The pathogenic relationship between neuromyelitis optica (NMO) and multiple sclerosis (MS) continues to be debated despite mounting evidence that these are distinct entities.1-3 The NMO-IgG, which targets the water channel protein aquaporin-4 (AQP4), is the first confirmed serum biomarker for any form of central nervous system inflammatory demyelinating disease and reliably distinguishes NMO from MS and other neurological diseases. Four immunopathological patterns (IP I-IV) have been described in early active MS lesions.4 Some investigators have interpreted humoral MS IP II as having an immunopathogenic link with NMO because both share complement and immunoglobulin deposition and have a greater likelihood than other forms of MS to respond favorably to plasma exchange therapy.4,5 Here, we describe the NMO-IgG status of a cohort of patients with biopsy-proven early active lesions consistent with MS.

Methods. All patients had biopsy-proven central nervous system inflammatory demyelination consistent with MS (n=85; 43 women), were classified immunohistochemically (IP I-IV),4 were enrolled into the MS lesion project (National Multiple Sclerosis Society RG 3185), and, at the last visit, were bled to test serum for NMO-IgG using indirect immunofluorescence.

Results. Clinical Characteristics of Biopsy Cohort. Enrolled patients had a spectrum of disease courses (relapsing remitting, 57; monophasic, 20; primary progressive, 0; secondary progressive, 7; and uncertain, 1 patient). The median age at biopsy was 38 years (interquartile range, 27-46 years), expanded disability status scale score at biopsy was 2.0 (interquartile range, 1.0-3.5), and disease duration prior to biopsy was 1.4 months (interquartile range, 0.6-4.9 months). At the last follow-up (median, 3.6 years from disease onset), 85% of patients were defined as having definite (n=65) or probable MS (n=7). The remaining 13 patients (15%) were classified as having a clinically isolated syndrome.

NMO-IgG Status Of Biopsy MS Cohort. The distribution of immunopathological patterns for the patients was as follows: IP I, n=15; IP II, n=53; IP III, n=17; IP IV, n=0. All were seronegative for NMO-IgG. Eighteen of 85 patients (22%) had received 1 or more immunosuppressant medication or plasma exchange in the 3-month period prior to blood draw (intravenous methylprednisolone, 6; short-term prednisone, 6; long-term prednisone, 5; methotrexate, 1; cyclophosphamide, 1; mitoxantrone, 2; and plasma exchange, 2). A minority (45%) were receiving immunomodulatory medications (interferon beta or glatiramer acetate) in the 3-month period prior to blood draw.

Comment. This study shows a lack of detectable NMO-IgG in pathologically confirmed patients with MS including those with evidence of humoral MS pathology (IP II), supporting the idea that MS and NMO are distinct clinicopathologic entities. The low percentage of patients receiving immunosuppressant therapy at the time of blood draw minimizes the potential for treatment to have been a determinant of seronegativity. Although immune complex deposition is a characteristic immunopathological finding for both NMO and MS IP II, the distribution of immune complexes is distinct.3 In MS IP II lesions, complement is deposited at sites of active myelin destruction with increased AQP4 expression, even in regions of immune complex deposition (Figure, A and B). In active NMO lesions, complement is deposited in a vasculocentric rim and rosette pattern similar to the normal distribution of AQP4 (C); C9 neo reactivity is associated with a complete loss of AQP4 immunoreactivity in this same region (D). Immunocytochemistry for C9 neo antigen is red; AQP4, brown.

Figure. Comparison of C9neo and aquaporin 4 (AQP4) immunoreactivity in multiple sclerosis pattern II and neuromyelitis optica active lesions. A and B, Pattern II active multiple sclerosis brain lesion is shown; immunoreactivity to C9neo antigen is noted within myelin-laden macrophages (arrows), but absent around blood vessels (arrowhead) (A). This corresponds to a region of increased AQP4 immunoreactivity, with prominent staining of the cytoplasmic surface and processes of reactive astrocytes (B). C and D, Active neuromyelitis optica spinal cord lesion is shown. The C9neo antigen is deposited in a vasculocentric rim and rosette pattern similar to the normal distribution of AQP4 (C); C9neo reactivity is associated with a complete loss of AQP4 immunoreactivity in this same region (D). Immunocytochemistry for C9 neo antigen is red; AQP4, brown.
of immune complex deposition (Figure, C and D). In vitro, NMO-IgG binds selectively to target cell membranes expressing AQP4 and causes complement activation or rapid downregulation of AQP4 expression, implicating a complement-activating AQP4-specific autoantibody in the pathogenesis of NMO lesions. Thus, NMO-IgG is not an epiphenomenon of antibody-mediated pathology, but rather a specific biomarker that reliably distinguishes NMO-related disorders from MS and plausibly allows the classification of NMO as an autoimmune channelpathy selectively targeting the central nervous system.

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Financial Disclosure: All coauthors have seen and agreed with the contents of the manuscript. In accordance with the Bayh-Dole Act of 1980 and Mayo Foundation policy, Drs Lennon and Lucchinetti report that they stand to receive royalties for intellectual property related to the aquaporin-4 autoantigen. This intellectual property is licensed to a commercial entity for development of a simple antigen-specific assay to be made available worldwide for patient care. The test will not be exclusive to Mayo Clinic. To date, the authors have received a total of less than $10 000 in royalties. Mayo Clinic offers the test as an in-house test with the options of reporting patient care. The test will not be exclusive to Mayo Clinic. The authors have received a total of less than $10 000 in royalties. Mayo Clinic offers the test as an in-house test with the options of reporting patient care. The test will not be exclusive to Mayo Clinic.

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COMMENTS AND OPINIONS

Notice of Incomplete Referencing

A s the Editor of the Archives of Neurology, I am writing to inquire about your article titled “Cross-reactive T-Cell Receptors in Tumor and Para-neoplastic Target Tissue,” which was published in the May 2009 issue of the Archives.1

You recently wrote to the Editor of The Journal of the Neurological Sciences (JNS) that:

“I wanted to let you know that we have used biological material from the patient described in full detail in our paper 10974 in another paper just appearing in Arch Neurol (attached). In that paper we report CDR3 spectratyping data of tumor and CNS. However, in the “methods” section, we very briefly scratch the clinical scenario so readers understand the CDR3 data presented. We have always felt that this would not be a problem.”

Actually, there is a problem, which requires a candid explanation from you so I can make a judgment about how this happened and what should be reported to our readers. The JNS article was accepted August 6, 2008, and the Archives of Neurology article was accepted October 1, 2008. The 2 articles shared biological material from 1 patient, which was not disclosed to the Archives. In addition to making a timely, voluntary disclosure to me and my editors, your article should have included a reference to the JNS article. Both the disclosure of the duplicate biological material and the reference to the JNS article in the Archives article should have been made to us before publication. These facts may have influenced our decision to accept and publish your study in our journal, and most certainly would have been shared with our readers. The AMA Manual of Style sections 5.3 and 5.3.2 indicate that you should have informed and consulted me about these facts when you submitted your manuscript.2

You apparently had months to alert and consult me between the time of acceptance by JNS and publication in that journal on May 15, 2009. We are grateful that Raymond Voltz, MD, the only author of both articles, revealed this lack of disclosure now, but we require a full explanation to set the record straight in our journal.

The Archives of Neurology takes duplicate publication and the concurrent submission of studies seriously, so we require an explanation, and perhaps an apology, depending on the circumstances. A timely response to this letter would be appreciated. We often contact the