Myelin-oligodendrocyte glycoprotein antibody-associated disease

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Myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently identified autoimmune disorder that presents in both adults and children as CNS demyelination. Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis, and aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder (NMOSD) cumulative biological, clinical, and pathological evidence discriminates between these conditions. Patients should not be diagnosed with multiple sclerosis or NMOSD if they have anti-MOG antibodies in their serum. However, many questions related to the clinical characterisation of MOGAD and pathogenetic role of MOG antibodies are still unanswered. Furthermore, therapy is mainly based on standard protocols for aquaporin-4 antibody-associated NMOSD and multiple sclerosis, and more evidence is needed regarding how and when to treat patients with MOGAD.

Introduction

Myelin-oligodendrocyte glycoprotein (MOG) constitutes a quantitatively minor component (0·05%) of CNS myelin[1] and is expressed on the outer lamella of the myelin sheath.[1,2] Although MOG knockout mice display normal myelin ultrastructure and no distinctive phenotype,[3] in humans MOG is thought to be involved in completion and maintenance of the myelin sheath and in cell–cell communication. MOG has been controversially discussed as a putative autoantigen in autoimmune CNS demyelinating diseases for decades,[4] but it is well established as an antigenic target in the experimental autoimmune encephalomyelitis mouse model.[5,6] The emergence of protein conformation-dependent assays[7] for the detection of anti-MOG antibodies has revealed distinct clinical phenotypes in children and adults with CNS demyelination.[8,9] Different terms have been proposed to characterise patients with CNS syndromes associated with the presence of anti-MOG antibodies. We will use here the term MOG antibody-associated disease (MOGAD), which suggests that this is a distinct disorder but does not preclude the future incorporation of a yet unidentified clinical presentation, and does not imply pathogenicity of the antibody itself.

Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis, and neuromyelitis optica spectrum disorder (NMOSD) associated with anti-aquaporin-4 (AQP4) antibodies (AQP4-NMOSD), cumulative biological, clinical, and neuropathological evidence clearly discriminates between these conditions. In patients with MOGAD, lesions are characterised by inflammatory demyelination, and not astrocytopathy as seen in AQP4-NMOSD. The perivascular deposits of activated complement proteins and immunoglobulins that are typical for multiple sclerosis lesions are also rarely found in patient with MOGAD.[10] Furthermore, although MOGAD shares some pathological features with multiple sclerosis (eg, demyelination and immune-cell infiltration), the lesions in MOGAD are characterised by perivascular infiltrated MOG-laden macrophages and $CD4^+$ T-cell infiltration; by contrast, multiple sclerosis lesions are characterised by infiltration by $CD8^+$ T cells.[10]

There are many unanswered questions related to the clinical characterisation of MOGAD and the pathogenetic role of anti-MOG antibodies, and more evidence is needed regarding who, how, and when to treat. This Personal View is based on a focused workshop on MOGAD, organised by the European Committee for Treatment and Research in Multiple Sclerosis, held in Athens, Greece, March 7–9, 2019. Our aim is to review and discuss the immunology, pathology, clinical spectrum, and treatment of MOGAD.

Clinical features in adults and children

MOGAD accounts for approximately 1·2–6·5% of all demyelinating syndromes in adults.[11,12] In children (<18 years), the frequency of anti-MOG antibody seropositivity during a first acute demyelinating syndrome is high, with multinational studies from Europe,[13–15] North America,[16] and Australia[17] identifying these antibodies in about 40% of all acute demyelinating syndrome presentations.[18] The most common presentations, stratified according to the different demyelinating phenotypes, are summarised in table 1 (appendix pp 2–5).

In both adult and children, the frequency of MOGAD is phenotype dependent. A single-centre retrospective study detected anti-MOG antibodies in the serum of 12 (60%) of 20 of adults with acute disseminated encephalomyelitis either at onset or at follow-up.[19] A Danish population-based prospective study detected anti-MOG antibodies in two (4%) of 51 adults with a first episode of optic neuritis,[20] and the multicentre, randomised, placebo controlled Optic Neuritis Treatment Trial reported anti-MOG antibodies in three (2%) of 177 individuals.[21] In anti-AQP4

	Optic neuritis	Transverse myelitis	Acute disseminated encephalomyelitis
Clinical features	Up to 80% of patients, either at onset or during the disease course; simultaneous bilateral involvement in up to 40%; average high contrast visual acuity at nadir counting figures; optic nerve head swelling (papillitis); might have peripapillary haemorrhage; more steroid responsive than in AQP4-NMOSD and multiple sclerosis	Spinal cord involvement in 30% of episodes at onset and up to 50% during the disease course; motor disability might be similar to AQP4-NMOSD; urinary, bowel, and erectile dysfunction are common; more steroid responsive than AQP4-NMOSD and multiple sclerosis	Most frequent presentation in children (<18 years); only in about 5% of adult presentations; seizures at onset observed in up to 40% of children with acute disseminated encephalomyelitis; MOG antibody associated ADEM at higher risk of higher risk of post-acute disseminated encephalomyelitis epilepsy
Imaging	Extensive T2-weighted and gadolinium enhancing lesion in the optic nerve or chiasm, more evident on orbit MRI; predominates in the anterior parts of nerve but might extend to optic chiasm; perineural gadolinium enhancement; peripapillary retinal nerve fibre layer thinning frequent on OCT but clinical-radiological paradox (despite severe atrophy of retinal nerve fibre layer, visual acuity is preserved); attack related retinal nerve fibre layer thinning with temporal predominance; microcystic macular in 24%	Initially described as longitudinally extensive transverse myelitis but short myelitis in up to 40%; involvement of the conus medullaris (more frequent than in MS and AQP4NMOSD); abnormalities confined to grey matter (sagittal line and axial H sign) and nerve roots; less frequent gadolinium enhancement than AQP4-NMOSD and multiple sclerosis; initial spinal cord MRI negative in 10% of patients; frequent complete resolution at follow-up scan	Large, hazy, and poorly demarcated asymmetrical bilateral lesions; deep grey matter involvement, most commonly affecting the thalamus; lesions might be highly enhancing; corpus callosum, brainstem and cerebellum involved; frequently associated to spinal cord involvement; frequent complete resolution at follow-up scan
CSF	Rare oligoclonal bands (<10%); presence of frequent mild lymphocytic pleocytosis	Rare oligoclonal bands (<10%); presence of frequent mild lymphocytic pleocytosis	Rare oligoclonal bands (<10%); presence of frequent mild lymphocytic pleocytosis
Risk of relapse and outcome	Patients aged <45 years at higher risk of relapse than older ones (>18 years); permanent visual impairment (visual acuity <20/100) rare at 2 years; reversible visual dysfunction from first episode in up to 75%; progressive thinning of peripapillary retinal nerve fibre layer (but not of the combined ganglion cell and inner plexiform layer) might be observed in absence of new clinical attacks	Good or full recovery from the onset attack in 60% younger patients (<18 years); around 20% of patients had permanent motor disability at 2 years (disability status scale >3·0); irreversible motor disability at last follow-up was explained by disability at onset attack in 68·4% patients who reached DSS 3.0 and 87·5% who reached disability status scale EDSS 6.0; permanent bowel, bladder, and erectile dysfunction are frequent despite good motor recovery	Up to 50% of children (<18 years) will relapse after acute disseminated encephalomyelitis; phenotype at relapse might be multiple disseminated encephalomyelitis, or acute disseminated encephalomyelitis-optic neuritis; a small proportion of children (<18 years) will have a single relapse within 3 months; behavioural and cognitive problems might occur after acute disseminated encephalomyelitis and are more common in relapsing group (up to 50%); up to 10% (predominantly very young children [younger than 7 years]) can develop a leukodystrophy-like phenotype with large confluent highly enhancing lesions and significant brain atrophy over time

Other, less common, phenotypes have also been reported in patienst with MOG-Ab; (1) isolated brainstem involvement in about 7% of adults and 30% of children (younger than 18 years; postrema syndrome is rare); (2) cortical (unilateral or bilateral) encephalitis with or without white matter involvement; (3) cranial neuropathies or mixed central and peripheral syndromes; (4) features of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; (5) pseudotumour cerebri-like, associating bilateral papillitis to elevated CSF opening pressure. For references and information, please see appendix (pp 2–5). MOG=myelin-oligodendrocyte glycoprotein. AQP4-NMOSD=anti-aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder. OCT=optical coherence tomography. EDSS=expanded disability status scale. ADEM=acute disseminated encephalomyelitis

Table 1: **Main clinical and paraclinical features in anti-MOG antibody-associated disease**

antibody seronegative longitudinally extensive transverse myelitis, two retrospective studies reported that 16–23% of individuals were anti-MOG antibody seropositive.[22,23] MOG antibodies are identified in up to 64% of children with acute demyelinating encephalomyelitis[24] and in almost all those who relapse after acute disseminated encephalomyelitis (multiphasic acute disseminated encephalomyelitis or acute disseminated encephalomyelitis-optic neuritis),[25–28] but in 33–43% of children presenting with optic neuritis[14,16,28] and only three (6%) of 50 patients with paediatric myelitis.[28] Anti-MOG antibodies were identified in 26 (24%) of 110 children with relapsing demyelinating syndrome and 26 (54%) of 48 with non-multiple sclerosis relapsing demyelination.[9] Most studies describing the frequency of anti-MOG antibodies and the clinical phenotypes associated with them were done in tertiary referral centres for neuroinflammatory disorders, which might lead to selection bias. This is especially relevant when evaluating patients with clinical phenotypes such as optic neuritis or myelitis, who might be referred to such centres only because of severe or atypical presentation. In addition, the first cohorts evaluated for anti-MOG antibodies by cell-based assay were restricted to patients with monophasic or recurrent optic neuritis or myelitis, thus not reflecting the real frequency of anti-MOG antibodies across all acute and chronic inflammatory demyelinating CNS diseases.[29–32] Clinical phenotypes and paraclinical features stratified by age at onset are summarized in table 2.

No racial groups seem to be more or less likely to be diagnosed with MOGAD, by contrast with AQP4-NMOSD which is more common in non-White people. An equal number of males and females have MOGAD among young children (age <10 years), with a slight

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	Children			Adults			
	<10 years	10–17 years	All Children	18–39 years	40–59 years	≥ 60 years	All adults
Female to male ratio[33,38]	Similar	Similar	Similar	Slightly more female	Slightly more female	Slightly more female	Slightly more female
Presentation at onset[8,28,36,37]							
Optic neuritis	20–30%	50–60%	20–60%	50–65%	50–65%	50–70%	50–70%
Transverse myelitis	15–20%	15–20%	15–20%	20–40%	20–40%	20–40%	20–40%
Acute disseminated encephalomyelitis	50–60%	20–30%	20–60%	<8%	<8%	<8%	<8%
Brainstem demyelination	<10%	<10%	<10%	<10%	<10%	<10%	<10%
Patients relapsing at 2 years[8,15,33]	NA	NA	40%	NA	NA	NA	40–44%
Risk of relapse*[38]	Very low	Low	Low	Moderate	Moderate	Very low	Moderate
Mean annualised relapse rate (SD)[38]	0·17 (0·31)	0·28 (0·38)	0·23 (0·35)	0·39 (0·62)	0·31 (0·52)	0·15 (0·27)	0·35 (0·58)
CSF oligoclonal bands[54,55]	<5%	<12%	<10%	<10%	<10%	<10%	<10%
Motor disability (reaching EDSS 3·0)†[33,38]	<10%	<10%	<10%	20–30%	20–35%	30–40%	20–40%
Visual acuity disability (reaching visual acuity 0·2)†[38]	<10%	<10%	<10%	<10%	10–20%	10–20%	<20%
Bladder, bowel, and erectile dysfunction or all three[33]	NA	NA	20%	NA	NA	NA	28–46%

Annualised relapse rate was calculated as number of relapses per year before treatment (excluding index event) and on-treatment only in patients with at least 6 months follow-up after initiation of treatment. Relapses were analysed for up to 2 years before initiation of therapy and for the duration of the time on therapy. No data are evaluable on the risk of relapse and bladder, bowel, and erectile dysfunction or all three stratified to the different age groups. We have therefore included a reference for all children and all adults. Refrain from drawing definitive conclusions regarding visual acuity disability and bladder, bowel, and erectile dysfunction or all three in children due to probable recall bias. Very low=lower risk than the reference category. Low risk=0–30% higher risk than the reference category. Moderate risk=30–60% higher risk than the reference category. EDSS=expanded disability status scale. NA=not aplicable. *Age group <10 years old is the reference category. †Based on cohorts of patients with a median follow-up between 2 and 4 years.

Table 2: **Demographic, clinical, and laboratory differences according to age at onset in myelin-oligodendrocyte glycoprotein antibody-associated disease**

female predominance (less than in patients with AQP4-NMOSD) in older post-pubertal children and adults.[33] No definitive evidence has linked MOGAD with other autoimmune diseases or specific malignancy. Although an HLA association, similar to other autoantibody associated disease might be expected, a study of 43 Dutch patients with MOGAD showed no significant HLA association.[34] As in other genetic and acquired white matter diseases, there is an age-dependent phenotype in MOGAD:[35] Younger children are more likely to have brain involvement compared with older children and adults.[36,37] Similar to multiple sclerosis, both the severity of the attacks and the recovery from attacks are also age-dependent, with worse severity and more complete and faster recovery in children.[38] The risk of relapse is lower in children, with most remaining monophasic.[16] Less than 10% of children who relapse (typically very young children [<7 years]) develop a leukodystrophy-like phenotype, with large confluent highly enhancing lesions on MRI and substantial brain atrophy over time.[35] These children have poor outcomes, with permanent cognitive and motor disabilities.[35] Younger children (<7 years) are more likely to have symptomatic brain involvement compared with older children and adults.[37]

Cohort studies and case reports have shown that the disease course is heterogeneous. The number of clinical relapses itself does not accurately explain disability accrual at the individual level, possibly because of individual differences in the susceptibility for myelin damage and mechanisms of remyelination and repair. For instance, children younger than 9 years are more likely to have severe brain pathology, with higher lesion load detected on conventional imaging, than children aged 9 years and older;[37] nevertheless, recovery from acute attacks appears faster than in older children and adults. This finding might not be disease specific and was also observed in a comparison between adult and children with multiple sclerosis showing that every 10 years of age reduced recovery on the expanded disability status scale by 0·15 points.[39] It is estimated that about 40% of adults[40,33] and 30%[18] of children[28] with MOGAD present with a second clinical attack within 5 years.

Approximately 60% of adult patients develop permanent neurological deficits, including motor and visual symptoms[41] and about 50% of children with relapsing MOGAD and brain involvement develop cognitive problems.[37] Prediction of disability based on characteristics of the first attack remains elusive. Early studies suggested that high anti-MOG antibody titres could predict further clinical events,[15] but more recent data indicate that patients might remain seropositive for many years and not relapse, and even patients who become seronegative could still relapse (and become seropositive at time of relapse).[16] Antibody titres, even when measured longitudinally, did not clearly correlate with disability outcomes.[8] Similarly, baseline MRI parameters are not predictive of risk of relapse or disability.[16,33]

Biomarkers

Assays for anti-MOG antibody detection

Over the last 10 years, great efforts have been made to improve anti-MOG antibody detection techniques.[42] More consistent results were obtained when the substrate for the tests were recombinant antigens expressed on live cells. As glycosylation and conformation of the MOG protein play a key role in anti-MOG antibody recognition,[43–46] surface expression of the full-length human MOG protein (usually α-1 isoform, 218 aminoacids) expressed typically on human embryonic kidney (HEK293) cells[7] is used to detect pathogenic anti-MOG antibodies accurately. The immunopathology in MOGAD is summarised in the figure and the panel. Their titres are higher during the acute attack in young children than in adolescents or adults[32] but more likely to become negative after the attack.[16] Timing of testing is important as antibody titres fluctuate and can decrease over months from presentation, and some patients can subsequently be tested negative.[16] A higher cutoff for seropositivity and use of specific secondary antibodies to IgG1 or IgG-Fcγ[47] increases specificity (ranging from 99·6% to 100%).[48] The use of anti-IgG (heavy and light chain) secondary antibodies is a matter of debate. It was previously shown that using IgG (heavy and light chain) secondary antibodies could cross react with anti-MOG-IgM, which can be found in healthy controls.[47] However, two studies showed that IgG (heavy and light chain), IgG1, and IgG-Fcy antibodies were similar, and no IgM binding was observed.[49,50] These discrepancies could be due to differences in assay methods. Of note, the sensitivities and specificities reported in all these studies[15,16,47–51] were evaluated in the research setting, and applicability remains to be evaluated in the clinical context. In a recent large multicentre comparative study, anti-MOG antibody cell-based assays showed excellent agreement with each other for high positive and negative samples, but low positive or borderline samples were more frequently discordant.[51] Such titres represent an undefined group of patients and are likely to affect the sensitivity and specificity of the results across all anti-MOG antibody testing laboratories. Each credited laboratory uses a specific cut off for positivity. As with any test, low positive or borderline results are more frequently discordant and should be evaluated as such.

Anti-MOG antibodies are now rarely found in patients with typical multiple sclerosis using cell-based assays. Only one (0·4%) of 244 patients with multiple sclerosis was found to be anti-MOG antibody positive by live-cell-based assay in a multicentre study.[52] Accordingly, two cross-sectional studies reported no detection of anti-MOG antibodies in 200 patients with progressive multiple sclerosis[53] and in two (<1%) of 685 patients with relapsing or progressive multiple sclerosis from two tertiary centres.[11] It is exceptionally rare for any patient to have serum antibodies to both MOG and AQP4.[8,42] Patients who are anti-MOG antibody positive with clinical and paraclinical features discordant or uncommon for MOGAD must be closely monitored to determine the positive predictive value of this antibody for clinical management. This is particularly relevant in adults with suspected multiple sclerosis, in whom testing of all patients with suspected demyelinating disease would result in many borderline results and probably false positives. With the absence of established criteria for MOGAD, diagnosis in antibody-positive patients with atypical presentation rests on the rigour of the test method and the expertise of the clinician.

One half of patients with MOGAD present with pleocytosis (predominantly lymphocytes and monocytes) with cell numbers that tend to be higher than in multiple sclerosis.[54,55] Severity of pleocytosis correlates more strongly with the rostral extent of lesions in people with acute disseminated encephalomyelitis or longitudinally extensive transverse myelitis than it does in people with optic neuritis.[8] Oligoclonal bands and a positive IgG index are found in less than 15% of people with MOGAD, mainly during attacks.[54,55] Similar to patients with AQP4-NMOSD, CSF cytokine profile is elevated during an acute

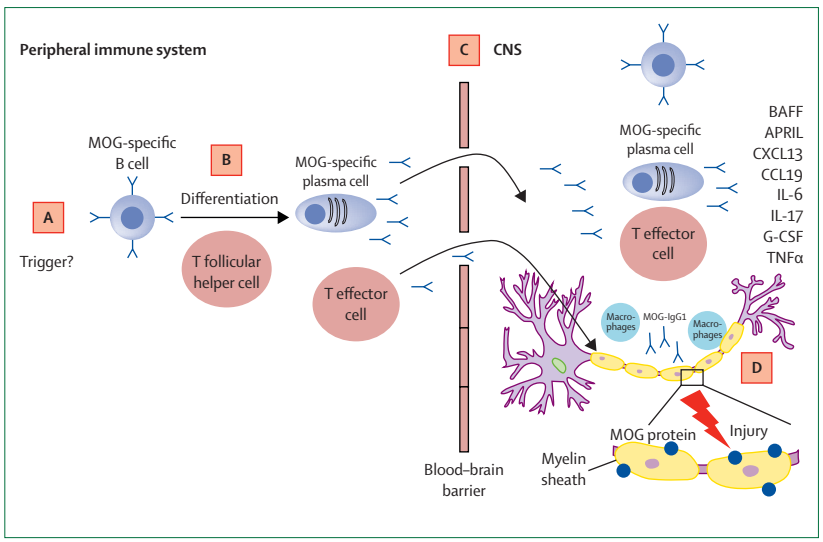

Figure: **Proposed model for immunopathology of anti-MOG antibody-associated disease and potential treatment strategies**

(A) The trigger for anti-MOG antibody production is unknown, but the autoimmune induction is thought to occur in the peripheral immune system. Although post-infection autoimmunity is a probable trigger, no disease-specific pathogens have been identified. Potential mechanisms for post-infectious autoimmunity, either in isolation or in combination, include molecular mimicry, bystander activation, epitope spreading, B-cell receptor mediated co-capture of antigens, and polyclonal activation of B cells. (B) In addition to anti-MOG antibodies and anti-MOG antibody-producing cells (B cells[98] and plasma cells), antigen-specific T follicular helper cells are also probably involved. As human anti-MOG antibodies are mainly of the IgG1 phenotype, T follicular helper cells are required for differentiation of B cells into plasma cells that produce MOG antibodies. (C) B cells, plasma cells, and autoantibodies have to cross the blood–brain barrier to interact with their autoantigen, and mediate their pathogenic effects. Anti-MOG antibodies might enter the CNS when the blood–brain barrier is damaged after binding to Fc receptors and release from endothelial cells. (D) Once in the CNS, anti-MOG antibodies presumably bind MOG (dark blue circles) expressed on myelin (yellow ovals) where they lead to myelin injury (red flash) and subsequent demyelination.[56,97] In parallel, anti-MOG antibodies and plasma cells might also enhance activation of cognate MOG-specific CD4+ T cells or myelin basic protein-specific T effector cells and macrophages in the CNS.[99] Indeed, there is an increase of proinflammatory cytokines (IL-6, IL-17, G-CSF, and TNFα) as well as B cell cytokines and chemokines (BAFF, APRIL, CXCL13 and CCL19) in the CSF of patients with anti-MOG antibody-associated disease, compared with CSF from healthy controls.[56] MOG=myelin-oligodendrocyte glycoprotein. MG-CSF=granulocyte colony stimulating factor. TNF=tumour necrosis factor. IL=interleukin. BAFF=B cell activating factor. APRIL=a proliferation inducing ligand.

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See Online for appendix

Panel: **Proposed immunopathology of myelin-oligodendrocyte glycoprotein (MOG)-antibody associated disease**

- Human anti-MOG antibodies are typically of the IgG1 isotype[42]
- The hypothesis of their pathogenic potency was derived from a monoclonal mouse antibody against MOG[93]
- The transfer of this monoclonal antibody to rodents that already have complement-dependent experimental autoimmune encephalomyelitis enhances demyelination[94]
- Studies looking at the effect of anti-MOG antibodies both *in-vivo* and *in-vitro* reveal primary demyelination[95] with loss of the microtubule cytoskeleton in oligodendrocytes, resulting in altered axonal expression of proteins[96]
- The study of presence of $CD4^+$ T cells in lesions from patients with anti-MOG antibody-associated disease, and data from rat models, suggest that T cells are important in pathogenesis[10, 97]
- MOG-specific B cells have been identified in the peripheral blood from patients with anti-MOG antibody-associated disease, defined by the presence of anti-MOG antibodies in the serum[98]

attack compared with that in patients with multiple sclerosis.[56] Finally, the usefulness of anti-MOG antibody detection in the CSF is not yet fully evaluated. When paired samples are analysed, there is a good concordance between serostatus and CSF status (ie, most CSF-positive patients are seropositive), but not all seropositive patients are CSF-positive, and only a small proportion are seronegative and CSF-positive.[57]

Imaging biomarkers

Brian and spinal cord MRI

Brain MRI in MOGAD can be abnormal in more than 50% of patients, regardless of the clinical presentation.[8] In general, brain lesions are more widespread in children than in adults, reflecting a higher disease burden. In addition to the deep white and grey matter lesions found in acute disseminated encephalomyelitis-like presentations, brainstem lesions are found in up to 40% of patients with MOGAD, frequently involving the pons and middle cerebellar peduncles.[9,58–60] Interestingly, in a discriminant analysis using only routine clinical scans obtained on different MRI machines, anti-MOG and anti-AQP4 antibody related diseases could not be distinguished, but displayed different imaging characteristics from multiple sclerosis:[58] lesions were poorly demarcated, fewer in number, and so-called Dawson fingers or lesions adjacent to the body of lateral ventricles were less frequent.[58,61] Other studies have suggested that the involvement of cerebellum, brainstem, or both as a part of a multifocal CNS episode is more likely to indicate the presence of anti-MOG antibodies when compared with multiple sclerosis, but not with anti-AQP4-positive patients.[62] Dramatic lesion resolution on MRI, sometimes within a month of presentation, is not rare in MOGAD.[59] Patients with MOGAD are less likely to develop clinically silent MRI lesions than are patients with multiple sclerosis.[63]

Although initially thought to be associated predominantly with white matter disease, both adults[64,65] and children[24,66,67] with MOGAD can experience cortical encephalitis and seizures. Brain MRI in these patients can be normal or have reversible cortical changes occasionally with leptomeningeal enhancement.[64] Reports of isolated seizures (with normal brain MRI) during the first episode of what later turned out to be MOGAD in children[66] and reports of aseptic meningoencephalitis and pseudotumour cerebri-like presentations[68] highlight that normal conventional imaging should not preclude the diagnosis of MOGAD and that contrast-enhanced scans can increase the diagnostic yield in symptomatic patients.[64]

Spinal cord MRI findings in MOGAD such as the presence of longitudinally extensive T2 lesions, spanning at least three vertebral segments on sagittal sequences, or the hyperintensity of grey matter on axial sequences (longitudinally extensive transverse myelitis), can resemble those commonly seen in AQP4-NMOSD.[69] MRI features suggesting a diagnosis of MOGAD rather than AQP4-NMOSD or multiple sclerosis are involvement of the conus medullaris, abnormality confined to grey matter (sagittal line and axial H sign) and nerve roots, and scarcity of or minimal gadolinium enhancement.[69] Occasionally, large lesions might be associated with mild clinical impairment, a clinical-radiological paradox, particularly in children.[35]

MRI of the optic nerves can show extensive T2 hyperintensity and T1 gadolinium enhancement that predominates in the anterior portion of the nerve. These features together with severe swelling of the optic nerve head with or without haemorrhage on fundoscopy can help differentiate MOGAD from episodes of optic neuritis in AQP4 NMOSD and multiple sclerosis. Perineural oedema is another radiological finding in up to half of patients with MOGAD with optic neuritis.[70–72]

Optical coherence tomography

Patients usually display a thickening of the peripapillary retinal nerve fibre layer, probably due to optic disc swelling during the acute phase of an optic neuritis attack.[73] Subsequently, the peripapillary retinal nerve fibre layer progressively thins, which is greater in the temporal quadrants. Although findings are still inconsistent, on average, optic neuritis associated with anti-MOG antibodies causes less retinal damage than optic neuritis associated with anti-AQP4 antibodies.[74] In affected eyes, longitudinal optical coherence tomography has found a decrease of the peripapillary retinal nerve fibre layer but not of the combined ganglion cell and inner plexiform

layer in the absence of new clinical attacks,[73] in contrast to the reduction of both layers observed in optic neuritis associated with ant-AQP4 antibodies or multiple sclerosis over time.[74,75] In non-affected eyes, subclinical neuroaxonal retinal damage has been found with a decrease in thickness of the ganglion cell and inner plexiform layer.[74] Conflicting results have been reported regarding the peripapillary retinal nerve fibre layer in this subgroup of patients with non-affected eyes.[73,76] Subclinical chiasmal or optic nerve inflammation are the most probable explanation. Similar to the MRI paradox, a clinical-radiological discordance has also been observed with optical coherence tomography, in patients with MOGAD whom preserved visual acuity despite severe atrophy of the retinal nerve fibre layer[77] compared with to optic neuritis in patients with multiple sclerosis or AQP4-NMOSD, in which retinal nerve fibre layer thickness and visual acuity frequently correlate.[78–80]

Treatment

Attack treatment

There are currently no randomised control trials or evidence-based guidelines for the acute treatment of MOGAD relapses. There is no evidence that anti-MOG antibody positivity should influence acute attack treatment and most neurologists treat these patients according to the demyelinating phenotypes. Importantly, in most circumstances, anti-MOG antibody results are not available within the first few days of acute presentation, and thus do not guide immediate therapies.

Observational studies show that patients with MOGAD are highly sensitive to corticosteroids and can achieve complete and dramatic symptom remission after a short course of intravenous steroids.[26,33,63,81] First line immunotherapy therefore consists of intravenous methylprednisolone (30 mg/kg per day or 1 g per day, for 3–5 days). Treatment escalation is warranted for patients who do not improve after intravenous methylprednisolone or individuals with a severe attack such as complete loss of vision, paralysis, or severe encephalopathy requiring admission to intensive care. In the absence of evidence directly related to MOGAD, the treatment algorithm proposed for CNS demyelination[18] is followed in most expert centres, adapted to local clinical practice or age group. Escalation therapies include plasma exchange (five exchanges on alternative days), immunoadsorption, intravenous immunoglobulins (total of 2 g/kg over 2 or 5 days), or plasma exchange followed by intravenous immunoglobulins.[18] As is the case in AQP4-NMOSD,[82] we anticipate that time to initiation of acute treatment is a predictor of long-term outcome.

The decision for how long and whether to wean the patient from corticosteroids is debated. The choice depends on the severity of the attack, the risk of flare-up if weaning from steroids is too early, and timing and mode of action of the chosen relapse treatment and maintenance therapies. Classically, in adults with MOGD, some centres proposed the use of 1 mg/kg per day for 3 months and then progressive tapering over the next 3 months.[63] In a study of 59 patients with MOGAD, of the 146 episodes treated with oral prednisolone taper, most of the 103 subsequent episodes occurred towards the end of the taper or shortly after prednisone cessation.[63] For children (<16 years), the prolonged use of oral corticosteroids is also debated. Some paediatricians among the authors of this Personal View apply a protocol similar to the one used for adults, with 3–6 months of oral steroids (akin to protocols used in rheumatological conditions); other paediatricians among the authors alternatively think that the steroids course should be less than 4 weeks to avoid side- effects and propose use of intravenous immunoglobulins for 3 to 6 months.

Chronic treatment for relapse prevention

The accumulation of disability in patients with antibody-mediated diseases, such as MOGAD, is thought to be primarily relapse related. Because of the risk of disability due to incomplete relapse recovery, identifying patients at risk for relapse, and treating those with relapses, is the focus of current management. The clinical differentiation between true relapse, disease rebound (during steroid wean or shortly after discontinuation of steroids), and pseudo-relapses secondary to intercurrent infection illness is challenging. Clinical history and examination, preferably in specialist centres, are important when making treatment decisions.

Currently there are no predictors of relapse risk and long-term outcome. Because around 70% of paediatric patients with MOGAD will have a monophasic outcome,[16] the decision to initiate chronic immunosuppression in paediatric patients is more controversial than in adults. Currently, with the absence of natural history studies and the known infectious risks of current immunosuppressive agents, most clinicians would start treatment only after a second event. The decision regarding continuous immunotherapy for relapse prevention is typically influenced by several factors: response to treatment of the initial attack; severity of the initial attack; risk of short-term disability (associated with the first episode or accumulation of episodes); risk of short-term and long-term immunosuppression; and age.

No clinical trials have been done for patients with MOGAD and the current literature reports real-world clinical data, which are not optimal for evaluation of treatment efficacy. Data from the six largest retrospective studies on treatment of relapsing MOGAD[37,63,81,83–85] revealed that, at a median of 9–16 months after the start of treatment, the number of relapse free patients was 20 (69%) of 29 patients on intravenous immunoglobulin monotherapy, 30 (47%) of 63 on mycophenolate mofetil, 21 (39%) of 55 on azathioprine, and 47 (50%) of 94 on rituximab. Of note, although anti-CD20 therapy seems to show some effect, it appears to be less efficacious than in AQP4-NMOSD.[86] In AQP4-NMOSD,

relapses mostly occur when the biological effect of rituximab decreases, whereas patients with MOGAD can relapse despite absent B cells.

A human being cannot be alive without B cells.[86,87] Importantly, time to treatment efficacy is highly variable between different immunotherapies, and needs to be taken into account.

First-line injectable multiple sclerosis treatments (interferon-beta and glatiramer acetate) were shown to be ineffective in preventing relapses in both adults[85] and children[37] with relapsing MOGAD, with no change in annual relapse rate. Although conceptually the use of natalizumab might prevent autoreactive T cells from accessing the brain, in case reports of natalizumab use in six patients with suspected multiple sclerosis but finally diagnosed with MOGAD, severe relapses were reported in five patients.[37,81] There are only anecdotal reports for use of alemtuzumab, dimethyl fumarate, and fingolimod, precluding judgment of treatment efficacy.

Conclusions and future directions

The keys to improving outcomes in MOGAD are (1) making early diagnosis based on accurate and reproducible detection of anti-MOG antibodies, (2) improving understanding of the disease mechanisms that lead to relapses and disability accumulation, and (3) establishing treatment protocols. There are currently no formal criteria for the diagnosis of MOGAD. Once established and validated, these should improve time to diagnosis and diagnostic accuracy criteria.

In view of the phenotypical heterogenicity of MOGAD, a key question is whether patients with anti-MOG antibodies presenting with NMOSD, acute disseminated encephalomyelitis, or cortical encephalitis might have different pathobiology driving their disease and should therefore be treated differently. To provide further evidence on the mechanisms involved in MOGAD, it is essential to improve our *in-vivo* and *in-vitro* models. Human-derived oligodendrocyte cultures, rodent models expressing humanised MOG, or animal models with MOG proteins that have a higher homology to human MOG than rodents (eg, rhesus monkeys) will provide a better basis to investigate the pathogenic mechanisms. The methodological challenge of measuring antigen specific CD4+ T-cells and B-cells, which are most likely present in the blood of patients with MOGAD at low frequency, are big obstacles that will have to be overcome to address frequency and phenotype of these cells.[88,89] These studies are important to better understand the mechanisms behind the development of an autoimmune response to MOG and might pave the way for antigen specific immune therapies.

With the rarity of the condition, multicentre international studies evaluating initial therapy and intensified therapies are required to determine their safety and efficacy. One approach would be to standardise treatment protocols across centres, similar to the approach used in oncology. Alternatively, the use of heterogeneous treatment protocols across centres might be a method for capturing real world data, without indication bias, as recently done in a study comparing clinical outcomes of escalation versus early intensive disease-modifying therapy in patients with multiple sclerosis.[90] Repurposing of medications tested for other antibody-mediated conditions with similar pathological mechanism might be explored while specific drugs are developed for MOGAD. Use of data from the randomised control trials for NMOSD and subanalysis of the treatment response in patients with anti-MOG antibodies (some were included in MNOSD trials as patients seronegative for AQP4 antibodies)[91,92] would be a quick approach to evaluate the efficacy of anti-interleukin-6 receptor antibodies and anti-CD19 antibodies. However, the numbers of patients are likely to be small and the trials were not powered for these analyses. Preliminary results from a phase 2 trial of rozanolixizumab (anti-FcRn) showing improvements in functional outcome measures in patients with myasthenia gravis and anti-acetylcholine receptor antibodies might also prove beneficial in MOGAD, as these conditions share similarities in terms of immunopathology.[100] Finally, in anticipating the launch of a randomised control trial in MOGAD, there is an urgent need to identify disease-specific biomarkers of outcomes and treatment response.

Search strategy and selection criteria

The reference list for this Personal View was based on discussions at the 2-day the European Committee for Treatment and Research in Multiple Sclerosis workshop March 7–8, 2019, and included topics and references discussed in the workshop meetings. These topics were selected by the authors as key priorities in the field of myelin-oligodendrocyte glycoprotein antibody-associated disease. Additionally, we searched PubMed for articles published in English between Jan 1, 1975, and March 1, 2021, using the search terms "myelin oligodendrocyte glycoprotein", "neuromyelitis optica spectrum disorders", "acute disseminated encephalomyelitis", "optic neuritis", "transverse myelitis", OR "demyelinating diseases" combined with "MOG" OR "autoantibodies". We prioritised articles published between 2016 and 2021, a period that corresponds broadly with that in which recombinant antigens expressed on cells (cell-based assays) have been used for myelin-oligodendrocyte glycoprotein IgG testing. We included older references only if they were seminal to the field. We excluded single case reports and data published only in abstract form, and reviewed the bibliographies of included articles for additional references.

Contributors

RM, YH, AC-C, TD, SV, BH, and A-KP contributed to study concept and design, acquisition of data, analysis and interpretation, writing. BW, EW, HJK, IK, HL, M-IL, CL, EM, JP, FP, AP, SP, MR, DKS, PWS, AT, MT,

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