A Benign Form of Neuromyelitis Optica

Does It Exist?

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Background: Few data exist on a possible benign form of neuromyelitis optica (NMO).

Objectives: To identify NMO with a good outcome (go-NMO) among a large population of patients and to describe demographic and clinical variables associated with go-NMO vs standard NMO and benign multiple sclerosis.

Design: Observational retrospective multicenter study.

Setting: Twenty-five medical centers in metropolitan France (MF) and 3 medical centers in the French West Indies (FWI).

Patients: A total of 175 patients with NMO were retrospectively analyzed from 2 cohorts: 125 in MF and 50 patients of nonwhite race/ethnicity in the FWI. Patients in MF fulfilled the 2006 NMO criteria, whereas patients in the FWI fulfilled the 1999 or 2006 NMO criteria. Neuromyelitis optica and multiple sclerosis databases were reviewed, and patients with a score of 3 or lower on the Expanded Disability Status Scale after a 10-year follow-up period were considered to have go-NMO.

Main Outcome Measures: Clinical, laboratory, and magnetic resonance imaging data and course of disability.

Results: In MF, go-NMO was observed in 11 patients, including 3 untreated patients. In the FWI, NMO was severe because of disability related to optic neuritis. Compared with standard NMO, go-NMO was associated with a lower annualized relapse rate (0.3 vs 1.0, \( P < .01 \)), and 8 of 11 patients with go-NMO showed complete regression of myelitis on magnetic resonance imaging during the disease course. Three patients experienced a disabling attack of NMO after 15 years of follow-up. A good outcome occurred less frequently among patients with NMO than among patients with multiple sclerosis (12.0% vs 22.4%, \( P = .03 \)).

Conclusions: Among patients in MF, go-NMO occurs rarely. However, because a disabling attack may occur after a long follow-up period, a benign form of NMO cannot be defined.

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EUROMYELITIS OPTICA (NMO) is a relapsing and disabling autoimmune disease of the central nervous system, characterized by severe optic neuritis and extensive myelitis. A direct consequence of NMO is disability, including complete vision loss or paraplegia, which may be lethal in 2.9% to 25% of patients, mainly through brainstem involvement.\(^1\)\(^2\) Optic neuritis is initially followed by severe residual vision loss (visual acuity [VA], \( \leq 0.1 \) minutes of arc [corresponding to 20/200 on Snellen visual acuity charts]) in 30% of patients descended from nonwhite populations and in 22% of patients descended from the white population.\(^6\) After a first episode of myelitis, ambulation is limited to 500 m, corresponding to a residual Expanded Disability Status Scale (EDSS) score of 4 or higher, in 37.3% of patients.\(^2\) These data argue for development of severe disabling inflammatory disease in the absence of immunosuppressive therapies among patients with NMO.

Despite the putative severity of NMO, there are rare reports of a benign course in patients with NMO.\(^7\)\(^8\) Such patients developed NMO secondary to celiac disease\(^7\) or dengue infection.\(^8\) In a third case report, NMO was observed in a patient without evidence of systemic autoimmune or infectious disease.\(^8\) These reported cases fulfilled the 2006 diagnostic criteria for NMO.\(^10\) Cohort investigations that included more than 30 patients with NMO have not estimated the proportion of patients with good outcome NMO (go-NMO) (ie, those with a
score of ≤3 on the EDSS after a 10-year follow-up period. Evaluation of disability in these cohorts suggests that the disease may be less severe among patients of white vs nonwhite race/ethnicity.

We analyzed 2 NMO cohorts, one in metropolitan France (MF) with 125 patients and the other in the French West Indies (FWI) with 50 patients of nonwhite race/ethnicity, to identify patients with go-NMO. We further describe demographic and clinical variables associated with go-NMO vs standard NMO and benign multiple sclerosis (MS) in these geographic areas to develop hypotheses about benign inflammatory disease of the central nervous system.

**METHODS**

We performed an observational retrospective multicenter study of NMO in France, including MF and the FWI. Data were collected from September 1, 2007, through September 1, 2010, corresponding to the end point of the study. In MF, 25 tertiary hospital centers recruited 200 patients with a suggested diagnosis of NMO; 125 of these fulfilled the 2006 NMO criteria and were included in the study. Data derived from this cohort have been published elsewhere. In the FWI, 3 tertiary hospital centers recruited 76 patients with a suggested diagnosis of NMO; 50 of these were included in the study (26 fulfilled the 1999 NMO criteria and 24 fulfilled the 2006 NMO criteria). Selection of patients with NMO for the study is shown in Figure 1A. Selection of patients with benign MS for the study is shown in Figure IB. Data were derived from hospital medical records and from a clinical information questionnaire specifically designed for NMO. If needed, additional data were obtained from the participating centers by e-mail or by telephone. All data were entered in the European Database for Multiple Sclerosis, recently modified to include NMO. In MF, MS data were obtained from the database for Alsace, a representative French region. In the FWI, MS data were obtained from the geographic Caribbean database. Data confidentiality and security were ensured consistent with recommendations of the French data protection authority (Commission Nationale de l’Informatique et des Libertés), which also approved the study.

Assessed for each patient with NMO were demographic data, medical history, treatment, laboratory test results, neuroimaging data, and key episodes in the course of NMO (relapses and successive disability score dates). In patients with go-NMO, initial spinal cord magnetic resonance (MR) imaging was performed a mean (SD) of 7.8 (6.5) years after disease onset, 4.8 (4.1) years after the first episode of myelitis. Imaging was performed immediately after the first episode of myelitis in patients 1, 2, 3, and 5 (Table 1). Initial brain MR imaging was performed a mean (SD) of 7.3 (6.2) years after disease onset and was classified as normal in the presence of criteria by Paty et al or by Barkhof et al or as abnormal in the absence of those criteria. Serum samples from 111 patients in MF and from 24 patients in the FWI were tested for NMO-IgG with an indirect immunofluorescence assay on a substrate of adult rat cerebellum and midbrain using a previously described technique. Among the MF cohort of patients with go-NMO in whom the immunofluorescence assay was negative (patients 1, 2, 3, and 11), anti-aquaporin 4 antibody detection was performed using a routinely used cell-based assay with aquaporin 4-transfected cells. For the other patients, the NMO-IgG test was unavailable at NMO onset and was not necessary to diagnose NMO according to the 1999 or 2006 criteria. Residual disability was assessed during at least 6 months using EDSS score and VA. An EDSS score of 3 corresponded to benign MS, and an EDSS score of 2 reflected better vision. Visual acuity was included in the vision variable of the EDSS score. An EDSS score of 3 was compatible with a maximum VA of 0.1 or less (20/200 Snellen) in the worse eye, and an EDSS score of 2 indicated a large scotoma or a maximum VA of 0.33 to 0.2 (20/60 to 20/100 Snellen) in the worse eye.

Comparisons of categorical data were performed using χ² test. Comparisons of quantitative data were conducted using Mann-Whitney test. Kaplan-Meier technique was used to estimate time to the second episode and time to initial treatment. Survival curves were compared using log-rank test. Two-
Patiens with go-NMO

Good-outcome NMO was observed in 11 patients, all of whom were in the MF cohort (Figure 1A). When 33 patients with an unknown long-term clinical course (ie, <10 years’ follow-up and EDSS score of ≤3) were excluded, 11 of 92 patients with go-NMO represented 12.0% of the NMO cohort. Table 1 gives individual demographic and clinical characteristics of 11 patients with go-NMO. The first episode of myelitis was characterized by an isolated sensitive symptom in 5 patients and by a sensorimotor deficit in 6 patients (5 with spinchter impairment). After intravenous corticotherapy, recovery from myelitis was complete in 5 patients, including 3 patients with myelitis at NMO onset. The initial episode of clinical optic neuritis was bilateral in 1 patient. Visual acuity was 0.1 or worse (20/200 Snellen) in 6 patients, and the mean VA was 0.2 (20/100 Snellen) in the disabled eye. After intravenous corticotherapy, recovery from optic neuritis was complete in 9 patients. After a mean (SD) follow-up period of 16.4 (3.9) years, the course of NMO was relapsing-remitting in 10 patients and monophasic in patient 8, who was lost to follow-up because of suicide 11.7 years after disease onset. Using an EDSS cutoff score of 2, patients 10 and 11 were not considered to have go-NMO. At the end of the follow-up period, patient 3 had an EDSS score of 7 because of severe myelitis, and patients 6 and 7 had EDSS scores of 4.5 and 5, respectively, because of combined severe VA loss and myelitis. Residual VA of 0.1 or worse (≤20/200 Snellen) in 1 eye was observed in patients 7 and 8, but the mean VAs among the entire go-NMO cohort at the end of the follow-up period were 0.8 (20/25 Snellen) in both eyes.

Longitudinal extensive transverse myelitis was observed a mean (SD) of 9.7 (5.8) years after NMO onset and a mean (SD) of 5.8 (4.3) years after the first episode of myelitis and was observed in 7 patients on initial spinal cord MR imaging. Patient 8 was free of extensive myelitis at the end of the follow-up period. Apparent complete regression of myelitis (Figure 2) was observed in 8 of 11 patients with go-NMO.

In the FWI cohort, no go-NMO was observed. Most patients had severe optic neuritis with residual VA of 0.1 or worse (≤20.200 Snellen), despite immunosuppressive therapy (Figure 1A).

Demographic and clinical data associated with NMO vs benign MS are summarized in Table 2. Excluding demographic data (higher ratios of female to male patients and nonwhite to white races/ethnicities in the FWI), disease-related characteristics of standard NMO were similar in the FWI and MF cohorts and allow a comparison between go-NMO and standard NMO. Compared with standard NMO, go-NMO was associated with a lower annualized relapse rate and demonstrated a trend to delayed time from onset to a second episode. Whereas patients with standard NMO were often treated with immunosuppression, 3 patients with go-NMO required no treatment, and 2 patients with go-NMO needed only immunomodulatory therapy.

A lower percentage of patients having NMO experienced a good outcome of the disease compared with patients having benign MS in Alsace (12.0% vs 22.4%, P=.03). Except for a predominance of nonwhite patients in the FWI cohort, demographic and clinical characteristics of patients with benign MS were identical in Alsace and in the FWI. Similar results were noted when the cutoff for go-NMO was an EDSS score of 2 or lower.
Our study found go-NMO in 12.0% of patients among the MF NMO cohort. No patients in the FWI NMO cohort had a good outcome because of severe optic neuritis among this population. Compared with patients having standard NMO, patients having go-NMO had a lower annualized relapse rate, and complete regression of myelitis on spinal cord MR imaging was observed in 8 of 11 patients with go-NMO.

Based on our results, it is difficult to conclude that a benign form of NMO exists. First, the term benign is based on an assessment of the natural history of the disease, whereas only 3 patients in our cohort with go-NMO were untreated. Second, the expression “benign form” implies a permanent condition, whereas patients with NMO may have a good outcome for many years and then have a disabling attack, as observed in 3 patients after 15 years of follow-up.

To date, the so-called benign form of NMO has been described only in case reports. Patients with opticospinal demyelination secondary to celiac disease or dengue infection dramatically improved after causative treatment and a short course of corticotherapy. Primary benign NMO has been described in a patient with opticospinal demyelination, longitudinal extensive transverse myelitis, and normal brain MR imaging. The disease was characterized by a 6-year interval between the first 2 attacks and by marked swelling of a cervical lesion, which was initially suggestive of a low-grade tumor. The patient responded to corticothereapy and experienced progressive improvement after a few months. Six years after this event, spinal cord MR imaging showed complete regression of the initial lesion. This is in accord with our description of go-NMO, including spontaneous improvement, regressive myelitis, and a low annualized relapse rate. In contrast, clinical predictors of death among the FWI cohort with NMO included a high frequency of episodes during the first year of disease, blindness or sphincter signs at onset, and lack of recovery after the first attack.

Among the MF cohort, independent risk factors for EDSS scores of 4, 6, and 7 were not identified, but a large number of lesions on brain MR imaging during the disease course of NMO may predict a VA outcome of 0.1 or worse (≤20/200 Snellen).

Results of this study suggest some possible explanations for low disability among patients with NMO. The most important of these relate to the low annualized relapse rate and the complete regression of myelitis on MR imaging in 8 of 11 patients with go-NMO. These observations indicate that disability may be exclusively linked to relapses in NMO, without progressive aggravation of disability between relapses. The findings underline a major difference in the pathophysiological processes between NMO and MS, in which a progressive course is common. Regression of myelitis on MR imaging in inflammatory demyelinating diseases of the central nervous system has been described in acute disseminated...
encephalomyelitis and in the pseudotumoral form of MS.\textsuperscript{20} Such observations are uncommon in classic MS, whatever the course of the disease. In NMO, this point is poorly documented, but reported cases demonstrate that marked swelling in myelitis can shrink after high-dose corticosteroids.\textsuperscript{9,21} In a study by Cassinotto et al\textsuperscript{21} that included 17 patients with NMO, complete regression was observed in only 2 patients after a 26-month follow-up period. In most cases, these spinal cord lesions progress to atrophy and necrosis, leading to syrinxlike cavities on T1-weighted images. From a pathological point of view, it would be relevant to correlate transient myelitis in NMO with the presence of NMO-IgG, which can appear and disappear during the course of the disease.\textsuperscript{22} Involvement of immunosuppressive therapies in this transitory detection was not demonstrated in a large prospective follow-up study,\textsuperscript{2} but our data show that the phenomenon can occur without any treatment.

Good-outcome NMO was observed in the MF cohort but not in the FWI cohort. Differences in genetic backgrounds may be a key factor in accounting for these results, as suggested by the low proportion of nonwhite patients with go-NMO in the MF cohort. Despite immunosuppressive therapy, the median time in the FWI cohort from NMO onset to an EDSS score of 3 was 1 year, and death occurred in 25% of patients.\textsuperscript{1} In other NMO cohorts of primarily white race/ethnicity, percentages of patients with NMO-related death were as follows: 2.9% in a Mexican cohort,\textsuperscript{14} 3.2% in an MF cohort,\textsuperscript{15} 13% in an Italian cohort,\textsuperscript{16} and 22.5% in a North American cohort.\textsuperscript{17} The apparent severity of NMO in the North American cohort may be related to the following: (1) the high proportion of untreated patients in 1999, when the new NMO spectrum was first described; (2) a selection bias for severe hospitalized cases; and (3) the unspecified proportion of nonwhite patients in this population. The severe disability in our FWI cohort was mainly because of early and severe vision impairment, characterized by a permanent loss of vision after 2 attacks in a given eye and by a median time of 2 years from onset to monocular vision loss.\textsuperscript{8} Nevertheless, some patients in the FWI cohort experienced complete regression of their myelitis and remained fully ambulatory. These data raise questions about the validity of the vision scale used to calculate the EDSS score when applied to patients with NMO.

Several biases may limit interpretation of our study results. First, we may have inadvertantly selected patients with good prognosis in the MF cohort, as demonstrated by the low proportion of deaths compared with that in the FWI cohort. This could have occurred because of selection bias, as all patients in the MF cohort were being followed up at the start of the study and the 2006 NMO criteria were used in this population. In contrast to the 1999 NMO criteria used in the FWI cohort, the 2006 NMO criteria do not include the severity of motor disability and vision impairment in the diagnosis and may select less disabled patients.\textsuperscript{23} Second, whereas the collected data among this NMO cohort were among the most complete in the literature, the retrospective study design induced a lack of power in the search for predictive factors of disability. For example, good recovery after the first clinical event reported among patients with go-NMO cannot be compared with that among patients of the entire MF and FWI cohorts because of the wide range of treatments used after the first event, as well as the difficulty of assessing this in patients with a 10-year follow-up period. Third, the definition used for go-NMO was derived from that used for MS. Visual acuity was included in the EDSS score, and a converted vision score of 3 was compatible with a maximum VA of 0.1 or worse (≤20/200 Snellen) in the worse eye, which raises questions about whether symptoms were benign. That is why we also considered an EDSS score of 2 compatible with a large scotoma or a maximum VA of 0.33 to

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**Table 2. Characteristics of Patients Having Neuromyelitis Optica (NMO) in Metropolitan France (MF) and in the French West Indies (FWI) and of Patients Having Benign Multiple Sclerosis (MS) in Alsace and in the FWI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NMO in FWI (n=50)</th>
<th>Standard NMO in MF (n=81)</th>
<th>go-NMO in MF (n=11)</th>
<th>Property Value</th>
<th>P Value</th>
<th>Benign MS in Alsace (n=232)</th>
<th>P Value</th>
<th>Benign MS in FWI (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-male ratio</td>
<td>9:1</td>
<td>2:5</td>
<td>1:75:1</td>
<td>.85</td>
<td>.28:1</td>
<td>.70</td>
<td>.81:13</td>
<td>.13</td>
<td>.13</td>
</tr>
<tr>
<td>White-nonwhite ratio</td>
<td>0:50</td>
<td>9:1</td>
<td>4:5:1</td>
<td>.79</td>
<td>.28:1</td>
<td>.70</td>
<td>.81:13</td>
<td>.13</td>
<td>.13</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>31.8 (13.0)</td>
<td>35.2 (14.0)</td>
<td>31.6 (12.6)</td>
<td>.36</td>
<td>.29:8:7</td>
<td>.71</td>
<td>.26:8:9</td>
<td>.13</td>
<td>.13</td>
</tr>
<tr>
<td>Disease course monophasic:remitting ratio</td>
<td>0:50</td>
<td>1:4</td>
<td>1:10:6</td>
<td>.66</td>
<td>.23:2:2</td>
<td>.03</td>
<td>.27:0:25</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Time from onset to second attack, mean (SD), mo</td>
<td>23.3 (45.0)</td>
<td>31.2 (44.6)</td>
<td>46.5 (40.2)</td>
<td>.08</td>
<td>.59:32:7</td>
<td>.17</td>
<td>.58:64:2</td>
<td>.17</td>
<td>.17</td>
</tr>
<tr>
<td>Annualized relapse rate, mean (SD), mo</td>
<td>0:9 (0.7)</td>
<td>1:0 (1.5)</td>
<td>0:3 (0.1)</td>
<td>&lt;.01</td>
<td>.04:0:2</td>
<td>.24</td>
<td>.04:0:2</td>
<td>.19</td>
<td>.19</td>
</tr>
<tr>
<td>Patients receiving treatments, No. (%)</td>
<td>39 (78.0)</td>
<td>76 (93.8)</td>
<td>8 (72.7)</td>
<td>.08</td>
<td>.18:70</td>
<td>.97</td>
<td>.20:74:0</td>
<td>.82</td>
<td>.82</td>
</tr>
<tr>
<td>No. of treatments received, mean</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>&lt;.01</td>
<td>.31</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>IM</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>&lt;.01</td>
<td>.14:0</td>
<td>.19</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>IS</td>
<td>30</td>
<td>48</td>
<td>4</td>
<td>.07</td>
<td>…</td>
<td>0</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>IM + IS</td>
<td>8</td>
<td>25</td>
<td>2</td>
<td>.26</td>
<td>…</td>
<td>1</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Time to first treatment, median (95% CI), y</td>
<td>4.5 (2:3-6.7)</td>
<td>2.1 (1:4-2.7)</td>
<td>12.0 (8:3-15.7)</td>
<td>.03</td>
<td>.11:5:17:0</td>
<td>.65</td>
<td>.11:9:6:12:4</td>
<td>.50</td>
<td>.50</td>
</tr>
<tr>
<td>NMO-IgG, No. (%)</td>
<td>15 (62.5)</td>
<td>34 (50.0)</td>
<td>6 (54.5)</td>
<td>.96</td>
<td>…</td>
<td>…</td>
<td>…</td>
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</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ellipse, not applicable; go-NMO, NMO with a good outcome; IM, immunomodulatory treatment; IS, immunosuppressive treatment.

\*Patients with an Expanded Disability Status Scale score lower than 3 and with less than 10 years’ follow-up are excluded.

\*Comparison between NMO subgroups in MF.

\*Comparison between go-NMO and benign MS in Alsace.

\*Comparison between benign MS in Alsace and in the FWI.

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0.2 (20/60 to 20/100 Snellen) in the worse eye. However, such considerations do not alter the results of the study.

Because a disabling attack may occur after a long follow-up period, a benign form of NMO cannot be defined. However, results of this study show that go-NMO exists. This finding is applicable to a small percentage of patients with NMO descended from white populations with a low annualized relapse rate of NMO. The result is independent of NMO-IgG seropositivity, which does not affect the course of NMO.1,16,22 As in MS, a long first interattack interval could be indicative of a less disabling course of NMO.23 Furthermore, the resolution of myelitis without sequelae on MR imaging (spontaneously or after a short course of oral corticotherapy) may suggest a potentially good outcome of NMO. When NMO is suspected, complete regression of symptoms and of signal abnormalities on MR imaging may also be indicative of a good outcome. These considerations are valid only in the absence of the predictors of severity mentioned herein.

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