Anti-myelin antibodies in multiple sclerosis: clinically useful?

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Anti-myelin antibodies may have predictive clinical value, but striking correlations as reported earlier are unlikely

Despite numerous studies on prognostic disease markers in multiple sclerosis (MS), very few markers have emerged as clinically relevant. Often, early studies show great potential, but subsequent reports on the same marker yield inconsistent or even contradictory results. It is crucial to understand the reasons why various studies of the same marker lead to different conclusions.

Recently, Berger *et al* have reported a promising predictor of clinically definite MS in a cohort of patients with clinically isolated syndrome (CIS), positive findings on brain magnetic resonance imaging, and oligoclonal bands in their cerebrospinal fluid.¹ Of the 103 patients in their cohort, 64 (62%) were seropositive for either anti-myelin oligodendrocyte glycoprotein (MOG) or anti-myelin basic protein (MBP) or both IgM antibodies. Patients who were seropositive for both anti-MOG and anti-MBP (22%) had more frequent and earlier relapses than those who were seronegative. The presence of both antibodies predicted the conversion to definite MS more robustly than the presence of anti-MOG IgM alone.¹

Whether serum anti-myelin antibodies can be used as a marker of MS or a predictor of disease course has been addressed in several subsequent studies. Using a liquid phase radiobinding assay, Lampasona *et al* found that anti-MOG IgM and IgG have the same low frequency (<10%) in MS patients as in control subjects,² whereas Lim *et al*³ could not confirm the predictive value of anti-myelin IgM antibodies, tested with western blotting,¹ for conversion of optic neuritis to definite MS. Mantegazza and colleagues⁴ investigated MOG autoreactivity by ELISA, using the recombinant extracellular domain of MOG as antigen, in 262 MS patients and 438 control subjects. They found anti-MOG antibodies in the serum of 13.7% of the MS patients and similar percentages in controls. Although anti-MOG appeared to be unspecific for MS, they found a correlation between disease severity and anti-MOG titre in patients with progressive

MS. Very recently, Lalive *et al* described a cell based assay that specifically measures antibodies directed against cell membrane expressed human MOG (hMOGcme).⁵ They evaluated the incidence of these antibodies in the serum of 92 MS patients, 36 patients with CIS, and 37 controls, and in *Callithrix jacchus* marmosets with MS-like experimental allergic encephalomyelitis (EAE). They found that hMOGcme IgG antibodies, although not specific, predominate during CIS and relapsing-remitting MS and can be detected during the preclinical stage of EAE.

In this issue of the journal, Rauer and colleagues present another interesting paper on anti-myelin antibodies in MS (see pages 739–42). Using western blot analysis,⁶ they found 31 patients (69%) were seropositive for either anti-MOG or anti-MBP or both IgM antibodies in their cohort of 45 CIS patients. Thus, the frequency of anti-myelin antibodies seems to agree with the previous paper.¹ However, although sub-analysis suggested that the presence of anti-MOG/MBP IgM is correlated to earlier development of relapses, the data do not confirm that anti-MOG/MBP antibody status predicts the risk for relapses. Furthermore, this study demonstrated the limited specificity of anti-myelin IgM antibodies; anti-MOG and anti-MBP IgM were found in 21% and 27% of healthy controls, respectively.

Several factors may be responsible for the seemingly conflicting results concerning anti-myelin antibodies in MS. First, different methods of laboratory measurement have been used; the exact conformation of the myelin components displayed in the assays (ELISA, western blot, liquid phase) may be difficult to control and may result in the presentation of (partially) aberrant epitopes that are not exposed under physiological conditions *in vivo*.⁵ The disease relevance of these antibodies is therefore uncertain. Second, study design and populations vary greatly; in addition to diverse genetic backgrounds, methods of patient selection and data analysis are dissimilar. It should be considered whether the

presence of these antibodies might allow identification of a subgroup characterised by a more or less homogeneous type of tissue injury, possibly responsive to B cell directed therapies.

The natural behaviour of IgM and IgG anti-myelin antibodies is incompletely understood. Rauer and colleagues restrict their report to IgM antibodies, whereas autoantibodies of the IgG class are, in general, more specific. It would be of interest to determine both IgM anti-myelin behaviour over time and seroconversion of IgM to IgG. Therefore, large longitudinal, prospective studies including serial sampling are strongly recommended. We believe that anti-myelin antibodies still could have (predictive) clinical value; however, lack of specificity makes striking correlations as reported earlier unlikely.

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