

ORIGINAL ARTICLE

Lack of Association between Antimyelin Antibodies and Progression to Multiple Sclerosis

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ABSTRACT

BACKGROUND

Patients with a single episode of neurologic dysfunction and brain magnetic resonance imaging (MRI) scans suggestive of multiple sclerosis are at high risk for clinically definite multiple sclerosis, but the outcome for individual patients is unpredictable. An increased risk of progression to clinically definite multiple sclerosis in patients with serum antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) has been reported.

METHODS

We measured serum anti-MOG and anti-MBP IgG and IgM antibodies in 462 patients with a first clinical event suggestive of multiple sclerosis and at least two clinically silent lesions on brain MRI. The patients were participating in a multicenter trial of treatment with interferon beta-1b. Antibodies were assessed by Western blot analysis at baseline, and the results compared with the time and rate of progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis as defined by an international panel (the McDonald criteria). Regular visits were scheduled for the assessment of neurologic impairment and for MRI before treatment and at months 3, 6, 9, 12, 18, and 24.

RESULTS

No associations were found between the presence of anti-MOG and anti-MBP IgM and IgG antibodies and progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis according to the McDonald criteria, either in the entire cohort or in any subgroups of the study population.

CONCLUSIONS

Serum antibodies against MOG and MBP, as detected by Western blot analysis, are not associated with an increased risk of progression to clinically definite multiple sclerosis in patients who have had a clinically isolated syndrome suggestive of multiple sclerosis.

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AFTER A FIRST EPISODE OF CENTRAL nervous system dysfunction that is suggestive of multiple sclerosis (known as a clinically isolated syndrome), it is difficult to predict the individual risk of multiple sclerosis. Berger et al.¹ reported a significantly increased risk of clinically definite multiple sclerosis among patients with a clinically isolated syndrome and serum antibodies against recombinant myelin oligodendrocyte glycoprotein (MOG) and purified myelin basic protein (MBP), detected by Western blot analysis.

MOG is a minor component of myelin (0.01 to 0.05% of central myelin protein) that is found exclusively in the central nervous system.² The N-terminal domain of MOG is expressed on the myelin surface and is easily accessible to antibodies.³ Several lines of evidence suggest that antibody-mediated demyelination plays a role in multiple sclerosis^{4,5}; anti-MOG antibodies are capable of inducing demyelination in animal models of autoimmune encephalomyelitis and in brain-cell cultures,⁶⁻⁸ and in one study they were detected in damaged myelin from patients with multiple sclerosis.⁹ MBP constitutes about 30% of the central myelin protein and is localized on the cytoplasmic side of the myelin sheath.¹⁰

The Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial was conducted to explore the effect of interferon beta-1b (Betaseron, Schering), given subcutaneously every other day, on the rate of progression to clinically definite multiple sclerosis in patients with a clinically isolated syndrome.¹¹ Using methods identical to those of Berger et al.,¹ we measured anti-MOG and anti-MBP antibodies in patients recruited for this trial and compared the results with the primary outcomes.

METHODS

PATIENTS AND STUDY DESIGN

The BENEFIT study was a double-blind, placebo-controlled, randomized, parallel-group, multicenter, phase 3 trial designed to evaluate the safety, tolerability, and efficacy of interferon beta-1b, at a dose of 250 μ g (8 mIU) given subcutaneously every other day, for the treatment of a first clinical episode that was suggestive of multiple sclerosis.¹¹ Eligible patients were between 18 and 45 years old, had presented with a first neurologic event

suggestive of multiple sclerosis, and had at least two clinically silent lesions on a T₂-weighted brain magnetic resonance imaging (MRI) scan. Patients with symptoms and signs indicative of a single lesion (monofocal presentation) or more than one lesion (multifocal presentation) in the central nervous system were eligible; their baseline score on the Expanded Disability Status Scale (EDSS)¹² had to be between 0 and 5 (on a scale of 0 to 10, with higher scores indicating greater disability). Patient eligibility was confirmed centrally before randomization. At the discretion of the treating neurologist, corticosteroids were used to treat the initial event before randomization. The research protocol was approved by the institutional review boards of the participating centers, and all participants gave written informed consent before being enrolled.

Patients were randomly assigned in a 5:3 ratio to receive 250 μ g of interferon beta-1b or placebo for up to 24 months or until clinically definite multiple sclerosis was diagnosed according to slightly modified Poser criteria.¹¹⁻¹³ Study treatment was initiated within 60 days after the occurrence of the first clinical event.

The EDSS score, other data, and blood samples were collected at screening, baseline, and months 3, 6, 9, 12, 18, and 24. MRI was performed at screening and at months 3, 6, 9, 12, 18, and 24. Analysis of cerebrospinal fluid was performed at the discretion of the investigators at the participating centers. Results were considered positive when oligoclonal bands or intrathecal IgG production was detected. Serum samples obtained at baseline, before treatment began, were used for analysis of anti-MOG and anti-MBP antibodies.

WESTERN BLOT ANALYSIS FOR ANTI-MOG AND ANTI-MBP ANTIBODIES

We performed the Western blot analysis exactly according to the protocol described by Berger et al. (with a serum dilution for IgG of 1:1000).¹ The human recombinant extracellular MOG domain (amino acids 1 through 125) was provided by Berger et al.,¹ and human myelin-derived MBP was obtained commercially (from Chemicon). Before performing the antibody measurements, we confirmed the reliability of the results of the Western blot analysis between our laboratory and that of Berger et al.¹⁴ The blots were assessed independently by two of the study investigators, who

had no access to clinical or MRI findings. A serum sample was considered to be positive if the immunoreactivity was greater than that of a standard negative control sample. Monoclonal antibodies to MBP (MAB381, Chemicon) and MOG (8.18-C5, M. Reindl, Innsbruck)³ and known positive and negative human serum samples were used as controls.

STATISTICAL ANALYSIS

The baseline characteristics of the patients were compared in the placebo and treatment groups according to antibody status with the use of the chi-square or Kruskal–Wallis test. The cumulative risk of progression to clinically definite multiple sclerosis¹³ or multiple sclerosis as defined by an international panel (the McDonald criteria)¹⁵ was calculated with the Kaplan–Meier method. Cox proportional-hazards analysis, adjusted for potential confounding variables, was used to assess whether antibody status predicted the development of clinically definite multiple sclerosis (as indicated by Berger et al.¹) or the development of multiple sclerosis according to the McDonald criteria. The final model also included adjustment for age, sex, use or nonuse of corticosteroid treatment for the first event, the effect of treatment with interferon beta-1b, multifocal or monofocal disease presentation, and the number of gadolinium-enhancing lesions on T₁-weighted MRI scans and the number of hyperintense lesions on T₂-weighted scans.

Analyses for IgG and IgM antibody status were performed separately. Cox proportional-hazards analysis was used for the subgroup of patients with positive cerebrospinal fluid findings, patients who received corticosteroid treatment for the initial episode and those who did not, and interferon beta-1b and placebo recipients. Subgroup analyses were also performed for patients with different lag times between the initial event and sample collection (i.e., patients with lag times within the first, second, third, and fourth quartiles of the total cohort). The results are expressed as medians and interquartile ranges.

The statistical analyses of anti-MOG and anti-MBP antibodies were performed on a post hoc basis, and P values were not adjusted for multiple testing. All reported P values are two-sided; a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Serum samples from 462 of the 468 patients included in the BENEFIT study were analyzed for anti-MOG and anti-MBP antibodies; baseline serum samples were not available for six patients. Four hundred thirty-two patients (94%) were followed for 24 months or until clinically definite multiple sclerosis was diagnosed; 30 patients (6%) dropped out of the study before clinically definite multiple sclerosis was diagnosed (median follow-up time for all patients, 699 days).

During the 2-year observation period, clinically definite multiple sclerosis was diagnosed in 150 patients (32%), and multiple sclerosis according to the McDonald criteria in 331 (72%). A total of 327 patients (71%) received corticosteroid treatment for the first event, and 245 (53%) had a monofocal disease presentation. The median number of lesions seen on T₂-weighted MRI scans was 17 (interquartile range, 7 to 38), and the median number of lesions seen on gadolinium-enhanced, T₁-weighted scans was 0 (interquartile range, 0 to 1). According to the randomization ratio of the study, 289 of 462 patients (63%) were randomly assigned to receive interferon beta-1b treatment and 173 (37%) to receive placebo. Of 310 patients who underwent cerebrospinal fluid testing, 263 (85%) had findings compatible with intrathecal IgG synthesis (a raised IgG index or oligoclonal bands). Blood samples were obtained for antibody analysis a median of 55 days after the onset of the first event (interquartile range, 46 to 59).

Table 1 shows the baseline characteristics of the patients according to whether they were positive or negative for anti-MOG and anti-MBP IgM and IgG antibodies. A significantly higher proportion of women had positive antibody findings for both IgM and IgG. The proportion of patients who had received corticosteroids was lower among those who were positive for anti-MOG and anti-MBP IgG antibodies and among those who were negative for anti-MOG IgG antibodies but positive for anti-MBP IgG antibodies; the proportion of patients treated with corticosteroids did not differ according to IgM antibody status (Table 1). No other significant differences between patient groups were observed.

As shown by the Kaplan–Meier plots in Figure 1, the risk of clinically definite multiple sclerosis over a period of 2 years was not influenced

Table 1. Clinical and Demographic Characteristics of the 462 Patients According to IgM and IgG Antibody Status.

Variable	IgM Antibodies		IgG Antibodies	
	Negative for Anti-MOG Antibodies and Positive for Anti-MBP Antibodies	Positive for Anti-MOG Antibodies and Negative for Anti-MBP Antibodies	Negative for Anti-MOG Antibodies and Positive for Anti-MBP Antibodies	Positive for Anti-MOG Antibodies and Negative for Anti-MBP Antibodies
All patients — no. (%)	221 (48)	119 (26)	76 (16)	33 (7)
Female sex — no. (%)	141 (64)	85 (71)	62 (82)†	30 (91)‡
Age — yr				
Mean	29	30	30	31
Interquartile range	24–36	24–37	25–38	27–39
Interferon beta-1b treatment — no. (%)	139 (63)	76 (64)	45 (59)	24 (73)
Corticosteroid treatment of first event — no. (%)	148 (67)	87 (73)	57 (75)	18 (55)¶
Cerebrospinal fluid analysis performed				
No. of patients	141	82	57	42
No. with positive results (%)	121 (86)	71 (87)	51 (89)	14 (78)
Monofocal presentation — no. (%)	117 (53)	67 (56)	39 (51)	14 (42)
No. of lesions on T ₂ -weighted MRI				
Median	17	19	16	21
Interquartile range	7–38	9–37	7–33	10–37
No. of lesions on gadolinium-enhanced, T ₁ -weighted MRI				
Median	0	0	0	0
Interquartile range	0–2	0–1	0–1	0–1
Time from disease onset to collection of blood sample — days				
Median	55	55	55	56
Interquartile range	47–59	44–58	45–59	48–59

* P=0.02 for the comparison with patients who were seronegative for anti-MOG and anti-MBP IgM antibodies.
 † P=0.004 for the comparison with patients who were seronegative for anti-MOG and anti-MBP IgM antibodies.
 ‡ P=0.008 for the comparison with patients who were seronegative for anti-MOG and anti-MBP IgG antibodies.
 § P=0.01 for the comparison with patients who were seronegative for anti-MOG and anti-MBP IgG antibodies.
 ¶ P=0.02 for the comparison with patients who were seronegative for anti-MOG and anti-MBP IgG antibodies.

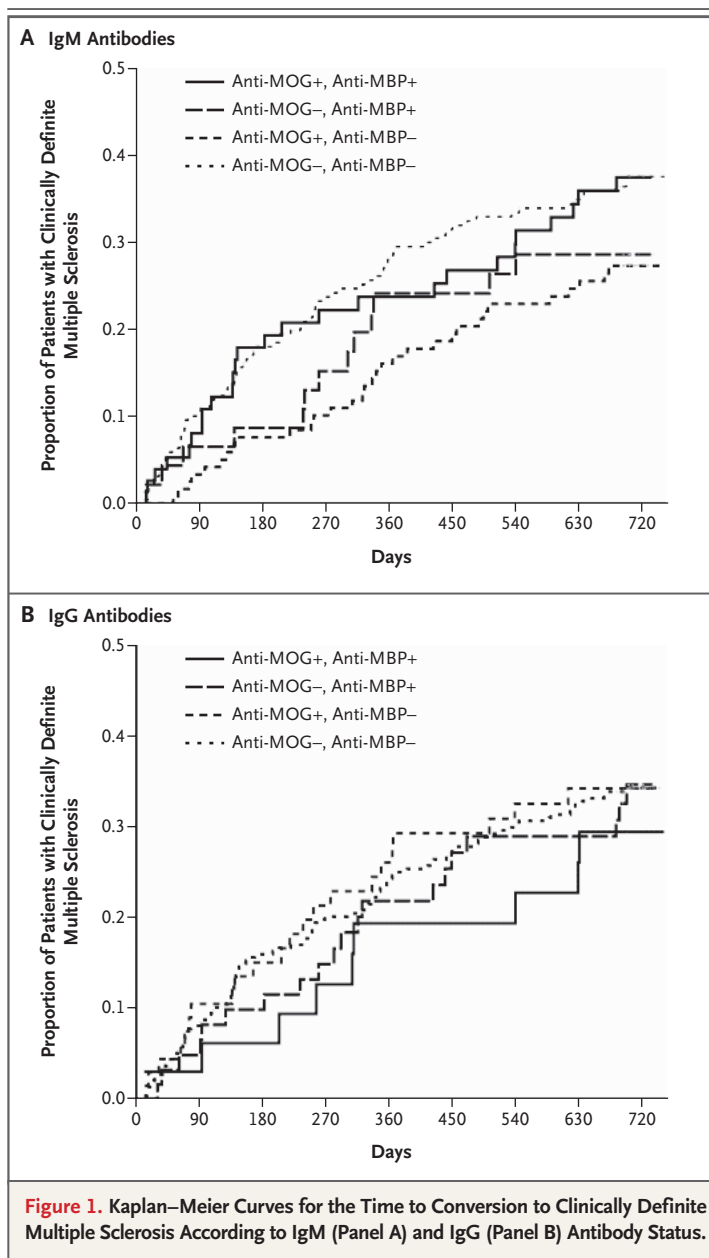
by antibody positivity. Adjusted Cox proportional-hazards analysis showed that the risk of clinically definite multiple sclerosis over the 2-year observation period was not increased in any of the patient groups with positive IgM antibody findings (Table 2). There was, however, an indication of a decrease in the risk of clinically definite multiple sclerosis in patients who were positive for anti-MOG IgM antibodies and negative for anti-MBP IgM antibodies. With respect to IgG antibody status, the risk of clinically definite multiple sclerosis was not increased in any of the patient groups, and hazard ratios were all close to 1.0. The risk of clinically definite multiple sclerosis was significantly decreased by treatment with interferon beta-1b and was increased among patients who had received corticosteroid treatment for the initial clinical event or who had gadolinium-enhancing lesions on T₁-weighted MRI scans at baseline.

The Cox proportional-hazards analyses for the development of multiple sclerosis according to the McDonald criteria provided similar results: the risk of multiple sclerosis was not significantly increased in any of the patient groups with positive IgM or IgG antibody findings, and hazard ratios were all below or close to 1.0 (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The distribution of IgM and IgG antibody status in the subgroups of patients with positive cerebrospinal fluid results, those randomly assigned to receive placebo or interferon beta-1b, and those who had received corticosteroid treatment, as well as the distribution of antibody status according to the interval between the initial episode and sample collection, was similar to the distribution in the entire patient cohort. The Cox proportional-hazards analyses for these subgroups did not reveal any significant increase in the risk of clinically definite multiple sclerosis among patients with positive antibody findings (IgM, IgG, or both) (see Table 2 of the Supplementary Appendix).

DISCUSSION

In this study, we attempted to reproduce the previously reported finding of an association between serum anti-MOG and anti-MBP IgM antibody status and the prognosis in the early phase of multiple sclerosis⁴; we were unable to confirm this



association. There was no increase in the risk of clinically definite multiple sclerosis or of multiple sclerosis according to the McDonald criteria among patients who were positive for anti-MOG antibodies, anti-MBP antibodies, or both. This was true for both IgM and IgG antibodies not only in the total study population but also in all subgroups analyzed: patients receiving placebo or interferon beta-1b, patients with positive cerebrospinal fluid findings, patients who had received corticosteroid treatment, and patients with shorter or longer in-

Table 2. Hazard Ratios for the Development of Clinically Definite Multiple Sclerosis According to IgM and IgG Antibody Status.*

Variable	IgM		IgG	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Antibody status				
Negative for anti-MOG and anti-MBP antibodies	1.00		1.00	
Negative for anti-MOG antibodies, positive for anti-MBP antibodies	0.70 (0.39–1.27)	0.24	0.97 (0.58–1.60)	0.90
Positive for anti-MOG antibodies, negative for anti-MBP antibodies	0.62 (0.41–0.94)	0.03	1.00 (0.63–1.6)	0.99
Positive for anti-MOG and anti-MBP antibodies	1.00 (0.63–1.57)	0.98	1.04 (0.52–2.11)	0.91
Covariates				
Female sex	1.06 (0.74–1.52)	0.74	1.03 (0.72–1.48)	0.87
Age at onset of disease (per yr)	0.96 (0.93–0.98)	<0.001	0.96 (0.94–0.98)	<0.001
Interferon beta-1b treatment	0.49 (0.35–0.67)	<0.001	0.49 (0.35–0.68)	<0.001
Corticosteroid treatment of first episode	1.59 (1.08–2.35)	0.02	1.58 (1.06–2.35)	0.02
Multifocal presentation	1.01 (0.73–1.41)	0.94	1.04 (0.75–1.46)	0.80
No. of lesions on T ₂ -weighted MRI (per lesion)	1.01 (1.00–1.01)	0.09	1.00 (1.00–1.01)	0.15
No. of lesions on gadolinium-enhanced, T ₁ -weighted MRI (per lesion)	1.06 (1.01–1.10)	0.01	1.06 (1.02–1.11)	0.003

* Hazard ratios were calculated with the Cox proportional-hazards model.

tervals between the initial clinical event and blood collection. Finally, we were unable to confirm the previously reported association between the number of lesions seen on gadolinium-enhanced MRI brain scans and the anti-MOG or anti-MBP antibody status.¹

We established and validated the Western blot method used by Berger et al.¹ in our laboratory with the active support of the original authors, who also provided their MOG antigen.¹⁴ Parallel measurements of independent samples in the two laboratories yielded highly consistent results.¹⁴ Our study and that of Berger et al.¹ identified similar distributions of positive anti-MOG and anti-MBP IgM antibody status. In both studies, women predominated in the groups of patients who were positive for anti-MOG and anti-MBP antibodies.

Both studies included patients with a clinically isolated syndrome who had clinically silent MRI lesions suggestive of multiple sclerosis, and the two studies were similar with respect to the age and sex of the patients. The patients in our study had a larger number of lesions on T₂-weighted MRI scans obtained at the time of the clinically isolated syndrome, whereas the number of gadolinium-enhancing lesions seen on T₁-weighted

scans was similar in the two studies. To account for the effect of such subclinical disease dissemination and activity on the predictive value of antibody testing, the hazard ratios for clinically definite multiple sclerosis were adjusted for MRI characteristics at baseline.

All the patients in the study by Berger et al.¹ had oligoclonal bands in the cerebrospinal fluid, whereas in the BENEFIT study, cerebrospinal fluid analysis was performed at the discretion of the investigator, and not all patients in whom the analysis was performed had findings indicating an intrathecal humoral immune response. However, a subgroup analysis of patients with positive cerebrospinal fluid findings also failed to show an association between IgM or IgG antibody status and the risk of clinically definite multiple sclerosis.

Another difference between the two studies arises from the analysis of antibodies in blood samples obtained at different times. We obtained serum samples for antibody analysis a median of 55 days (interquartile range, 46 to 59) after the first signs of a clinically isolated syndrome, at which time 327 (71%) of our patients had undergone corticosteroid treatment. Berger et al.,¹ however, obtained serum samples for antibody

analysis within 14 days after the initial event, and all the patients in their study received high-dose corticosteroid treatment after the samples had been collected.

It is possible that analysis of blood samples obtained earlier (within a few days after the first manifestation of clinical disease and before the administration of corticosteroids) might have shown a correlation between antibody status and outcomes. However, the similarity in the rates of positive tests for IgM antibodies in the two studies argues against the hypothesis that in our study, the longer interval between the first manifestations of disease and the collection of blood samples or the administration of high-dose corticosteroids before the samples were obtained had a profound effect on the test results. In addition, our subgroup analyses did not show any trend toward an association between higher rates of positive antibody tests or an increased predictive value of the test results and earlier rather than later collection of blood samples. Patients treated with corticosteroids had a somewhat lower rate of positive tests for anti-MOG and anti-MBP IgG antibodies but not for IgM antibodies, and there was no indication that the predictive value in the patients treated with corticosteroids differed from that in the patients who did not receive this treatment.

It should also be noted that the duration of follow-up in our study was limited to 2 years. It might be argued that a longer period of follow-up would have allowed for detection of a correlation between antibody status and a diagnosis of multiple sclerosis. However, in view of the number of patients in whom clinically definite multiple sclerosis or multiple sclerosis according to the McDonald criteria was diagnosed during the 2-year follow-up period, a major change in the results with longer follow-up would be highly improbable. Moreover, in the study by Berger et al.,¹ after a 2-year observation period, there was already a striking difference in the risk of clinically definite multiple sclerosis according to anti-MOG IgM antibody status.

The findings in the Barcelona cohort of patients with a clinically isolated syndrome¹⁶ further support our argument: over a mean follow-up period of 46 to 47 months (range, 12 to 105), there was no significant correlation between antibody status and clinical outcomes. Our findings are also in line with recently presented results of

smaller, single-center studies using the same Western blot method. In a cohort of 47 patients with a clinically isolated syndrome, the baseline anti-MOG and anti-MBP antibody status was not associated with the risk of clinically definite multiple sclerosis after a follow-up period of 1 year or with MRI findings at baseline or at 1 year.¹⁷ Similarly, in two other studies, involving 55 patients¹⁴ and 45 patients¹⁸ with a clinically isolated syndrome, the presence of anti-MOG antibodies, anti-MBP antibodies, or both was associated with more frequent or more rapid progression to clinically definite multiple sclerosis only in subgroup or secondary analyses.^{14,18}

Thus, our data, together with the findings in the Barcelona cohort,¹⁶ provide definitive evidence against the use of anti-MOG and anti-MBP antibody status, as determined by Western blot analysis, to predict the outcome in patients with a clinically isolated syndrome suggestive of multiple sclerosis.

Analysis of antibodies strongly depends on the detection method used and the conformation status of the antigen. In solid-phase assays, the antigen is transferred to an artificial surface. As a result, protein denaturation may occur, and new epitopes not present in the native tertiary structure of the folded MOG molecule may be exposed.¹⁹ The anti-MOG and anti-MBP responses measured by Western blot analysis or enzyme-linked immunosorbent assay are common findings in central nervous system inflammation rather than specific features of multiple sclerosis.²⁰⁻²² Liquid-phase assays, in which a protein is more likely to retain its original tertiary structure, might be a better approach to studying conformation-dependent antibodies and their possible disease specificity,²³ although in a recent study of multiple sclerosis these expectations were not met.²⁴ Recently, transfected mammalian cells and fluorescence-activated cell-sorter analysis were used to detect antibody binding to human MOG in its membrane-embedded conformation, demonstrating elevated levels of anti-MOG antibodies in serum samples from patients with a clinically isolated syndrome and relapsing–remitting multiple sclerosis.²⁵ Previous studies have also stressed the importance of the native glycosylation of MOG for detecting disease-specific antibodies.²⁶⁻²⁹ Our results strongly suggest that antimyelin antibodies have no role in the diagnosis of multiple sclerosis or in the identification of patients at

high risk for the development of clinically definite disease. Alternatively, there may be a role for such antibodies, but we may need more sophisticated methods to detect them.

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No potential conflict of interest relevant to this article was reported.

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REFERENCES

- Berger T, Rubner P, Schautzer F, et al. Antimyeloid antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. *N Engl J Med* 2003;349:139-45.
- Linnington C, Webb M, Woodhams PL. A novel myelin-associated glycoprotein defined by a mouse monoclonal antibody. *J Neuroimmunol* 1984;6:387-96.
- Brunner C, Lassmann H, Waehndt TV, Matthieu JM, Linnington C. Differential ultrastructural localization of myelin basic protein, myelin/oligodendroglial glycoprotein, and 2',3'-cyclic nucleotide 3'-phosphodiesterase in the CNS of adult rats. *J Neurochem* 1989;52:296-304.
- Lucchinetti CF, Bruck W, Rodriguez M, Lassmann H. Distinct patterns of multiple sclerosis pathology indicates heterogeneity on pathogenesis. *Brain Pathol* 1996;6:259-74.
- Storch MK, Steffler A, Brehm U, et al. Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. *Brain Pathol* 1998;8:681-94.
- Schluesener HJ, Sobel RA, Linnington C, Weiner HL. A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. *J Immunol* 1987;139:4016-21.
- Linnington C, Bradl M, Lassmann H, Brunner C, Vass K. Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein. *Am J Pathol* 1988;130:443-54.
- Kerlero de Rosbo N, Honegger P, Lassmann H, Matthieu JM. Demyelination induced in aggregating brain cell cultures by a monoclonal antibody against myelin/oligodendrocyte glycoprotein. *J Neurochem* 1990;55:583-7.
- Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. *Nat Med* 1999;5:170-5.
- Baumann N, Pham-Dinh D. Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiol Rev* 2001;81:871-927.
- Kappos L, Polman CH, Freedman MS, et al. Interferon beta-1b in patients with a first clinical event suggestive of multiple sclerosis. *Neurology* 2006;67:1242-9.
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;33:1444-52.
- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227-31.
- Kuhle J, Lindberg RL, Regeniter A, et al. Antimyeloid antibodies in clinically isolated syndromes correlate with inflammation in MRI and CSF. *J Neurol* (in press).
- 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;50:121-7.
- Pelayo R, Tintoré M, Montalban X, et al. Antimyeloid antibodies with no progression to multiple sclerosis. *N Engl J Med* 2007;356:426-8.
- Lim ET, Berger T, Reindl M, et al. Antimyeloid antibodies do not allow earlier diagnosis of multiple sclerosis. *Mult Scler* 2005;11:492-4.
- Rauer S, Euler B, Reindl M, Berger T. Antimyeloid antibodies and the risk of relapse in patients with a primary demyelinating event. *J Neurol Neurosurg Psychiatry* 2006;77:739-42.
- O'Connor KC, Chitnis T, Griffin DE, et al. Myelin basic protein-reactive autoantibodies in the serum and cerebrospinal fluid of multiple sclerosis patients are characterized by low-affinity interactions. *J Neuroimmunol* 2003;136:140-8.
- Reindl M, Linnington 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;122:2047-56.
- Mantegazza R, Cristaldini P, Bernasconi P, et al. Anti-MOG autoantibodies in Italian multiple sclerosis patients: specificity, sensitivity and clinical association. *Int Immunol* 2004;16:559-65.
- Markovic M, Trajkovic V, Drulovic J, et al. Antibodies against myelin oligodendrocyte glycoprotein in the cerebrospinal fluid of multiple sclerosis patients. *J Neurol Sci* 2003;211:67-73.
- Bonifacio E, Lampasona V, Bingley PJ. IA-2 (islet cell antigen 512) is the primary target of humoral autoimmunity against type 1 diabetes-associated tyrosine phosphatase autoantigens. *J Immunol* 1998;161:2648-54.
- Lampasona V, Franciotta D, Furlan R, et al. Similar low frequency of anti-MOG IgG and IgM in MS patients and healthy subjects. *Neurology* 2004;62:2092-4.
- Lalive PH, Menge T, Delarasse C, et al. Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. *Proc Natl Acad Sci U S A* 2006;103:2280-5.
- Marta CB, Oliver AR, Sweet RA, Pfeiffer SE, Ruddle NH. Pathogenic myelin oligodendrocyte glycoprotein antibodies recognize glycosylated epitopes and perturb oligodendrocyte physiology. *Proc Natl Acad Sci U S A* 2005;102:13992-7.
- Lolli F, Rovero P, Chelli M, Papini AM. Antibodies against glycosylated native MOG are elevated in patients with multiple sclerosis. *Neurology* 2005;65:781-2.
- Gaertner S, de Graaf KL, Greve B, Weisstrer R. Antibodies against glycosylated native MOG are elevated in patients with multiple sclerosis. *Neurology* 2004;63:2381-3.
- O'Connor KC, Appel H, Bregoli L, et al. Antibodies from inflamed central nervous system tissue recognize myelin oligodendrocyte glycoprotein. *J Immunol* 2005;175:1974-82.

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