Auto antibodies in inflammatory demyelinating diseases of the central nervous system

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Summary

The determination of disease-specific auto-antibodies (Abs) is a challenge in any autoimmune disease. The significance of Abs detected in inflammatory demyelinating diseases (IDD) of the central nervous system (CNS), such as multiple sclerosis (MS), is still unclear. Histopathological reports have demonstrated that a humoral (Abs)-mediated pattern of demyelination is detected in >50% of MS patients and is consistently associated with active demyelination. The observation that these patients specifically respond to plasmapheresis reinforces the hypothesis of a specific humoral MS subtype. One of the most intensively studied antigen targets in MS is a glycoprotein of the myelin sheath called the Myelin Oligodendrocyte Glycoprotein (MOG). Recent advances have shown that epitope specificity of MOG is crucial in terms of specificity of the Ab response.

Several other auto-Abs, including anti-myelin, oligodendrocyte and neuronal Abs have been studied in MS. These auto-Abs may have pathogenic or protective properties, but could also have no functional role. Recently, the demonstration of a highly specific auto-Ab in an IDD of the CNS called neuromyelitis optica (NMO), directed against the aquaporin-4 (AQP-4) located at the blood brain barrier (BBB), has allowed a refinement of the diagnostic criteria of NMO and classification of this disease as an autoimmune channelopathy. These recent advances have reinforced the interest in tracking the role of the humoral response in the different IDD of the CNS.

Key words: antibodies; autoimmunity; biomarker; central nervous system; demyelinating diseases; multiple sclerosis; neuromyelitis optica

List of abbreviations

Ab(s)	Antibody(ies)
ADEM	Acute Demyelinating Encephalomyelitis
Ag(s)	Antigen(s)
AQP4	Aquaporin-4
ATM	Acute Transverse Myelitis
BBB	Blood Brain Barrier
CNS	Central Nervous System
CNPase	2',3'-Cyclic Nucleotide 3' Phosphodiesterase
CSF	Cerebral Spinal Fluid
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-Linked Immunosorbent Assay
Galc	Galactocerebroside
HSP	Heat Shock Protein
hMOG$_{cme}$	(human MOG expressed on cell-membrane)
IDD	Inflammatory Demyelinating Diseases
IVIG	Intravenous Immunoglobulin
LETM	Longitudinal Extensive Transverse Myelitis
MAG	Myelin Associated Glycoprotein
MBP	Myelin Basic Glycoprotein
MOG	Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NF-L	Neurofilament Light Chain
NMO	Neuromyelitis Optica
PLP	Proteolipid Protein

The spectrum of inflammatory demyelinating diseases (IDD) of the central nervous system (CNS)

The spectrum of inflammatory demyelinating diseases (IDD) of the central nervous system (CNS) can be defined according to clinical course, severity and chronicity of the disease [1, 2]. Multiple sclerosis (MS) is the prototype of IDD of the CNS. At onset MS often exhibits a relapsing-remitting course and evolves into a secondary progressive phase during the later stages. Uncommon forms of IDD of the CNS, often called "MS variants", can be clinically classified into: i) fulminant course: Marburg'disease, Balo's concentric sclerosis, Schilder's disease and acute disseminated encephalomyelitis (ADEM); ii) monosymptomatic subtypes: transverse myelitis and optic neuritis (ON); iii) syndromes with a restricted topography: neuromyelitis optica (NMO), recurrent ONs and relapsing transverse myelitis [2] (fig. 1).

Whether these diseases should be considered as inflammatory-mediated or autoimmune remains an open question. To date, no specific aetiology has been determined for these entities. Nevertheless, these syndromes exhibit certain common features. They are all considered to be idiopathic, to involve exclusively the CNS with primary white matter demyelination, and to be characterised by a pronounced and complex inflammatory process. Distinctions between these entities rely on clinical history, paraclinical investigations including imaging and biological tests and the exclusion of other aetiologies (infection, genetic, tumoral or metabolic origins). The considerable overlap between some of these disorders may lead to diagnostic uncertainty.

Recent reports in the fields of clinical pathology and immunology have brought new insights regarding the complexity of these different subtypes of IDD. The physiopathology of MS is certainly more complex than the simplified image of a $CD4^+$-Th1 T-cell mediated disease following activation by a single putative antigen (Ag) as suggested by experimental autoimmune encephalomyelitis (EAE) studies. In addition, the view that MS is not only an autoimmune but also a neurodegenerative disease is supported by studies showing that axonal damage is an early phenomenon that can be detected in areas remote from inflammation or demyelination [3–5].

The role of the humoral response in MS pathogenesis and in other variants has always been challenged. Some of the reasons for this include the lack of a clear clinical response to humoral-targeted treatments (i.e., intravenous immunoglobulin/IVIG, plasmapheresis) [6–8], difficulties in demonstrating both a specific and a functional role of anti-myelin Abs [9, 10] and the absence of Ab deposition in the CNS of some IDD. Nevertheless, neuropathological studies have revealed that MS is a very heterogeneous disease including forms with a predominantly humoral response (Abs and complement) in a specific subtype and other subtypes seemingly mediated by a macrophage-driven toxicity or a primary apoptosis of oligodendrocytes [11]. These results have been substantiated by the demonstration that only patients with a humoral pattern respond to plasmapheresis [12]. These recent findings have modified the perception of IDD of the CNS and underlined its heterogeneity not only on the clinical but also the pathological side.

Figure 1

Spectrum of IDD of the CNS according to clinical observation. (Adapted from [2]).
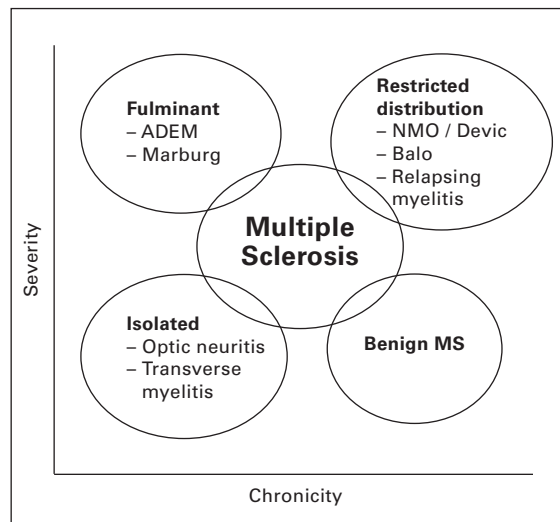
Multiple sclerosis

Multiple sclerosis (MS) is defined as a chronic immune-mediated inflammatory demyelinating disease of the CNS [13]. MS is the major idiopathic inflammatory demyelinating disease of the CNS. Prevalence is about 1/1000 among people living in Europe and the United States and the disease affects more than 10000 people in Switzerland and more than two million people worldwide. MS occurs more commonly among people with northern European ancestry, but people of African, Asian and Hispanic backgrounds are not exempt. The disease usually starts between 20 and 40 years of age and has a female predominance in a 2:1 ratio [1]. MS is not life shortening but its socioeconomic importance is second only to trauma among young adults. The neuropatho-

logical characteristics of MS are brain and spinal cord lesions with perivascular inflammatory infiltrates, demyelination, axonal loss and astrogliosis [14].

The origin of MS remains unknown, but environmental factors, genetic background and viral infections may contribute to the susceptibility to the disease. The disease develops in genetically predisposed individuals [15] and the prevalence increases in family members of MS patients [16]. First-degree relatives have a 2–5% increased risk of developing MS and the concordance rate in monozygotic twins vary between 20–35% [16]. In addition, HLA-DR and -DQ genes carry a higher risk of developing MS [15, 17] and the risk associated with a specific HLA haplotype seems to be dependent on the ethnical background[15]. Other factors such as viruses have been extensively investigated as MS triggers. MS relapses often follow viral infections [18] and temporal association during MS "epidemics", for example in the Faroe islands, have pointed to a possible association between infectious agents and MS. One hypothesis is that genetic predisposition under the influence of specific environmental factors may favour the penetration of the disease.

MS classification largely relies on the clinical course. There are two major forms of MS. The predominant one is the relapsing-remitting course (RRMS) that accounts for almost 85% of patients at disease onset and affects women about twice as often as men. After 10 years, approximately 50% of the RRMS patients will develop a secondary progressive phase of the disease (SPMS). This stage corresponds to a progression of the disease associated with a decrease or absence of relapses. The second form of MS accounts for 15% of patients. These patients initiate the disease with an insidious onset and a primary progressive course (PPMS, 10%) or as primary relapsing course (PRMS, 5%) which involve minor superimposed relapses [1, 19]. Finally, another subgroup, called clinically isolated syndrome (CIS), includes patients at disease onset and qualified by a single relapse. These patients are often considered as early RRMS but at the time of the initial consultation cannot be diagnosed as definite MS according to the revised McDonald MS criteria [20].

Histological classification

Important advances in the understanding of MS pathogenesis are based on a recent report that analysed a large collection of MS lesions from three international centres, bringing together material from 32 autopsies and 51 biopsies [11]. Criticisms regarding this report are based on the fact that the population studied came mostly from patients who underwent cerebral biopsy at disease onset because of an atypical clinical or radiological presentation. Thus, this study may not be representative of classic MS patients, nevertheless the results are of great interest. Several markers including the type of inflammatory cell, the detection of complement activation and the presence of auto-Abs were used to differentiate histological patterns. In the any one patient, the pattern of demyelination observed was homogenous within multiple active lesions. When the demyelinated lesions were compared between patients, four essential patterns were observed, although the last one (pattern IV) is rare and its reliability still unclear [11]. The first pattern (~20%) is associated with a predominant macrophage infiltration that mediates demyelination through the release of pro-inflammatory cytokines or proteases. The second pattern (~55%) is similar to the first pattern but includes the presence of auto-Abs and complement activation at the site of vacuolated myelin. The third and fourth patterns (~25%) are associated with less macrophage infiltration, no Abs deposition and no complement activation, but with a distal oligodendrogliopathy or oligo-

dendrocytes apoptosis. The latter patterns resemble a virus or toxin-induced demyelination. Interestingly, signs of remyelination were mainly found in inflammatory patterns (i.e., I and II) whereas remyelination was absent in pattern III and IV. A major issue of this study is to consider MS not only as a clinically but also a histopathologically heterogeneous disease. Moreover, these results indicate that Abs could play a crucial role in 50–60% of MS patients but do not participate in the pathogenic mechanism in the remaining 40–50%. These results may explain why the determination of auto-Abs as a highly specific biomarker of MS is likely to be difficult as MS may comprise different pathogenic entities. The possible pathogenic role of auto-Abs in MS was recently emphasised by a study examining the clinical response to plasmapheresis in relation to histological pattern. Only patients with pattern II (humoral pattern) responded to plasma exchange, whereas patients with pattern I (macrophage-induced demyelination) or with pattern III (primary oligodendrocyte death) did not respond [12].

Recently, the heterogeneity of MS lesions was challenged by another histopathological study in 39 MS patients [21]. Analysis of active demyelinated lesions revealed the presence of complement and Ab associated with phagocytic macrophages in areas of active demyelination, suggesting a humoral-associated phagocytosis as the dominant mechanism of demyelination in MS.

Immunology of multiple sclerosis: potential role of B cells and the humoral response

MS is considered as a predominantly cellular-mediated autoimmune disease [22] although other factors such as auto-Abs, pro-inflammatory cytokines and chemokines are involved in the pathogenesis, at least in specific subtypes.

The role of B cells and a humoral response in MS pathogenesis was initially suggested by the observation that Ig levels in the cerebral spinal fluid (CSF) were elevated [23] and that the mild CSF pleiocytosis was often associated with plasma B cells. Once inflammation has started, B cells and Abs may cross the BBB and participate in MS pathology through different mechanisms. Notably, B cells have been shown to potentially mediate damage in MS through: i) the deregulation of B cell production [24, 25] that may specifically target myelin Ag [26, 27] ii) the presence of ectopic B lymphoid structures in the meninges of MS patients [28, 29] iii) the presence of plasma cells producing auto-Abs to myelin and oligodendrocyte antigens in the CNS and peripheral circulation of MS patients [30] and iv) the B cell Ag presentation to T cells [31–33]. In some animal models, B cells have been shown to be critical for induction of EAE [34].

Recently, depletion of B cells with anti-CD20 monoclonal Abs (rituximab) has been tested in MS. The results of this clinical trial (HERMES trial) [35] represent a major breakthrough in the MS field for at least three reasons. Firstly, this phase II study revealed that depletion of B cell by a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. Secondly, these results bring new insights into MS pathogenesis revealing that B cells, whose function has certainly been underestimated, play an important role in MS pathogenesis. Thirdly, rituximab has been tested not only in MS but also in NMO [36, 37], with the main hypothesis that depletion of B cells may influence the humoral response and thus the clinical course of the disease. Nevertheless, recent studies showed that the main, or at least the initial and rapid effect of rituximab, was to influence the role of antigen-presentation by the B cell, rather that Ab secretion or cytokine production. Notably, rituximab targets the CD-20, a receptor located on pre-B to mature B cells but absent on the Ab-secreting plasma cells.

Further, a role for Abs in MS is supported by observations of intrathecal Abs synthesis, oligoclonal B cell expansion in the CSF, the frequent detection of immunoglobulin (Ig) deposition in MS lesions [11, 38] and by the fact that specific Abs can induce demyelination in animals [39, 40]. In EAE models, passive transfer of pathogenic myelin-reactive Abs (such as anti-MOG or anti-Galc Abs) are by themselves not sufficient to induce a phenotype but may induce a secondary demyelination after the BBB is artificially permeabilised [39–41].

Auto antibodies in multiple sclerosis

Anti-myelin antibodies

Myelin antigens are the prevalent targets studied in this field. Besides the understanding of MS pathogenesis, detection of MS-specific Abs has always been a goal in terms of diagnostic markers, classification of MS subtypes and prediction of disease course. However, the detection of auto-Abs in MS is not necessarily linked to the initial stage of the disease and can also be associated with a secondary response following "epitope/antigen spreading" (i.e., development of an immune response to epitopes distinct from, and noncross-reactive with, the disease-causing epitope). In addition, the presence of specific Abs in MS is not necessarily deleterious and may increase remyelination or induce neuroprotection. Thus, the presence of auto-Abs in MS can be associated with a primary pathogenic function, a secondary humoral reaction or even a repair function (i.e., remyelination/axonoprotection). In addition, the detection of Abs in MS may be useful in assessing the clinical course and prognosis or even predict response to treatment. Regardless of the heterogeneity of MS pathogenesis, it is noteworthy that Abs may be useful in revising the classification of MS subtypes, for example according to pathology specificity [11].

Anti-myelin oligodendrocyte glycoprotein (MOG)

Myelin oligodendrocyte glycoprotein (MOG) is a minor constituent specific to the CNS. The full-length protein contains 218 amino acids. MOG is a target myelin antigen (Ag) for both humoral and cellular CNS-directed immune responses. The encephalitogenic properties of MOG are believed to result from the extracellular location of its IgV-like domain on the outermost myelin lamellae, which makes it an exposed target accessible to initial autoimmune attack on compact myelinated axons [42]. In both rodent and primate MS models of EAE, Abs against MOG may directly induce demyelination [39–41, 43], whereas anti-MBP or anti-proteolipid protein (PLP) are not associated with an increase in

Table 1

Epitope recognition of MOG differentially influences Ab response and EAE phenotype.

EAE model	Immunization	Inflammation	Pathogenic Ab[d]
Mouse [44]	humanMOG[a]	+	+
	ratMOG[b]	+	−
	HuP42SMOG[c]	+	−
Rat [41]	Passive transfer Ab *(and adoptive T cell transfer)*	Inflammation	Demyelination
	anti-MOG Ab[e]	+++	+
	adoptive T cell transfer only[f]	+++	−
Marmoset [46]	Immunization	Inflammation	Demyelination
	1–125rMOG[g]	+++	+++
	pep-mixMOG[h]	+ to +++	+
	pep-aaMOG[i]	+ to +++	+

a. glycosilated human extracellular and conformational MOG; b. non-glycosilated rat MOG; c. non-glycosilated human MOG; d. determined by passive transfer experiments and in vitro assay; e. rat anti-MOG Ab (8–18C5); f. EAE splenocytes; g. recombinant human full extracellular MOG (aa 1–125); h. mixture of 11 20mer peptides overlapping by ten aa and spanning the sequence of MOG aa 1–120; i. isolated MOG peptides (1–40, 21–40, 51–90, 81–120).

myelin injury. In addition, anti-MOG Abs have been linked to myelin damage in MS lesions [38]. However, the demonstration of Abs pathogenicity in humans is still lacking, although some recent data suggest that specific anti-conformational MOGs are pathogenic when transferred to the animal [44].

The influence of epitope recognition of MOG on EAE phenotype has been explored in different animal models. Table 1 summarises reports on the influence of the MOG epitope in mouse [45], rat [41] and monkey [46] EAE. Interestingly, anti-MOG Abs appear to be more pathogenic (increase the level of demyelination) when Abs are directed against the conformational epitope of human MOG that preserves glycolisation. Thus, specific epitope presentation of MOG is crucial to elicit an Ab response that induces demyelination in EAE models.

The major limitation in the detection of anti-MOG Abs in human studies is related to the fact that different assays testing different MOG preparations may give different results. In addition, cohorts of MS patients and proper definition of MS subtypes may differ between hospitals and laboratories. Almost 30 publications on anti-MOG Abs in MS have been published so far (reviewed in reference [47]). Results differ considerably and can be summarised according to i) the technique used in the assay, ii) the Ig isotype detected or, iii) the sequence/conformation and origin of MOG used as antigen (table 2). The table 3 summarises the results of anti-MOG assay according to the technique used. It only contains reports that assess MS-specificity of anti-MOG

Abs. Notably, the demonstration of anti-MOG Abs increase in MS does not necessarily imply MS-specificity since most anti-MOG Abs are also found in controls, including healthy donors and patients with other neurological diseases.

The general trend shows an increase of anti-MOG Abs in MS. Nevertheless, the specificity and sensitivity of anti-MOG Abs differ considerably among studies. For example, recent studies assessing the role of anti-MOG Abs by Immunoblot in the early phase of MS show various interpretations of the results. Indeed, one of the most promising studies on Abs detection in MS analysed the prevalence of anti-MOG (peptide) IgM as well as anti-myelin basic protein (MBP) Abs by Immunoblot among patients with Clinically Isolated Syndrome (CIS, i.e., first demyelinating clinical event) [9]. This study demonstrated that the presence of anti-myelin Abs (i.e., anti-MOG and anti-MBP Abs) was a prognostic factor for a short duration until relapse. In 2007, the results of a similar but double blind study [10] failed to reproduce the results of the first study.

One major issue discussed here is the question of Ag and epitope specificity of MOG-Abs. Since none of the current solid or liquid phase assay (i.e., enzyme-linked immunosorbent assay/ELISA, Immunoblot, liquid-phase assay) take into account the native oligodendrocyte-expressed conformation of MOG, a new cell-based assay was designed to specifically measure Abs directed against conformationally folded, cell membrane-embedded human MOG and evaluated the prevalence of these anti-native MOG Abs in serum of humans [48]. The results showed no correlation

Table 2

Summary of MOG preparations and assays used for anti-MOG Abs detection in MS.

Type of MOG	rhMOG expressed: – in mammalian cells – in E. Coli – by in vitro translation	Synthetic Peptides (1 to 125 aa)	Purified from human myelin	Tetramer
Ig isotype	IgG, IgM, IgA			
Assay	ELISA, Immunoblot, Fluid phase, Elispot, FACS			

rhMOG: recombinant human MOG.

Table 3

Anti-MOG Abs studies classified according to the technique of detection.

	N# publications "increased in MS vs controls"	References
ELISA	6/7	146–152
Immunoblot	6/7	9, 10, 26, 153–156
Liquid phase solution-phase RIA LiPHELIA	0/3	26, 49, 157, 158
FACS	3/3	44, 48, 159

in the Clinically Isolated Syndrome cohort (CIS, onset MS) between serum reactivity against hMOG (solid phase ELISA, linear epitopes) and hMOG$_{cme}$ (human MOG expressed on cell-membrane of transfected Chinese Hamster Ovarian (CHO) cells). Further, pre-absorption studies demonstrated the absence of cross-reactivity between epitopes of MOG displayed in these two different assays. Analysis of reactivity against hMOG$_{cme}$ in the different MS clinical subtypes showed a prominent response in CIS, RRMS and to a lesser degree SPMS, compared to HC and PPMS. There is therefore a humoral immune response specifically directed against intact MOG expressed on myelin/oligodendrocytes in these groups of patients. The predominance of hMOG$_{cme}$specific Abs in CIS suggests that these Abs represent early stages of the immune response against intact (as opposed to degraded) myelin, and thus may represent a marker of inflammatory phases of disease related to BBB permeabilisation and/or molecular mimicry. These patterns of humoral reactivity may be exploited to refine our understanding of disease stages, cause and prognosis.

The basis of the discrepancy between conformational and non-conformational presentation of MOG was examined by comparing how ELISA and a liquid-phase assay (LiPhELIA) performed in conditions of specific, epitope-defined anti-MOG responses [49]. An identical MOG protein was used in order to explore the biophysical conformations of the antigen in the two systems. The results demonstrate the absence of Ab reactivity against soluble MOG in human serum and the fact that immunodominant epitopes of MOG were not properly displayed on its soluble form. Self-assembling radiolabelled tetramers (radioimmunoassay) may also discriminate Abs against folded or denatured MOG by selective unfolding of the antigen domain. With this technique, MOG-specific autoAbs were mostly identified in a subset of ADEM but only rarely in adult-onset MS cases [50]. These results emphasise the interest for novel cell-based assays that have been created and validated in order to measure reactivity against native membrane-embedded MOG [44, 48] and for which some pathogenicity of the Abs was demonstrated [44].

Anti-Myelin Basic Glycoprotein (MBP)

Myelin basic protein (MBP) is a major glycoprotein of the inner myelin sheath, thus less accessible to a primary humoral autoimmune response when the myelin sheath is intact. Anti-MBP Abs were found to be augmented in both sera and CSF of MS patients [51–55]. Nevertheless, a recent study describing the potential value of anti-MBP (combined with anti-MOG Abs) as predictive factors in early MS [9] could not be statistically reproduced [10]. Thus, the usefulness of anti-MBP testing in MS is still matter of debate.

Anti-Myelin Associated Glycoprotein (MAG)

Myelin Associated Glycoprotein (MAG) is a glycoprotein that constitutes approximately 3% of the myelin sheath and is, like MOG, located at the surface of the myelin sheath and easily accessible to an early immune response. Anti-MAG Abs are validated markers that assess a peripheral neuropathy associated with monoclonal gammapathy or lymphoproliferative disorders [56]. Reports have shown that low titres of anti-MAG are present in the CSF of MS patients and may be associated with disease progression [57, 58].

Anti-Galactocerebroside (Galc)

Galactocerebroside is a major lipid constituent of the myelin sheath that accounts for about 30% of the myelin content. Beside anti-MOG Abs, anti-Galc Abs are also described as having encephalitogenic properties when passively transferred to the animal during EAE [59, 60]. Anti-Galc Abs has been proposed as a staging marker in MS. In both animal and in human studies, these Abs are not detected in healthy controls and are preferentially found among the RRMS subtype [61]. Since these Abs are not found in early MS (CIS stage) they could be useful in detecting progression of the disease.

Anti-Proteolipid Protein (PLP)

Proteolipid Protein (PLP) is another abundant glycoprotein in the myelin sheath. It is commonly used to induce a relapsing-remitting form of EAE in some animal models [62]. An increase of auto-Abs directed against PLP has been described in the CSF of MS patients [53, 54, 63].

Anti-Phosphatidylcholine

The presence of IgM anti-myelin/lipid has been found among oligoclonal bands in the CSF [64]. These Abs were specific to phosphatidylcholine and were described as predictive of an aggressive disease course in MS.

Anti-oligodendrocyte antibodies
Anti-alu repeats

Screening of sera and CSF from MS patients showed that almost 50% reacted with the Alu peptides, an OPC antigen [65]. In addition, some samples selected according to their reactivity with Alu peptides stained the cytoplasm of OPC intensively but not the cytoplasm of astrocytes. It was therefore hypothesised that auto-Abs to the OPC epitope could contribute to the pathogenesis in a subgroup of MS patients.

Anti-AN-2 (NG2)

NG2 (oligodendrocyte surface glycoprotein) is a surface marker of oligodendrocyte precursor cells (OPC). Notably, the process of remyelination involves migration and differentiation of OPC into demyelinated areas of the CNS [66]. Thus, auto-Abs directed against OPC could be a trigger that restricts remyelination. Anti-NG2 have been reported in both CSF and serum of MS patients [67].

Anti 2',3'-cyclic nucleotide 3' phosphodiesterase (CN-Pase)

2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) is a protein associated with oligodendrocyte/myelin membranes that is also present in lymphocytes and retina. It has been shown that CNP might be a major target for the humoral response [68]. Anti-CNP Abs were detected in sera of 74% of MS patients. These IgM Abs were present in serum in high titre as well as in CSF. In addition, the Ab response is consistent with a persistent antigenic stimulation.

Anti-neuronal antibodies

The concept of primary myelin and oligodendrocyte damage with axon sparing as a hallmark of multiple sclerosis (axon-myelin dissociation) has recently been challenged with the demonstration that neuro-axonal lesions are an early phenomenon [69] linked to the inflammatory process [69, 70] that can be observed outside demyelinated areas [3], and correlated with the progression of the disease [71]. Neurodegeneration in MS, long considered as a late process following recurrent episodes of demyelination, is now accepted as an early and major trigger of MS pathogenesis. Interestingly, when serum Abs are tested against cell surface Ags from glial and neuronal cell-lines (including astrocytes, oligodendrocytes and neurons), more than 70% of primary progressive forms of MS (PPMS) and 25% of classical RRMS have Abs binding neurons [72].

Anti-light chain neurofilament (NF-L)

Most of the studies assessing auto-Abs against neuronal Ag are targeting cytosqueletal neurofilament proteins. These auto-Abs are related to an unspecific axonal damage more than to a specific disease. One of the most promising neuronal Ag in terms of biomarker is the neurofilament light chain (NF-L). An increase of auto-Abs targeting NF-L was found in progressive forms of MS (primary and secondary MS) [73, 74] and the titres correlated with both disability score (expanded disability status scale/EDSS) [74] and magnetic resonance imaging (MRI) measures of brain atrophy [75].

Anti-Gangliosides

Gangliosides are surface markers of axons that are not CNS-specific but also found on peripheral nerves. Anti-Gangliosides Abs are rou-tinely tested to investigate polyradiculoneuritis. Plasma samples from MS patients and controls were tested for Abs against gangliosides GM1, GM3, GD1a, GD1b, and GD3 using ELISA. The percentages of subjects with increased anti-GM3 responses were described to be higher in the primary and secondary progressive MS compared to controls [76, 77].

Other auto antibodies
Anti-neurofascin

These auto antibodies recognise the native form of the extracellular domains of both neurofascin 186 (NF186), a neuronal protein concentrated in myelinated fibres at the nodes of Ranvier, and NF155, the oligodendrocyte-specific isoform of neurofascin. In vitro studies with hippocampal slice cultures have shown that anti-neurofascin Abs inhibit axonal conduction in a complement-dependent manner. In EAE studies, these Abs selectively target nodes of Ranvier, resulting in deposition of complement, axonal injury and disease exacerbation [78]. In MS, disruption of neurofascin localisation reveals early changes preceding demyelination and remyelination [79]. Further studies are required to assess the exact role of these auto-Abs in MS pathogenesis.

Anti-oligodendrocyte-specific protein (OSP/Claudin-11)

OSP/Claudin-11 is the tight junction inducing protein claudin-11, which was shown to induce the parallel strand tight junction in the myelin sheath. A study analysed the presence of these Abs with different techniques including Western blot analysis, peptide blots and ELISA. The results show that anti-OSP/Claudin-11 Abs were present in the CSF of MS patients, although the results varied according to the technique used [80]. In addition, EAE studies have demonstrated that pathogenic autoimmunity against OSP/claudin-11 may also involve a specific T cell response [81].

Anti-proteasome

Proteasome are ubiquitous protease complexes composed of 14 different subunits involved in processing and chaperone function. By using recombinant proteasomal subunits, the presence of specific auto-Abs directed against some specific subunits has been shown to increase in about two thirds of MS patients [82]. The humoral response against proteasome was associated with a specific T-cell proliferative response against some specific subunits.

Anti-glycopeptide

Most of the myelin proteins and myelin lipids are glycolysated. It has been speculated that glycosilation is important for epitope recognition. Specific serum IgM directed against the artificial glycopeptides CSF114(Glc) was found among

MS patients but not in healthy controls or in other inflammatory autoimmune conditions [83]. In addition, these Abs are described as being myelin- and oligodendrocyte-specific and correlate with MRI and clinical activity. Similar results where obtained with MS serum applied on another glycosilated Ag (Glc(alpha1,4)Glc(alpha) [84].

Anti-DNA

Anti-DNA Abs are frequently detected in serum of patients with connective tissue diseases or systemic autoimmune diseases, but can also be found in serum of MS patients. High-affinity anti-DNA Abs were described as a major component of the intrathecal IgG response in an MS patient in whom the IgG repertoire from active plaques and B cells recovered from the CSF was cloned [85]. Nevertheless, the lack of specificity of anti-DNA Abs remains a major problem.

Antibodies and remyelination/neuroprotection

The function of auto-Abs is sometimes difficult to assess and to predict. On the one hand, Abs directed against acetylcholine receptor (AchR), detected in myasthenia gravis, are known to be pathogenic. On the other hand, the function of most neurological paraneoplastic auto-Abs is still unclear. In addition, some Abs may play a protective role. For example, Abs directed against oligodendrocytes surface markers have been shown to promote myelin repair in an animal model of MS using viruses [86, 87].

Anti-heat shock protein (HSP)

Abs directed against heat shock protein (HSP)-60 [88–90] have been associated with promotion of remyelination in animal and in vitro models. By contrast, another report showed that anti-Alpha-B-crystallin Abs (a small molecular weight heat shock protein (HSP)) was associated with an increase in relapse rate [91, 92].

Anti-Nogo

Nogos (neurite outgrowth inhibitors) play an important role in myelin-axon interaction. An original attempt to promote remyelination was to selectively block Nogo-A by means of anti-Nogo-A Abs or vaccination with Nogo Ag [93]. Interestingly, IgM directed against Nogo was found to increase in both CSF and serum of RRMS patients [94], but was also found in controls.

Anti-Lingo

Nogo receptor-interacting protein (Lingo-1) has been recently identified as a negative regulator of oligodendrocyte differentiation and myelination. The loss of Lingo-1 function by Lingo-1 gene knockout or by treatment with an antibody antagonist of Lingo-1 function leads to functional recovery in the EAE model. This was reflected biologically by improved axonal integrity and by newly formed myelin sheaths [95]. Antagonism of Lingo-1 or its pathway is therefore a promising approach in the treatment of demyelinating diseases of the CNS.

Neuromyelitis optica (NMO) / Devic syndrome

Neuromyelitis optica (NMO) or Devic's disease is a severe, frequently recurrent and progressive demyelinating disease of the CNS primarily affecting the optic nerves and the spinal cord [96–98] (fig. 2). After five years of disease progression, ~50% of patients are blind in one or both eyes and cannot walk unaided. NMO may account for 1% of IDD of the CNS among Caucasians, but represents almost 30% of total IDD in Japan, where it is described as "optic-spinal multiple sclerosis" (OSMS). The first case was described in 1894 by Devic at the Hôtel-Dieu Hospital in Lyon but it is only over a century later that new insights on NMO pathogenesis and the discovery of a specific auto-Abs has led to a better distinction between this entity and MS. Until recently, NMO was often mistaken for MS. On the one hand both diseases may start with identical symptoms involving white matter of the CNS. On the other hand they both classically progress with a relapsing pattern. A secondary progressive course is frequent in MS, but rather rare in NMO [99]. Recently, NMO has been described as a predominantly B-cell and Ab-mediated autoimmune condition, due to evidence that autoAbs and complement played a major role in pathogenesis [97]. This concept was recently reinforced by the demonstration of disease-specific Ab [100–102], sustained by the clinical response to plasmapheresis [103] and the beneficial effect of B-cell depletion [104]. These findings lead to a revision of diagnostic criteria for NMO in 2005 (table 4).

Pathogenesis of neuromyelitis optica

The importance of the humoral response and the role of auto-Abs in NMO pathogenesis was underlined by a recent work based on nine NMO-autopsy cases examining 82 lesions in total [97]. The pathology observed was identical in all nine patients and consisted of extensive demyelination, necrosis and acute axonal loss. The pathology of NMO involves both white and grey matter, whereas MS pathology is mostly focused on white matter [11]. Histology demonstrates extensive macrophage infiltration associated with granulocytes and eosinophils. Contrary to typical MS le-

Figure 2

MRI findings in a patient with NMO. (A) Longitudinal extensive spinal cord lesion starting on the medulla oblongata and extending over >8 vertebral segments (white arrows). (B) Lesion of the left optic nerve (optic neuritis, white arrow). (C) At disease onset, brain MRI is often normal. (D and E) 5 years after disease onset, brain lesions are detectable.
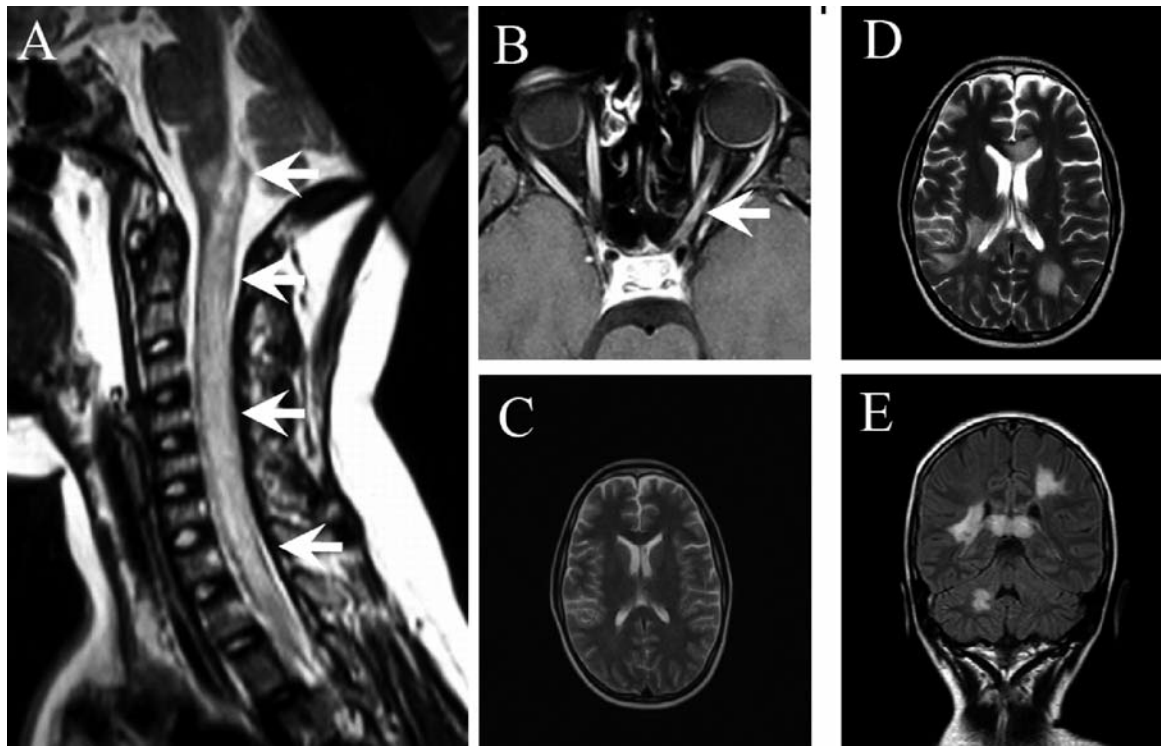
sions, a rare infiltration of CD3^{+} and CD8^{+} T lymphocytes is observed in NMO lesions. Notably, a pronounced deposition of immunoglobulin and complement C9neo associated with both fibrosis and hyalinization was depicted in active lesions around vessels. These findings indicate that different tissue injury mechanisms are operative in both disorders.

Biological distinctions between multiple sclerosis and neuromyelitis optica

Biological differences between MS and NMO are frequently observed in both serum and CSF (table 5). CSF pleiocytosis in NMO, contrary to MS, is frequently above 50 WBC/mm³, [105] and can be associated with predominant neutrophilia. Oligoclonal bands are more frequently found in MS [104–107] whereas association with systemic auto-Abs (such as anti-nuclear or anti-DNA Abs) are more frequent in NMO but should be interpreted with caution when there is no clinical sign of autoimmune disease [101, 104, 108].

NMO-specific antibodies

The prevalence of the humoral response in NMO along with the pronounced fibrosis and hyalinization around vessels was retrospectively a strong argument for the detection of auto-Abs di-

rected against the vessel membrane. In 2004, a report described the finding of a specific auto-Ab directed against the blood-brain barrier (BBB), the so-called NMO-IgG [101]. The specific Ag targeted by the auto-Ab was recognised a year later and was found to be a transmembrane water channel called aquaporin-4.

NMO-IgG

The technique of NMO-IgG detection is based on an indirect immunoflorescence staining with diluted patient serum applied on murine CNS tissue. The presence of NMO-IgG is further revealed by indirect immunofluorescence (fig. 3). NMO-IgG outlines CNS microvessels, pia, subpia and Virchow-Robin spaces. Patients tested in the first report included Caucasian and Japanese NMO (n = 56) as well as those with a high-risk syndrome (n = 36) defined as recurrent optic neuritis or longitudinal extensive myelitis with no evidence of MRI brain lesion. Controls consisted of patients with MS or miscellaneous disorders. Based on several studies, NMO-IgG test is reported with a sensitivity of 58–76% and a specificity of 85–99% for NMO [96, 101, 109–111]. Notably, for the first time a biological marker was able to differentiate two closely-related IDDs of the CNS.

Anti-Aquaporin-4 (AQP4) antibodies

The Ag targeted by NMO-IgG was recognised in 2005. By means of brain mouse tissue knockout for aquaporin-4 (AQP4) and AQP4-transfected cells, it was shown that NMO sera specifically bind to a water channel called aquaporin-4 [100]. AQP channels were initially discovered by Peter Agree (Nobel Prize, 2003) and more than ten different water channels have so far

Table 4

New diagnostic criteria (2005) for definite NMO [96].

1. Optic neuritis	
2. Acute myelitis	
3. At least 2/3 supportive criteria	i) Contiguous spinal cord MRI lesion extending ≥3 vertebral segment
	ii) Brain MRI not meeting diagnostic criteria for MS*
	iii) NMO-IgG seropositive status

* Paty MRI criteria

Figure 3

NMO test. Immuno-fluorescent staining of serum IgG from a NMO patient. Serum is diluted 1/100 and applied on tissue from monkey's brain. Anti-NMO IgG are revealed by a 2nd anti human IgG (magnitude x 200). The CNS microvessels of the blood brain barrier are targeted by these NMO-IgG (arrows). Control: MS serum at the same dilution (personal data).

Control (MS)
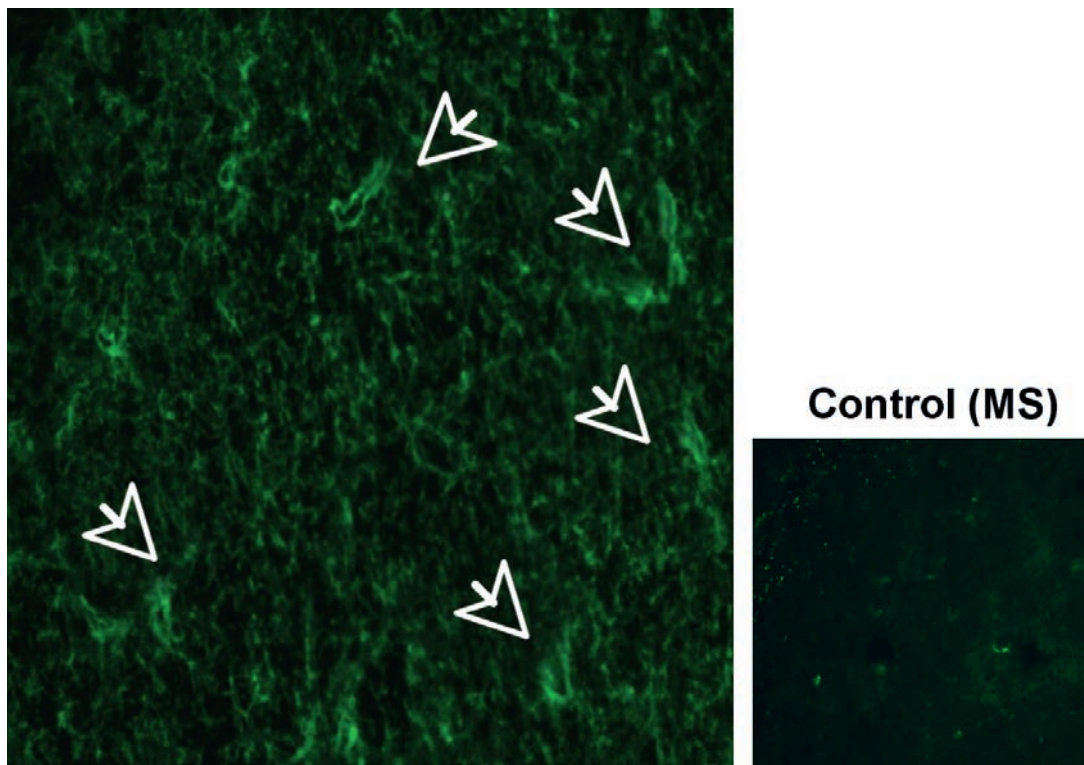
been described in humans. AQP4 is located in astrocytic foot processes at the blood brain barrier. The reasons why lesions are predominant in optic nerves and spinal cord, although AQP4 is ubiquitous in the CNS, are still unclear. One hypothesis is that AQP4 predominates in optic nerve and spinal cord [112]. The anti-AQP4 test has a sensitivity of 58–91% and a specificity >90% for NMO. A recent publication showed that AQP4 Abs tested with a cell based assay can reach a sensitivity of 91% and specificity of 100% to detect NMO, demonstrating that some specific AQP-4 tests can be more accurate than the original NMO-IgG (immunofluorescence) assay [110, 113]. Thus, anti-NMO/AQP4 Abs are diagnostic markers of a new autoimmune channelopathy specific to the CNS.

Limited or widespread B cell immune response in neuromyelitis optica?

NMO patients often have circulating auto-Abs that exceed the level usually seen in MS. For example, Anti-nuclear Abs (ANA) are seen in less than 30% of MS but in more than 50% of NMO cases and other systemic auto-Abs are frequently increased [105]. In NMO, prominent Ab response against myelin Ags such as MOG and MBP is frequent [114], and protein microarray techniques have detected several new auto-Abs of unknown function [115]. Hence, the B cell response in NMO is more consistent with a widespread immune response rather than an isolated immune response targeting only one putative Ag. These results indicate that several Ags might be involved in NMO pathogenesis, as it is frequently seen in other autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome or myasthenia gravis. The results of these studies [114, 115] do not contradict the relevance of the NMO/AQP-4 specific Abs since some NMO patients can be negative for this marker [101].

Finally, these findings emphasise the role of the humoral response in NMO and the fact that the B-cell immune response is possibly directed against several targets following epitope and Ag spreading.

Table 5

Biological characteristics of MS and NMO [104, 108, 160].

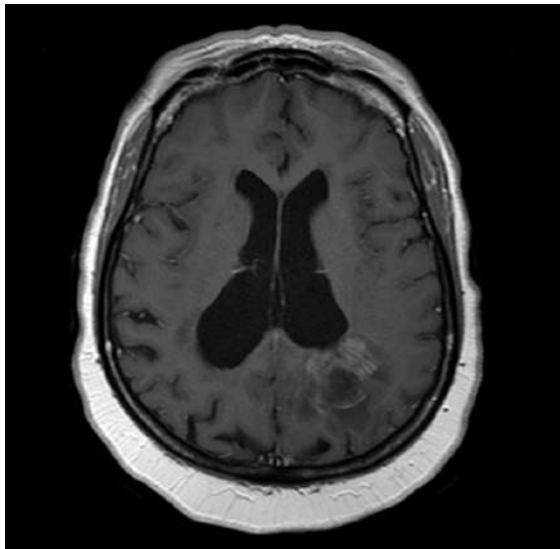|	MS	NMO
CSF:		
Pleocytosis	5–50 cells/mm^3	5–50 cells/mm^3 >50 cells/mm^3: 32%
Cell repartition	Lympho-monocytes	Lympho-monocytes Neutrophils: 25–50%
Oligoclonal bands	90%	30%
Serum:		
Anti-nuclear Abs (ANA)	20–30%	>50%
Other auto-Abs (systemic autoimmune diseases)	rare	frequent
NMO-IgG	absent	>70%

Balo's concentric sclerosis

Balo's concentric sclerosis is a rare IDD of the CNS, usually considered as a variant of MS, the diagnosis of which largely relies on MRI examination (fig. 4) [116–120]. More than 60 cases are reported in the literature and most died within a period of weeks or months [121], although a benign course with clinical and radiological remission has been described [118, 122]. It was first detailed by Balo in 1928 as "leukoencephalitis periaxialis con-

Figure 4

Balo's concentric sclerosis. T1-weighted MRI of a 60-year-old woman presenting with a typical image of Balo's concentric sclerosis. The concentric lesion appears to extend centrifugally by adding rims of myelin breakdown (personal data).

centrica" and is characterized by lesions of alternating bands of demyelinated and myelinated white matter forming concentric rings or irregular stripes. Lesions are typically multiple but can also be mixed with typical MS plaques [123]. The bands of myelinated white matter may include remyelinated fibres but usually consist in myelin sheath of normal thickness and preserved oligodendrocytes. A recent report analysed autopsy-derived CNS tissue from 14 patients with Balo's concentric sclerosis [123]. It was observed that demyelinated bands of white matter were consistent with the immunohistological features of type III MS pattern [11]. Demyelinated bands were associated with an increase of nitric oxide synthase (iNOS) in macrophages and microglia, whereas oligodendrocytes in the preserved white matter expressed the protective inducible facor-1α (HIF-1α and heat shock protein 70 (hsp 70). The fact that no Abs have been found to be involved in Balo's pathogenesis is consistent with the features of Type III MS classification that relies on the presence of primary oligodendrocyte degeneration. These histopathology-based results may explain the absence of auto-Abs found in Balo's concentric sclerosis, although no substantial study has addressed this question to date.

Marburg's disease

The first case was reported by Marburg in 1906 He described a patient, who developed sleepiness, headache, nausea, vomiting and paresis and died four weeks later. Post mortem examination showed extensive acute and sub acute demyelination in the CNS. Marburg's disease is defined by a severe demyelinating encephalomyelitis leading to death within weeks or months. Contrary to acute demyelinating encephalomyelitis (ADEM), it displays widespread demyelination occurring either diffusely in the white matter or with multifocal lesions forming large plaques by confluence and not restricted to the perivascular area as in ADEM [124–126]. The plaques found in Marburg's disease resemble the pathological change found in chronic active MS but can show,

in contrast to ADEM, different ages [127, 128]. The acute lesions are hypercellular with giant astrocytes, swollen axons, rare necrosis and predominance of MBP-positive macrophages. Determination of Ab deposition and complement activation within lesions has not been explored in Marburg's disease. Nevertheless, lesions encountered in Marburg's disease resemble those seen in some EAE models [1, 129], where anti-myelin (especially anti-MOG) Abs have been associated with the pattern of demyelination. Moreover, a single case report has shown that plasmapheresis can be helpful in Marburg's disease as in most acute variant IDDs of the CNS [130], indicating that B cells and auto-Abs might be involved in the pathogenesis of Marburg's disease.

Schilder's myelinoclastic diffuse sclerosis

This acute variant of IDD of the CNS does not represent a specific neuropathological entity and is applied to a wide variety of diseases of the CNS including pseudotumoral MS, ADEM and other leukodystrophies [2, 127, 131–133]. This term is commonly used by neuropaediatricians to

qualify atypical MS in children, starting with extensive lesions that may include a whole cerebral hemisphere. Further development such as a classic MS is often described [134]. Schilder's disease is often restricted to acute or chronic cases with at least one large area of demyelination present in

the cerebral hemispheres. One attempt to define "true" Schilder's disease includes the presence of bilateral large plaques (>3x2 cm) in the centrum semiovale of the hemispheres with histology identical to MS [131]. These lesions may co-exist with more typical MS lesions although demyelinated areas are often more spongy or cystic.

Due to the absence of rigorous clinical and neuropathological definition of Schilder's disease and the lack of a well defined neuropathological study, it is currently difficult to address the question of the role of the humoral response in this disease.

Acute demyelinating encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is defined as a typically monophasic autoimmune demyelinating disease of the CNS predominantly affecting children [135, 136]. The clinical diagnosis of ADEM is strongly suggested by a close temporal relationship between an acute infection or an immunisation followed in days or weeks by symptoms of encephalomyelitis [137]. MRI usually shows disseminated multifocal, subcortical white matter abnormalities with signs of blood barrier dysfunction. Oligoclonal bands are less frequently found in ADEM than in MS and, if found, may be transient [137].

The distinction between early signs of MS and ADEM remains controversial. A major difference between MS and ADEM is the course of the disease. Whereas MS is defined by relapses or at least progression of disability over time, ADEM is commonly seen as an acute monophasic disease with rare descriptions of relapsing or progressive cases [136, 138] that frequently lead to a final diagnosis of MS [135]. The pronounced perivascular inflammation is often associated with minor signs of demyelination restricted to the vicinity of the perivascular inflammatory infiltrates [125]. Thus, ADEM pathology resembles the pathological pattern found in myelin-induced EAE dominated by CD4+ T-cell infiltration with moderate demyelination, whereas MS pathology is associated with a predominant demyelinating feature. In addition, Theiler's murine encephalomyelitis, a virus-induced encephalomyelitis, is also considered to be a good model to study post infectious mechanisms that may contribute to ADEM

pathogenesis. Some vaccine-associated ADEM cases, such as the live attenuated rabies virus or the Japanese B encephalitis, have been directly linked to the contamination with CNS tissues [139, 140]. In these cases, specific anti-myelin Abs have been detected and correlated with the onset of encephalitis.

ADEM is often associated with the detection of auto-Abs that may be related to a secondary B-cell response to spreading CNS/myelin antigens. An autoimmune response against MBP is thought to be a potential aetiological factor in the pathogenesis of ADEM. This assumption is based on the observation that ADEM shares a typical pattern found in EAE after immunisation with MBP [125].

A recent study used an assay based on self-assembling radiolabelled tetramers allowing discrimination of Abs against folded or denatured myelin oligodendrocyte glycoprotein (MOG). It showed that auto-Abs from patients with ADEM selectively bound the folded MOG tetramer, whereas sera from mice with EAE induced with MOG peptide only immunoprecipitated the unfolded tetramer [50]. With this technique, MOG-specific auto-Abs were mostly identified in a subset of ADEM but only rarely in MS patients. It was concluded that auto-Abs against folded MOG were specifically increased in ADEM. Although there are no specific Abs available to detect ADEM, this work highlights the association of humoral response and specific anti-myelin Abs in ADEM.

Longitudinal extensive transverse myelitis (LETM)

Acute transverse myelitis (ATM) may have different origins. With the exclusion of infection, tumour, paraneoplastic syndrome, compressive origin, infarction, sarcoidosis, connective tissue disease, radiation and vitamin deficiency, most of the remaining cases are attributed to idiopathic myelitis mediated by autoimmunity [141]. Following a better understanding of NMO pathogenesis and the notion of specific extensive myelitis [96], a sub-category of myelitis was defined as longitudinal extensive transverse myelitis

(LETM). On the one hand, patients with a spinal cord lesion in MRI that spans less than two vertebral segments in length and extends asymmetrically within the cross-section of the cord are at high risk of developing MS [142]. On the other hand, patients with complete transverse myelitis associated with extensive longitudinal lesions spanning three or more vertebral segment are at low risk of developing MS [143] and are often suggestive of NMO [96] or idiopathic LETM [144]. NMO-IgG are detectable in 25% of recur-

rent optic neuritis and 52% of LETM [101]. A recent study tested the predictive value of the NMO-IgG for relapse or later development of optic neuritis (i.e., fulfilling NMO criteria) after a first event of LETM [144]. It was observed that 38% of patients with inaugural LETM were NMO-IgG positive and that most of them experienced relapses. By contrast, none of the NMO-IgG negative patients presented relapses at one year follow up. In addition, systemic auto-Abs directed against extractable nuclear Ag (ENA) (i.e., SSA and SSB) and antinuclear Ab (ANA) were also detected in LETM, but only NMO-IgG was increased in relapsing forms. When testing AQP4 Abs with transfected cell lines, the prevalence of specific Abs in LETM appears to increase, in comparison with the classical NMO-IgG test [145]. This suggests that IDDs of the CNS such as LETM could be better defined with specific auto-Abs.

Conclusion and perspectives

Inflammatory demyelinating diseases (IDD) of the CNS include MS and MS variants. These entities are defined according to clinical course, radiology, and to a lesser extent, biological examination. Nevertheless, these diseases clearly exhibit distinct immunopathological features. Some doubts arise as to whether to classify MS as a single disease or a complex syndrome because its pathogenesis appears to be very heterogeneous. Should not the so-called "MS variants" be viewed as specific subtypes still lacking histopathological or biological markers?

Notably, a predominant cellular autoimmune response is present in all cases of IDDs of the CNS, but the pathology, the clinical course and the therapeutic response depend on additional immune factors. The humoral response is heterogeneous among the different IDDs of the CNS. Whereas MS appears to be a heterogeneous disease, with about one half of the patients presenting an Ab-superimposed pattern, other IDDs of the CNS could certainly be better defined in the future according to the humoral response. For instance, NMO was until recently viewed as an unclear MS variant. The recent observation that this condition was essentially mediated by a humoral response and the demonstration of a NMO-specific Ab has brought new hope to achieving a better distinction between patients affected by other IDD of the CNS. Auto-Abs are also suspected to play a role in the pathogenesis of other rare IDD of the CNS such as Marburg's syndrome and ADEM.

A better distinction between IDD variants will probably be determined by new histopathological studies, which in turn need to be confirmed by independent research groups. In this regard, the demonstration of biomarkers specificity, such as auto-Abs, and their link with a clinical or histopathological subtype is a major challenge for the next decades. The finding of specific/sensitive diagnostic parameters that allow differentiation between diseases and MS subtypes will help to better define the most suitable therapeutic option or to develop new therapeutic agents. Beside the immunological approach, it is noteworthy that molecular and genetic markers might also help achieve distinction among demyelinating diseases. Although different research approaches may help to classify IDD of the CNS, the study of auto-Abs is certainly an important way to better understand the pathogenesis and to specify the different subtypes of CNS demyelinating diseases.

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