

ARTICLES

NMO-IgG predicts the outcome of recurrent optic neuritis

Reprinted with permission from **Neurology**, 2008; 70:2197-2200.
Neurology is a copyrighted publication of Lippincott Williams & Wilkins (LWW).

M. Matiello, MD
 V.A. Lennon, MD,
 PhD
 A. Jacob, MD
 S.J. Pittock, MD
 C.F. Lucchinetti, MD
 D.M. Wingerchuk,
 MD
 B.G. Weinshenker,
 MD

Address correspondence and
 reprint requests to Dr. Brian
 Weinshenker, Department of
 Neurology, Mayo Clinic
 College of Medicine, 200 First
 St SW, Rochester, MN 55905
 weinb@mayo.edu

ABSTRACT

Objective: To determine the prognostic value of neuromyelitis optica (NMO)-immunoglobulin G (IgG) in patients with recurrent optic neuritis (ON). The aquaporin-4-specific serum autoantibody, NMO-IgG, is a biomarker for NMO and relapsing transverse myelitis. Recurrent ON may herald multiple sclerosis (MS) or NMO, or it may occur as an isolated syndrome. The prognosis and response to therapy differs in each of these contexts.

Methods: We evaluated 34 patients who were tested for NMO-IgG between 2000 and 2007 and who had two or more episodes of ON without satisfying a diagnosis of MS or NMO prior to serologic testing. Clinical data were available for 25 Mayo Clinic patients (5 NMO-IgG positive and 20 NMO-IgG negative) and for an additional 9 seropositive patients whose serum was referred to the Mayo Clinic Neuroimmunology laboratory for testing.

Results: Twenty percent of the patients with recurrent ON seen at Mayo Clinic were seropositive. All NMO-IgG-positive patients (vs 65% NMO-IgG-negative patients) had at least one attack with visual acuity in the affected eye worse than 20/200 ($p = 0.05$). In seropositive patients for whom long-term follow-up was possible (median 8.9 years after the initial ON), 6 of 12 (50%) experienced an episode of myelitis and fulfilled criteria for NMO. In contrast, 1 of 15 seronegative patients (6.7%) fulfilled McDonald criteria for MS ($p = 0.03$). Seropositive patients had a final visual score which was worse than that of seronegative patients ($p = 0.02$).

Conclusions: Neuromyelitis optica (NMO)-immunoglobulin G seropositivity predicts poor visual outcome and development of NMO. Seropositive recurrent optic neuritis is a limited form of NMO.
Neurology® 2008;70:2197-2200

GLOSSARY

IgG = immunoglobulin G; **LETM** = longitudinally extensive transverse myelitis; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **ON** = optic neuritis; **RON** = recurrent ON; **TM** = transverse myelitis; **VA** = visual acuity.

Optic neuritis (ON) is an acute inflammatory demyelinating syndrome of the CNS that may occur in isolation or may herald multiple sclerosis (MS), neuromyelitis optica (NMO), or recurrences of ON without other CNS manifestation (idiopathic recurrent ON [RON]).¹ The diagnosis of NMO, rather than MS, in a patient with a history of ON and myelitis is largely dependent on documentation of longitudinally extensive spinal cord lesions, which are common in NMO and rare in MS. The prognosis for NMO is worse than for MS,² and current evidence suggests that conventional immunomodulatory treatments for MS are ineffective for NMO.³⁻⁶ Therefore, early distinction between NMO (and its related spectrum of disorders) from MS is clinically important.

Editorial, page 2192

e-Pub ahead of print on April 23, 2008, at www.neurology.org.

From the Departments of Neurology (M.M., V.A.L., A.J., S.J.P., C.F.L., B.G.W.) and Laboratory Medicine and Pathology (V.A.L., S.J.P.), Mayo Clinic College of Medicine, Rochester, MN; and Department of Neurology (D.M.W.), Mayo Clinic College of Medicine, Scottsdale, AZ.

Dr. Matiello is supported by a du Pré fellowship grant provided by the Multiple Sclerosis International Federation (www.msif.org). This research is sponsored in part by a grant to Dr. Weinshenker from the Olson Foundation.

Disclosure: Drs. Marcelo Matiello, Ann Jacob, and Sean Pittock have nothing to disclose. Drs. Brian Weinshenker, Vanda Lennon, and Claudia Lucchinetti have intellectual property associated with the discovery of NMO-IgG, which has been licensed to a commercial entity. The NMO-IgG test is offered on a service basis by Mayo Collaborative Service Inc., an agency of Mayo Foundation. Dean Wingerchuk and Brian Weinshenker have served as consultants for Genentech for development of a clinical trial for neuromyelitis optica. Dr. Wingerchuk has consulted for Teva pharmaceuticals. Drs. Weinshenker and Wingerchuk have also been investigators in clinical trials for MS.

The serum autoantibody, NMO-IgG, detected by indirect immunofluorescence,² binds to the CNS-dominant water channel, aquaporin-4, and has high sensitivity and specificity for NMO.^{2,7} Recent incorporation of NMO-IgG seropositivity as a diagnostic criterion for NMO⁸ has been validated independently.⁹ Detection of NMO-IgG in patients with idiopathic longitudinally extensive transverse myelitis (LETM) predicts recurrence or development of ON within 1 year in 55% of cases.¹⁰ The goal of the current study was to evaluate the diagnostic and prognostic value of NMO-IgG in patients with RON.

METHODS The study was approved by the Mayo Clinic Institutional Review Board (IRB# 1036-04). Eligible patients fulfilled the following inclusion criteria: 1) tested for NMO-IgG between 2000 and 2007 in the Mayo Clinic Neuroimmunology Laboratory; 2) at least two clinical episodes of ON separated by 30 days or more and documented before NMO-IgG testing; 3) no other neurologic signs or symptoms prior to the NMO-IgG test that suggested a diagnosis of MS or NMO.

Blinded indirect immunofluorescence testing for NMO-IgG was performed on a service basis.⁴ We reviewed medical records for patients evaluated at Mayo Clinic (5 NMO-IgG positive and 20 NMO-IgG negative) and abstracted data provided by referring physicians for patients not evaluated at Mayo Clinic. Data for patients evaluated elsewhere were ascertained only for seropositive RON patients (identified serologically in the Mayo Clinic Neuroimmunology Laboratory [$n = 9$], in the course of contacting physicians of NMO-IgG-positive patients in routine laboratory physician-initiated consultative and quality assurance activities). Thus, only patients evaluated at Mayo Clinic were informative regarding the seroprevalence of NMO-IgG in RON. Data for both groups were used to evaluate demographic characteristics and outcome data associated with NMO-IgG seropositive RON.

Visual acuity (VA) was assessed in each eye by an ordinal scale: 0 = 20/20; 1 = scotoma but better than 20/30; 2 = 20/30 to 20/59; 3 = 20/60 to 20/199; 4 = 20/200 to 20/800; 5 = count fingers only; 6 = light perception; 7 = no light perception.¹¹ The final visual outcome was the sum of the last assigned visual score for each eye.

Follow-up information included additional relapses of ON, development of transverse myelitis (TM) or other neurologic manifestations, and the patient's most recent visual and motor status.

We determined whether the patients satisfied criteria for MS or NMO.^{8,12} We used the statistical package JMP 6.0 (SAS Institute, Cary, NC, 2005) to analyze the significance of differences between the seropositive and seronegative groups using χ^2 or Fisher exact test for frequency data, and Wilcoxon or t test for continuous data, as appropriate. We used a Kaplan-Meier analysis to evaluate differences in incidence of TM in the seropositive and seronegative groups following the first episode of ON.

RESULTS Five of the 25 patients (20%) evaluated at Mayo Clinic were NMO-IgG-positive. Seropositivity was not associated with sex, age at onset, number of ON episodes prior to serologic testing, interval between the first and the second episodes, or occurrence of bilateral episodes of ON. Among patients for whom ethnicity information was available, non-Caucasian ancestry was more common in the seropositives (5 of 12; 41.7%) than in the seronegatives (2 of 19; 10.5%, $p = 0.07$).

The initial ON episode was more severe in seropositive patients ($p = 0.05$) and VA in the affected eye was worse than 20/200 at the nadir in all seropositive patients (one or more ON episodes) compared to 64.7% in seronegative patients ($p = 0.05$). Thirty-one patients had a brain MRI after the first ON; none fulfilled MRI criteria for MS,¹² 6 of 11 seropositive patients (55%) and 12 of 19 seronegative patients (63%) had normal brain MRI or changes restricted to the optic nerve. The remainder had nonspecific MRI signal changes.

Follow-up data were available for 12 seropositive and 15 seronegative patients, representing 79.4% of the population studied. The interval was similar in the two groups: 8.95 ± 2.0 years for seropositive vs 8.02 ± 5.1 years (mean \pm SD) for seronegative patients ($p = 0.73$). Four seropositive and 7 seronegative patients had ON relapses after NMO-IgG testing ($p = 0.69$). The final visual status score was worse in the seropositive group: 10.22 ± 9.0 (mean \pm SD) vs 6.38 ± 1.0 in the seronegative group ($p = 0.02$) (table).

One seronegative patient (6.6%) and 6 seropositive patients (50%) experienced TM episodes during the follow-up period ($p = 0.03$) (figure). The seronegative patient experienced a band-like sensation around her chest accompanied by paresthesia of the lower extremities; MRI of thoracic spine revealed two small lesions adjacent to vertebra T11 each measuring about 3 mm, likely unrelated to her symptoms considering the dermatome level of sensory disturbance. Minor sensory disturbances accompanied by small spinal cord MRI lesions also occurred in one seropositive patient while she was receiving monthly IVIg therapy. The other five seropositive patients experienced severe TM, leading either to quadriplegia or paraplegia, accompanied by severe sensory and sphincter deficits. Spinal cord lesions longer than three vertebral segments were present in the four patients on whom we had information about their MRI scans. Two seropositive pa-

Table Patient demographic, clinical, and MRI characteristics and outcome information stratified by neuromyelitis optica (NMO)-immunoglobulin G (IgG) serologic status			
Baseline characteristics (prior to NMO-IgG testing)	Seronegative (n = 20)	Seropositive (n = 14)	p Value
Age at onset, y, median (IQR)	28.9 (14.8-43.7)	31.0 (23.7-42.3)	0.45*
Sex, F:M	18:2	14:0	0.5*
Ethnicity, n (%)			0.07*
Caucasian	17 (89.5)	7 (58.3)	
Other	2 (10.5)	5 (41.7)	
Unknown	1	2	
No. of ON episodes, mean ± SD	3.05 ± 1.65	4.14 ± 2.95	0.14*
Interval between first and second episodes, d, median (IQR)	131 (50.5-912.3)	258 (70.75-1,255)	0.19*
First ON visual score at nadir, mean ± SD	4.53 ± 2.26	6.12 ± 1.12	0.07†
ON event with visual acuity worse than 20/200, n (%)	11/17 (64.7)	10/10 (100)	0.05†
No. of patients with bilateral episodes of ON	6	3	0.7†
At least one episode with no light perception, n (%)	7/17 (41.2)	7/10 (70)	0.14‡
Follow-up outcomes	Seronegative (n = 15)	Seropositive (n = 12)	p Value
No. of patients with ON episodes after NMO-IgG serologic testing, n (%)	7 (46.7)	4 (33.3)	0.69†
Visual score at last follow-up, sum of both eyes, mean ± SD	6.38 ± 3.42	10.22 ± 3.89	0.02†
Transverse myelitis episodes, n (%)	1 (6.6)	6 (50)	0.03§

*Wilcoxon test.

†Fisher exact test.

‡t test.

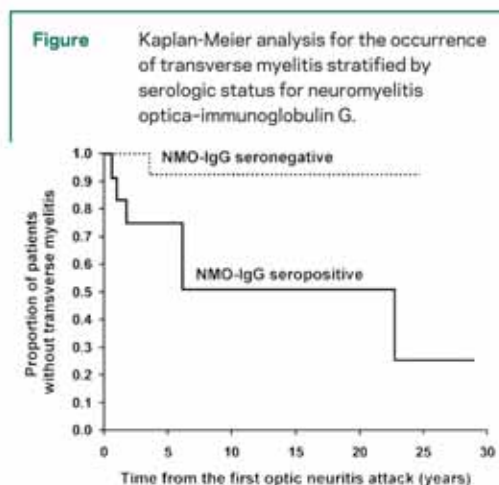
§Chi-square.

¶Log-rank.

IQR = interquartile range; ON = optic neuritis.

tients died shortly after developing TM, one from a pulmonary embolism and the other from uncertain cause.

NMO-IgG titers among seropositive cases were higher in those who developed myelitis than in those who did not. TM developed in 5 of 7 patients (71.4%) whose NMO-IgG was positive at a serum dilution greater than 1:480, but in only 1 of 5 patients (20%) whose serum was positive at a dilution of 1:480 or lower ($p = 0.07$).



DISCUSSION The 20% seroprevalence of NMO-IgG among patients presenting with RON was similar to the frequency we originally reported for NMO-IgG among patients with RON. In the original report, 2 of 8 patients (25%) with simultaneous or sequential RON were NMO-IgG positive.²

The visual disability recorded for patients in this report is consistent with previous reports for patients with NMO. In a study conducted before the advent of NMO-IgG testing, the initial ON episode and final visual outcome of patients with RON were worse in the NMO-conversion group than in those who did not convert to NMO.¹ Similarly, in comparing visual status immediately after an ON episode and then 6 months later in Afro-Caribbean patients with NMO or MS, the number of attacks in the first 2 years (2.0 ± 1.3 vs 0.97 ± 0.7), the annual relapse rate (0.39 ± 0.33 vs 0.27 ± 0.29), and the final visual acuity impairment ($20/50$ vs $20/25$) were greater in NMO than in MS.¹¹

NMO-IgG is not restricted to patients fulfilling all criteria for a definite diagnosis of NMO.^{10,14-16} The seropositivity rate in patients with recurrent LETM was 52%² and 40% in pa-

tients with a single episode of LETM.¹⁰ This study provides support for RON being a limited or inaugural symptom of NMO in at least 20% of patients.

No clinical trial has established the most efficacious treatment for preventing relapses in NMO. However, case series strongly supports the use of immunosuppressant drugs rather than interferon beta.³⁻⁶ Patients with RON who are seropositive for NMO-IgG are at high risk for development of TM and severe disability. Therefore, we advocate testing patients with RON for NMO-IgG and favor use of immunosuppressive therapy in treating NMO-IgG-seropositive patients with RON, as we also recommend for patients with LETM who are NMO-IgG seropositive.¹⁰

ACKNOWLEDGMENT

The authors thank Denice Bredlow for editing the manuscript.

Received August 2, 2007. Accepted in final form October 18, 2007.

REFERENCES

1. Pirko I, Blauwet LK, Lesnick TG, Weinshenker BG. The natural history of recurrent optic neuritis. *Arch Neurol* 2004;61:1401-1405.
2. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;364:2106-2112.
3. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 1998;51:1219-1220.
4. Wingerchuk DM. Diagnosis and treatment of neuromyelitis optica. *Neurologist* 2007;13:2-11.
5. Warabi Y, Matsumoto Y, Hayashi H. Interferon beta-1b exacerbates multiple sclerosis with severe optic nerve and spinal cord demyelination. *J Neurol Sci* 2007;252:57-61.
6. Papeix C, Vidal JS, de Seze J, et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. *Mult Scler* 2007;13:256-259.
7. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 2005;202:473-477.
8. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485-1489.
9. Saiz A, Zuliani L, Blanco Y, et al. Revised diagnostic criteria for neuromyelitis optica (NMO): Application in a series of suspected patients. *J Neurol* 2007;254:1233-1237.
10. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 2006;59:566-569.
11. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;53:1107-1114.
12. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50:121-127.
13. Merle H, Olindo S, Bonnan M, et al. Natural history of the visual impairment of relapsing neuromyelitis optica. *Ophthalmology* 2007;114:810-815.
14. Jarius S, Franciotta D, Bergamaschi R, et al. NMO-IgG in the diagnosis of neuromyelitis optica. *Neurology* 2007;68:1076-1077.
15. Scott TF, Kassab SL, Pittock SJ. Neuromyelitis optica IgG status in acute partial transverse myelitis. *Arch Neurol* 2006;63:1398-1400.
16. Matsuoka T, Matsushita T, Kawano Y, et al. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain* 2007;130:1206-1223.

The Transverse Myelitis Association is proud to be a source of information about Transverse Myelitis and the other neuroimmunologic disorders. Our comments are based on professional advice, published experience and expert opinion, but do not represent therapeutic recommendations or prescriptions. For specific information and advice, consult a qualified physician. The Transverse Myelitis Association does not endorse medications, treatments, products, services or manufacturers. Such names appear in this publication solely because they are considered valuable information. The Transverse Myelitis Association assumes no liability whatsoever for the contents or use of any medications, treatments, products or services mentioned.
