Myelin oligodendrocyte glycoprotein antibodies in neurological disease

Markus Reindl[1]* *and Patrick Waters*[2]

Abstract | Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies (MOG-Abs) were first detected by immunoblot and enzyme-linked immunosorbent assay nearly 30 years ago, but their association with multiple sclerosis (MS) was not specific. Use of cell-based assays with native MOG as the substrate enabled identification of a group of MOG-Ab-positive patients with demyelinating phenotypes. Initially, MOG-Abs were reported in children with acute disseminated encephalomyelitis (ADEM). Further studies identified MOG-Abs in adults and children with ADEM, seizures, encephalitis, anti-aquaporin-4-antibody (AQP4-Ab)-seronegative neuromyelitis optica spectrum disorder (NMOSD) and related syndromes (optic neuritis, myelitis and brainstem encephalitis), but rarely in MS. This shift in our understanding of the diagnostic assays has re-invigorated the examination of MOG-Abs and their role in autoimmune and demyelinating disorders of the CNS. The clinical phenotypes, disease courses and responses to treatment that are associated with MOG-Abs are currently being defined. MOG-Ab-associated disease is different to AQP4-Ab-positive NMOSD and MS. This Review provides an overview of the current knowledge of MOG, the metrics of MOG-Ab assays and the clinical associations identified. We collate the data on antibody pathogenicity and the mechanisms that are thought to underlie this. We also highlight differences between MOG-Ab-associated disease, NMOSD and MS, and describe our current understanding on how best to treat MOG-Ab-associated disease.

Myelin oligodendrocyte glycoprotein (MOG) was first identified 40 years ago as a target of demyelinating antibodies in guinea pigs[1]. MOG is a glycoprotein (218 amino acids, molecular mass 26–28 kDa) that is uniquely expressed in oligodendrocytes in the CNS of mammals, and is highly conserved between species[2–4]. In humans, MOG has been detected in the corpus callosum at around the time of birth, and transcript and protein levels throughout the CNS increase until ~2 years of age[4–6]. MOG expression starts later than that of other myelin proteins and therefore has potential as a marker of oligodendrocyte maturation and of myelin compaction. Primates, but not rodents, express multiple isoforms of MOG that have identical extracellular immunoglobulin (Ig) domains, but differentially spliced intracellular C-termini[5,7] (FIG. 1). The isoforms are divided into α or β isoforms on the basis of their C-terminal amino acids.

The biological role of MOG and its isoforms is not clear. Several (mostly single) studies have indicated that the protein could be a cellular receptor, an adhesion molecule or a regulator of microtubule stability[8,9]. MOG binds to C1q, the first component of the classical complement pathway, and to nerve growth factor[9,10]. Expression of MOG seems to make cells permissive to entry of Rubella virus, and when the single *N*-linked glycosylation site on MOG contains a glycan with terminal fucose residues, MOG becomes a ligand for DC-SIGN, a C-type lectin receptor that is expressed on the surface of dendritic cells and macrophages[11,12] (FIG. 1). However, genetic inactivation of MOG in mice has no clinical or histological consequences[13,14].

Despite our lack of knowledge about the biological role of MOG, we do know that it is an encephalitogenic protein that can elicit a demyelinating immune response in numerous experimental models of inflammatory demyelinating diseases[15,16]. These findings have motivated investigation into the role of anti-MOG antibodies (MOG-Abs) in neurological diseases. In this Review, we summarize the current knowledge about MOG, compare assays for the detection of MOG-Abs and describe the identified clinical associations with MOG-Abs. We review studies of antibody pathogenicity and the underlying mechanisms of this pathogenicity. Finally, we highlight differences between MOG-Ab-associated disease, anti-aquaporin-4-antibody (AQP4-Ab)-positive neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS), and describe our current understanding of how best to treat MOG-Ab-associated disease.

[1]*Clinical Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria.*

[2]*Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.*

**e-mail: Markus.Reindl@i-med.ac.at*

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Key points

- Antibodies against myelin oligodendrocyte glycoprotein (MOG-Abs) that are detectable with cell-based assays are associated with non-MS acquired demyelinating syndromes of the CNS.
- MOG-Ab-associated disorders account for a larger proportion of paediatric patients than that of adult patients who present with acquired demyelinating disease.
- The clinical presentation of MOG-Ab-associated disorders changes with age: MOG-Abs are associated with an ADEM-like presentation in young children and an opticospinal presentation in children aged >9 years and adults.
- Most patients with MOG-Ab-associated disorders have favourable outcomes, but a subset are left with permanent disability, usually as a result of the initial attack.
- Many patients develop relapsing disease; relapses usually involve optic neuritis and often occur during steroid weaning or soon after steroid cessation, suggesting that a longer initial treatment duration is required.
- Investigation of human MOG-Ab pathogenicity is hampered by their limited binding to rodent MOG; nevertheless, the place of MOG-Ab-associated disorders in the spectrum of inflammatory demyelinating diseases is becoming clearer.

Detecting MOG-Abs

Immunoblotting and ELISA. Early studies of serum immunoglobulin G (IgG) MOG-Abs suggested that the number and proportion of MOG-Abs in people with MS is higher than that in healthy individuals or people with other neurological diseases[17–19]. However, follow-up studies in which different control populations were used demonstrated no association of MOG-Abs with MS. Current interpretation of these data is that immunoblots or an enzyme-linked immunosorbent assay (ELISA) in which the linear or refolded recombinant protein is used as the assay substrate (usually residues 1–125) largely detect antibodies against non-native MOG epitopes. These antibodies occur frequently in the general population and do not cause disease.

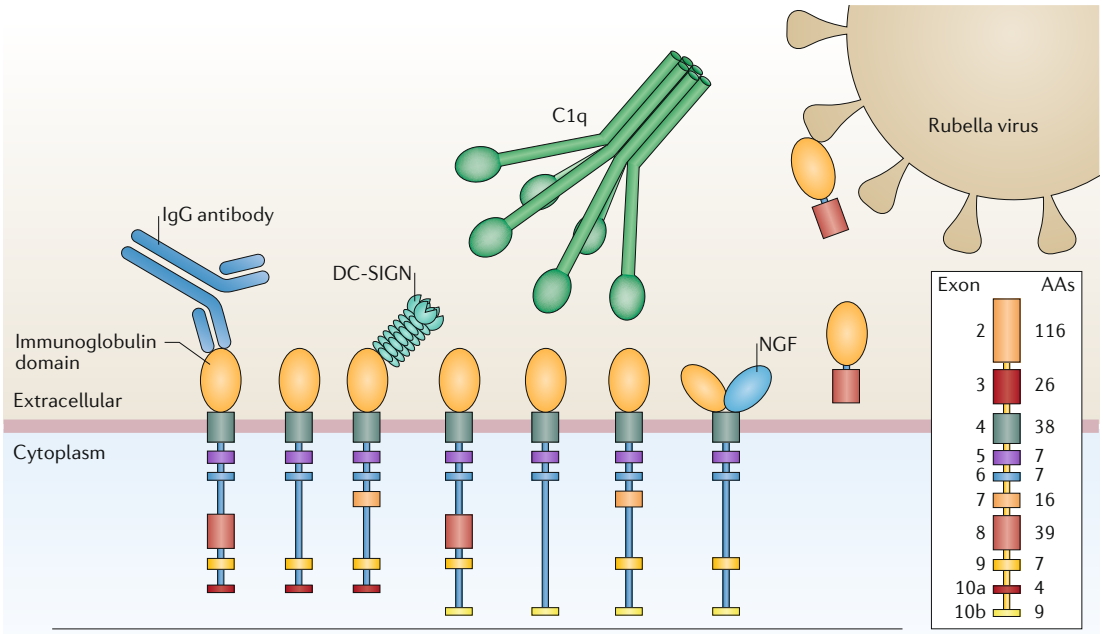
Numerous studies of MOG-Ab expression have been conducted. Summary data from studies that included at least ten people per group (FIG. 2; Supplementary Tables 1–5) show that MOG-Abs were detected in 423 (20%) of 2,111 people with MS in 16 studies in which immunoblotting (seven studies) or ELISA (nine studies)[17–32] were used. This proportion of people with MS who were positive for MOG-Abs is substantially higher than that of healthy individuals and people with headache, back pain, neurodegenerative diseases, infections and other inflammatory diseases (221 (13%) of 1,726)[17–19,21,22,24–26,28–33]. However, the lack of consistency between studies and the presence of antibodies in >10% of the control populations cast doubt on the findings.

Subsequent testing for MOG-Abs in people with aquired demyelinating syndromes of the CNS other than MS finally demonstrated that the antibodies are not clinically associated with MS. A single study in which ELISA was used showed that MOG-Abs were present in 6 of 11 patients (54%) with AQP4-Ab-positive NMOSDs[34]. Finally, in seven studies in which immunoblotting (two) or ELISA (five) were used, MOG-Abs were detected in people with atypical demyelinating disorders (such as clinically isolated syndrome (CIS), AQP4-Ab-negative NMOSDs[35], optic neuritis, myelitis, brainstem syndrome, acute demyelinating encephalomyelitis (ADEM), multiphasic demyelinating encephalomyelitis (MDEM) and encephalitis) at a similar frequency (41 (16%) of 252) to that in people with MS[18,19,28,30–32,34]. However, a high degree of heterogeneity is seen in the results (FIG. 2), suggesting that immunoblotting and ELISA are inconsistent as detection methods for MOG-Abs and that they cannot be used to define a distinct clinical entity. This conclusion is strengthened by the observation that MOG-Abs are absent in patients with MS and controls when more-specific radioimmunoprecipitation assays (RIAs) are used[25,28,36] (FIG. 2).

Specific tests show clinical associations. Kevin O'Connor's work provided the breakthroughs necessary to suggest that MOG-Ab detection could be clinically useful. His seminal work demonstrated the requirement for natively-folded MOG as an assay substrate, and for inclusion of children with ADEM, a non-MS demyelinating disease, as a control population. In an elegant experiment, he created a soluble MOG-Ig-domain tetramer by covalently linking MOG to streptavidin via an amino acid linker. Use of this tetramer as the substrate in an RIA identified enrichment of MOG-Abs in 19% of people with ADEM but only in 1% of healthy or neurological controls and in 2% of people with MS[28]. With this work, O' Connor defined the clinical association of MOG-Abs with a demyelinating phenotype that was not MS (FIG. 2; Supplementary Tables 1, 2 and 4).

At a similar time, cell-based assays (CBAs) that enabled screening for native proteins were emerging. This relatively simple technology involves transient or stable transfection of mammalian cells with plasmids that encode subunits of individual surface receptors or ion channels[37]. Human embryonic kidney (HEK) cells, Chinese hamster ovary cells (CHO) or other cells express sufficient amounts of the proteins transcribed from the plasmid to enable surface expression of single-chain or multi-subunit protein complexes. Antibodies that are present in serum or cerebrospinal fluid (CSF) samples can then interact with the extracellular surface of proteins. This method was first used >20 years ago to detect serum antibodies against the glutamate receptor GluR3 in Rasmussen encephalitis[38], and in 2005 for the detection of AQP4-Abs in NMOSD[39].

In CBAs for the detection of MOG-Abs, cells that express MOG are incubated with human serum samples, usually for 1 h at room temperature. Antibodies that bind to the cells are detected with different anti-human, specific secondary antibodies that recognize total human IgG (heavy and light chain), IgG-Fc (constant chain) or IgG1. Binding is quantified by either flow cytometry (CBA-FACS) or visual scoring by microscopic evaluation of the immunofluorescence (CBA-IF), which is often titrated. In the majority of established CBAs for detection of MOG-Abs, the α-1 isoform of MOG (FIG. 1) is used, although an alternative in which a truncated version of MOG that contains only the extracellular immunoglobulin and the transmembrane domain has also been tested. These assays were first used for the detection of MOG-Abs in a subset of people with MS in 2001 (REF.[40]) and then in two studies after the first international multicentre evaluation experiment of MOG-Abs in 2006 (REFS[41,42]). These studies



Isoforms	α1	α2	α3	β1	β2	β3	β5	α4 and β4
Size kDa	25.1	20.5	22.2	25.6	20.2	22.7	21.0	16.3
Amino acids	218	179	195	223	177	200	184	142

Fig. 1 | **The structures and functions of myelin oligodendrocyte glycoprotein isoforms.** The differences in the primary structures and membrane localizations of the MOG isoforms are determined by amino acids outside the N-terminal immunoglobulin domain. Exon 10a and 10b encode C-terminal amino acids (AAs) that define the α and β isoforms. The shortest isoforms (α4 and β4) are identical soluble immunoglobulin domains with an additional 26 amino acids that are encoded by exon 3. The other isoforms differ in their inclusion of exons 7, 8 and 9. The extracelluar immunoglobulin-domain mediates biological functions by recognition of several binding partners, including IgG antibodies, DC-SIGN (a C-type lectin receptor that is expressed on the surface of dendritic cells and macrophages), complement component C1q, nerve growth factor (NGF) and the Rubella virus, and might also form multimers. MOG has a single glycosylation site at Asn31, which mediates the binding of DC-SIGN. IgG, immunoglobulin G.

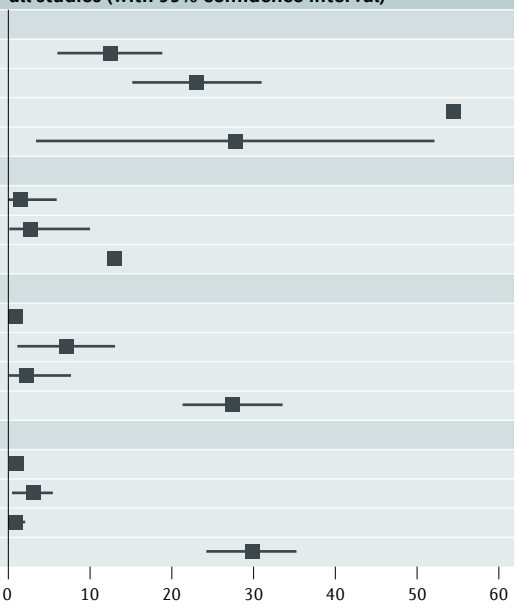
yielded inconsistent results, but O'Connor's important work motivated numerous researchers to use CBAs to detect MOG-Abs in patients with a non-MS aquired demyelinating syndrome.

In the initial MOG CBA studies, a lack of disease specificity was revealed by detection of MOG-Abs at low titres in people with MS or other neurological diseases and in healthy individuals[30,41–45]. These observations suggest that factors in the serum might bind to MOG and produce a nonspecific positive signal, or that these antibodies belong to the class of natural antibodies that are relatively common at low levels and are not removed by B cell tolerance mechanisms (particularly in young children), but do not cause disease. This nonspecific low-titre positivity is seen in studies of other CNS autoantibodies, such as the NMDA receptor, which are also common at low titres[46,47].

Regardless of the explanation for the observed non-specificity, the association of MOG-Abs with a non-MS acquired demyelinating clinical phenotype was re-established by improving specificity through the use of a higher serum dilution of 1/160 for CBA-IF, higher cut-off values for CBA-FACS, or by use of an IgG1-specific secondary antibody. Continuous dialogue between the laboratory and clinic has led to further improvements in the MOG-Ab CBA metrics (FIG. 2; Supplementary Tables 1–5). In more than 70% of CBA studies, all of the healthy or neurological controls were negative (that is, specificity was 100%)[24,27,28,35–65]. In five-sixths of CBA-FACS studies, people with AQP4-Ab-positive NMOSD were MOG-Ab seronegative[44,48–52], and from 24 CBA-IF studies, fewer than 1% (7 of 1,520) of people with AQP4-Ab-positive NMOSD were found to be positive for MOG-Abs[45,53–75]. Similarly, use of CBA-IF has demonstrated that patients with relapsing–remitting or primary progressive MS are predominantly MOG-Ab negative: only 24 (1%) of 1,608 people with MS were positive for MOG-Abs across 25 studies, and half of these were children[30,45,54,59–64,67,69,71–73,75–85]. In these studies, most samples from patients with MS that were positive for MOG-Abs had a low titre that is considered to be borderline or equivocal. Patients with MS who are clearly seropositive for MOG-Abs often have atypical MS that includes features usually associated with MOG-Ab-associated disorders, such as optic neuritis, longitudinal transverse myelitis and atypical brain lesions. The exception to these observations is the results of CBA-FACS studies (mostly those published before 2016), in which 105 (6%) of 1,771 people with MS (57 of whom were children) were considered to be MOG-Ab seropositive[40–42,46–51,53,56,61,63–74,86]. This observation might reflect use of a sub-optimal assay cut-off. Regardless, the availability of this new non-MS biomarker

a

Disease group	Number of studies	Number of MOG-Ab positive individuals
IB/ELISA		
Controls	14	221/1726 (12.8%)
MS	16	423/2111 (20.0%)
AQP4-Ab⁺NMOSD	1	6/11 (54.5%)
Other non-MS	7	41/252 (16.3%)
RIA		
Controls	3	3/236 (1.3%)
MS	3	8/264 (3.0%)
Other non-MS	1	13/101 (12.9%)
CBA-FACS		
Controls	18	15/1173 (1.3%)
MS	21	105/1771 (5.9%)
AQP4-Ab⁺NMOSD	6	10/317 (3.2%)
Other non-MS	20	273/1026 (26.6%)
CBA-IF		
Controls	17	45/5504 (0.8%)
MS	25	24/1608 (1.5%)
AQP4-Ab⁺NMOSD	24	7/1520 (0.5%)
Other non-MS	41	757/2639 (28.7%)



b

Assay	Studies	Patients with MOG-Ab positive non-MS	Patients with MOG-Ab positive MS
AQP4-Ab negative other demyelinating disease versus MS			
IB/ELISA	6	39/240 (16%)	77/677 (11%)
RIA	1	13/101 (13%)	3/140 (2%)
CBA-FACS	19	265/997 (27%)	75/1380 (5%)
CBA-IF	23	550/1918 (29%)	22/1353 (2%)

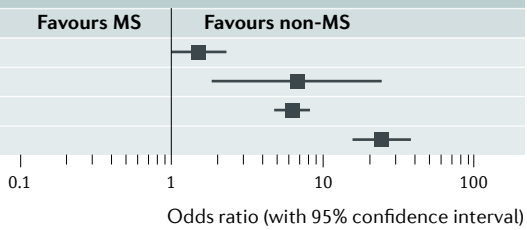


Fig. 2 | **Anti-MOG antibodies are associated with anti-aquaporin-4-antibody-negative non-multiple sclerosis demyelinating diseases. a** | Summary data from studies in which the frequency of anti-MOG antibodies (MOG-Abs) in controls (people with other neurological disease and healthy individuals), people with multiple sclerosis (MS), people with anti-aquaporin-4-antibody (AQP4-Ab)-seropositive neuromyelitis optica spectrum disorder (NMOSD) and people with other demyelinating diseases were analysed with different immunoassays (Supplementary Tables 1–4). The forest plot shows the mean percentages (squares) of individuals who were positive for MOG-Abs across the studies with 95% confidence intervals (error bars). Means and confidence intervals were calculated from the frequencies reported in the individual studies (Supplementary Tables 1–4). **b** | Comparison of MOG-Abs in MS and other AQP4-Ab-negative demyelinating diseases across multiple studies (Supplementary Table 5). Estimated odds ratios of the pooled studies are shown as squares with 95% confidence intervals (error bars). Odds ratios >1 indicate that the presence of MOG-Abs favours a non-MS disease course. CBA-FACS, cell-based assay with flow cytometry; CBA-IF, cell-based assay with immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IB, immunoblot; MOG, myelin oligodendrocyte glycoprotein; RIA, radioimmunoprecipitation assay.

has encouraged use of novel diagnostic criteria for critical re-examination of children who have previously been diagnosed with MS[87].

The development of highly specific assays has revealed that the MOG-Ab-associated clinical phenotype accounts for a proportion of people with non-MS acquired demyelinating syndromes (ADEM, AQP4-Ab-negative NMOSD, optic neuritis, myelitis, encephalitis and other syndromes). In 20 studies in which CBA-FACS was used, 27% of people with these conditions were MOG-Ab-positive[28,31,41,43,44,48–52,88–96], and in 41 studies in which CBA-IF was used, 29% were MOG-Ab-positive[30,45,53–77,79–82,86,97–105]. On the basis of these data, the presence of MOG-Abs is a convincing indicator of a non-MS demyelinating disease rather than clinically definite MS. Odds ratios for the different assays are 6.75 for RIA (95% CI 1.87–24.35)[28], 6.29 for CBA-FACS (95% CI 4.80–8.23)[28,31,41,43,44,49,51,52,86,88–96] and 24.32 for CBA-IF (95% CI 15.95–37.90)[30,45,53,54,59–64,67,69,71,73,75–77,79–82,84]. By contrast, the odds ratio when immunoblotting or ELISA are used is 1.51 (95% CI 1.00–2.28)[18,19,28,30–32]. Serum MOG-Ab assays with a high specificity can be used to define a non-MS demyelinating disease in adults and children

Box 1 | **Recommendations for anti-MOG antibody testing**

- Only cell-based assays (flow cytometry or immunofluorescence) in which full-length MOG (such as the α-1 isoform) is expressed in human cells should be used. Immunoblotting and enzyme-linked immunosorbent assays are of no use for detection of disease-relevant anti-MOG antibodies (MOG-Abs).
- For the detection of immunoglobulin G (IgG), only IgG-Fc or IgG1 secondary antibodies should be used. Total anti-IgG (heavy and light chain) secondary antibodies identify all antibody subclasses to some degree, meaning that results obtained with these secondary antibodies must be interpreted with caution.
- A second method should be used to confirm positive results, particularly borderline positive samples. At a minimum, the assay should be repeated and an assay with a control antigen should be used to confirm specificity.
- Given that a proportion of serum MOG-Abs are transient and associated with a monophasic disease course[30,69,80,93,113,114], MOG-Ab testing should be repeated after 6 months and 1 year to identify patients with persistent MOG-Abs, who are most likely to experience a relapse.
- As for anti-aquaporin-4 antibodies, MOG-Abs should be measured in serum because they are present in the cerebrospinal fluid (CSF) only at low levels, indicating that they have a peripheral origin[30,64,163]. In a few cases, intrathecal production of MOG-Abs is seen, but the relevance of this finding remains to be clarified[156,164].

with ADEM, seizures, encephalitis, optic neuritis, myelitis or brainstem encephalitis. In 2016, this spectrum of inflammatory demyelinating syndromes of the CNS was classified as atypical demyelination[106]. By contrast, MOG-Abs are only rarely found in people with MS, AQP4-Ab-positive NMOSD or other neurological diseases and in healthy controls.

MOG-Ab assay recommendations. Currently, MOG-Abs are best detected by use of a CBA in which the recombinant antigen is expressed in its natural conformation on the surface of human cells. However, further improvements could be made on the basis of biochemical examination of the MOG isoforms and their associated membrane proteins. For example, a better understanding of the native quaternary structure and the glycosylation state of MOG in CNS tissue compared with MOG that is expressed in CBAs could help to improve MOG-Ab assays. A deeper understanding of any functional or physical differences between antibodies separated by the assay cut-off could also help. Even without these improvements, the reproducibility of the different technologies that are currently used to detect MOG-Abs needs to be compared, as has been carried out for assays of AQP4-Abs[107].

In the absence of the studies suggested above, we propose recommendations (BOX 1) for MOG-Ab testing (as has recently been done for autoimmune encephalitis[108]) on the basis of our own data, findings from the literature and recently published recommendations from an international expert panel[109]. In summary, these recommendations are the use of CBAs with only full-length MOG, use of IgG1-specific secondary antibodies, use of a second method as confirmation, and measurement of levels only in the serum (BOX 1).

Clinical features

Frequency in children. Most studies of MOG-Abs have been retrospective, and the patient samples used were collected for other purposes. Only in a few of the latest studies have MOG-Abs been analysed in a prospective, population-based manner. MOG-Abs were detected in 65 (31%) of 210 children with acquired demyelinating disease[70] in a large study conducted in Austria and Germany, in 76 (32%) of 237 (REF.[80]) children in a UK study and in 31 (22%) of 151 children in a study from the Netherlands, but not all participants were tested for MOG-Abs[90]. These studies have also demonstrated that MOG-Abs are present in children more frequently than are AQP4-Abs (31% versus 3%[80] and 32% versus 6%[71] in two studies).

Summary data from 61 studies reveal the association of MOG-Abs with non-MS inflammatory demyelinating CNS diseases by age (FIG. 3), and demonstrates that the proportion of individuals with an acquired demyelinating disease who are positive for MOG-Abs is greater among children (40%) than among mixed cohorts (29%) and adults (22%). Most of these studies included selected populations, and CBAs (CBA-FACS or CBA-IF) were used to analyse MOG-Abs in children (18 studies)[31,43,59,71,76,79,80,84,89–93,95,97,100–102], mixed cohorts of children and adults (16 studies)[28,30,53,56,57,62–66,69,73,81,86,96,103] or adults (27 studies)[41,44,45,48–52,54,55,58,60,61,67,68,70,72,74,75,77,82,88,94,98,99,104,105]. On this basis, the frequency of MOG-Abs and their titres are higher among young children than among adolescents or adults[80]. However, MS and AQP4-Ab-positive NMOSD are known to be less common among children[110,111], so the higher seroprevalence of MOG-Abs in children could be a consequence of age-dependent manifestations of demyelinating diseases.

The prevalence of MOG-Abs in adults is lower than in children. In two population-based studies in adults with optic neuritis, the seroprevalence of MOG-Abs was low. The frequency of MOG-Ab seropositivity was similar in the two cohorts: 2 (4%) of 51 in a cohort from Denmark[82] and 3 (2%) of 177 in the Optic Neuritis Treatment Trial in the USA[88]. All individuals who were MOG-Ab positive developed a non-MS course. A large study conducted in Korea identified a similarly low frequency (22 (4%) of 505) of MOG-Abs among adult patients with acquired demyelinating diseases of the CNS[69]. Finally, analysis of the prevalence of MOG-Abs in NMOSD diagnosed according to the 2015 criteria[112] in two studies has revealed similarly low frequencies of MOG-Ab seropositivity in their cohorts. In one study, 9 (12%) of 74 patients in a cohort from Catalonia, Spain, were seropositive[68], and in the other, 15 (11%) of 132 patients in a UK cohort were seropositive[70]. In both studies, ~50% of all individuals who were seronegative for AQP4-Abs were seropositive for MOG-Abs.

Age dependence of clinical features. In the past 3 years, 23 studies have been published in which the clinical and MRI characteristics of large groups of people who are positive for MOG-Abs (20–252 patients per study, median 33) have been studied[50,51,71,75,79–81,86,90,102,103,113–123]. Cohorts in these studies included children, adults or both. In four of these studies, only patients with relapsing disease courses were included, whereas patients with monophasic and recurrent disease were included in the other 19. In addition, some of these studies focused on patients with an opticospinal phenotype, whereas

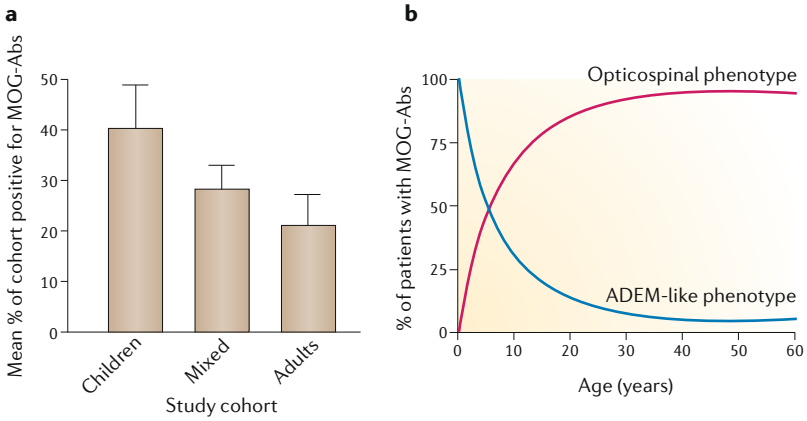


Fig. 3 | **The seroprevalence and clinical presentations associated with anti-MOG antibodies are age-dependent. a** | A comparison of 61 studies in which immunoprecipitation or cell-based assays (using either flow cytometry or immunofluorescence) were used to measure anti-myelin oligodendrocyte glycoprotein (MOG) antibodies (MOG-Abs) in children (18 studies), mixed cohorts of children and adults (16 studies) and adults (27 studies) with anti-aquaporin-4-antibody-negative non-multiple-sclerosis (MS) demyelinating diseases. The mean percentages of MOG-Ab-positive patients (bars) are shown for each subpopulation with 95% confidence intervals (error bars). **b** | The clinical phenotype associated with MOG-Abs changes with age, from acute disseminated encephalomyelitis (ADEM)-like (ADEM, ADEM–optic neuritis, multiphasic disseminated encephalomyelitis (MDEM) or encephalitis) to opticospinal (optic neuritis, myelitis, neuromyelitis optica spectrum disorder, brainstem) with increasing age. Data from REFS[80,113].

other studies were less biased, and some patients were included in more than one study. Nevertheless, the clinical characteristics of patients were generally comparable across studies, although the clinical outcome (prognosis or disability) of patients was sometimes different between studies. Across all the studies, the age of onset ranged from 0 to 90 years, the number of women was slightly higher than that of men, and no associations of MOG-Abs were apparent with ethnicity or, unlike AQP4-Ab-associated NMOSD, other autoimmune diseases. CSF parameters were normal in most patients, although up to 50% had elevated CSF leukocyte cell counts or protein levels. Unmatched IgG oligoclonal bands were present in only 10% of patients, and MOG-Abs were only rarely found in the CSF. Such studies have contributed to our understanding of the major differences between MOG-Ab syndrome, AQP-Ab-NMOSD and MS (TABLE 1).

These 23 studies, and older studies, clearly indicate that the clinical phenotype associated with the presence of MOG-Abs (TABLE 2) changes with age from ADEM-like (ADEM, ADEM–optic neuritis, MDEM and encephalitis) in children to opticospinal (optic neuritis, myelitis and brainstem encephalitis)[80,113] in adults. Young children most often present with ADEM, whereas optic neuritis is the most common feature in children older than ~9 years of age and in adults. Fewer patients present with myelitis, brainstem features, or the more recently described encephalitis with steroid-responsive seizures (FIG. 3). Finally, symptoms that are associated with involvement of the area postrema, such as nausea, vomiting and hiccups, occur in a subset of patients (at or before presentation), although associated imaging findings are inconsistent[124,125].

MOG-Abs in ADEM and encephalitis. The seminal description of MOG-Abs in children with ADEM, published in 2007 (REF.[28]), has been consistently replicated. MOG-Abs are found in a large proportion of children with ADEM[30,93,96,101], and these children have different MRI features to children who are negative for MOG-Abs: MOG-Abs are associated with large, hazy and bilateral lesions, an absence of small lesions and/or well-defined lesions, and involvement of more anatomical areas, often with longitudinally extensive transverse myelitis[126]. Importantly, children who have ADEM and are positive for MOG-Abs are at high risk of relapses that often include optic neuritis, leading to a diagnosis of MDEM, ADEM associated with recurrent optic neuritis or NMOSD[71,79,80,96,101,120,121,126–128]. The persistent presence of MOG-Abs is associated with a recurrent disease course or poor recovery, whereas the transient presence of the antibodies characterizes a monophasic disease course[30,79,80,93,96]. These associations are also seen in patients with an opticospinal phenotype[69,79,80,113,114]. Consequently, repeated MOG-Ab testing after 6 months and 1 year is recommended to identify the patients who are most likely to experience a relapse.

The frequently observed clinical phenotype of ADEM in children has a rare counterpart in adults. In 2017, an adult was described who had treatment-responsive focal seizures that generalized and who was eventually shown to be positive for MOG-Abs in the serum and the CSF[129]. When the patient's treatment of prednisolone was tapered, a relapse occurred with optic neuritis, supporting the association of this novel disease phenotype with MOG-Abs.

Two further retrospective case series confirm the association between MOG-Abs and seizures in adults[105,130]. In a single-centre study conducted in Japan, three of twenty-four consecutive adult patients with steroid-responsive encephalitis presented with swollen unilateral cerebral cortical lesions and epileptic seizures[105]. All three patients had generalized tonic–clonic seizures and were positive for MOG-Abs at symptom onset. MOG-Abs were also detected in the CSF of two patients for whom a sample was available. Retrospective study of the other series, in the UK, identified five patients who were positive for MOG-Abs who had cortical brain lesions and experienced seizures; in three of these five, seizures were the presenting feature[130]. All had a relapsing disease course and remained seropositive for MOG-Abs at the last follow-up, 2–12 years after onset. Two patients with recurrent seizures had residual cognitive impairment. Since these initial descriptions, this novel clinical phenotype associated with MOG-Abs has been confirmed in other studies[86,114,131].

Treatment response and clinical outcomes. MOG-Ab-associated demyelinating disease was initially described as being monophasic with complete recovery[56,57]. However, as testing became more widespread, it became clear that up to 70% of patients with these conditions have a relapsing disease that affects the eyes in most individuals, irrespective of the site of the onset attack site[50,51,71,75,79–81,86,90,102,103,113–122]. Interestingly, relapses are

Table 1 | **Demographic, clinical and MRI features of MS, AQP4-Ab-NMOSD and MOG-Ab-associated disease**

Feature	Disease[a]		
	MS	**AQP4-Ab-associated NMOSD**	**MOG-Ab-associated disease**
Clinical presentation	Optic neuritis, myelitis, brainstem or cerebellar syndrome, cognitive dysfunction and symptoms caused by involvement of other brain regions typically involved in MS	Optic neuritis, myelitis, area postrema syndrome, brainstem syndrome, narcolepsy or acute diencephalic syndrome, cerebral syndrome with NMOSD-typical brain lesions	ADEM-like (ADEM, MDEM, ADEM–optic neuritis, encephalitis), or opticospinal (optic neuritis, myelitis) or brainstem encephalitis
Female:male ratio	3:1	8–9:1	1–2:1
Age at onset	20–30 years	>40 years	More often in childhood than adulthood
Prevalence (per 100,000)	80–300	1–4	1–4
Disease course	Relapsing–remitting or chronic progressive	More often recurrent than monophasic	Monophasic and recurrent (recurrence often presents as optic neuritis)
Brain MRI findings[117,154]	Multiple focal white matter lesions, ovoid lesions adjacent to the body of the lateral ventricles, Dawson fingers and T1 hypointense lesions	No brain lesions or lesions atypical of MS and/or lesions in the brainstem and/or pons	ADEM-like, no brain lesions or lesions atypical of MS (fluffy lesions or three lesions or fewer)
Spinal MRI findings	Short-segment (<3 vertebral segments) lesions	Long-segment (>3 vertebral segments) lesions	Long-segment (>3 vertebral segments) lesions involving the lumbar segment and conus
Optic neuritis	More often unilateral than bilateral	Bilateral or unilateral, severe and often recurrent	Bilateral or unilateral, sparing of the optic chiasm and often recurrent
CSF OCBs	Common (>90% of patients)	Rare (<10% of patients)	Rare (<10% of patients)
CSF pleocytosis	Moderate (<50% of patients)	Common (>70% of patients)	Common (>70% of patients)
Neuropathology	Demyelination, axonal injury and astrogliosis	Astrocytopathy	Oligodendrocytopathy
Risk of future disability	High, owing to disease progression	High, owing to poor recovery from attacks and a high relapse rate	Low, owing to good recovery from attacks; in a subset of patients, recovery from the initial attack is poor
Treatment	Immunomodulatory, immunosuppressive	Immunosuppressive	Immunosuppressive

ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin-4; AQP4-Ab, anti-AQP4 antibody; CSF, cerebrospinal fluid; MDEM, multiphasic disseminated encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MOG-Ab, anti-MOG antibody; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder, according to the 2015 diagnostic criteria[112]; OCBs, oligoclonal immunoglobulin G bands. [a]Data summarizes several studies of MS[87,111], AQP4-Ab-associated NMOSD[112,117,154,162,165] and MOG-Ab-associated disease[50,51,71,75,79–81,86,90,102,103,113–123,154].

frequently observed either during steroid weaning or within 2 months of steroid withdrawal[113,114,116,121,122]. Most relapses occur in adults who are being treated with <10 mg prednisolone daily (range 0–25 mg) or in children who are receiving prednisolone at <0.5 mg/kg daily. The duration of treatment might also be important. Patients whose treatment lasts for less than 3 months are twice as likely to relapse as those who are treated for longer, suggesting the need for a biomarker for the response to treatment. Several studies suggest that relapses occur in patients who remain seropositive despite treatment — this group of patients often have high initial antibody titres, and includes ~80% of adult patients but fewer in paediatric populations. These observations suggest that prospective follow-up of MOG-Ab titres might help with treatment decisions[30,69,80,93,113,114].

The most common neurological symptom in people with MOG-Ab-associated disorders is optic neuritis. Studies in which optical coherence tomography has been used to compare the optic neuritis associated with MOG-Abs and with AQP4-Abs have demonstrated that severe damage to the optic nerve can be observed in MOG-Ab-associated disorders[132,133]. Neuroradiologically, MOG-Ab-associated optic neuritis is characterized by optic nerve head swelling, retrobulbar involvement, a long lesion length and, frequently, bilateral involvement[134]. MOG-Ab-associated optic neuritis often involves the anterior optic pathway,

Table 2 | **Demographic and clinical features of cohorts in three large studies of MOG-Ab-associated disease**

Feature of cohort	Study		
	Hennes et al. 2017 (REF. [80])[a]	**Jurynczyk et al. 2017** (REF. [113])[b]	**Cobo-Calvo et al. 2018** (REF. [114])[c]
Number of patients	65	252	197
% female	54	57	49
% children	100	29 ($n=75$[d])	0
Age at onset	Median 6 years (range 0–17 years)	Mean 30 years (standard deviation 18 years)	Median 36 years (range 19–77 years)
% with ADEM at onset	52	18	5
% with optic neuritis at onset	29	55	61
% with myelitis at onset	13	18	22
% with optic neuritis and myelitis at onset	5	9	8
% with brainstem, cerebral or multifocal symptoms at onset	1	0	5
Median months of follow-up (range)	24 (24–86)	26 (0–492)	16 (1–557)
% with relapsing disease	34	44	42
% that met 2015 criteria for NMOSD[112]	5	40 ($n=75$[d])	19
Annualized relapse rate	0.40	0.20 ($n=75$[d])	0.37
% with EDSS score of ≥3 at follow-up	5	NA	25 ($n=77$[d])
% with EDSS score ≥4 at follow-up	3	7[d]	NA
% in which MOG-Abs persisted	71 ($n=51$[d])	72 ($n=57$[d])	92 ($n=24$[d])
% with CSF OCBs	11 ($n=63$[d])	12 ($n=24$[d])	6 ($n=175$[d])
% with CSF pleocytosis (>5 cells/μl)	49 ($n=61$[d])	38 ($n=138$[d])	44 ($n=138$[d])

ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; IgG, immunoglobulin G; MDEM, multiphasic disseminated encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MOG-Ab, anti-MOG antibody; NA, not available; NMOSD, neuromyelitis optica spectrum disorder; OCBs, oligoclonal IgG bands. [a]MOG-Abs were detected in a cell-based assay with an anti-human IgG (total molecule)-specific secondary antibody and visualized by immunofluorescence (CBA-IF). A titre ≥1/160 was considered seropositive. Borderline seropositive samples (titres of 1/160 to 1/1,280) were confirmed with an anti-human IgG heavy chain-specific secondary antibody. [b]MOG-Abs were detected in a cell-based assay with an anti-human IgG1-specific secondary antibody and visualized by immunofluorescence. A titre of 1/20 was considered seropositive. [c]MOG-Abs antibodies were detected in a cell-based assay with an anti-human IgG heavy chain-specific secondary antibody and visualized by flow cytometry (CBA-FACS). A titre ≥1/640 was considered seropositive. [d]Only data from a subset of patients (*n* as indicated) were included.

whereas AQP4-Ab-associated optic neuritis affects the posterior optic pathway, but there is also considerable overlap between the conditions and long optic nerve lesions occur in both diseases. In contrast to AQP4-Ab-associated optic neuritis in which damage is caused by the severity of an attack, the damage associated with MOG-Abs seems to be driven by the frequency of attacks in patients who recover from the initial episode. Despite the potential for a higher relapse rate in MOG-Ab-associated optic neuritis, outcomes are generally better than in AQP4-Ab-associated optic neuritis[51,56,57,66,84,94,103,104,113–115,123,134].

Most people with MOG-Ab-associated disease recover well from attacks but some studies have shown that up to 45% can be left with severe disability[69,113,114,116,118]. Importantly, >70% of this disability results from the onset attack. In one study of 17 Korean patients with MOG-Ab-associated disease, four had a poor outcome, and in three of these, the outcome was a result of the onset attack; the fourth patient had experienced five optic neuritis attacks over 2 years despite maintenance steroids and azathioprine treatment[69]. A second study from the UK supported these findings[113]. In 25 (71%) of 35 patients who were disabled as a result of MOG-Ab-associated disease, the disability was a result of the onset attack. Vision, motor and bladder functions were affected: 9 of 12 patients whose visual system was affected had a visual acuity score of 6/36 or less; 3 of 5 patients with motor disability had an EDSS score ≥4; and 15 of 21 patients with affected bladder function had permanent bladder dysfunction. Similar results were also seen in a large national study conducted in France[114]. These studies suggest that there is room for improvement in the acute management of MOG-Ab-associated disease, and that time to treatment might be important for the prevention of permanent disability, as is the case in anti-LGI1 antibody-associated autoimmune encephalitis[135]. If patients recover from the onset attack, the chances of developing a severe disability are lower.

Only a limited amount of data are available on prospective treatment of MOG-Ab-associated disease, and current treatment is based on clinical experience with similar antibody-mediated diseases, such as AQP4-Ab-positive NMOSD and myasthenia gravis. Most disease-modifying treatments that are used in MOG-Ab-associated disease — which include corticosteroids, intravenous immunoglobulin, immunosuppressive

drugs (such as mycophenolate mofetil, azathioprine and methotrexate) and rituximab — are associated with a reduction in annual relapse rate[113,114,116,121,122]. By contrast, immunomodulatory treatments for MS, such as interferon-β and glatiramer acetate, are ineffective[116,121]. In a study of children and adults in Australia, maintenance treatment with oral prednisolone was associated with fewer treatment failures than were other treatment modalities[122], whereas a retrospective study of children confirmed that all treatment modalities reduced annualized relapse rates but had limited effects on disability[121]. However, these studies included few groups of individuals who were from different countries and were treated with the same modality, and positivity for MOG-Abs was often identified retrospectively. Therefore, as for AQP4-Ab-associated NMOSD, randomized controlled treatment trials are needed but difficult to perform owing to the rarity of the conditions.

Pathogenic role of MOG-Abs

The pathogenicity of autoimmune responses to MOG has been well established for almost 40 years and has been reviewed in detail elsewhere[16,136]. To summarize previous findings from animal models, MOG is encephalitogenic in many different species and the associated pathology is mediated by T cells and complement-fixing antibodies. Importantly, as is the case for AQP4-Abs, pathogenic MOG-Abs can be present in the circulation and have no effect unless they gain access to the CNS via an opening of the blood–brain barrier that results from an inflammatory environment. Experiments in animal models have also demonstrated that only MOG-Abs that recognize conformational epitopes are pathogenic. MOG-mediated experimental autoimmune encephalomyelitis (EAE) models are, like human MOG-Ab-associated disease, clinically heterogeneous, and the most common clinical phenotypes seen in humans (ADEM and opticospinal) also dominate in these models. The type of pathology seen in MOG-mediated EAE depends upon the balance between levels of encephalitogenic T cells and demyelinating MOG-Abs: an excess of T cells leads to an ADEM phenotype whereas an excess of MOG-Abs leads to focal confluent demyelinated lesions[137]. The opticospinal or cerebral distribution of inflammatory demyelinating lesions in the CNS after immunization with MOG is further influenced by polymorphisms in major histocompatibility complex genes[138–141]. Transgenic mice that express MOG-Abs develop either spontaneous opticospinal EAE if MOG-specific T cell receptors are also present, or an ADEM-like disease after infection with encephalitogenic viruses[142–144]. These observations might also explain the disease phenotypes in humans, as ADEM is often associated with infection or immunizations[106].

Studies in which the pathogenic role of human MOG-Abs has been investigated in vivo have been only partially successful. In vitro, human MOG-Abs can activate complement and cellular-dependent cytotoxicity[42,43,53,145]. However, in mice, intracerebral injection of human MOG-Abs caused no complement-mediated demyelination and only subtle effects on oligodendrocytes[146]. Similarly, peripheral injection of human MOG-Abs into rats with T cell-mediated EAE did not cause demyelination[42,145,147]. These findings indicate that, in contrast to human AQP4-Abs, human MOG-Abs are not pathogenic in vivo in rodent models[136]. There are several possible explanations for this finding. First, most human MOG-Abs do not react with rodent MOG[118,145,148,149]. In vitro, only human MOG-Abs that can cross react with rodent MOG can bind to rodent CNS myelin tissue and induce complement-mediated demyelination[118,145]. The lack of pathogenicity after injection of human MOG-Abs in rodents might simply be explained by the absence of pathogenic MOG epitopes. Second, the pathogenic role of MOG-Abs might be different from that of AQP4-Abs. Whereas AQP4-Abs directly cause tissue injury, two studies published in 2016 demonstrated that MOG-reactive T cell-induced inflammation is increased in the presence of specific MOG-Abs owing to an increased uptake of MOG by antigen-presenting cells[147,150], indicating that these antibodies have an indirect effect in pathology. Third, the amount of human MOG-Abs needed to induce tissue damage is higher than that of AQP4-Abs owing to the differential localization and expression of the antigens. Peripheral injection of 100 μg of monoclonal AQP4-Abs leads to pronounced effects, but ≥1 mg of monoclonal MOG-Abs is necessary to achieve pathological effects[136]. Given that MOG-Ab purified from human serum has been used in all previous studies, the likelihood that this pathological amount was achieved in the polyclonal mixture of antibodies is low. Therefore, different models in which lower concentrations of human MOG-Abs that react with rodent MOG can be used are needed. Indeed, intrathecal injection of small amounts of MOG-Abs that react with rodent MOG into rats with T cell-mediated EAE resulted in inflammation and complement-mediated demyelination, proving that MOG-Abs can be pathogenic in vivo[151].

To summarize, human MOG-Abs can be pathogenic in rodents if they cross react with rodent MOG and if the titres and affinities of these antibodies are sufficiently high. Tissue injury can occur via two possible mechanisms: antibody-mediated injury or MOG-reactive T cell-induced inflammation. However, the vast majority of MOG-Abs in patients are reactive only to human epitopes and we currently have no test system available to determine their in vivo pathogenicity.

The place of MOG-Ab-associated disease

The use of CBAs has enabled a complete clinical description of MOG-Ab-associated disease, which will facilitate treatment decisions and prognosis. People who are seropositive for MOG-Abs do not have MS and they rarely fulfil the most recent clinical criteria for MS (FIG. 2). In a UK cohort of 75 individuals who were MOG-Ab-positive, only one adult fulfilled the 2010 McDonald criteria for MS, but also exhibited red flags of bilateral optical neuritis and, within weeks, developed short transverse myelitis and NMOSD-like thalamic and brainstem lesions[113]. Other individuals with apparent MS and who were seropositive for MOG-Abs have had either atypical features or low antibody titres[69,80,81,85,86,113,114,152].

Studies published in the past 2–3 years have identifed brain imaging features that can distinguish between MS, MOG-Ab-associated disease and AQP4-Ab-associated disease[117,134,153,154]. MRI characteristics of MOG-Ab-associated disease were distinct from those of MS but overlapped with those of AQP4-Ab-associated NMOSD. MS could be clearly separated from both antibody-associated diseases by the presence of ovoid lesions adjacent to the body of the lateral ventricles, Dawson fingers, T1 hypointense lesions (fluffy lesions) and more than three lesions. Experts from the European Magnetic Resonance Network in MS (MAGNIMS) have defined clinically useful MRI features that differentiate AQP4-Ab-associated and MOG-Ab-associated conditions from MS[155]. Importantly, a comparable percentage (12–27%) of people with AQP4-Ab-associated disease or MOG-Ab-associated disease fulfil the Barkhof MRI criteria for MS, so some of them might also fulfil the 2010 McDonald criteria for MS without having MS. This overlap of imaging features in MS and antibody-associated aquired demyelinating diseases was one reason for the development of the more stringent 2017 revision of the McDonald criteria[87]. Testing for MOG-Abs should, therefore, be avoided if the clinical criteria for MS are fulfilled according to the MAGNIMS imaging recommendations and/or the 2017 revision of the McDonald criteria for MS. A diagnosis of MS in individuals who are clearly positive for MOG-Abs should be reconsidered.

To date, only a few studies of patients who are MOG-Ab-positive have included neuropathological investigations by biopsy or autopsy[85,149,156–159]. Despite the heterogeneous clinical presentations of these cases (optic neuritis, myelitis, brainstem syndrome, ADEM, cerebral CIS and encephalomyelitis), lesions fulfilled the pathological criteria for inflammatory demyelinating lesions with antibody and complement deposition at sites of activity (MS Pattern II)[160]. However, additional pathological hallmarks of MS, such as chronic inflammation, progression, axonal damage and astrogliosis, were missing. In MOG-Ab-associated disease, the pathological hallmarks were primary demyelination, axonal preservation, loss of MOG reactivity and increased numbers of MOG-negative pre-oligodendrocytes. Thus, the pathology was very similar to that seen in MOG-Ab-associated EAE. In contrast to AQP4-Ab-positive NMOSD, which is a primary astrocytopathy, the immune attack in MOG-Ab-associated disease is directed against myelin and oligodendrocytes[136]. This pathological difference is also reflected by the fact that glial fibrillary acidic protein (GFAP) levels are increased in AQP4-Ab-positive NMOSD whereas levels of myelin basic protein are increased in MOG-Ab-associated disease[161]. However, the increased levels of myelin basic protein do not differentiate MOG-Ab-associated disease from MS.

These findings, together with the heterogenous clinical presentations of MOG-Ab-associated disease — optic neuritis, myelitis, brainstem syndromes, encephalomyelitis, ADEM, relapsing forms, encephalitis and seizures — raise the question of the place of MOG-Ab-associated diseases in the spectrum of inflammatory demyelinating CNS diseases. The broad clinical spectrum associated with MOG-Abs is often used as an argument against any clinical relevance of the antibodies, but the breadth of this spectrum is not really so much different from that of other currently defined diseases, such as NMOSD, myasthenia gravis and autoimmune encephalitis. The currently used criteria for NMOSD includes a similarly broad spectrum of core clinical characteristics under the umbrella of 'seropositive NMOSD'[112]. Previous attempts to include some aspects of MOG-Ab-associated diseases under the umbrella of 'seronegative NMOSD' have only been partially successful because only a subset of people who are positive for MOG-Abs fulfil these criteria. For these reasons, a new classification is needed that should be, in our opinion, based mainly on biological criteria, specifically antibody status. Such a classification has recently been proposed[96] and includes seropositivity for MOG-Abs detected with CBA, a characteristic clinical presentation (any one or a combination of ADEM, optic neuritis, myelitis, brain or brainstem syndrome compatible with demyelination) and the exclusion of alternative diagnoses. An expert panel has also suggested that the indications for MOG-Ab testing should overlap with all of these criteria and also include the 'red flag' of MS[109]. Such discussions of biological classifications are controversial because tests to determine the correct antibody status might not be available or affordable, and standardization of these tests is in the early stages. Similar discussions in the NMOSD field led to the 2015 diagnostic criteria, in which the AQP4-Ab serostatus is an important (but not conclusive) part of the diagnostic process that is guided by clinical features[112]. However, these criteria turned out to be of little use for the classification of MOG-Ab-associated diseases, and we doubt whether classification of an autoantibody-associated disease is useful without inclusion of the autoantibody status.

Future directions

In our opinion, the most important issue that needs to be addressed in future is the standardization of MOG-Ab assays. A few published studies[45,60,64,77,148] and regular exchanges between laboratories suggest overall agreement between some centres in which MOG-Ab CBAs are used, but no blinded, multicentre validation experiments have been conducted to compare MOG-Ab assays. These studies are needed to evaluate assay reproducibility between centres and will help to further define the clinical phenotypes that are associated with MOG-Abs. Only then will we be able to determine the diagnostic sensitivity and specificity of assays and to define cut-off values that ensure high specificity (when compared with patients with MS and healthy controls who are MOG-Ab-negative) and sensitivity for non-MS demyelinating diseases. Longitudinal studies will inform us about the prognostic role of MOG-Abs and establish clinical correlates of MOG-Ab persistence.

Several other research avenues are likely to be informative. The development of transgenic rodents that express human MOG and monoclonal antibodies derived from human B cells, as has been done for AQP4-Abs to study NMOSD, would also be useful to improve our understanding of the pathological role of MOG-Abs, if they have any[162]. In addition, information on tolerance mechanisms and developmental anatomy might be

gained from further investigation into the clinical observations of high MOG-Ab levels in young children and the age-dependent involvement of different anatomical sites in relapses. Any genetic associations with MOG-Ab-associated disease need to be established. Finally, given that MOG-Ab-associated disease is rare, clinical associations need to be determined in large, multicentre studies that combine as many patients as possible.

Conclusions

Multiple studies have confirmed the existence of an age-dependent autoimmunity to MOG. Specific diagnostic tests have revealed a clinical association between MOG-Abs and a non-MS acquired demyelinating syndrome that is often relapsing in nature. Young children most often present with ADEM and multiphasic forms of this disease (MDEM, ADEM–optic neuritis), whereas optic neuritis is the most common feature in children >9 years of age and in adults. Some older children and adults present with myelitis (longitudinally extensive or non-extensive), brainstem encephalitis and/or encephalitis with seizures. Optic neuritis is the most common single manifestation at onset and more so in relapses. Only a subset of patients who are positive for MOG-Abs fulfil the clinical criteria for NMOSD, and fulfilment of the clinical criteria for MS is rare. However, in these cases, the clinical diagnosis and the assay result should be carefully considered.

Most patients with MOG-Ab-associated disease recover well from attacks, but a subset are left with severe, permanent disability. Disability is mostly a result of the onset attack. In these severe cases, early treatment might not be sufficient or is administered too late to prevent damage. Once patients are treated with immunotherapy, the percentage who will go on to develop permanent disability is lower than in AQP4-Ab-positive NMOSD. The presence of MOG-Abs is consistently associated with neuropathology that affects myelin and oligodendrocytes despite the association with different clinical phenotypes. Some evidence indicates that human MOG-Abs have a pathophysiological role, but an appropriate model system is lacking, in part owing to poor binding of human MOG-Abs to rodent MOG. Finally, the place of MOG-Ab-associated disease in the spectrum of inflammatory demyelinating diseases of the CNS is becoming clearer.

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Review criteria
We searched PubMed for original articles that were published between 1990 and 2018 and focused on anti-MOG antibodies in neurological diseases. We used the search terms "myelin oligodendrocyte glycoprotein", "MOG", "antibodies", "autoantibodies", "cell based assay", "immunofluorescence", "flow cytometry", "multiple sclerosis", "acute disseminated encephalomyelitis", "neuromyelitis optica", "optic neuritis" and "myelitis" alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers. For the summaries of study results, only studies in which there were more than 10 patients per group were included.

Supplementary information
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