

Early indicators of relapses vs pseudorelapses in neuromyelitis optica spectrum disorder

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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

MRC = Medical Research Council; **NMO** = neuromyelitis optica; **NMOSD** = neuromyelitis optica spectrum disorder; **UTI** = urinary tract infection.

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

Supplemental data
at Neurology.org/nn

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Table 1 Demographics of the neuromyelitis optica cohorts

Demographics	Relapse patients (n = 36); no. of relapses = 57	Pseudorelapse patients (n = 15); no. of pseudorelapses = 17	Difference (p)
Date range of admission	2009–2015	2009–2015	
AQP4 IgG serostatus			0.686
Positive	27 (75)	9 (60)	
Negative	9 (25)	4 (25)	
Unknown	0 (0)	2 (13)	
Age at presentation, y			0.353
Mean ± SD	41.2 ± 20.0	37.7 ± 21	
Median	47	42	
Sex			0.561
Female	26 (72)	12 (80)	
Female/male ratio	13/5	12/3	
Race			0.915
African descent	20 (56)	8 (53)	
Asian	1 (3)	0 (0)	
Caucasian	14 (39)	6 (40)	
Latin American	1 (3)	1 (7)	

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G.

Unless otherwise noted, data are expressed as n (%) of patients. Percentages have been rounded and may not add up to 100.

health care costs, decreased quality of care, diminished patient satisfaction, and patients' lost time from work.³ In contrast, failing to identify a true relapse can cause potentially irreversible harm to the patient and accruing disability.⁴ Thus, missing a true relapse or inappropriately immunosuppressing a pseudorelapse both carry significant risks and implications for overall patient care, and clinical characteristics differentiating these 2 phenomena must be delineated.

Signs and symptoms that predict whether an admitted patient with a history of NMO is experiencing a true relapse or a pseudorelapse have not been previously described. The objectives of this retrospective study were to identify the clinical characteristics of patients with NMO presenting with true relapses or pseudorelapses, and to subsequently describe early clinical features that distinguish between them at onset of symptoms.

METHODS This retrospective review was conducted through a medical record search to identify all patients with a diagnosis of NMO or transverse myelitis admitted from the emergency department at Johns Hopkins Hospital. Patients were included in this study if they had a history of NMO as defined by the

2006 clinical diagnostic criteria,⁵ were admitted to the hospital between 2009 and 2015, and presented with an acute exacerbation defined as new or worsening neurologic symptoms in the setting of a presumed relapse. Workup for all patients included neurologic examination, MRI at the time of admission, and hematologic and urine studies. Demographic information, data on signs, symptoms, workup on admission, and information on final diagnosis were aggregated. Two distinct NMO cohorts were subsequently described: one group consisting of patients diagnosed with true relapses and the other with pseudorelapses.

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.

MRIs 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/nn). 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.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Johns Hopkins institutional review board. This was a retrospective study that did not require informed consent from the participants.

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

Table 2 Clinical presentations of the neuromyelitis optica cohorts

	Relapses		Pseudorelapses		Difference (p value)
	Symptoms	Signs	Symptoms	Signs	
Weakness	64		53		0.410
None		0		33	NA ^a
Mild		57		33	0.179
Moderate		31		33	0.872
Severe		12		0	0.295
Numbness^b	52		24		0.053
Bowel/bladder^b	21		41		0.123
Visual	41		12		0.039 ^c
Reduced acuity		96		0	0.008 ^c
New field cut		16		0	1.000
New APD		19		0	1.000

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

Data are expressed as percentages.

^aTrue relapses for the purposes of this study required at least mild weakness on examination.

^bSensory and bowel/bladder examinations were not sufficiently documented to determine severity.

^cSignificant.

patient population in Baltimore, MD. Of the patients who presented with true relapses, 75% had a positive anti-aquaporin-4 immunoglobulin G serostatus. Similarly, 60% of pseudorelapse patients had a positive anti-aquaporin-4 immunoglobulin G serostatus.

Of the 57 hospital admissions for true relapses, 64% demonstrated upper and/or lower extremity weakness (table 2); 53% of the 17 admissions for pseudorelapses also had documented weakness compared to prior baseline. The degree of weakness between both groups was not different. Of note, more than half of all true relapses were graded as mild with only a 1-point worsening in the MRC score (table 2). Numbness or worsening sensory loss was recorded in 52% of true relapse patients and 24% of pseudorelapse patients, which was not different. Twenty-one percent of true relapse and 41% of pseudorelapse admissions presented with bowel and/or bladder symptoms, including urinary incontinence and increased frequency and urgency. Thirty percent of relapse and 35% of pseudorelapse admissions had documented UTIs. In sum, there were no differences

Table 3 Laboratory testing

	Relapses	Pseudorelapses	Difference (p)
Urinary tract infection	30	35	0.669
WBC count >10k	32	24	0.576

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.⁶ 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,⁷ our data support the observation that worsening visual acuity sustained for more than 24 hours is more concerning for a true relapse.⁸ 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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REFERENCES

1. Oh J, Levy M. Neuromyelitis optica: an antibody-mediated disorder of the central nervous system. *Neurol Res Int* 2012;2012:460825.
2. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: clinical predictors of a relapsing course and survival. *Neurology* 2003;60:848–853.
3. Emanuel EJ, Fuchs VR. The perfect storm of overutilization. *JAMA* 2008;299:2789–2791.
4. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. *Neurology* 2007;68:603–605.
5. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485–1489.
6. Kimbrough DJ, Fujihara K, Jacob A, et al. Treatment of neuromyelitis optica: review and recommendations. *Mult Scler Relat Disord* 2012;1:180–187.
7. Fraser CL, Davagnanam I, Radon M, Plant GT. The time course and phenotype of Uhthoff phenomenon following optic neuritis. *Mult Scler* 2012;18:1042–1044.
8. Frohman TC, Davis SL, Beh S, Greenberg BM, Remington G, Frohman EM. Uhthoff's phenomena in MS—clinical features and pathophysiology. *Nat Rev Neurol* 2013;9:535–540.