | MS-Like         | Extension into |
|                            | (Median Time, mo)| (Median Time, mo)| to MRI (IQR)     | (Barkhof et al\textsuperscript{9} Criteria) | Brainstem       |
| First Brain MRI            | to MRI (IQR)     |                  |                  |                  |                  |
| Onset MRI Within 6 mo of Initial Symptoms (n = 27) | 27 (0.8) [0-1.9] | 17 (24.0) [10.4-93.6] | 3 5 3 (3) 4* | 2 |
| Normal                     | 14 (0.48) [0-1.5]* | 9 (30.7) [7.8-93.6] | 3 2 0 2* | 2 |
| Nonspecific                | 10 (1.6) [0.8-2.4] | 6 (13.6) [6.4-49.2] | 0 2 2 (2) | 2 0 |
| MS-like (Barkhof et al\textsuperscript{9} criteria) | 1 (1) | 1 (24) | 0 0 1 (1) 0 0 | |
| Atypical                   | 0 0 NA NA NA NA NA | |
| Extension into brainstem   | 1 (1.6) | 0 NA NA NA NA NA | |
| Other                      | 1 (0.5)† | 1 (133) | 0 1 0 0 1 | |
| Late MRI >6 mo After Initial Symptoms (n = 32)‡ | 32 (30.5) [14.7-80.4] | 12 (73.3) [25.2-136.8] | 5 5 1 (1) 1 0 | |
| Normal                     | 16 (35.8) [13.2-80.4] | 6 (122) [40.8-147.6] | 5 0 1 (1) 0 0 | |
| Nonspecific                | 14 (30.5) [13.9-99.2] | 6 (43.7) [18.0-109.8] | 0 5 0 1 0 | |
| MS-like (Barkhof et al\textsuperscript{9} criteria) | 2 (34.8) [20.4-51.0] | 0 NA NA NA NA NA | |
| Atypical                   | 0 0 NA NA NA NA NA | |
| Extension into brainstem   | 2 (Also nonspecific) | 0 NA NA 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). |

![Figure 1.](image-url)
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 hemispheric 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 immunohistochemical 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.

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

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.

### 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 Attacks, y</th>
<th>No. of Myelitis Attacks</th>
<th>EDSS Score at Last Follow-up Visit</th>
<th>Extensive White Matter Lesions</th>
<th>Diencephalic Involvement</th>
<th>Brainstem</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>+</td>
<td>−</td>
<td>−</td>
<td>Extension into L posterior limb internal capsule and deep white matter of R cerebellum</td>
<td>−</td>
<td>Encephalopathy, agitation and coma with recovery; residual dysarthria and emotional lability</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>−</td>
<td>−</td>
<td>Mild L facial droop and conjugate eye movements</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>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>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>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.
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 \( \leq 16 \) 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-
ucts and infiltration by eosinophils and granulocytes as are characteristic in NMO spinal cord lesions.13

In the original cohort of patients used by Wingerchuk et al2 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,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.2 Several clinicopathological series have reported a subset of cases with extension of lesions into the medulla or whole brainstem.12,15 O’Riordan et al16 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 NMO1,2,17,18 while immunomodulatory therapies such as interferon-beta and glatiramer acetate are promoted for early treatment of MS.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 al20 suggests that these lesions are specific for NMO and, thus, a clue to its pathogenesis. Vernant et al21 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.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.13 The autoantigen of NMO-IgG has been identified as the water channel protein, aquaporin 4.22 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.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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