Multiple sclerosis (MS) is the most common chronic disabling disease of the central nervous system (CNS) in young adults in Western countries, with a lifetime risk of 1 in 400 and an incidence of 80-110 in 100,000. It is characterised by a profound heterogeneity in clinical expression, prognosis and response to therapies. There are two major clinical subtypes of the disease. Relapsing-remitting (RR)-MS is the more frequent (85%-90%), affecting twice as many women as men. The majority of all RR-MS patients go on to develop secondary progressive (SP)-MS at a later stage. The other clinical MS subtype is primary progressive (PP)-MS that is present in 10%-15% of patients who have a disease onset and steady progression. The neuropathological hallmarks of the disease, namely inflammation, demyelination, axonal damage, gliosis and partial remyelination, are not uniformly represented throughout the patient population. Multiple genes contributing to disease susceptibility add further to the complexity of the disease. Although its aetiology and pathogenesis remain controversial, several lines of evidence indicate that MS is mediated by a misdirected immune response against one or several myelin antigens. Another frequently discussed possibility is that the inflammatory reaction is primarily directed against an unknown infectious agent.

As a result of finding activated T cells in MS plaques and by analogy with animal models of MS, the principal research focus in MS has for a long time been on T cells. However, recently the role of B cells, plasma cells and immunoglobulins in MS has been re-examined. Current findings indicate that humoral immunity also plays a major role in disease pathogenesis. Several mechanisms could explain how antibody responses to myelin components arise in MS. Activation of B cells may result from antigenic stimulation targeted at a specific molecule which could be driven by cross-reactivity with infectious agents (molecular mimicry).

Activation could also be a random bystander effect of the inflammatory response observed in MS lesions triggered by B cell superantigen stimulation. Another reason for the activation of B cells could be the production of neoantigens resulting from active transcription of hypermutable areas during viral infections. Once an antibody response has been generated, pathogenic antibodies against specific myelin antigens could mediate demyelination. Natural autoantibodies could enhance demyelination and antibodies directed against myelin components could participate in anti-idiotypic networks, which may regulate the disease course of MS [Figure 1].

Current immunomodulatory and immunosuppressive therapies, including interferon-β1a, IFN-β1b, glatiramer acetate and mitoxantrone, do produce beneficial clinical effects in different forms of MS. However, they are only partially effective, particularly with regards to the prevention of SP-MS. One very likely reason for this limited efficacy is the practice of using a single immunomodulatory or immunosuppressive therapy across a heterogeneous group of MS patients who have a wide variety of disease courses, ranging from benign to aggressive, and possibly very different underlying pathogenic mechanisms. There is therefore an urgent need not only to identify such pathogenic processes in individual patients, but also to be able to predict the individual clinical development as well as to optimise individual therapy so as to prevent future disability.

**Autoantibodies as diagnostic markers in MS**

Historically, the presence of autoantibodies in other autoimmune diseases has been a significant indicator of the role of B cells. In these other autoimmune diseases, the autoantibodies have been implicated in the mechanisms of disease pathogenesis, have a diagnostic and prognostic role and can also serve as surrogate markers of disease activity.

The biological rationale behind autoantibodies as paraclinical markers in MS is principally based on the early findings of increased intrathecal immunoglobulin IgG synthesis and the presence of oligoclonal IgG bands in more than 95% of patients with clinically definite MS. This is the most common abnormality detected in MS patients and therefore an important diagnostic tool in MS. The oligoclonal IgG response in MS appears early in the disease course and typically persists over time. This is in contrast to acute infectious diseases, where the presence of oligoclonal bands is often transient and disappears within a few months. The importance of humoral factors in the pathogenesis of MS has been further underlined by the observation that B cells are frequently found in the CNS of MS patients as well as the finding that autoantibodies can cause demyelination in experimental allergic encephalomyelitis (EAE), the animal model of MS.

Many studies have tried to identify autoantibodies directed against various myelin and nonmyelin target antigens in the serum and cerebrospinal fluid (CSF) of MS patients [Table 1]. However, none of these studies revealed convincingly an MS-specific antibody response against CNS antigens. Most antibodies detected in MS are also found in other neurological and systemic conditions and to a lesser extent, in healthy controls. There are several possible explanations for these disappointing results. First, the causative autoantigen(s) in MS has not been identified so far, possibly again due to the fact that MS is very heterogeneous in its clinical course and presentation. In addition, the fact that these studies were carried out in different patient populations, regardless of the genetic background and different clinical courses, may also explain the disappointing results. Finally, technical issues concerning the difference between assay systems and the antigen preparations used in the assays also add to the controversy surrounding previous findings on autoantibodies in MS. A further question that has not been addressed conclusively enough is the potential biological role of the detected antibodies. This is probably a complex one, ranging from a mere bystander phenomenon to demyelinating and even remyelinating properties.

However, there are promising studies that support the use of antibodies in subtyping MS patients by immunological and neuroradiological means. Antibodies directed to the myelin oligodendrocyte glycoprotein (MOG), a central nervous system specific component of the myelin surface sheath that is highly immunogenic, have been repeatedly shown in CSF and sera in a...
subset of MS patients and patients with other inflammatory neurological conditions. These antibodies persisted over time only in MS patients and were present early in the disease course. This persistent antibody response may play an important role in lesion formation in a subset of MS patients and is consistent with reports demonstrating antibody and complement precipitation in an immunopathologically defined subset of MS patients. This specific subset of MS patients may therefore benefit from therapies targeting the humoral arm of the immune response such as plasma exchange or intravenous immunoglobulins.

Although further studies are needed to support these initial findings and to clarify whether these markers are useful, they are a first step towards a more hypothesis driven approach to subtype the heterogeneous disease complex, which finally may result in a more distinct treatment approach.

**Autoantibodies as surrogate markers in MS**

Once the diagnosis of possible MS has been made, reliable markers are needed that are able to predict the likely individual clinical course in a patient. Thus, disease type and disease activity should be described in terms of the likely occurrence of future relapses and overall disease progression, especially the time point of conversion to clinically definite as well as to secondary progressive MS.

The diagnosis of clinically definite MS still needs long observation periods and repetitive MRI investigations. The identification of immunological prognostic markers for progression to clinically definite MS has therefore been of particular interest for many years. Antimyelin antibodies were recently demonstrated to be able to predict the risk of a second relapse in patients with a clinically isolated syndrome suggestive of MS. Patients who were seropositive for anti-MOG and anti-MBP antibodies had a second relapse within a mean of eight months, as compared to 45 months in patients who were seronegative for these antibodies. These findings are consistent with previous reports demonstrating that intrathecal IgG antibody production, dominance of B cells and oligoclonal anti-lipid immunoglobulin M (IgM) bands in the CSF are associated with a more progressive disease course. Thus an increased activation of B cells in MS may identify patients with a more severe disease course.

Promising markers for monitoring axonal damage, and therefore the conversion to chronic progressive MS, are neuronal neurofilament proteins. Axonal damage occurs early in the disease course and once a certain threshold of damaged or degenerated axons is reached, secondary progression in MS occurs. Increased levels of antibodies to the light subunit of the neurofilament proteins have been found repeatedly in the primary or secondary chronic progressive phase of the disease course. Whether these antibodies have a pathogenic role in axonal destruction or are rather an epiphenomenon secondary to massive release of axonal proteins remains unclear. Nevertheless they have also been correlated with clinical disability and brain atrophy in MS.

**Concluding remarks**

There is currently no antibody available that fulfills the criteria of a mere diagnostic or predictive marker in MS. Disappointing as this conclusion may be, it is also clear that antibodies play a very important role in clinical practice and research in a disease that is far from being a single neurological disorder. Promising studies have shown that antibodies can help in subtyping individual MS patients according to their pathogenesis and in enabling the provision of the most adequate therapy available. It is unlikely, however, that an antibody will be found that fulfills all the criteria of a surrogate endpoint in MS. The establishment of a panel of antibodies that could provide combined criteria for inflammation, demyelination, axonal degeneration and remyelination could be of significant help in the optimisation of therapy and the prevention of disability.

<table>
<thead>
<tr>
<th>Table 1. Antibodies to myelin proteins and other CNS antigens in MS.</th>
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<tr>
<td><strong>Target antigen</strong></td>
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<tr>
<td>Myelin-oligodendrocyte glycoprotein (MOG)</td>
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<td>Myelin basic protein (MBP)</td>
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<td>Myelin proteolipid protein (PLP)</td>
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<td>Myelin-associated glycoprotein (MAG)</td>
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**References**


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