The Natural History of Recurrent Optic Neuritis

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Background: Optic neuritis (ON) may occur in isolation or may herald multiple sclerosis (MS) or neuromyelitis optica (NMO). Occasionally, ON may recur many times without intervening evidence of dissemination in space.

Objective: To define the clinical course and prognosis of patients with recurrent ON.

Design: Retrospective medical record review and telephone follow-up survey.

Setting: Clinic-based practice in a large tertiary referral institution.

Main Outcome Measures: Survival analysis of conversion to MS and NMO and final visual impairment. We studied the association of clinical and demographic factors, the presence of brain lesions on magnetic resonance images, and the use of corticosteroid treatment at the time of the first ON occurrence with conversion to MS and NMO.

Results: We identified 1274 patients with ON between 1994 and 2000 and selected 72 (5.7%) with recurrent ON without intervening symptoms of a disseminated demyelinating condition for further analysis. The 5-year conversion rate to NMO was 12.5% and to MS, 14.4%. Among 5 patients with 2 or more lesions consistent with MS on brain magnetic resonance images, 2 (40.0%) converted to MS and none to NMO, while among 11 patients without such lesions, none converted to MS and 2 (18.2%) converted to NMO (P = .16). Conversion to MS occurred in 7 (19.4%) of 36 individuals treated for their first ON episode with corticosteroids vs 4 (44.4%) of 9 untreated individuals (P = .19). There was no difference in the conversion rate to MS between those treated with intravenous steroids (4 [16.7%] of 24) vs oral steroids (3 [25.0%] of 12) (P = .33). Conversion to NMO occurred earlier than conversion to MS (2.3 ± 1.6 vs 5.3 ± 4.3 years, respectively; P = .01). Women tended to convert to NMO more frequently than men (female-male ratio for NMO converters, 7:1; MS converters, 2:1; nonconverters, 2:1; P = .56), as did those with a higher annual frequency of ON episodes (NMO converters, 2.0 ± 1.3; MS converters, 1.0 ± 1.0; nonconverters, 0.6 ± 0.5; P = .04). The number of ON events in the first 2 years following the first ON episode was higher in the NMO group (NMO converters, 2.4 ± 0.9; MS converters, 1.9 ± 1.1; nonconverters, 1.7 ± 0.7; P = .04). The final visual impairment was greatest in the NMO group (P = .02).

Conclusions: Patients with rapid succession of severe ON events are more likely to develop a generalized demyelinating disease. Patients with NMO had a worse visual outcome.

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OPHTIC NEURITIS (ON) IS AN inflammatory demyelinating syndrome of the central nervous system. It may occur in isolation or as part of multiple sclerosis (MS) or neuromyelitis optica (NMO) (Devic disease). It results in loss of vision and may be associated with eye pain and color vision and visual field deficits and phosphenes. It can affect either or both eyes, sequentially or simultaneously. Optic neuritis is considered idiopathic when symptoms develop across hours to days and remit spontaneously following corticosteroid therapy and when various toxic, nutritional, metabolic, vascular, hereditary, infectious, infiltrative, autoimmune, or compressive etiologies have been excluded.

Some patients experience recurrent ON without events referable to other parts of the central nervous system. Recurrent ON has been classified as MS in some studies but not in others. Classification of recurrent ON contributes to the controversy about the risk of developing MS following ON episodes. By strict application of MS criteria, including criteria of McDonald et al., recurrent ON affecting both optic nerves could be considered MS. However, if recurrent ON were not considered to be MS by definition, the frequency with which it would herald MS or NMO is unknown.
We describe the demographic and clinical features of 72 patients with recurrent ON, with special attention to the risk of developing MS or NMO.

**METHODS**

**CASE ASCERTAINMENT**

Using the central records system of Mayo Clinic, Rochester, Minn, we reviewed the medical records of patients diagnosed with ON, retrobulbar neuritis, inflammatory optic neuropathy, papillitis, and neuroretinitis between 1994 and 2000. Patients without follow-up data for the last 2 years of the study were contacted by telephone. The Mayo Clinic institutional review board approved the study. Patients consented to follow-up.

**CASE DEFINITION**

All patients with 2 or more ON events before reaching the end point were studied. The end point was development of clinical evidence for MS, NMO (criteria of Wingerchuk et al), or the end of the observation period. All patients classified as having NMO met the absolute criteria (ON, myelitis, and no other neurological features aside from ON or myelitis). They all had normal brain and spinal cord magnetic resonance imaging (MRI) findings consistent with 1 of the major supportive criteria (longitudinally extensive lesions extending over 3 or more vertebral segments). Spinal fluid analysis was documented in 5 of 8 cases with findings supporting NMO (>50 leukocytes and/or >3 neutrophils/mm3). An episode of visual loss in the same eye was considered a recurrent episode only if it occurred at least 3 months after the previous event. Brief events attributable to the Uhthoff phenomenon were not included. Specificity of the diagnosis of ON was based on criteria published earlier by Rodriguez et al. A neurologist or ophthalmologist verified the diagnosis in all cases but not of each episode of ON. Besides visual loss, at least 2 of the following criteria were required: afferent papillary defect, color vision abnormalities, pain on eye movement, abnormal visual evoked response, and cecocentral field defect. Patients with a macular star suggesting neuroretinitis were excluded.

**DATA COLLECTION**

To assess visual impairment, we used an ordinal scale described by Wingerchuk et al where 0 = normal; 1 = scotoma but visual acuity better than 20/30; 2 = visual acuity of 20/30 to 20/59; 3 = visual acuity of 20/60 to 20/199; 4 = visual acuity of 20/200 to 20/800; 5 = visual acuity of counting fingers only; 6 = visual acuity of light perception; 7 = visual acuity of no light perception; and 8 = unknown visual acuity. To characterize the final visual outcome, we added the last known individual visual scores of both eyes. We collected data about each ON event, including date of onset, laterality, severity (visual acuity, color vision impairment), the presence of afferent pupillary defect and eye pain; acute and preventive treatment; and response to treatment. We determined whether the follow-up data satisfied criteria for MS or NMO.

**STATISTICAL METHODS**

We used the JMP 5.0 software package (SAS Institute Inc, Cary, NC). For quantitative data with skewed distributions, medians and ranges are presented. Otherwise, quantitative data are presented as means±standard deviations. We used Wilcoxon rank sum tests and Kruskal-Wallis tests to assess differences between groups when the data were skewed. To compare means, we used 1-way analysis of variance with Tukey-Kramer tests for pairwise differences of groups. We used the Fisher exact test to assess differences in categorical data between groups. A log-rank test was used to compare survival between groups.

**RESULTS**

**PATIENT CHARACTERISTICS**

Of 1274 patients with ON, 72 (5.7%) met the inclusion criteria. We classified patients as converters to MS (MS group), NMO (NMO group), or neither (nonconverters). The demographics and clinical characteristics are summarized in Table 1. The mean ± SD age of onset (32.9 ± 12.8 years) did not differ between groups. The overall female: male ratio was 2.1:1.0; the sex ratio was greatest in the NMO group (7:0.1:0). The median number of ON events per patient was 3 (range, 2-14) in men and 2 (range, 2-9) in women (Figure 1).

The same eye was involved for all ON events in 14 patients (19.4%); 46 (63.9%) had ON in both eyes at some time without simultaneous bilateral events. Ten (13.9%) had at least 1 simultaneous bilateral ON episode; 2 converted to NMO.

### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients Who Converted to MS</th>
<th>Patients Who Converted to NMO</th>
<th>Nonconverters</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>20</td>
<td>8</td>
<td>44</td>
<td>NA</td>
</tr>
<tr>
<td>Female-male ratio</td>
<td>1.9:1.0</td>
<td>7.0:1.0</td>
<td>1.9:1.0</td>
<td>P = 0.56</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>33.4 (10.3)</td>
<td>29 (17.0)</td>
<td>33.4 (13.1)</td>
<td>P = 0.82</td>
</tr>
<tr>
<td>Total ON events</td>
<td>3.0 (2.0-14.0)</td>
<td>2.5 (2.0-6.0)</td>
<td>2.0 (2.0-9.0)</td>
<td>P = 0.61</td>
</tr>
<tr>
<td>Severity of first ON</td>
<td>2.0 (1.0-7.0)</td>
<td>5.5 (3.0-7.0)</td>
<td>4.0 (1.0-7.0)</td>
<td>P = 0.04‡</td>
</tr>
<tr>
<td>Interval between 2 ON events, mo</td>
<td>12.0 (1.0-96.0)</td>
<td>6.0 (2.0-44.0)</td>
<td>11.5 (1.0-252.0)</td>
<td>P = 0.21</td>
</tr>
<tr>
<td>No. of ON episodes per year until end point*</td>
<td>1.0 (1.0)</td>
<td>2.0 (1.3)</td>
<td>0.56 (0.50)</td>
<td>P = 0.04‡</td>
</tr>
<tr>
<td>No. of ON episodes in the first 2 years after index event*</td>
<td>1.9 (1.1)</td>
<td>2.4 (0.9)</td>
<td>1.7 (0.7)</td>
<td>P = 0.04‡</td>
</tr>
<tr>
<td>Time to end point**</td>
<td>5.3 (4.3)</td>
<td>2.3 (1.6)</td>
<td>8.7 (7.2)</td>
<td>P = 0.01‡</td>
</tr>
<tr>
<td>Combined final outcome (VAleft + VAright)*</td>
<td>4.3 (2.4)</td>
<td>5.9 (2.8)</td>
<td>3.2 (2.8)</td>
<td>P = 0.02‡</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica; NA, not applicable; ON, optic neuritis; VA, visual acuity.

*Values expressed as mean (SD).
†Values expressed as median (range).
‡Statistically significant.
MS and 1 to NMO. Two (2.8%) had recurrent bilateral ON only, 1 of whom converted to NMO and 1 to MS.

CONVERSION TO MS OR NMO

The conversion rate to MS or NMO, combined, after the first ON event was 26.9% at 5 years and 42.3% at 10. Based on survival analysis (Figure 2), the 1-, 5-, and 10-year conversion rates to NMO after the first ON event were 5.6%, 12.5%, and 12.5%, respectively, and to MS, 2.8%, 14.4%, and 29.8%, respectively. The median number of events was similar: 3 (range, 2-14) in the MS group, 2.5 (range, 2-6) in the NMO group, and 2 (range, 2-9) in nonconverters ($P = .61$) (Table 1). However, the mean ± SD annualized ON event rate was 1.0 ± 1.0 event per year in the MS group, 2.0 ± 1.3 events per year in the NMO group, and 0.6 ± 0.5 event per year in nonconverters ($P = .04$). Because of differences in follow-up, the number of ON episodes in the first 2 years after the initial event was also considered and was significantly higher in the NMO group ($P = .04$). Conversion to NMO occurred earlier than conversion to MS (NMO, mean ± SD, 2.3 ± 1.6 years; MS, 5.3 ± 4.3 years; $P = .01$). In the MS group, the median interval was longer than in the NMO group and was approximately the same as in nonconverters. We observed a trend toward a shorter interval between the first attacks in the NMO group ($P = .21$).

Four patients had a preexisting history of other autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, and Hashimoto thyroiditis). Two converted to MS and 2 to NMO.

SEVERITY OF FIRST EPISODE

Data were available from 14 MS converters (70%), 4 NMO converters (50%), and 27 nonconverters (61.4%). Converters to NMO experienced the worst and MS converters the mildest first ON events ($P = .04$) (Table 1).

BRAIN MRI AT FIRST EXAMINATION

Data were available for 16 cases (22.2%) (Table 2). Five had at least 2 T2-weighted hyperintense lesions in the juxtacortical, periventricular regions or cerebellum. Two (40%) developed MS during the observation period, and 3 (60%) were nonconverters. Eleven patients had no detectable T2-weighted hyperintense lesions on MRI of the head. Two of these patients (18.2%) developed NMO, while 9 (81.8%) remained nonconverters ($P = .16$).

CORTICOSTEROID TREATMENT OF FIRST EPISODE

Data were available on 45 patients (63.9%) (Table 3). Patients were treated at different centers using different protocols. Conversion to MS occurred less frequently in those treated with corticosteroids, though not significantly so (7 [19.4%] of 36 vs 4 [44.4%] of 9, respectively; $P = .19$). There was no difference in the conversion rate to MS (4 [16.7%] of 24 vs 3 [25.0%] of 12, respectively) between those treated with intravenous vs oral steroids ($P = .33$).

TREATMENT WITH IMMUNOMODULATORS

Eleven patients (15.3%) were treated with disease-modifying therapies. Among the eventual NMO converters, 1 patient was treated with interferon-β-1a following his second ON event and had no further ON events. Azathioprine and prednisone were substituted after diagnosis of NMO. Among the eventual MS converters, 3 were treated with interferon-β-1a following their second or third
ON events and 2 continued to have further attacks of ON. Among nonconverters, 2 were treated with interferon-β-1a, 3 with interferon-β-1b, 1 with azathioprine, and 1 with intravenous immunoglobulin and oral prednisone. Three continued to have further ON events. Conversion to MS occurred in 4 (36.4%) of those treated with immunomodulators vs 24 (39.3%) of those not taking immunomodulators (P = .90, using the Fisher exact test).

**FINAL VISUAL OUTCOME**

Patients in the NMO group had worse visual impairment at last assessment than patients who remained nonconverters (mean ± SD Wingerchuk et al scale score, NMO group, 5.9 ± 2.8; nonconverters, 3.2 ± 2.8; P = .02). The MS group had an intermediate outcome (mean ± SD, 4.3 ± 2.4); the difference between the MS group and nonconverters was not significant (P = .34).

**COMMENTS**

Others have studied the association between ON, MS, and NMO. In a population-based study in Olmsted County, Minnesota, the incidence of ON was 5 in 100,000. By definition, ON occurs in every patient with NMO. Whether recurrent episodes of ON are associated with increased risk for developing MS or NMO has been controversial. Early recurrence of ON was shown to increase the risk of MS. However, Francis et al did not reach the same conclusion. In the Optic Neuritis Treatment Trial, recurrent ON episodes occurred in 30% of all studied patients within 5 years, including patients who met diagnostic criteria for MS after their first episode of ON. Lucchinetti et al reported that in the pediatric age group, recurrent ON without other evidence of MS represented 3% of cases, similar to the frequency we report (5.6%). We excluded patients with optic neuropathy of other causes, including those with neuroretinitis, which is distinct from MS and not associated with increased risk of MS. We included the previously mentioned search terms to ensure complete ascertainment.

The mean age at onset of the first ON event and the sex ratio in our study do not differ from previous reports. The association of coexisting autoimmune conditions with demyelinating diseases has been well described in NMO and may also occur in MS.

The survival analysis showed that the 10-year conversion rate to MS is 29.8% and to NMO, 12.5%. Rodriguez et al reported the largest population-based study describing the natural history of ON and found that the conversion rate to MS was 39% at 10 years. Others reported the 10-year conversion rate to be between 24% and 39%. A common conclusion arising from these studies is that the cumulative conversion rate increases most rapidly in the first 10 years, after which it continues to rise, albeit more slowly. The severity of the first event was worse in NMO converters, which corresponds with previous observations of more severe visual loss in NMO. In NMO converters, subsequent events tended to occur earlier than in MS converters or nonconverters. The annualized ON event rate underlines that a rapid succession of ON episodes is predictive of NMO conversion. The annualized rates were approximately 2 events per year for the NMO group, 1 event per year in the MS group, and 1 event every other year in the nonconverters. The difference was owing to a shorter interval to diagnosis (development of myelitis) rather than to the occurrence of a greater number of ON events.

Our observations regarding the brain MRI findings are consistent with previous articles suggesting a higher likelihood of conversion when brain MRI shows lesions similar to those seen in patients with MS. Most patients did not have brain MRI at first episode, but only following their recurrent episodes; hence, the rarity of MRI at the time of the first episode does not reflect practice patterns at Mayo Clinic.

The Optic Neuritis Treatment Trial suggested that treatment of the first episode of ON with intravenous steroids may reduce the chance of subsequent conversion to MS. This had not been independently confirmed. Our results agree with the Optic Neuritis Treatment Trial and support long-term benefits of steroid treatment in first attacks of ON.

Among the strongest predictors of visual outcome is whether patients “convert” to NMO or MS. The final visual outcome was worst in the NMO group.

Only 11 (15.3%) individuals in this cohort were treated with immunomodulatory therapies. The majority (6 [54.5%]) continued to have further episodes. While undergoing disease-modifying therapy, 4 (36.4%) converted to NMO or MS. There was no difference in the rate of conversion to MS or NMO in those who were treated. However, owing to the small sample size, uncontrolled treatment assignment, and the heterogeneity of treat-
ments, it is impossible to draw valid conclusions about potential benefits of immunomodulatory therapies.

While our study has limitations because of its retrospective nature, it would not be feasible to ascertain sufficient numbers of patients with recurrent ON prospectively to obtain this type of long-term follow-up. We made every effort to exclude cases with other optic neuropathies due to, for example, sarcoidosis, vasculitis, temporal arteritis, and anterior ischemic optic neuropathy. However, in a retrospective study, it is possible that some cases of optic neuropathy due to other causes may have been diagnosed as idiopathic ON.

The follow-up for these cases is variable and in some cases, short. The group with “recurrent ON only” may convert to MS or NMO later. Thus, further follow-up is required.

Magnetic resonance imaging and treatment data were not available for all patients. Since this is a retrospective study, biases unknown to the investigators may have influenced why some patients received steroid treatment and others did not. Similarly, unknown biases may have determined why MRI of the head was done in some cases but not in others. Nonetheless, this study provides useful data for counseling patients with recurrent ON regarding the risk of conversion to MS or NMO and the prognosis for recovery of vision.

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REFERENCES