Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more

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Abstract: B cells and antibodies constitute an important element in different inflammatory diseases of the central nervous system (CNS). Autoantibodies can serve as a biomarker to identify disease subgroups and may in addition contribute to the pathogenic process. One candidate autoantigen for multiple sclerosis (MS) is myelin oligodendrocyte glycoprotein (MOG). MOG is localized at the outermost surface of myelin in the CNS and has been the focus of extensive research for more than 30 years. Its role as an important autoantigen for T cells and as a target of demyelinating autoantibodies has been established in several variants of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The literature regarding antibodies to MOG in MS patients is confusing and contradictory. Recent studies, however, have described high levels of antibodies to conformationally correct MOG in pediatric acquired demyelination, both acute disseminated encephalomyelitis (ADEM) and MS. In adult MS, such antibodies are rarely found and then only at low levels. In this review, we summarize key findings from animal models and patient studies, discuss challenges in detecting anti-MOG antibodies in patients and present recent approaches to identifying new autoantigens in MS.

Keywords: Myelin oligodendrocyte glycoprotein, detection methods of autoantibodies, multiple sclerosis, ADEM

Introduction

Inflammatory demyelinating diseases of the central nervous system (CNS) comprise a broad spectrum of mechanistically heterogeneous disorders of which multiple sclerosis (MS) is the most common [Meinl *et al*. 2010]. There is strong evidence based on histopathological investigations and clinical response to plasma exchange [Keegan *et al*. 2005] that antibody-dependent mechanisms contribute to the pathogenesis in at least a subset of patients with CNS inflammation [Meinl *et al*. 2006]. The recently discovered aquaporin (AQP)4-specific autoantibodies allow the differentiation of neuromyelitis optica (NMO) from MS [Weinshenker *et al*. 2006]. It is tempting to speculate that certain subsets of MS patients can be identified based on their autoantibody profile. Myelin oligodendrocyte glycoprotein (MOG) is one of the best studied candidates, and is the focus of this review.

Historically: why is MOG interesting as a target?

The interest in MOG is based on animal experiments showing that MOG is a target of demyelinating antibodies. Initially, it was described that CNS homogenate contains a target of antibodies mediating complement-dependent demyelination in guinea pigs [Lebar *et al*. 1976, 1986]. A monoclonal antibody (mAb), 8-18C5 against rat cerebellar glycoproteins was raised in mice [Linnington *et al*. 1984] and used to define a glycoprotein in CNS myelin that was later named MOG [Linington and Lassmann, 1987]. With the help of this mAb, rat MOG cDNA was isolated and subsequently sequenced [Gardinier *et al*. 1992]. The sera of experimental autoimmune encephalomyelitis (EAE) guinea pigs were shown to have a demyelinating activity which was correlated to anti-MOG antibody titers [Linington and Lassmann, 1987].

Lessons from animal models

MOG can be involved in CNS autoimmunity in principally two different ways. First, MOG-specific T cells evoke CNS inflammation. Second, anti-MOG antibodies lead to the induction of demyelination. Demyelination is a characteristic feature of MS lesions indicated by the presence of naked demyelinated axons.

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The development of encephalitogenic T cells and demyelinating antibodies upon immunization with MOG depends largely on the strain of mice or rats. In Dark Agouti (DA) rats, immunization with MOG in complete Freund's adjuvant (CFA) results in a prominent T-cell response with only slight demyelination [Storch *et al*. 1998]. Brown Norway (BN) rats, on the other hand, develop a strong antibody response upon active immunization with MOG and incomplete Freund's adjuvant (IFA) [Storch *et al*. 1998]. Immunizing Lewis rats with murine MOG and CFA causes a rather mild form of EAE, characterized by occasional focal demyelination with only small numbers of T cells in the CNS, suggesting that MOG is a poor encephalitogen in the Lewis rat [Adelmann *et al*. 1995]. It has been proposed that this difference is due to higher expression of MOG in the CNS of BN rats compared with Lewis rats and that this increase in protein expression is caused by polymorphisms in the non-coding region of the MOG gene [Pagany *et al*. 2003].

SJL/J mice, but not C57Bl/6 mice, are able to mount a pathogenic anti-MOG antibody response upon active immunization with recombinant rat MOG and IFA [Bourquin *et al*. 2003]. The inability of C57BL/6 mice to produce antibodies against rat MOG that recognize MOG on the cell surface seems to be caused by the MHC class II haplotype H-2^b [Bourquin *et al*. 2003]. This animal model has unfolded interesting differences between human and rodent MOG. Immunizing with human MOG, instead of rat MOG, leads to B-cell dependent EAE in these mice [Marta *et al*. 2005]. Although anti-MOG antibodies are generated in both cases, only antibodies generated against human MOG, but not those generated against rat MOG, are pathogenic and cause EAE upon transfer to recipient mice. B-cell-independent EAE, in contrast, cannot be generated with human MOG in these mice, because the encephalitogenic T-cell response is dependent on a serine at position 42, where human MOG comprises a proline [Oliver *et al*. 2003]. Substituting proline with serine in human MOG allows B-cell-independent EAE induction with the human MOG mutant in C57Bl/6 mice [Marta *et al*. 2005].

Using anti-MOG-antibodies, a two-hit model for the induction of demyelination was developed. Encephalitogenic T cells initiate an inflammation and compromise the integrity of the blood–brain barrier. Anti-MOG antibodies are then able to access the CNS and mediate demyelination [Linington *et al*. 1988; Schluesener *et al*. 1987]. The two-hit model is also supported by experiments with mice carrying a MOG-specific transgenic B-cell receptor or T-cell receptor (TCR): C57Bl/6 mice with a knock-in of the H chain of the pathogenic MOG-specific mAb 8-18C5 were generated [Litzenburger *et al*. 1998]. These mice have high titers of functional autoreactive MOG-specific B cells and serum antibodies but the mice do not develop spontaneous EAE. Upon a slight challenge with encephalitogenic T cells, a fulminant demyelination develops [Litzenburger *et al*. 1998]. A spontaneous relapsing–remitting mouse has been developed [Pollinger *et al*. 2009]. These transgenic SJL/J mice carry a TCR specific for the MOG peptide 92-106 and develop EAE with a high frequency. The mice produce MOG-specific antibodies; depletion of B cells with an anti-CD20 mAb suppresses spontaneous EAE development. MOG-deficient TCR transgenic mice, in contrast, do not produce anti-MOG antibodies and do not develop relapsing–remitting EAE [Pollinger *et al*. 2009].

Anti-(AQP)-4 antibodies from NMO-patients have been shown to induce lesions in the CNS of mice and rats after opening of the blood–brain barrier by encephalitogenic T cells [Bennett *et al*. 2009; Bradl *et al*. 2009; Kinoshita *et al*. 2009]. When injected directly into the brain together with complement, rather than peripherally, these anti-(AQP)-4 antibodies are even able to induce lesions in mice lacking T cells [Saadoun *et al*. 2011].

Also in primates, such as common marmosets (*Callithrix jacchus*), MOG immunization induces demyelinating antibodies and encephalitogenic T cells ['t Hart *et al*. 2004]. Immunization of *C. jacchus* with myelin basic protein (MBP) results in clinically mild EAE without demyelination. Subsequent passive transfer of IgG against whole white matter causes demyelination and clinical aggravation, this effect is also achieved by passive transfer of either polyclonal antirat MOG antibodies or the anti-MOG mAb 8-18C5 [Genain and Hauser, 1996]. Immunizing marmosets with either the extracellular domain of rat MOG or synthetic 20-mer peptides revealed that only antibodies generated against the protein, but not against the peptides, cause demyelination and severe EAE in marmosets [von Budingen *et al*. 2002].

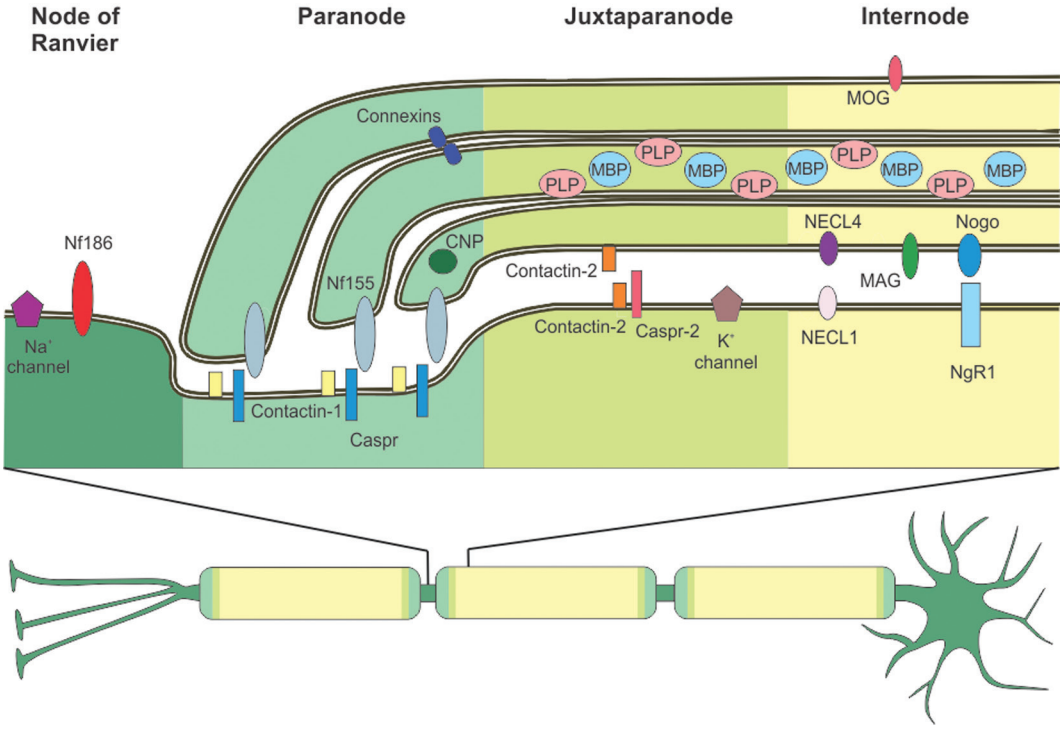

Figure 1. Distribution of central nervous system (CNS) myelin proteins. A neuron with a myelinated axon is depicted. Myelin enwraps the axon at intervals called internodes omitting small openings termed nodes of Ranvier. Adjacent to the nodes of Ranvier are the paranode and the juxtaparanode. All four zones have a characteristic protein composition, as depicted in the upper part of the picture. At th nodes of Ranvier, Neurofascin 186 (NF186) supports the clustering of Na+ channels. To allow saltatory conduction, the nodal Na+ channels are separated from the juxtaparanodal K+ channels via the paranode, where the myelin protein Neurofascin 155 (NF155) binds tightly to the axonal complex of Contactin-1 and Contactin-associated protein (Caspr). Connexins form gap junctions between myelin layers at the paranode. 2'3'-cyclic-nucleotide 3'-phosphodiesterase (CNP) is an abundant cytoplasmic myelin protein, predominantly found at the paranode. At the juxtaparanode, clustered K+ channels are associated to Caspr-2 and Contactin-2 is found both at the innermost myelin-sheath and the axon, allowing it to bind to itself. Typical myelin proteins are found at the internode: Proteolipid protein (PLP) and Myelin basic protein (MBP) are the major myelin proteins, the quantitatively minor Myelin oligodendrocyte glycoprotein (MOG) is found at the outermost surface of the myelin sheath. Nectin-like (NECL) adhesion proteins and Myelin associated glycoprotein (MAG) are found at the periaxonal space. Nogo is also predominantly found at the adaxonal myelin membrane, its receptor Nogo-receptor 1 (NgR1) is found at the axonal membrane.

Structure, abundance and localization of MOG

MOG is a quantitatively minor component of CNS myelin (less than 0.05% of all CNS myelin proteins) but its localization on the outermost surface of myelin [Brunner *et al.* 1989] makes it accessible for antibodies (Figure 1). Other more abundant myelin components, such as myelin basic protein, are inaccessible for antibodies. Rat MOG together with the Fab fragment of the mAb 8-18C5 [Breithaupt *et al.* 2003] and mouse MOG [Clements *et al.* 2003] have been crystallized. The demyelinating mAb 8-18C5 recognizes two residues (His103 and Ser 104) at the membrane-distal surface of MOG [Breithaup *et al.* 2008]. MOG features an IgV-like fold with a single glycosylation site (Asn-31). Similarities in the amino acid sequence and in the three-dimensional structure of MOG and the milk protein butyrophilin (BTN) put forward a role for BTN in the sensitization of T and B cells against MOG [Breithaupt *et al.* 2008; Guggenmos *et al.* 2004].

The exact function of MOG remains unclear but its structure and localization suggest a role as an adhesion molecule, possibly gluing CNS myelin fibers together [Clements *et al.* 2003]. MOG itself is also able to bind the complement component C1q and might therefore regulate the classical complement pathway [Johns and Bernard, 1997]. A recent study [Cong *et al.* 2011] showed that MOG might also function as a host cell receptor for the rubella virus. A MOG knockout mouse, however, showed no obvious phenotype

Table 1. Important features of MOG.

Size	218 amino acids/27 kDa
Abundance and occurrence	Restricted to CNS, on the outermost surface of myelin sheaths and on oligodendrocytes 0.05% of myelin proteins
Membrane topology	Single span transmembrane protein: – extracellular domain (amino acids 1–117) – one transmembrane domain – one C-terminal integral membrane domain [Della Gaspera *et al*. 1998]
Function	Unknown. No phenotype in knockout mouse [Delarasse *et al*. 2003]. Probably adhesion of myelin fibers [Clements *et al*. 2003] or regulator of classical complement pathway [Johns and Bernard, 1997]. Potential host cell receptor of the rubella virus [Cong *et al*. 2011].
Structure	IgV-like fold, single glycosylation site (Asn-31), one disulphide bond (Cys24–Cys98) [Breithaupt *et al*. 2003; Clements *et al*. 2003].
Sequence conservation	More than 90% among mammals [Pham-Dinh *et al*. 1993].
Possible pathogenic relevance	Target of encephalitogenic T cells. Target of demyelinating Abs in many species including primates.

MOG, myelin oligodendrocyte glycoprotein; CNS, central nervous system; IgV, immunoglobulin V; Abs, antibodies.

[Delarasse *et al*. 2003]. Essential features of MOG are summarized in Table 1.

Anti-MOG antibodies in adult MS patients: different detection methods and contradictory results

Enzyme-linked immunosorbent assay

Table 2 gives an overview over important studies assaying anti-MOG antibodies in patients with CNS inflammation and controls with different techniques. The first studies of anti-MOG antibodies in MS patients employed enzyme-linked immunosorbent assay (ELISA) assays with MOG purified from human brain white matter to determine the anti-MOG antibody titer in patients' sera and cerebrospinal fluid (CSF) [Xiao *et al*. 1991]. Using this approach, anti-MOG antibodies were detected in the CSF of a subset of MS patients, but also in the control groups. Similar results were obtained in a later study for which the extracellular domain of human MOG was expressed in *Escherichia coli*, without refolding of the antigen [Reindl *et al*. 1999]. Using native full-length mouse MOG from transfected mammalian cells, anti-MOG antibodies in both MS patients and healthy controls were detected and it was shown that the levels of IgM antibodies were higher in patients with a first demyelinating event, as compared with MS patients with a relapse or healthy donors [Gaertner *et al*. 2004]. The group also claimed to observe a correlation of anti-MOG IgG levels and disease activity, as those IgG antibodies were found to be higher in MS patients with a relapse or secondary progressive MS patients, as compared with healthy donors and MS patients in remission [Gaertner *et al*. 2004].

Seemingly healthy young adults with sera containing anti-MOG IgG antibodies, as determined by ELISA using recombinant human MOG, were reported to have a slightly higher risk of developing MS, compared with matched controls [Wang *et al*. 2008]. This association between anti-MOG status and disease risk disappeared after normalizing for the anti-EBNA IgG titer [Wang *et al*. 2008]. Another group [Klawiter *et al*. 2010] detected antibodies against human MOG expressed in insect cells with a secondary antibody recognizing all antibody isotypes in sera and CSF of both MS patients and controls. The group calculated an rMOG index as a marker for intrathecal anti-MOG Ig production and reported that this index was slightly higher in MS patients than in controls [Klawiter *et al*. 2010].

Anti-MOG antibodies were isolated by affinity chromatography to MOG coupled agarose and the binding of these antibodies to synthetic MOG peptides was assessed in an ELISA [Haase *et al*. 2001]. Antibodies from both patients and

controls bound to several peptides, without showing a specific MS-associated binding pattern. By comparing the binding of the same antibodies to cell-bound MOG in a flow-cytometry assay, one out of 17 MS samples and none of the nine healthy controls bound MOG in its native conformation [Haase *et al*. 2001].

In a recent study [Gori *et al*. 2011], rat MOG was expressed in *E. coli* and refolded. The correct folding of the antigen was demonstrated by far-UV circular dichroism. No antibodies in either MS patients or controls were detected.

Antibody binding to the extracellular domain of recombinant human MOG, expressed in *E. coli*, was not seen in solution, but in solid-phase, antibodies from both MS patients and healthy controls bound to the same MOG construct [Menge *et al*. 2007b]. It seems conceivable that the affinity of anti-MOG antibodies is not high enough to allow detection of antibody binding in solution.

Anti-MOG Ig in MS tissue

IgG from the CNS parenchyma of autopsy samples from MS patients were isolated and their binding to refolded *E. coli* MOG in solid phase and to *in vitro* translated human MOG in solution phase was assessed [O'Connor *et al*. 2005]. The group identified IgG binding to MOG in solid phase in a subgroup of MS patients, but not in the CSF or serum. One out of 37 MS patients and no controls showed binding to the solution-phase MOG protein [O'Connor *et al*. 2005]. Binding of immunogold-labeled MOG and MBP peptides to CNS tissue of MS patients and marmosets with MOG-induced EAE was described [Genain *et al*. 1999]. The group concluded that these MOG peptides bind to anti-MOG antibodies present on the tissue. This intriguing finding awaits further confirmation and elaboration.

Western blot

Western blot analysis detects antibodies to denatured proteins. Using this technique, antibodies to MOG were found in MS patients and in healthy controls [Lindert *et al*. 1999; Reindl *et al*. 1999]. It had been proposed that the anti-MOG and anti-MBP antibody status of clinically isolated syndrome (CIS) patients, as determined by Western blotting using MOG expressed in *E. coli*, could be predictive of the progression to MS [Berger *et al*. 2003]. In this study, patients with antibodies against both MBP and MOG had a significantly higher relapse risk, compared with antibody-seronegative CIS patients. These results were refuted by later studies [Kuhle *et al*. 2007; Pelayo *et al*. 2007] that used the same methods.

Cell-based assays

To detect antibodies to native MOG, cell lines were transfected to express MOG on the surface. Binding of antibodies to this surface expressed MOG can be detected and quantified by fluorescence-activated cell sorting (FACS) or immunocytochemistry [Brilot *et al*. 2009; Di Pauli *et al*. 2011; Haase *et al*. 2001; Lalive *et al*. 2006, 2011; McLaughlin *et al*. 2009; O'Connor *et al*. 2007; Probstel *et al*. 2011; Zhou *et al*. 2006]. The first study [Haase *et al*. 2001] that used MOG-transfected cells initially obtained MOG-binding IgG from 200 to 300 ml of serum using *E. coli* produced MOG for affinity purification. As mentioned above, antibody binding to MOG-transfected cells was seen in material obtained from 1/17 MS patients and in 0/9 preparations from controls.

A major advance in our understanding of antibodies to MOG was obtained in a study that analyzed acute disseminated encephalomyelitis (ADEM) patients along with adult MS patients [O'Connor *et al*. 2007]. ADEM is an acute disorder of the CNS affecting mostly children under the age of 10. This typically monophasic disease is characterized by an acute inflammation and demyelination of the CNS and usually succeeds a viral infection or vaccination [Tenembaum *et al*. 2002]. This study [O'Connor *et al*. 2007] used both cell-bound MOG and a tetramer-based assay (see below). It showed that a proportion of patients with ADEM have high antibodies to MOG, whereas in adult MS patients, such antibodies are barely detectable.

All subsequent studies that used a cell-based assay and included ADEM, pediatric and adult MS, basically confirmed this observation [Brilot *et al*. 2009; Di Pauli *et al*. 2011; Lalive *et al*. 2011; McLaughlin *et al*. 2009; Probstel *et al*. 2011].

A MOG tetramer radioimmunoassay

Further analysis showed that the proportion of anti-MOG positive children can be identified

with a tetramer radioimmunoassay in which four human MOG extracellular domains are tetramerized and used to detect antibodies via immunoprecipitation [O'Connor *et al.* 2007]. This technique is more sensitive than conventional solution-phase assays, as the avidity of the antigen is higher and it detects antibodies to the correctly folded MOG protein more specifically than conventional ELISA, because the MOG tetramer does not bind antibodies to linear MOG epitopes. With this technique, the group was able to detect high levels of anti-MOG antibodies in ADEM patients, but hardly in MS patients and control groups. The tetramer radioimmunoassay and the cell-based assay essentially identified the same group of anti-MOG positive patients.

Anti-MOG antibodies in a proportion of pediatric MS and ADEM

Using a tetramer radioimmunoassay, antibodies to conformationally intact MOG were detected in a subset of ADEM patients and these antibodies are rather rare in adult-onset MS cases [O'Connor *et al.* 2007]. Anti-MOG antibodies were also found in the serum of a subset of pediatric MS cases using cells transfected with MOG-GFP [McLaughlin *et al.* 2009]. All studies analyzing anti-MOG reactivity in pediatric patients noted a higher reactivity in young children (age <10 years) [Brilot *et al.* 2009; McLaughlin *et al.* 2009; Probstel *et al.* 2011]. No linkage between anti-MOG and anti-Epstein–Barr virus (EBV) antibodies was seen [Selter *et al.* 2010]. Cells transfected with hMOG are significantly more prone to natural killer (NK)-mediated cytotoxicity after incubation with purified serum IgG from anti-MOG positive patients, as compared with IgG from anti-MOG negative patients [Brilot *et al.* 2009]. Another group [Di Pauli *et al.* 2011] used immunocytochemistry to assess anti-MOG staining in a longitudinal study. They found a correlation between a decline in antibody titers and full recovery in ADEM patients. In a 5-year follow up, all 16 ADEM patients studied showed a rapid decline of anti-MOG antibodies [Probstel *et al.* 2011]. Strikingly, anti-MOG antibodies detected in the same study in pediatric MS patients persist in six of eight patients with fluctuations and were even shown to increase. High titer anti-MOG-antibodies are also present in a proportion of children with optic neuritis (ON) and are more frequent in children with recurrent ON, as compared to children with monophasic ON [Rostasy *et al.* 2012].

Summarizing view on anti-MOG Ig in pediatric and adult MS and ADEM

Technical challenges

Taken together, a general view is emerging that cell-bound assays are the best suited tools for analyzing antibodies to conformationally correct MOG. With a cell-bound assay and with the tetramer assay a proportion of children with ADEM or MS can be identified and clearly distinguished from controls. ELISA and Western blotting detect antibodies to incorrectly folded or denatured MOG. Those antibodies are not pathogenic, because they do not necessarily recognize MOG as it is present in the CNS. The disadvantage of using cell-bound assays, on the other hand, is that the cell surface is a very complex, indefinable milieu, compared with an ELISA plate. This high complexity makes it difficult to compare the results of different groups working with different cell lines and different protocols. It would therefore be worthwhile to develop an ELISA assay in which the human MOG protein is provided in its correctly folded structure only.

Anti-MOG Ig in adult and childhood MS/ADEM

Antibodies against correctly folded MOG are preferably found in pediatric MS and ADEM patients. In adult MS patients, such anti-MOG antibodies are rarely detected. The reason for this phenomenon is yet uncertain, but the different pathogeneses of these two CNS disorders (ADEM and MS) might play a role. ADEM usually succeeds a viral infection or vaccination and it has been proposed that antibodies produced against a viral structure might attack the immune system [Menge *et al.* 2007a]. Another explanation for the absence of anti-MOG antibodies in adult MS patients might be that anti-MOG antibodies are present in a few patients at the time of initiation of CNS inflammation, but disappear in the following years. A recent longitudinal study noted the persistence of anti-MOG IgG with fluctuations for a period of up to 5 years in children with MS [Probstel *et al.* 2011]. The further long-term follow up of these and other anti-MOG positive patients will provide further insight.

Possible pathogenic relevance of anti-MOG Ig in childhood demyelination

The formal proof of pathogenicity of human anti-MOG IgG might require transfer experiments which have not yet been performed. However, the

features of anti-MOG IgG in pediatric demyelination strongly suggest that these antibodies are pathogenic. This view is based on the comparison with prerequisites of pathogenicity of anti-MOG antibodies established in animal experiments. First, pathogenic anti-MOG antibodies recognize the conformationally correct MOG in a cell-bound assay [Brehm *et al*. 1999]. As discussed above, several groups have now identified anti-MOG antibodies in a proportion of pediatric demyelination with such an assay. Second, in animal models the complement fixing ability of anti-MOG was linked to their demyelinating activity [Piddlesden *et al*. 1993]. The pediatric anti-MOG antibodies are mostly of the complement-activating isotype IgG1 [McLaughlin *et al*. 2009; Probstel *et al*. 2011]; *in vitro* experiments examining their complement fixing activity in the context of myelin and oligodendrocytes are still missing. In addition to complement, antibody-dependent cellular cytotoxicity might also contribute to tissue destruction and antibody-dependent cellular cytotoxicity activity of human anti-MOG antibodies has been observed *in vitro* [Brilot *et al*. 2009]. Third, a breached blood–brain barrier, e.g. in the context of a T-cell-mediated encephalitis is crucial for the pathogenicity of anti-MOG antibodies, since anti-MOG antibodies are not pathogenic in the absence of CNS inflammation [Litzenburger *et al*. 1998]. Gadolinium-enhanced lesions are found in the majority of pediatric MS and ADEM patients [Poser and Brinar, 2007; Waubant *et al*. 2009]. These MRI data point out the disturbed blood–brain barrier in pediatric demyelination indicating that anti-MOG antibodies will have access to CNS myelin.

Consequences for the therapy of anti-MOG positive patients?

The number of drugs available for the therapy of inflammatory CNS diseases is increasing [Kieseier and Stuve, 2011]. This offers the possibility for further treatment optimization, provided biomarkers are available to identify patient subgroups. An example is the detection of anti-aquaporin-4 antibodies in NMO patients. The presence of these autoantibodies has therapeutic consequences, since many observations support the application of anti-CD20 treatment in NMO patients [Pellkofer *et al*. 2011]. In contrast, IFNβ might not be the ideal treatment for many NMO patients, since it may worsen the disease [Palace *et al*. 2010]. This might be due to the induction of the B-cell survival factor BAFF by IFNβ [Krumbholz *et al*. 2008]. Up to now experiences with IFNβ treatment in anti-MOG positive patients have not been reported. It seems plausible that patients with anti-MOG antibodies rather benefit from plasma exchange or a B-cell-directed therapy. A reduction of anti-MOG antibodies after B-cell-directed therapy would be expected, if short-lived plasma blasts rather than long-lived plasma cells are the source of these antibodies. The rapid decline of anti-MOG Ig in ADEM patients [Probstel *et al*. 2011] suggests that in these patients the antibodies are derived from short-lived plasma cells.

In search for other targets

The clinical observation that a proportion of MS patients benefit from plasma exchange [Keegan *et al*. 2005] and the absence of a decent MOG reactivity in the vast majority of adult MS patients suggests that targets of pathogenic antibodies in MS have yet to be identified. In a proteomic approach, glycoproteins were purified from human myelin, separated by two-dimensional gel electrophoresis and probed with patients' sera for antigen recognition. The purification of myelin glycoproteins has two reasons. First, it enhances the sensitivity to detect antibodies to minor components of the myelin and second, glycoproteins (such as MOG) are frequently displayed on the cell surface and accessible for antibodies. Proteins recognized by patients' Ig can be identified by mass spectrometry. With this approach, the two antigens neurofascin and contactin-2/TAG-1 have been identified [Derfuss *et al*. 2009; Mathey *et al*. 2007]. These two proteins are expressed by both oligodendrocytes and neurons and localized around the node of Ranvier [Derfuss *et al*. 2010]. A mAb to neurofascin mediated axonal injury in an animal model [Mathey *et al*. 2007], while T cells specific for contactin-2 directed encephalitis to the gray matter [Derfuss *et al*. 2009]. Another group also employed two-dimensional gel electrophoresis and mass spectrometry, without specific purification of glycoproteins, and found antibodies against transketolase and CNPaseI in the CSF of MS patients [Lovato *et al*. 2008]. Further work still has to identify the relevance of the reactivity to these new autoantigens for individual patients.

Patterns of autoantibody reactivities in the serum and CSF of MS patients have been described [Quintana *et al*. 2008]. Only binding to artificial peptides, but not to correctly folded proteins are

Table 2. Methods and studies for anti-MOG antibody detection in patients with CNS inflammation and controls.

Study	Technique	Antigen	Patient sample tested	Percentage of patients with demyelinating disorders declared anti-MOG positive	Percentage of controls declared anti-MOG positive
[Xiao *et al*. 1991]	ELISA	MOG from human white matter	Plasma and CSF from adult MS patients and controls	Plasma: 0% CSF: 23%	Plasma: 0% CSF: 3–7%
[Lindert *et al*. 1999]	Western Blot	Human MOG expressed in *E. coli*	Plasma from adult MS patients and controls	54%	22%
[Reindl *et al*. 1999]	Western Blot, ELISA	Human MOG expressed in *E. coli*	Serum and CSF from adults MS patients and controls	Serum: 38% CSF: 33%	Serum: 3–53% CSF: 0–53%
[Haase *et al*. 2001]	Cell-based assay (flow cytometry), peptide ELISA	Human MOG transfected LTK3$^-$ cells, Synthetic human MOG peptides	Purified anti-MOG antibodies from serum of adult MS patients and controls	ELISA: 100% Flow cytometry: 6%	ELISA:100% Flow cytometry: 0%
[Berger *et al*. 2003; Kuhle *et al*. 2007; Pelayo *et al*. 2007]	Western blot	Human MOG expressed in *E. coli*	Serum of adult CIS patients	62%	No controls
[Gaertner *et al*. 2004]	ELISA	Mouse MOG transfected AG8 cells	Serum from adult MS patients and controls	N/S	N/S
[O'Connor *et al*. 2005]	ELISA (DELFIA), solution-phase RIA	Refolded human MOG, expressed in *E. coli*; *in vitro* translated human MOG	Purified IgG from MS lesions, serum and CSF from adult MS patients and controls	CNS tissue: 50% CSF: 5% Serum: 3%	CNS tissue: 0–25% CSF: 0% Serum: 0%
[Zhou *et al*. 2006]	Cell-based assay (flow cytometry, Immunocytochemistry)	Human MOG transfected LN18 cells	Serum of adult MS patients and controls	22-41%	4%
[Lalive *et al*. 2006]	Cell-based assay (flow cytometry), ELISA	Human MOG transfected CHO cells, human MOG expressed in *E. coli*	Serum of adult MS patients and controls	N/S	N/S
[O'Connor *et al*. 2007]	Tetramer radioimmunoassay, cell-based assay (flow cytometry), ELISA (DELFIA)	Tetramers of human MOG extracellular domain; Jurkat cells transfected with MOG-EGFP; human MOG expressed in *E. coli*, refolded	Serum and CSF of pediatric ADEM and MS patients and adult MS patients and controls	Serum and CSF: ADEM: 19% MS: 0-8% CIS: 0%	Serum: 1% CSF: 6%
[Menge *et al*. 2007b]	ELISA, LiPhELIA	Human MOG, expressed in *E. coli*	Serum of adult MS patients and controls	LiPhELIA: 0%	LiPhELIA: 0%
[Wang *et al*. 2008]	ELISA	Human MOG, expressed in *E. coli*	Serum of MS patients before and after disease onset and controls	52%	43%

Table 2. (Continued)

Study	Technique	Antigen	Patient sample tested	Percentage of patients with demyelinating disorders declared anti-MOG positive	Percentage of controls declared anti-MOG positive
[McLaughlin *et al*. 2009]	Cell-based assay (Flow cytometry)	Human MOG-GFP transfected Jurkat cells	Serum and CSF pediatric MS and ADEM patients, serum of adult MS patients and controls	Pediatric: 21% Adult: 4%	Pediatric: 0–6% Adult: 0–5%
[Brilot *et al*. 2009]	Cell-based assay (Flow cytometry)	Human MOG transfected LN18 cells	Serum and CSF of pediatric ADEM and CIS patients; Serum of adult MS patients and controls	ADEM and CIS children: 47% Adult MS: 0%	Pediatric: 0–7%
[Klawiter *et al*. 2010]	ELISA	Human MOG, expressed in insect cells	Serum and CSF of MS patients and controls	37% (rMOG index >0.7)	8% (rMOG index >0.7)
[Selter *et al*. 2010]	Cell-based assay (Flow cytometry)	Human MOG transfected LN18 cells	Serum of pediatric ADEM and CIS patients and controls	ADEM: 47% CIS: 36%	0%
[Probstel *et al*. 2011]	Cell-based assay (Flow cytometry)	Human MOG, transfected TE671 cells	Serum of pediatric ADEM, CIS and MS patients, adult MS patients and controls	ADEM: 35% CIS: 29% Pediatric MS: 15% Adult MS: 6%	0%
[Lalive *et al*. 2011]	Cell-based assay (flow cytometry), ELISA, LiPhELIA,	Human MOG transfected CHO cells, human MOG expressed in *E. coli*	Serum of pediatric ADEM, MS and viral encephalitis patients and controls	Flow cytometry: ADEM: 27% MS: 5% Viral encephalitis: 0% ELISA: ADEM 55% MS: 14% LiPhELIA: 0% Viral encephalitis: 0%	0%
[Di Pauli *et al*. 2011]	Cell-based assay (Immunocytochemistry), ELISA	Human MOG-EmGFP transfected HEK293A cells, human MOG expressed by *E. coli*, refolded	Serum and CSF of pediatric and adult ADEM, CIS and MS patients and controls	Immunocytochem: ADEM: 44% CIS: 8% MS: 2% ELISA: ADEM: 24% CIS:8% MS: 15%	Immunocytochem: 0-2% ELISA: 4–11%
[Gori *et al*. 2011]	ELISA	Rat MOG expressed in *E. coli*, refolded	Serum and CSF from adult MS patients and controls	0%	0%

MOG, myelin oligodendrocyte glycoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; MS, multiple sclerosis; ELISA, enzyme-linked immunosorbent assay; CIS, clinically isolated syndrome; ADEM, acute disseminated encephalomyelitis; LiPhELIA, liquid phase enzyme-linked immuno assay, DELFIA, dissociation enhanced lanthanide fluoroimmunoassay; RIA, radioimmunoassay; CHO, Chinese hamster ovary.

observed in this study. The antigen recognition tested with these microarrays will therefore not necessarily mirror the reaction in the CNS of the patients and it remains open whether the detected antibodies, which may serve as a biomarker, are also pathogenic. The same might be true for lipid microarrays probing MS patients' sera for binding to myelin sheath lipids [Kanter *et al.* 2006]. Hence, antigen microarrays can only give an idea of which antigens might play a role in MS.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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