Early indicators of relapses vs pseudorelapses in neuromyelitis optica spectrum disorder

**ABSTRACT**

**Objective:** The purpose of this study was to review cases of neuromyelitis optica spectrum disorder (NMOSD) relapses and pseudorelapses to identify early features that differentiate between them at onset of symptoms.

**Methods:** This was a retrospective analysis of 74 hospitalizations of patients with NMOSD who were admitted to the Johns Hopkins Hospital for workup and treatment of a presumed relapse. Standard workup included MRI and blood and urine testing for metabolic and infectious etiologies. The gold standard for a relapse was defined as new or worsening symptoms and a change in neurologic examination correlating with a new or enhancing MRI lesion. A pseudorelapse was a clinical exacerbation with similar symptoms and signs but the MRI was negative, and workup identified an alternative cause for the symptoms that, when treated, resulted in the improvement of neurologic symptoms. Factors considered to be early predictors of relapses vs pseudorelapses were analyzed using the Fisher test.

**Results:** Among 74 NMOSD hospitalizations for presumed relapse, 57 were confirmed relapses while 17 had a negative MRI and an identifiable cause of pseudorelapse. The most common causes of pseudorelapse were infection, pain, and dysautonomia. The only early predictor that reliably differentiated relapse from pseudorelapse among this NMOSD patient population was vision loss (p = 0.039). Race, sex, presentations of weakness, numbness, and bowel/bladder dysfunction, white blood cell count, and urinary tract infection were not different among patients with relapses vs pseudorelapses.

**Conclusions:** Vision loss in NMOSD is strongly suggestive of a true relapse vs a pseudorelapse. Pseudorelapses localized to the spinal cord in patients with previous myelitis presented similarly to true relapses and could only be ruled out by a negative MRI. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e269; doi: 10.1212/NXI.0000000000000269

**GLOSSARY**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>MRC</td>
<td>Medical Research Council; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; UTI = urinary tract infection.</td>
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</table>

Neuromyelitis optica (NMO) is a severe inflammatory demyelinating disease of the CNS that primarily causes recurring episodes of optic neuritis and transverse myelitis.1 Historically, NMO relapses contributed to cumulative long-term visual and motor disability, such that 62% were functionally blind at 5 years and 50% of patients were dependent on a wheelchair.2

Differentiating symptoms between a true relapse, defined as an immune-mediated attack of the CNS, and a pseudorelapse, in which systemic metabolic factors can cause preexisting neurologic symptoms to worsen, is a diagnostic challenge even for expert clinicians. This distinction has significant implications for the type and duration of treatment provided. Misdiagnosis of pseudorelapses often leads to inappropriate immunosuppressive therapy incurring unnecessary risks and side effects. In addition, pseudorelapse admissions to the hospital result in increased
The gold standard for a relapse in this study was defined as a clinical exacerbation presenting with new or worsening symptoms with a change on neurologic examination that correlated with a new or enhancing MRI lesion. At least 30 days must have elapsed since the previous relapse. The gold standard for a pseudorelapse in this study was defined as a clinical exacerbation with similar symptoms and signs, but the MRI was negative for a new or enhancing lesion and there was an alternative cause for the symptoms that, when treated, resulted in the improvement of neurologic symptoms. These gold standard definitions for relapse and pseudorelapse do not encompass the full spectrum of NMO spectrum disorder (NMOSD) disease in practice. The purpose for including only cases that met these strict criteria is to identify early clinical and objective measures that could definitively exclude a pseudorelapse. The motor examination was scored as no change (none), a 1-point change in the Medical Research Council (MRC) motor scale (mild), a 2-point MRC change (moderate), or 3+ change (severe). The standard ophthalmologic examination included visual acuity, visual fields, and pupillary examination.

MRRs were obtained by using either 1.5- or 3-tesla scanners: Philips Healthcare (Best, the Netherlands), GE Healthcare (Milwaukee, WI), and Siemens (Erlangen, Germany). Diffusion-weighted imaging and T1-weighted, fast spin-echo T2-weighted, and postgadolinium T1-weighted imaging were performed. All patients were given IV gadolinium-based contrast media. Data analysis was performed using GraphPad Prism statistical software (GraphPad Software, La Jolla, CA) to compare differences between the 2 cohorts (see table e-1 at Neurology.org/nm). Age at presentation and white blood cell count were analyzed using Mann–Whitney statistical tests. The Fisher exact probability test was used to test statistical significance in race, sex, urinary tract infection (UTI), weakness, numbness, bowel/bladder symptoms, and vision complaints on admission. A p value of less than 0.05 was considered statistically significant.

RESULTS Seventy-four individual hospital admissions met criteria for inclusion, 57 of which met gold standard criteria for true relapses and 17 met the criteria for pseudorelapses. The average age at presentation in the true relapse cohort was 41.2 years (range 3–78) and was 37.7 years (range 3–71) in the pseudorelapse cohort (table 1). The sex distribution was skewed toward female in both groups, with a female to male ratio of 13:5 and 12:3 in the relapse and pseudorelapse cohorts, respectively. There was also a higher proportion of African American patients overall, with 56% of the relapse cohort and 53% of the pseudorelapse cohort, reflecting the NMOSD.
Abbreviation: APD = afferent pupillary defect; NA = not applicable.
Data are expressed as percentages.

a True relapses for the purposes of this study required at least mild weakness on examination.
b Sensory and bowel/bladder examinations were not sufficiently documented to determine severity.
c Significant.

Table 2  Clinical presentations of the neuromyelitis optica cohorts

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Mild</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Moderate</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Severe</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Numbnessb</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Bowel/bladderb</td>
<td>21</td>
<td>41</td>
</tr>
<tr>
<td>Visual</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>Reduced acuity</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>New field cut</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>New APD</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: APD = afferent pupillary defect; NA = not applicable.

Table 3  Laboratory testing

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Relapses</th>
<th>Pseudorelapses</th>
<th>Difference (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>30</td>
<td>35</td>
<td>0.669</td>
</tr>
<tr>
<td>WBC count &gt;10k</td>
<td>32</td>
<td>24</td>
<td>0.576</td>
</tr>
</tbody>
</table>

Abbreviation: WBC = white blood cell.
Data are expressed as percentages.

In the following between the 2 groups: age at presentation, sex, race, UTI, white blood cell count, weakness, numbness, and bowel/bladder symptoms (table 3).

The only difference found between the groups at presentation was unilateral or bilateral worsening of visual acuity, both by symptomatic presentation and visual acuity examination, consistent with an acute optic neuritis. The prevalence of visual symptoms was notably different between the 2 cohorts: 41% of true relapse admissions vs 12% of pseudorelapse admissions presented with complaints of changes in visual acuity (p = 0.039, table 2). Neither of the 2 subjects in the pseudorelapse group presenting with visual complaints had detectable changes on visual acuity testing or any other ophthalmologic finding.

Of the 24 patients with true optic neuritis relapses presenting with visual complaints, all had ophthalmologic findings on examination, and all but one had reduced visual acuity compared to baseline.

Among admissions with true relapses, 93% were treated with a course of steroids and 30% required plasma exchange. Among patients with pseudorelapses who were ultimately determined to have an alternative, noninflammatory etiology for their worsening neurologic symptoms, 35% were initially treated with a course of high-dose steroids.

The most common cause of pseudorelapses included infections, hyperglycemia, pancreatitis, hypomagnesemia, lupus, dysautonomia, medication withdrawal, medication overuse, and conversion disorder.

DISCUSSION For patients with true relapses, defined as an inflammatory attack of the CNS causing neurologic dysfunction, delaying or deferring immunosuppressive treatment may result in permanent damage and increasing disability. However, unnecessarily immunosuppressing patients with NMO presenting with pseudorelapses can worsen metabolic syndromes, contribute to long-term steroid toxicity, and accrue costly, and avoidable, medical expenses. Therefore, correctly distinguishing between true relapses and pseudorelapses in patients with NMO with new or worsening symptoms can significantly change their long-term medical and neurologic outcome.

In this analysis, we found that worsening visual acuity is a sensitive biomarker of a true relapse of acute optic neuritis in patients with NMO. While inflamed optic nerves in multiple sclerosis are susceptible to Uhthoff phenomenon and other metabolic abnormalities early in the first 2 months of the recovery period, our data support the observation that worsening visual acuity sustained for more than 24 hours is more concerning for a true relapse. In contrast, loss of motor function in patients with NMO is
not a sensitive marker for a true relapse. Pseudorelapses and true relapses were equally likely to present with worsening weakness with no threshold for severity of motor dysfunction that rules out pseudorelapses. Numbness just failed to reach statistical significance, which may have been attributable to a small sample size. Therefore, we conclude that for patients with NMO presenting with symptoms and signs of a transverse myelitis relapse, an MRI is necessary to rule out a pseudorelapse.

There are several limitations to our study. First, data collection for this retrospective study was based on extraction of relevant patient information from electronic medical records. Second, selection bias is present because Johns Hopkins Hospital is a tertiary NMO referral center; however, this bias applies to both the relapse and pseudorelapse groups. Third, our definition of a true relapse based on MRI evidence may be too restrictive as we did not look for other evidence of inflammation such as spinal fluid pleocytosis, in all pseudorelapse cases. And finally, our study is limited in sample size because of the rarity of NMOSD and the number of NMOSD relapses and pseudorelapses that met our strict gold standard criteria.

**AUTHOR CONTRIBUTIONS**

R.A.K.: contributed to the design and conceptualization of the study, analysis and interpretation of the data, and drafting of the manuscript. M.A.M.: contributed to the design and conceptualization of the study, analysis and interpretation of the data, and drafting of the manuscript. M.L.: contributed to the design and conceptualization of the study, analysis and interpretation of the data, and drafting of the manuscript.

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Remi A. Kessler, Maureen A. Mealy and Michael Levy

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