CLINICAL SCIENCES

Clinical Course of Optic Neuritis in Patients With Relapsing Neuromyelitis Optica

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Objective: To describe the clinical characteristics, course, and prognosis of optic neuritis in recurrent neuromyelitis optica.

Methods: We analyzed 60 patients diagnosed using 1999 Mayo Clinic criteria who were seen between 1985 and 2004 at Hospital da Lagoa (Rio de Janeiro, Brazil).

Results: Optic neuritis was the initial feature in 53.3% of patients, most with unilateral disease. Recurrent optic neuritis before myelitis occurred in 18.3%. The visual impairment was severe at nadir of the visual index event in 78.3%, with a high remission rate. In the median disease duration of 8 years (range, 0.5-30 years), 380 relapses (118 optic neuritis, 223 myelitis, 39 optic neuritis and myelitis) occurred. At the last follow-up, 53.3% of patients had bilateral visual impairment and 63.3% were blind in at least 1 eye. A high mortality rate (23.3%) was due to cervical myelitis. Mortality rates were significantly higher among Afro Brazilian patients (58.3%).

Conclusions: Optic neuritis in patients with recurrent neuromyelitis optica has a severe and acute onset, with predominantly unilateral lesions followed by improvement of clinical symptoms. In the long-term, the disease leads to severe bilateral visual impairment. Mortality rates are higher among patients of Afro Brazilian descent.

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THE FIRST DESCRIPTION OF BILATERAL AMAUROSIS ASSOCIATED WITH SUBACUTE MYELITIS AND A FATAL COURSE WAS PROVIDED BY EUGÈNE DEVIC AT THE END OF THE 19TH CENTURY IN LYON, FRANCE. FOR MORE THAN A CENTURY, THESE CLINICAL PARAME-TERS WERE THE BASIS FOR THE DIAGNOSIS OF A RARE NEUROLOGICAL DISEASE RESTRICTED TO THE OPTIC NERVE AND SPINAL CORD, CALLED NEUROMYELITIS OPTICA (NMO) OR DEVIC DISEASE. At present, this condition is classified as an idiopathic inflammatory demyelinating disease of the central nervous system (CNS). Based on case studies published in different countries within the last decade, a relapsing type of NMO (RNMO) was identified. It is clinically characterized by 2 index events (optic neuritis [ON] and transverse myelitis [TM]) separated by an interval of days, weeks, months, and even years, with variable remission followed by new clinical events restricted to the optic nerve and spinal cord. In 1999, Wingerchuk et al from the Mayo Clinic proposed diagnostic criteria for NMO with the aim of differentiating this condition and multiple sclerosis (MS), the most common demyelinating disorder with a relapsing-remitting clinical course. Magnetic resonance imaging (MRI) of the brain and spinal cord as well as cerebral spinal fluid (CSF) analysis were the complementary methods indicated for laboratory support. IgG oligoclonal bands in CSF and multiple brain MRI lesions that are typical in MS are uncommon in NMO.

Monophasic NMO often occurs after infections or vaccinations. Relapsing NMO is an immunomediated disease that especially involves humoral mechanisms. Identification of an NMO-specific IgG antibody in the sera of patients with NMO brought new support for the hypothesis that RNMO is distinct from MS, despite its recurrent clinical course.

In this article, we will describe the clinical course of ON in a series of patients with RNMO from the Hospital da Lagoa, a referral center for the treatment of demyelinating disorders in Rio de Janeiro, Brazil.

METHODS

Eighty-two cases of ON and TM were identified from a group of 640 cases of demyelinating disease of the CNS. The cohort was followed up for editorial comment see page 128

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between 1985 and 2004 at the Hospital de Lagoa, a public tertiary hospital in Rio de Janeiro run by the Ministry of Health that is a referral center for patients with MS. From a database (SIAPEM12) and medical files, we extracted clinical data and complementary examination results (MRI of the brain and spinal cord and CSF analysis) in order to apply the 1999 Mayo Clinic diagnostic criteria for NMO, which require the presence of all absolute criteria and 1 major supportive criterion or 2 minor supportive criteria.5 By case definition, NMO with recurrent clinical examination and manual campimetric test were done. An or-

Results

We selected for this study 60 patients with relapses after the index event (ON and TM) that fulfilled the diagnostic cri-

teria. Table 2 elucidates the frequency of absolute, major, and minor supportive criteria presented in this series.

Epidemiological and clinical characteristics of the patients are presented in Table 3. The female-male ratio was 9:1 and 58.3% were of Afro Brazilian ethnicity (black and mixed race). Most of these patients (63%) sought the Hospital da Lagoa by spontaneous demand or by referral from other medical services; 30% of patients were originally seen in private practices by neurologists belonging to the Hospital da Lagoa team and were invited to participate in the study, while the other 7% came from other states in search of a definitive diagnosis for their condition.

Isolated ON was the initial feature in 32 patients, of whom 11 had 2 or more visual events before conversion to NMO. Demographic and clinical characteristics of patients with a single visual event at onset (n = 11) were indistinguishable from those with recurrent ON (n = 21) except for the median age at onset (isolated ON, 25 years; recurrent ON, 35 years) and a shorter median interval between the first visual event and the occurrence of myelitis (isolated ON, 8 months; recurrent ON, 34 months) (data not shown).

In the most severe phase of the visual index event, 65% of patients showed signs of unilateral visual damage and 35% showed signs of bilateral damage. There was severe loss of vision (visual acuity ≤ 20/200) in at least 1 eye in 78.3% of patients, followed by spontaneous remission or remission through the use of corticosteroids. However, severe visual deficits remained in 33% of patients.

Figure 1 shows the evaluation of visual impairment conducted at the nadir and at the best recovery of the visual index event and at the last follow-up according to an or-

Table 1. Quantification of Optic Nerve Impairment13 and Correlation Between VA and Percentage of Visual Loss13

<table>
<thead>
<tr>
<th>Ordinal Scale Score</th>
<th>Description of Visual Function</th>
<th>Estimate of Visual Loss, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal VA</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Scotoma, but VA (corrected) &gt; 20/30</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>VA (corrected) 20/30-20/59</td>
<td>10-34</td>
</tr>
<tr>
<td>3</td>
<td>VA (corrected) 20/60-20/999</td>
<td>35-79</td>
</tr>
<tr>
<td>4</td>
<td>VA (corrected) 20/200-20/800</td>
<td>≥ 80</td>
</tr>
<tr>
<td>5</td>
<td>Counting fingers</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Light perception</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>No light perception</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: VA, visual acuity.

Table 2. Frequency of Absolute and Supportive Criteria for NMO14

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Absolute Criteria</th>
<th>Minor Supportive Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optic neuritis</td>
<td>60 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Acute myelitis</td>
<td>60 (100.0)</td>
</tr>
<tr>
<td></td>
<td>No clinical evidence of disease outside of the optic nerve or spinal cord</td>
<td>60 (100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; MRI, Medical Research Council; MRI, magnetic resonance imaging; NMO, neuromyelitis optica.

a Data source: SIAPEM database.12
b Spinal cord MRI showed multiple lesions in fewer than 3 vertebral segments in 4 patients (7.4%) and 1 lesion in fewer than 3 vertebral segments in 1 patient (1.8%) and was normal in 2 patients (3.7%) after intravenous methylprednisolone treatment.
At the last follow-up, 50 patients showed signs of visual impairment (18 unilateral and 32 bilateral) and the following scores were identified: score 0 (normal vision) in 16.7% of patients; score 1 in 5.0%; score 2 in 8.3%; score 3 in 6.7%; score 4 in 13.3%; score 5 in 6.7%; score 6 in 20.0%; and score 7 in 23.3%. The median score for the classification of the visual deficit was 7 in the most severe phase of the index event, 2 in the remission phase, and 4 in the last follow-up.

When we compared the rates of severe visual dysfunction (loss of vision ≥80%) observed in the most severe phase of the index event (78.3%) and in the remission phase (35.0%), a statistically significant difference was observed (P < .001). However, when we compared the difference between the rate of severe visual dysfunction in the most severe phase of the index event (78.3%) and the final evaluation (63.3%), we did not get a statistically significant value (P = .07). Furthermore, ocular pain was mentioned in the clinical histories of 27% of patients.

The median disease duration at the last follow-up was 8 years (6 months–30 years). The median number of events per patient was 5 (range, 3–18 per patient). Acute TM was the most common event (58.7%), followed by visual events (31.0%) and optical spinal syndromes occurring in the same day (10.3%), as shown in Table 3.

Concerning the evolution of the visual impairment, the median time for the occurrence of 80% or more visual loss in 1 eye (visual score = 4), observed in 37 patients (61.7%), was 0.08 years (1 month), varying between 0.008 (1 day) and 26 years; complete loss of vision (score ≥6) in both eyes was observed in 22 patients (36.7%) and occurred in a median of 2.0 years, varying between 0.25 (3 months) and 30 years (Figure 2). The occurrence of 80% or more visual loss in 1 eye (white Brazilian patients, 40.0% vs Afro Brazilian patients, 77.1%; P = .004) and in both eyes (16.0% vs 72.0%, respectively; P = .004) were statistically different according to race.

Finally, there were 14 deaths (23.3%), and the median survival was 8 years (range, 1–30 years). The cause of death was directly related to cervical spinal cord damage with tetraplegia and respiratory failure in 13 patients (92.9%). Of the 14 patients whose course ended in death, 12 were Afro Brazilian and 2 were white. These numbers lead to a 34.3% mortality rate among Afro Brazilian patients and 8.0% among white Brazilian patients, a difference that is statistically significant (P = .02).

The diagnosis of idiopathic ON, as well as all the inflammatory demyelinating syndromes, depends on the exclusion of vascular, infectious, degenerative, metabolic, and tumoral diseases. In some patients, ON manifests by a single episode (monophasic ON) or develops into outbreaks and remissions (recurrent ON), but it could also be the onset manifestation of MS or the index event of NMO.

In 1991, the Optic Neuritis Treatment Trial presented the results of its analysis of the clinical profile of demyelinating ON in 448 American patients (77.2%, female; 85%, white). The acute phase was characterized by alteration of visual acuity (85.9%) and ocular pain (92.2%). The median visual acuity was 20/60 and severe visual loss (≥20/200) occurred in only 35.9% of cases. One-third of the patients developed MS.

Phillips et al compared clinical characteristics of demyelinating ON in black and white patients seen between 1989 and 1996 in the United States. They concluded that visual acuity was more severely affected in African American individuals, both in the initial phase of the disease and in the period 1 year later. Furthermore, the African American individuals with initial-phase ON that evolved into demyelinating disease most often developed NMO.

The natural history to recurrent ON was described by Pirko et al in a series of 72 patients. The 5-year conversion rate to NMO was 12.5% and to MS was 14.4%. The comparison among clinical and demographical characteristics of nonconverters (40 of 72), converters to NMO (8 of 72), and converters to MS (20 of 72) showed in the NMO group a high female-male ratio (7:1) and the greatest final visual impairment.

Herein, the spectrum and natural history of ON in relapsing NMO was described from a longitudinal analysis of a large series of patients from Rio de Janeiro. Most of the patients were female and Afro Brazilian. Development of the disease occurred between 30 and 40 years of age. Severe isolated unilateral ON was the initial mani-
festation of the disease in most of the patients. Few patients had recurrent visual events before conversion to NMO. As is characteristic of the natural course of inflammatory CNS disease, a high rate of remission took place spontaneously or after the use of corticosteroids following the first optic event. However, two-thirds of the patients developed severe unilateral visual impairment after a short period of disease, one-third had bilateral amaurosis in a median time of 2 years, and most patients had severe visual damage in at least 1 eye at the last follow-up, thereby confirming the high morbidity of ON. Considering the ethnic characteristics of the population, ON morbidity and mortality were significantly greater in Afro Brazilian patients.

We found a low frequency of ocular pain (27%) in the medical records. However, most of the patients with retrolubal neuritis had retro-orbital pain or ocular pain related to eye movement.19 Reviewing 8 case studies of patients with ON published between 1904 and 1994, Volpe20 found a prevalence of ocular pain that varied between 33% and 92%. In 2005, Agostoni et al19 called attention to the difficulty of evaluating pain in patients with ON. They said that in clinical practice, ON is diagnosed mostly by ophthalmologists and less frequently by neurologists. They emphasize that although pain is “the bedrock” of this diagnosis, it is often neglected by patients and by physicians. One limitation of the present study is that most of the information obtained concerning the initial events was done retrospectively. It is clear from the clinical descriptions that the attention of both the specialists and the patients was directed toward the loss of vision, with no emphasis on ocular pain, which may explain its low prevalence in this case study (27%).

Optic neuritis as a clinical event of NMO has been previously analyzed in other case studies.4-8 O’Riordan et al4 described in London 10 of 12 patients (83.3%) with a severe loss of vision (the patients could not count fingers). Wingerchuk et al5 analyzed the visual acuity at the last available assessment of 43 patients with relapsing disease at the Mayo Clinic and found complete blindness (acuity ≤20/200) in at least 1 eye in 60%. Papais-Alvarenga et al6 pro-

![Figure 1. Quantification of optic nerve impairment by an ordinal scale (Table 1) in the most severe phase of remission of the visual index event and at the last evaluation (n=60). Scores indicate the following: 0, normal visual acuity (VA); 1, corrected VA better than 20/30; 2, VA 20/30 to 20/59; 3, VA 20/60 to 20/199; 4, VA 20/200 to 20/800; 5, counting fingers; 6, light perception; and 7, no light perception. Data source: SIAPEM database.12]

![Figure 2. Progression of optic nerve impairment. A, Time to 80% or more visual loss in 1 eye (visual score = 4) (n=60). B, Time to bilateral loss of vision (visual score ≥ 6) (n=60). Data source: SIAPEM database.12]
spectively studied 24 Brazilian patients (22 with recurrent disease) and found, at last follow-up, permanent visual loss in 63% (unilateral in 21% and bilateral in 42%). De Seze et al22 described 13 French patients diagnosed with NMO during the period of 1985 through 1999, 10 of them with a relapsing-remitting pattern. The initial symptom was ON in only 2 cases; ON was bilateral at onset in 11 patients. After a mean period of 8.6 years, 53% had severe abnormalities in visual function (visual acuity ≤ 20/200). The Italian Devic’s Study Group23 gathered 46 patients in a multicenter study in 2004. They found that the initial event was unilateral ON in 37.0%, bilateral ON in 19.6%, and simultaneous myelitis and ON in 4.5%; in the remainder of the group, the onset of the disease was myelitis.

The recurrent type of NMO, clinically characterized by ON and TM followed by new clinical events restricted to the optic nerve and spinal cord, has been clearly recognized as distinct from MS in the last decade.3 Wingerchuk et al24 analyzed 71 patients, 23 with monophasic-type disease and 48 with recurrent-type disease, who were seen between 1951 and 1992 and clearly distinguished the clinical course and outcome of the 2 subtypes. Based on the analysis of the clinical data and laboratory information, they proposed absolute and supporting criteria for the diagnosis, which were used in this study. These criteria were validated in a study of Brazilian patients published in 200521 where it was shown that 85% of patients with NMO seen in Rio de Janeiro fulfilled the Mayo Clinic criteria, despite the ethnic differences. Of the 71 Rochester, Minnesota, cases, only 6 (8.4%) were nonwhite, while 28 of the 54 patients (51.8%) from Rio de Janeiro were Afro Brazilian. Most of the patients in both case studies3,22 had normal brain MRI results at onset, extensive inflammatory lesions in the spinal cord, and, from a clinical point of view, severe visual and motor damage, as well as a high prevalence of bilateral visual impairment. These epidemiological, clinical, and laboratory data distinguish RNMO from MS.

Recently, Wingerchuk et al22 proposed a revision to improve the diagnostic properties of NMO criteria. They removed the absolute restriction on CNS involvement beyond the optic nerves and spinal cord and incorporated the NMO-IgG biomarker. One limitation of the present study is that patients with RNMO were not evaluated with serological tests because the cohort predated the availability of these tests.

We found a high frequency of women (90%) and Afro Brazilian patients (58.3%). One of the characteristics associated with RNMO is female sex (91%, 83%, 90%, 76%, and 80%). The syndrome also is more frequent in nonwhite individuals, particularly Asian23 and African17 populations. As opposed to MS, which has high prevalence rates in white individuals living in the Northern hemisphere, NMO is a rare syndrome in these regions, constituting less than 1% of demyelinating disease.22 The frequency of selective and severe involvement of the optic nerve and spinal cord (optic spinal AS) in Japan is 1.5% to 40%.23 Data from a national study (South Atlantic Project, 1997) showed that 14% of the patients with MS living in Rio de Janeiro, in fact, had NMO syndrome.23 Considering the high rates of mortality and morbidity of NMO, all therapeutic efforts should be considered as possible treatments during the acute phase of ON or TM and as prevention of severe events.

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REFERENCES


