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Editorial

Anti-myelin oligodendrocyte glycoprotein antibodies in multiple sclerosis

Anthony T. Reder, MD; and Joel J. Oger, MD, FRCPC

Can serum antibodies to myelin oligodendrocyte glycoprotein (MOG) be used as a marker of multiple sclerosis (MS) or to predict the course of MS? Recent articles present conflicting data in response to these questions. Berger et al.[1] tested for presence of serum antibodies to MOG in patients experiencing a first clinically isolated syndrome suggestive of MS. Those who progressed almost invariably had anti-MOG antibodies. Conversely, Lampasona et al.[2] in this issue of *Neurology* report only low levels of anti-MOG antibodies in patients with MS and control subjects.

Autoantibodies to many myelin constituents are present in patients with MS. These antibodies may be an autoimmune reaction to an "MS antigen" or simply part of a generalized "nonsense" antibody response. In either case, the antibodies may affect the pathology of MS. Potential myelin autoantigens include myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG), 2',3'-cyclic nucleotide 3'-phosphodiesterase, and MOG. Because MBP accounts for ~30% of central myelin protein, it has traditionally been viewed as the major target for immune responses in MS and experimental allergic encephalomyelitis (EAE). However, MBP and PLP are in compact myelin and not easily accessible to the immune system. Although MOG is only a minor constituent of myelin proteins (at most 0.05%), this 218-amino acid glycoprotein may be an important immune target in MS.

MOG is unique to the brain; it is located on the outer lamellae of oligodendroglial membranes and myelin; it is highly immunogenic; and MOG immunization induces severe relapsing EAE in rodents and marmosets.[3] The extracellular portion of MOG protein is the dominant target in EAE induced by brain homogenates. It is recognized by encephalitogenic T cells and antibodies, with these two arms of immunity synergizing to cause CNS destruction. IV anti-MOG antibodies convert EAE from a nondemyelinating, moderately inflammatory disease to a severe inflammatory disease with extensive demyelination.[3] T cells proliferate to MOG more than to other myelin antigens in patients with MS.[4] Anti-MOG antibodies fix complement and are bound to disintegrating myelin in acute MS lesions.[5] Anti-MOG antibodies are present in serum and CSF of one-third of patients at the time of their first attack of MS.[6] The antibodies persist at a stable titer (usually 1:1000 to 1:2000) and are present at the same frequency in all stages of MS. More than two-thirds of patients with MS have T cells in the blood that proliferate when exposed to purified human MOG; in the CSF, T cells from 12 of 14 patients were responsive.[7] There are also immunoglobulin (Ig) G anti-MOG responses in viral and bacterial meningitis. However, these antibodies disappear as the meningitis resolves, but the CSF anti-MOG index is persistently higher in MS.

Why do these results seem to conflict with those of Lampasona et al.?[2] A difference in patient populations is unlikely because the MOG response seems to be present in all forms and all stages of MS in multiple studies. Technical differences are more likely and suggest important immune principles in MS.

Berger et al.[1] used the first 102 N-terminal amino acids of recombinant human MOG, expressed in *Escherichia coli*, as the antigen in their Western blot analyses and previous ELISAs.[6] Sugar groups are missing from the recombinant molecule, yet MOG is a brain glycoprotein. When antigens are directly isolated or expressed in mammalian cells,[2] they are glycosylated; when they are expressed in bacteria, as in the report of Berger et al.,[1] sugar moieties are lost. Glycosylated proteins conserve their tertiary structure better, and tertiary structure is necessary for antibody binding. Sugars can also protect some otherwise hidden antibody-binding sites. Therefore, glycosylated and unglycosylated proteins may have different antibody-binding patterns.

Smaller unglycosylated MOG peptides have varying antigenicity. Sera from patients with MS bind to several members of a panel of overlapping 25 amino acid peptides; however, the same sera do not bind to native MOG on the oligodendrocyte surface.[8] Antibodies induced by vaccination with DNA encoding

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From the Department of Neurology, University of Chicago, IL.
Address correspondence and reprint requests to Dr. Anthony T. Reder, Department of Neurology, MC 2030, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637; e-mail: areder@neurology.bsd.uchicago.edu

the glycosylated, mature MOG protein are highly dependent on conformation. However, denatured, poorly refolded, recombinant MOG extracted from bacteria generates a much more complex antibody response.[3]

Western blot analyses and ELISAs can alter protein conformation and tertiary structure. Western blot analyses require solubilization in sodium dodecyl sulfate detergent, destruction of sulfhydryl bonds, and boiling. In direct-binding ELISA, the antigen is bound to plastic by electric charges at pH 9.0, a procedure that tends to change the tertiary structure of the proteins. Nonspecific binding is also more difficult to avoid in direct ELISA assays. The liquid phase-radiobinding assay used by Lampasona et al.[2] avoids both of these problems. Here, the protein floats in solution in its natural state.

Assays with glycosylated MOG (Lampasona et al.[2]) reflect the immune response to intact MOG. However, damaged myelin or macrophage-processed myelin (possibly reflected by the assays of Berger et al.[1]) could allow generation of new antigens. Thus, results will change with different methods.

These papers support earlier work showing that low and high affinity antibodies are increased in MS. There are antibodies with multiple specificities in MS plaques: some against myelin proteins, some against viruses, and most with unknown "nonsense" specificities.[9] There are also higher than normal titers of antibodies in the serum and CSF directed against multiple viruses (e.g., measles and Epstein–Barr virus), against MBP (present in normal family members at the same rate but greater than control subjects; also true for MOG), and against nuclear and thyroid microsomal antigens.[10,11] IgM appears early in the immune response, has low binding avidity, and is less specific than IgG. Certain other CNS antigens are bound mainly by IgM in MS plaques, e.g., CNPase and nitrosylated cysteine residues (present in 50–60% of patients with secondary progressive MS).[13] This may merely reflect the increased immunoglobulin secretion in MS, but could be a specific response with pathogenic importance of IgM in MS lesions. Second, there is nonspecific B-cell activation in MS patients that generates antibodies to multiple antigens. MS B cells respond more vigorously to pokeweed mitogen, especially before exacerbations and during progressive disease.[12]

Patients with "clinically isolated syndrome" (CIS) included in the study of Berger et al. had CSF oligoclonal bands and old and new MRI lesions.[1] It is possible that with this definition of CIS, MS has been present for some time, allowing epitope spread and responses to multiple antigens. Another control would be acute disseminated encephalomyelitis (ADEM) or postinfectious encephalomyelitis, a multifocal, yet monophasic disease that usually does not evolve into the continuous immune response of MS. The early assay in ADEM or at the CIS stage in the course of MS could explain the type of antibody. The constant prevalence of IgM antibodies across MS disease states and duration argues that either 1) a continuous exposure to MOG or a related antigen allows maximal anti-MOG antibody generation even before the CIS; or 2) nonspecific immune activation with antibodies is part of the immune makeup of patients with MS, possibly even before MS develops.

We suggest that the authors of the papers comment on their techniques to facilitate clinical neurologists' interpretation of the data. The take-home message is that most of these findings represent nonsense antibodies that measure the antigenicity of the proteins involved more than a specific root cause of MS. The antibodies may reflect the increased immune response of MS patients more than the pathogenicity of the antibodies, yet still could have predictive value.

The MS field is increasingly exciting with the arrival of new and powerful imaging techniques and therapies. We look forward to tests that characterize the immune response, genes, transcriptional profile, and protein response. This will provide an "MS signature" in individual patients, allowing physicians to make firm diagnoses, determine prognosis, and direct therapy.

References

1. Berger T, Rubner P, Schautzer F, et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med 2003;349:139–145.
2. Lampasona V, Franciotta D, Furlan R, et al. Similar frequency of anti-MOG IgG and IgM in MS patients and healthy subjects. Neurology 2004;62:2092–2094.
3. Iglesias A, Bauer J, Litzenburger T, Schubart A, Linington C. T- and B-cell responses to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis and multiple sclerosis. Glia 2001;36:220–234.
4. Kerlero de Rosbo N, Milo R, Lees MB, Burger D, Bernard CCA, Ben-Nun A. Reactivity to myelin antigens in multiple sclerosis. Peripheral blood lymphocytes respond predominantly to myelin oligodendrocyte glycoprotein. J Clin Invest 1993;92:2602–2608.
5. Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med 1999;5:170–175.
6. Reindl M, Linington C, Brehm U, et al. Antibodies against the myelin oligodendrocyte glycoprotein and the myelin basic protein in multiple sclerosis and other neurological diseases: a comparative study. Brain 1999;122:2047–2056.
7. Sun J, Link H, Olsson T, et al. T and B cell responses to myelin-oligodendrocyte glycoprotein in multiple sclerosis. J Immunol 1991;146:1490–1495.
8. Haase CG, Guggenmos J, Brehm U, et al. The fine specificity of the myelin oligodendrocyte glycoprotein autoantibody response in patients with multiple sclerosis and normal healthy controls. J Neuroimmunol 2001;114:220–225.
9. Mattson DH, Roos RP, Arnason BGW. Isoelectric focusing of IgG eluted from multiple sclerosis, subacute sclerosing panencephalitis and normal brains. Nature 1980;287:335–337.
10. Hughes LE, Bonell S, Natt RS, et al. Antibody responses to *Acinetobacter* spp and *Pseudomonas aeruginosa* in multiple sclerosis: prospects for diagnosis using the myelin-*acinetobacter*-neurofilament antibody index. Clin Diagn Lab Immunol 2001;8:1181–1188.
11. Reder AT. Multiple sclerosis. In: Gilman S, ed. Neurobase, Medlink Neurology. San Diego: Medlink Corporation, www.medlink.com, 2004.
12. Oger J, Kastrukoff LF, Li DKB, Paty DW. Multiple sclerosis: in relapsing remitting patients, immune functions vary with disease activity as assessed by MRI. Neurology 1988;38:1739–1744.
13. Boullerne AI, Rodriguez JJ, Touil T, et al. Anti-S-nitrosocysteine antibodies are a predictive marker for demyelination in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. J Neurosci 2002;22:123–132.