Neuromyelitis Optica IgG Serostatus in Fulminant Central Nervous System Inflammatory Demyelinating Disease

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Background: The aquaporin-4–specific serum autoantibody neuromyelitis optica (NMO) IgG is a validated biomarker distinguishing NMO spectrum disorders from multiple sclerosis (MS). Because fulminant attacks are more common in NMO spectrum disorders than in MS, some investigators suggest that NMO IgG may be a marker of destructive demyelination rather than a disease-specific biomarker. To our knowledge, this study is the first to compare NMO IgG serostatus among patients with fulminant central nervous system inflammatory demyelinating disease (CNS IDD).

Objective: To determine whether NMO IgG distinguishes patients with NMO spectrum disorders from those with other fulminant corticosteroid-refractory CNS IDD.

Design: Descriptive historical cohort.

Setting: Neuroimmunology laboratory and neurology practice, Mayo Clinic College of Medicine, Rochester, Minnesota.

Patients: Serum samples from 74 patients who underwent plasmapheresis between February 24, 1993, and November 22, 2007, for a corticosteroid-refractory CNS IDD were tested for NMO IgG by indirect immunofluorescence assay.

Main Outcome Measures: Two blinded observers scored serum samples tested at 1:120 dilution. Clinical data were obtained by medical record review.

Results: Preplasmapheresis serum samples were available from 74 patients (ratio of women to men, 2:5); the mean interval between blood draw and plasmapheresis was 13 days. At the time of plasmapheresis, the mean age of patients was 46 years (age range, 7-80 years); the mean Expanded Disability Status Scale score was 7.0 (score range, 3.5-9.5 [10.0 is death]). Diagnoses included MS (18 patients with definite and 11 patients with probable), longitudinally extensive transverse myelitis involving at least 3 vertebral segments (20 patients), NMO (14 patients), transverse myelitis involving fewer than 3 vertebral segments (8 patients), optic neuritis (2 patients), and acute disseminated encephalomyelitis (1 patient). Neuromyelitis optica IgG was detected in 20 patients (27%) (10 with longitudinally extensive transverse myelitis, 9 with NMO, and 1 with recurrent optic neuritis) and was not detected in any patient with MS, short transverse myelitis, monophasic optic neuritis, or acute disseminated encephalomyelitis.

Conclusion: Neuromyelitis optica IgG is a specific biomarker for NMO spectrum disorders and is not simply a marker of destructive CNS IDD.

Arch Neurol. 2009;66(8):964-966

EUROMYELITIS OPTICA (NMO) is a severe demyelinating disease of the central nervous system (CNS), conventionally recognized for its propensity to preferentially affect the optic nerves and spinal cord. Typically, NMO has a worse clinical outcome than multiple sclerosis (MS), with more frequent and earlier relapses.1 Prototype MS is not usually fulminant in nature, and MS lesions are not typically destructive. This is in contrast to NMO. It tends to be more fulminant and is characterized immunopathologically by destructive lesions affecting gray and white matter, with necrosis, vascular hyalinization, eosinophilic and neutrophilic inflammatory infiltrates, and extensive vasulocentric deposits of immunoglobulins and complement.2 Early distinction of NMO from MS is prognostically and therapeutically important because their optimal treatments differ (immunosuppression for NMO and immunomodulation for MS).1 Although the aquaporin-4–specific autoantibody NMO IgG has been convincingly shown to be a biomarker that reliably distinguishes NMO spectrum disorders from classic MS, to our knowledge, no previous study has investigated the specificity of NMO IgG expressly in the setting of fulmi-
nant NMO compared with fulminant CNS inflammatory demyelinating disease (CNS IDD).\textsuperscript{3-13} Fulminant attacks are more common in NMO than in MS; therefore, some investigators suggest that NMO IgG may simply be a marker of fulminant CNS IDD rather than a specific identifier for NMO.\textsuperscript{1} Plasmapheresis is an effective treatment for corticosteroid-refractory fulminant attacks of CNS IDD.\textsuperscript{14} In this study, we analyze NMO IgG serostatus among a cohort of patients with CNS IDD who underwent plasmapheresis for a fulminant attack to determine whether NMO IgG is merely a marker of a destructive CNS demyelinating process or is, indeed, a specific biomarker for NMO spectrum disorders.

**METHODS**

Mayo Clinic patients treated between February 24, 1993, and November 22, 2007, by plasmapheresis for a fulminant corticosteroid-refractory attack of CNS IDD were identified from a larger cohort undergoing plasmapheresis (n = 212). Inclusion criteria were the following: (1) CNS IDD, (2) plasmapheresis for a fulminant corticosteroid-refractory CNS IDD attack, and (3) archival serum samples collected 0 to 3 months before plasmapheresis. Serum samples were tested for NMO IgG by indirect immunofluorescence assay (doubling dilutions, starting at 1:120).\textsuperscript{4} Titers were the reciprocal of the last dilution scored positive. Two independent observers (S.J.P. and V.A.L.) blinded to diagnosis scored the typical immunostaining pattern as positive (titer $\geq 120$) or negative. Clinical data were obtained by medical record review. Diagnoses were based on the following published criteria: monophasic optic neuritis (ON), MS (probable or definite),\textsuperscript{13,18} acute disseminated encephalomyelitis (ADEM),\textsuperscript{17} short transverse myelitis (TM) involving fewer than 3 vertebral segments,\textsuperscript{19} and NMO and NMO spectrum disorders (longitudinally extensive transverse myelitis [LETM] involving $\geq 3$ vertebral segments and recurrent ON).\textsuperscript{1} Before serum sampling, all patients had received immunosuppressive or immunomodulatory therapies.

**RESULTS**

Preplasmapheresis serum samples were available from 74 patients (ratio of women to men, 2:5). The mean interval between blood draw and plasmapheresis was 13 days (range, 0-95 days). The mean age of patients at the time of plasmapheresis was 46 years (age range, 7-80 years), and the mean Expanded Disability Status Scale score was 7.0 (score range, 3.5-9.5 [10.0 is death]). Diagnoses at attack onset included the following: MS (29 patients [18 definite and 11 probable]), LETM (20 patients [7 monophasic and 13 recurrent]), NMO (14 patients [1 monophasic and 13 recurrent]), short TM (8 patients [6 monophasic and 2 recurrent]), ON (2 patients [1 monophasic and 1 recurrent]), and ADEM (1 patient). Neuromyelitis optica IgG was detected in 20 patients (27%) (10 with LETM, 9 with NMO, and 1 with recurrent ON). Neuromyelitis optica IgG was undetected in any patient with ADEM, short TM, monophasic ON, or definite or probable MS. Titer values ranged from 240 to 61,440 (Figure). The mean disease duration at the last follow-up was 4.8 years (range, 48 days to 38 years). At the last follow-up, 10 of 20 patients (50%) with NMO IgG seropositivity had subsequent relapses, and 5 patients with LETM (3 with NMO IgG seropositivity) had progressed to meet diagnostic criteria for definite NMO. Patient diagnoses at the last follow-up included 27 with MS (22 definite and 5 probable), 19 with recurrent NMO, 14 with LETM (4 monophasic and 10 recurrent), 7 with short TM (5 monophasic and 2 recurrent), and 1 each with ADEM, recurrent ON, monophasic ON, and clinically isolated demyelinating syndrome. Diagnoses were unknown for 3 patients.

**COMMENT**

Neuromyelitis optica is often misdiagnosed as MS and is still considered by some to be a variant of MS. Recently reported clinical, radiographic, pathologic, and immunologic characteristics of NMO have led to recognition of NMO as a distinct entity from prototypic MS.\textsuperscript{1} Discovery of the aquaporin-4-specific autoantibody NMO IgG defined a specific humoral immune response associated with NMO and supported the existence of distinct underlying immunopathogenic mechanisms in NMO and MS.\textsuperscript{2,14-16} However, these previous studies examined the specificity of NMO IgG in the setting of classic nonfulminant MS. Because fulminant attacks are more frequent in NMO spectrum disorders and only equal in MS, the question of whether NMO IgG is simply a marker of fulminant CNS IDD has remained unaddressed, to our knowledge. The present study confirms previous findings that NMO IgG is a specific biomarker for NMO and its spectrum disorders and establishes that it is not an accompaniment of other severe inflammatory CNS demyelinating diseases, even in fulminant cases.\textsuperscript{2} Neuromyelitis optica IgG was restricted to patients with NMO or an NMO spectrum disorder. It was not detected in any patient with fulminant MS or another CNS IDD. Our observations further support that NMO is a distinct entity from MS and emphasize the necessity for early diagnosis to ensure early initiation of appropriate immunosuppressive therapies.
Author Contributions: Study concept and design: Magaña, Pittock, Lennon, and Lucchinetti. Acquisition of data: Magaña and Pittock. Analysis and interpretation of data: Magaña, Pittock, Weinshenker, and Lucchinetti. Drafting of the manuscript: Magaña. Critical revision of the manuscript for important intellectual content: Magaña, Pittock, Lennon, Keegan, Weinshenker, and Lucchinetti. Obtained funding: Lennon. Administrative, technical, and material support: Magaña and Pittock. Study supervision: Magaña, Pittock, Lennon, and Lucchinetti.

Financial Disclosure: In accord with the Bayh-Dole Act of 1980 and Mayo Foundation policy, Drs Lennon, Weinshenker, and Lucchinetti stand to receive royalties for intellectual property related to the aquaporin-4 autoantigen. To date, the authors have received less than $10,000 in royalties. Dr Weinshenker served as a consultant to Genentech Inc for development of a clinical trial for NMO, in royalties. Dr. Weinshenker was an author of a textbook and received royalties on the textbook. Dr. Weinshenker is a co-founder of the biotechnology company Genecious, Inc. Dr. Weinshenker has served as a consultant to several companies involved in the development of treatments for multiple sclerosis, in royalties. Dr. Weinshenker has served as an advisor to several companies involved in the development of treatments for multiple sclerosis, in royalties.

This work was supported by Clinical and Translational Science Awards grant 1 TL1 RR024152-01 from the National Institutes of Health (Ms Magaña) and by the Guthy-Jackson Charitable Foundation (Drs Lennon, Weinshenker, and Lucchinetti).

Additional Contributions: Lea Dacy, AB, provided assistance in the preparation of the manuscript.

REFERENCES