MOG-antibody associated disease

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MOGAD: review from the ECTRIMS workshop

Abstract

MOG-antibody-associated disease (MOGAD) is a recently identified autoimmune disorder presenting in both adults and children with central nervous system demyelination. Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis (MS), and aquaporin-4 antibody (AQP4-Ab) neuromyelitis optica spectrum disorder (NMOSD), cumulative biological, clinical and pathological evidence clearly discriminates between these conditions. Here we advocate that the diagnosis of MS or NMOSD should no longer be used in the presence of MOG antibodies in the serum (MOG-Ab). Yet, many questions related to the clinical characterization and pathogenetic role of MOG-Ab are still open. Furthermore, current concepts on MOGAD therapy are mainly based on AQP4-Ab NMOSD and MS standard protocols, and more evidence is needed regarding who, how and when to treat MOGAD.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) constitutes a quantitatively minor component (0.05%) of the central nervous system (CNS) myelin [1] and is expressed on the outer lamella of the myelin sheath[1, 2] Though MOG knock-out mice display normal myelin ultrastructure and no apparent phenotype[3]**,** in human, MOG is thought to be involved in completion and maintenance of the myelin sheath and in cell-cell communication, While MOG has been controversially discussed as a putative autoantigen in autoimmune CNS demyelinating diseases for decades[4], it is a well-established antigenic target in the experimental autoimmune encephalomyelitis (EAE) model[5, 6]. Emergence of protein conformation-dependent assays[7] for the detection of MOG-antibodies (MOG-Ab) has revealed a distinct clinical phenotypes in adults and children with CNS demyelination[8, 9]. Different terms have been proposed to characterize patients with CNS syndromes associated with the presence of MOG-Ab. We will use here the term "MOG-Ab-associated disease" (MOGAD), which suggests the concept of an autonomous entity but does not preclude the incorporation of a heretofore unidentified clinical phenotype, and does not imply pathogenicity of the antibody itself.

Although there are clinical phenotypic overlaps between MOGAD, multiple sclerosis (MS), and aquaporin-4 antibody (AQP4-Ab) neuromyelitis optica spectrum disorder (NMOSD), cumulative biological, clinical and pathological evidence clearly discriminates between these conditions. In patienst with MOGAD the characteristics of lesion pathologies is characterized by inflammatory demyelination and not astrocytopathy as seen in AQP4-Ab disease. The perivascular deposits of activated complements and immunoglobulins which are typical for MS leisons are also rarely found. Furthermore, although MOGAD shares some overlapping pathological features with MS (such as demyelination and immune cell infiltration), the lesions in MOGAD are characterized by perivascular infiltrated MOG-laden macrophages, and CD4+ T cells infiltation by contrast to MS lesion which are characterized by CD8Tcells infiltration , [10].

Many questions, related to the clinical characterization and the pathogenetic role of MOG-Ab, are still open, and more evidence is needed regarding who, how and when to treat MOGAD. This review is based on a Focused Workshop on MOGAD, organized by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

The purpose of this Personal View paper was to review and discuss the immunology and pathology, the clinical spectrum and the current knowledge on treatment of MOGAD, from a large panel of expert in the field.

Search strategy and selection criteria

The review was composed from the 2-day ECTRIMS workshop and included topics and referances discussed in the meetings. These topics were selected as key priorities in the field of MOGAD. 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, which correspond to the broadly use of recombinant antigens expressed on cells (cell-based assay, CBA) as the substrate for the MOG-IgG testing. We only included older material if it was seminal to the field. We excluded single case reports and data only published in abstract form and reviewed the bibliographies of included articles for additional references.

1. Clinical features in adults and children

MOGAD accounts for approximately 1.2-6.5% of all demyelinating syndromes in adults[11, 12]. In children, the frequency of MOG-Ab seropositivity during a first acute demyelinating syndrome (ADS) is high, with multinational studies from Europe[13-15], North America[16] and Australia[17] identifying these antibodies in about 40% of all ADS presentations[18]. The most common presentations, stratified to the different demyelinating phenotypes, are summarized in **Table 1; for references see appendix pp 3–5).**

In both adult and children the frequency is phenotype dependent. A single center retrospective study detected MOG-Ab in 12/20 (60%) of adults with ADEM either at onset or at follow-up[19]. A Danish population-based prospective study detected MOG-Ab in 2/51 adults with a first ON[20], and the multicenter, randomized, placebo controlled Optic Neuritis Treatment Trial reported identified MOG-Ab in 3/177 (1.7%)[21]. In AQP4-Ab seronegative longitudinally extensive transverse myelitis (LETM), two retrospective studies reported that 16-23% of individuals were MOG-Ab seropositive [22, 23]. In children, MOG-Ab are identified most frequently in children with acute demyelinating encephalomyelitis (ADEM, up to 64%[24]) and in almost all those who relapsed following ADEM (multiphasic ADEM or ADEM-ON)[25-28];

33-43% of children presenting with ON[14, 16, 28]; but in only 6% (3/50) pediatric myelitis[28]. MOG-Ab were identified in 26/110 (23.6%) children with relapsing demyelinating syndrome and 26/48 (54.2%) of non-MS relapsing demyelination[9]. Most of the studies describing the frequency of MOG-Ab and the clinical phenotypes associated with it were performed in tertiary referral centers for neuroinflammatory disorders, which may lead to selection bias. This is especially relevant when evaluating clinical phenotypes such as optic neuritis (ON) or myelitis that might be referred only because of severe or atypical presentation. In addition, the first cohorts evaluated for MOG-Ab by CBA were restricted to patients with monophasic or recurrent ON or myelitis thus not reflecting the real frequency of MOG-Ab across all acute and chronic inflammatory demyelinating CNS diseases. [29-32]Clinical phenotypes and paraclinical features stratified to the age of onset are summarized in **Table2.**

No racial groups seem to be more or less likely to be diagnosed with MOGAD,by contrast to AQP4-Ab which is more common in non-Caucasians. There is an equal number of males and female in young children (<10y) and a slight female predominance (less so than in AQP4-Ab) in older post-pubertal children and adults[33]. No definitive evidence has been reported linking MOGAD with other autoimmune diseases or specific malignancy.Although an HLA association, similar to other autoantibody associated disease is likely, in a recent study of 43 Dutch patients with MOGAD no significant HLA association was found[34]. As found 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 to older children and adults[36, 37]. Similar to MS both the severity of the attacks and the recovery from attacks is also age-dependent, with with worse severity and better recovery in children[38]. The risk of relapse is lower in children with the majority remaining monophasic[16]. Less than 10% of children who relapse (typically very young children), can develop a leukodystrophy-like phenotype with large confluent highly enhancing lesions on MRI and significant brain atrophy over time [35]. These children have poor outcome with permanent cognitive and motor disabilities[35]. Younger children are more likely to have symptomatic brain involvement compared to older children and adults[37].

Recent cohort studies and case reports have shown that the disease course is very heterogeneous. The number of clinical relapses itself does not accurately explain the 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 under 9 years of age are more likely to have a severe brain pathology with higher lesion load detected on

conventional imaging than children older than 9 years of age[37]; nevertheless, recovery from acute attacks appears faster than in older children and adults. This may not be disease specific and was also observed in comparison between adult and children with MS demonstrating that every 10 years of age, reduced EDSS recovery by 0.15 points[39]. It is estimated that about 40% of adult[40]s[33] and 30%[18] of children[28] with MOGAD present with a second clinical attack within five 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. Earlier studies suggested that high MOG-Ab titres could predict further clinical events[15], but more recent data indicate that patients may remain seropositive for many years and not relapse, and even patients who become seronegative may 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] .

2. Biomarkers

Assays for MOG-Ab detection

Over the last years, great efforts have been made to improve MOG-Ab detection techniques[42]. More consistent results have occurred when the substrate for the tests were recombinant antigens expressed on live cells (live cell-based assay, CBA). As glycosylation and conformation of the protein play a key role in MOG-Ab recognition[43-46], surface expression of the full-length human MOG protein (usually α-1 isoform, 218 aminoacids) expressed typically on human embryonic kidney cells (HEK293)[7] is used to detect pathogenic MOG-Ab more specifically. A summary of the immunopathology in MOGAD is ilustarted in **Figure 1 and panel 1**. The frequency of MOG-Abs and their titers are higher during the acute attack among young children than among adolescents or adults[32] but more likely to become negative after the attack[16]. Timing of testing is important as antibody titers fluctuate and may decrease over months from presentation, and some can serorevert and being subsequently tested negative[16]. A higher cut-off for seropositivity and use of specific secondary antibodies to IgG1 or IgG-Fcγ[47] increased specificity (ranging from 99.6% to 100%)[48]. The use of anti-IgG (H+L) secondary antibody is a matter of active debate. It was previously shown that using IgG (H+L) secondary antibodies may cross react with MOG-IgM which can be found in healthy contols[47].

However, two recent studies demonstrated that IgG (H+L), IgG1 and IgG-Fcy antibodies were comparable, and no IgM binding was observed[49, 50]. These discrepancies are likely due to assay methodologies. Of note, the sensitivities and specificities reported in all these studies[15, 16, 47-51] were evaluated in the research setting, and the applicability of this remains to be evaluated in the clinical context. Importantly, in a recent large multicenter comparitive study MOG-Ab CBAs showed excellent agreement with each other for high positive and negative samples. Low positive/bordeline samples were more frequently discordant[51]. These borderline/low MOG-Ab titers represent a currently undefined group and are likely to impact the sensitivity and specificity of the results across all MOG-Ab testing laboratories. Each credited laboratory uses specific cut off for positivity. Like with any test, low positive/borderline results are more frequently discordant and should be evaluated as such.

MOG-Ab are now rarely found in patients with typical MS using CBA. Only 0.4 % (1/244) MS patients were found MOG-Ab positive by live-CBA in a multicenter study[52]. Accordingly, two cross-sectional studies reported detection of MOG-Ab in 0/200 patients with progressive MS[53] and in 2/685 patients with relapsing or progressive MS from two tertiary centers[11]. It is exceptionally rare for any patient to have serum antibody to MOG and AQP4[8, 42]. MOG-Ab-positive patients 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 adult patients with MS, in whom testing of all patients with suspected demyelinating disease would result in many borderline results and probably false positives. With thecurrent absence of established criteria for MOGAD, diagnosis in antibody-positive patients with atypical presentation, rests on the rigor of the test method and the expertise of the clinician.

One half of the patients presents with CSF pleocytosis (predominantly lymphocytes and monocytes) with cell numbers that often tend to be higher than in MS[54, 55]. Pleocytosis correlates with the extension of the disease being higher in ADEM or LETM phenotypes than in ON[8]. Oligoclonal bands and a positive IgG index are found in less than 15%, mainly during attacks[54, 55]. The CSF cytokine profile during attacks in MOGAD seems to be more similar to AQP4-Ab NMOSD compared to MS[56]. Finally, the usefulness of MOG-Ab detection in the CSF is not yet fully evaluated. When paired serum and CSF are analyzed, there is a good concordance between serostatus and CSF status; i.e. most CSF-positive patients are seropositive. Not all seropositive patients are CSF-positive, and only a small percentage are seronegative and CSF-positive[57].

3.Imaging Biomarkers

Brain MRI in MOGAD can be abnormal in more than 50% of patients, regardless the clinical phenotype at presentation[8]. In general, brain lesions are more widespread in children compared to adults reflecting a higher disease burden. Apart from the deep white and grey matter lesions found in ADEM-like phenotypes, brainstem lesions are found in up to 40%, **f**requently 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, MOG-Ab and AQP4-Ab related diseases could not be distinguished, but displayed different imaging characteristics from MS[58] : lesions were poorly demarcated, fewer in number, and 'Dawson fingers' or lesions adjacent to the body of lateral ventricles were less frequent[58, 61]. Others 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 MOG-Ab when compared with MS, but not with 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 patients with MS[63].

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

Spinal cord MRI findings, such as the presence of longitudinally extensive T2 lesions spanning at least 3 vertebral segments on sagittal sequences or the hyperintensity of the grey matter on axial sequences (longitudinally extensive transverse myelitis), may resemble those commonly seen in AQP4-Ab positive NMOSD[69]. MRI features suggesting a diagnosis of MOG-Ab over AQP4-Ab or MS are involvement of the conus medullaris, abnormality confined to grey matter (sagittal line and axial H sign) and nerve roots, and lack of or minimal gadolinium enhancement[69]. Occasionally, large lesions may be associated with mild impairment, a clinical-radiological paradox, particularly in children[35].

MRI of the optic nerves may demonstrate 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 hemorrhage on fundoscopy can help differentiate MOGAD from episodes of ON in AQP4-Ab NMOSD and MS. A perineural edema is another radiological finding which is observed in up to half of MOGAD patients with optic neuritis[70-72].

Optical coherence tomography (OCT): Patients usually display a thickening of the peripapillary retinal nerve fiber layer (pRNFL), likely due to the optic disk swelling at the acute phase of an ON attack[73]. Subsequently, the pRNFL progressively evolves towards a progressive thinning which is greater in temporal quadrants. Although findings are still inconsistent, on average, optic neuritis associated with MOG-Ab causes less retinal damage than optic neuritis associated with AQP4-Ab [74]. In affected eyes, longitudinal OCT analysis has found a decrease of the pRNFL but not of the combined ganglion cell and inner plexiform layer (GCIP) in the absence of new clinical attacks[73], in contrast to the reduction of both layers observed in AQP4-ON and MS-ON over time[74, 75]. In non-affected eyes, a subclinical neuroaxonal retinal damage has been found with a decrease of the GCIP[74]. Conflicting results have been reported regarding the pRNFL involvement in this subgroup of patients[73, 76] A subclinical chiasmal or optic nerve inflammation are the most likely explanation. Similarly to the MRI paradox, a clinical-radiological discordance has also been observed with OCT , with preserved visual acuity despite severe atrophy of RNFL[77], in contrast to MS or AQP4-ON, in which RNFL thickness and visual acuity frequently correlate[78-80].

4. Treatment

Attack treatment

There are currently no randomized control trial or evidence-based guidelines for the acute treatment of MOGAD relapses. There is no evidence that MOG-Ab positivity should influence acute attack treatment and most neurologists treat these patients according to the demyelinating phenotypes. Importantly, in most circumstances, MOG-Ab 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 may achieve complete and dramatic symptom remission following a short course of intravenous steroids [26, 33, 63, 81]. First line immunotherapy therefore consists of intravenous

methylprednisolone (IVMP) (30mg/kg/ day or 1g; for 3-5days). Treatment escalation is warranted for patients who do not improve following IVMP or individuals with a severe attack such as complete loss of vision, paralysis or severe encephalopathy requiring intensive care admission. In the absence of evidence directly related to MOGAD, the treatment algorithm proposed for CNS demyelination[18] is followed in most expert centers, adapted to local clinical practice or age group. Escalation therapies include plasma exchange (PLEX, 5 exchanges on alternative days), immunoadsorption or intravenous immunoglobulins (IVIG, total of 2g/kg over 2 or 5days), or PLEX followed by IVIG. As, it is trhe case in AQP4-Ab NMOSD[82], it may be anticipated that time to initiation of acute treatment is one of the predictors of long-term outcome.

The decision for how long and whether to wean the corticosteroids is a matter of active debate. The choice is dependent on the severity of the attack and the risk of flare-up while weaning the steroids too early. The decision of a prolonged oral steroid treatment probably depends also on timing and mode of action of the chosen relapse treatment and maintenance therapies. Classically, in adults, some centers proposed to use 1 mg/kg/day for 3 months and then progressively taper over the next 3 months. In a study of 59 patients with MOGAD, of the 146 episodes treated with oral prednisolone taper, the majority of the 103 subsequent episodes occurred towards the end of the taper or shortly after prednisone cessation [63]. For children, the use of prolonged course of oral corticosteroids is also a matter of active debate. Some paediatricians apply a protocol similar to the one used for adults with 3-6 months oral steroids (akin to protocols used in rheumatological conditions); others feel strongly that the steroids course should be less than 4-weeks to avoid side effects and propose alternatively intravenous immunoglobulins for 3 to 6 months (expert opinion).

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. Given the risk of disability due to incomplete relapse recovery, identifying patients at risk for relapse, and treating those with relapses, is the main focus of current management. The clinical differentiation between true relapse, disease rebound (during steroid wean or shortly after discontinuation of steroids) or pseudo-relapses secondary to intercurrent illness is challenging. Clinical history and examination, preferably in specialist centers, are crucial when making treatment decisions.

Currently there are no predictors of risk of relapse and long-term outcome. Given that ~70%[16] of pediatric patients will have a monophasic outcome, the decision to intiate chronic

immunosuppression in a pediatric patient is even more controversial. 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 the need for a continuous immunotherapy for relapse prevention is typically influenced by (i) the response to treatment of initial attack; (ii) the severity of initial attack; (iii) risk of short-term disability (associated to the first episode or accumulation of episodes); (iv) risk of short- and long-term immunosuppression. ; and (v) age.

No clinical trials have been performed 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 month, 20/29 (69%) of patients remained relapse free on IVIG monotherapy, 30/63 (47%) on mycophenolate mofetil, 21/55 (39%) on azathioprine and 47/94 (50%) on rituximab. Of note, although anti-CD20 therapy seems to show some effect, it appears less potent than in AQP4-Ab NMOSD[86]. In AQP4-Ab NMOSD, relapses mostly occur when the biological effect of rituximab decreases, whereas in MOGAD patients may relapse despite absent B-cells[86],[87]. Importantly, time to treatment efficacy is highly variable, and need to be taken into account.

First-line injectable MS 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 may prevent autoreactive T-and B-cells from accessing the brain case reports of natalizumab use in patients with suspected MS but finally diagnosed with MOGAD, severe relapses were reported in 5 out of 6 patients[37, 81]. There are only anecdotal reports for alemtuzumab, dimethyl fumarate, and fingolimod, not allowing judgement of treatment efficacy.

5. Conclusions and future directions

The key to improving outcomes in MOGAD is (i) making early diagnosis based on accurate and reproducible detection of MOG-Ab (ii) improved understanding disease mechanisms leading to relapses and disability accumulation and (iii) establishing treatment protocols.

There are currently no formal criteria for the diagnosis of MOGAD. Once established and validated, these will improve time to diagnosis and diagnostic accuracy.

A key question in view of the phenotypical heterogenicity seen with MOGAD, is whether patients with MOG-Ab presenting with NMO, ADEM or cortical encephalitis may infact 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 with humanized MOG or animal models with a higher homology to human MOG (e.g. rhesus monkeys) will provide a better basis to investigate the pathogenic mechanisms. The methodological challenge of measuring antigen specific CD4+ T and B cells, which are most likely present in the peripheral blood of MOGAD patients at low frequency, are major obstacles that will have to be overcome in order 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 may pave the way for antigen specific immune therapies.

With the rarity of the condition, multicenter multinational studies evaluating initial therapy and intensified therapies are required to determine efficacy and side effects of treatment. One approach would be to standardize treatment protocols across centers similar to the approach used in oncology. Alternatively, the heterogeneous treatment protocols across centers may be a method in capturing real world data, without indication bias, and answer important clinical questions as recently done comparing clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with MS[90]. Repurposing of medications tested for other antibody mediated conditions with similar pathological mechanism may be explored while specific drugs are developed for MOGAD. Utilization of data from the randomized control trials for NMOSD and subanalysis of the treatment response in patients with MOG-Ab (some of them included in the seronegative NMOSD[91, 92]) would be a quick approach to evaluate the efficacy of anti-IL-6R and anti-CD19.However the number of patients are likely to be small and the trials were not primary power for thes analyses. Preliminary results from phase II trial of Rozanolixizumab (anti-FcRn) demonstrating improvements in functional outcome measures in patients with myasthenia gravis and acetylcholine receptor antibodies may also proove beneficial in MOGAD as these two conditions share similarities in tem of immunopathology. Finally, in anticipating the launch of a randomized control trial in MOGAD, there is an urgent need to identify disease specific biomarkers of outcomes and treatment response.

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References

1. Johns TG, Bernard CC. The structure and function of myelin oligodendrocyte glycoprotein. J Neurochem 1999;72:1-9.
2. Reindl M, Di Pauli F, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nat Rev Neurol 2013;9:455-461.
3. Delarasse C, Daubas P, Mars LT, et al. Myelin/oligodendrocyte glycoprotein-deficient (MOG-deficient) mice reveal lack of immune tolerance to MOG in wild-type mice. J Clin Invest 2003;112:544-553.
4. Hemmer B, Archelos JJ, Hartung HP. New concepts in the immunopathogenesis of multiple sclerosis. Nat Rev Neurosci 2002;3:291-301.
5. Lassmann H, Bradl M. Multiple sclerosis: experimental models and reality. Acta Neuropathol 2017;133:223-244.
6. Iglesias A, Bauer J, Litzenburger T, Schubart A, Linington C. T- and B-cell responses to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis and multiple sclerosis. Glia 2001;36:220-234.
7. O'Connor KC, McLaughlin KA, De Jager PL, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med 2007;13:211-217.

8. Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. Neurology 2018;90:e1858-e1869.
9. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology 2017;89:269-278.
10. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. Brain 2020;143:1431-1446.
11. Cobo-Calvo A, d'Indy H, Ruiz A, et al. Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: A multicenter cross-sectional study. Neurol Neuroimmunol Neuroinflamm 2019 Dec 13;7(2):e649.
12. Kunchok A, Chen JJ, McKeon A, Mills JR, Flanagan EP, Pittock SJ. Coexistence of Myelin Oligodendrocyte Glycoprotein and Aquaporin-4 Antibodies in Adult and Pediatric Patients. JAMA Neurol 2020;77:257-259.
13. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurol Neuroimmunol Neuroinflamm 2015;2:e81.
14. Ketelslegers IA, Van Pelt DE, Bryde S, et al. Anti-MOG antibodies plead against MS diagnosis in an Acquired Demyelinating Syndromes cohort. Mult Scler. 2015 Oct;21(12):1513-20.
15. Hennes EM, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology 2017 Aug 29;89(9):900-908.
16. Waters P, Fadda G, Woodhall M, et al. Serial Anti-Myelin Oligodendrocyte Glycoprotein Antibody Analyses and Outcomes in Children With Demyelinating Syndromes. JAMA Neurol 2019.
17. Brilot F, Dale RC, Selter RC, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann Neurol 2009;66:833-842.
18. Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Curr Treat Options Neurol 2019;21:2.
19. Lopez-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG Serostatus With Relapse After Acute Disseminated Encephalomyelitis and Proposed Diagnostic Criteria for MOG-IgG-Associated Disorders. JAMA Neurol 2018;75:1355-1363.
20. Soelberg K, Jarius S, Skejoe H, et al. A population-based prospective study of optic neuritis. Mult Scler 2017;23:1893-1901.
21. Chen JJ, Tobin WO, Majed M, et al. Prevalence of Myelin Oligodendrocyte Glycoprotein and Aquaporin-4-IgG in Patients in the Optic Neuritis Treatment Trial. JAMA Ophthalmol 2018;136:419-422.
22. Cobo-Calvo A, Sepulveda M, Bernard-Valnet R, et al. Antibodies to myelin oligodendrocyte glycoprotein in aquaporin 4 antibody seronegative longitudinally extensive transverse myelitis: Clinical and prognostic implications. Mult Scler 2016;22:312-319.
23. Jitprapaikulsan J, Chen JJ, Flanagan EP, et al. Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Autoantibody Status Predict Outcome of Recurrent Optic Neuritis. Ophthalmology 2018. Oct;125(10):1628-1637
24. Rossor T, Benetou C, Wright S, et al. Early predictors of epilepsy and subsequent relapse in children with acute disseminated encephalomyelitis. Mult Scler 2019:1352458518823486.
25. Baumann M, Hennes EM, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG):

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26. Wong YYM, Hacohen Y, Armangue T, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. Eur J Neurol 2018;25:782-786.
27. Rostasy K, Mader S, Hennes EM, et al. Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica. Mult Scler 2013;19:1052-1059.
28. Duignan S, Wright S, Rossor T, et al. Myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies are highly specific in children with acquired demyelinating syndromes. Dev Med Child Neurol 2018 Sep;60(9):958-962.
29. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. JAMA Neurol 2014;71:276-283.
30. Hoftberger R, Sepulveda M, Armangue T, et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. Mult Scler 2015 Jun;21(7):866-874.
31. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014;82:474-481.
32. Probstel AK, Rudolf G, Dornmair K, et al. Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype. J Neuroinflammation 2015;12:46.
33. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017;140:3128-3138.
34. Bruijstens AL, Wong YYM, van Pelt DE, et al. HLA association in MOG-IgG- and AQP4-IgG-related disorders of the CNS in the Dutch population. Neurol Neuroimmunol Neuroinflamm 2020 Mar 20;7(3):e702.
35. Hacohen Y, Rossor T, Mankad K, et al. 'Leukodystrophy-like' phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease. Dev Med Child Neurol 2018 Apr;60(4):417-423.
36. Fernandez-Carbonell C, Vargas-Lowy D, Musallam A, et al. Clinical and MRI phenotype of children with MOG antibodies. Mult Scler 2016;22:174-184.
37. Hacohen Y, Wong YY, Lechner C, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. JAMA Neurol 2018;75:478-487.
38. Cobo-Calvo A, Ruiz A, Rollot F, et al. Clinical Features and Risk of Relapse in Children and Adults with Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. Ann Neurol 2021;89:30-41.
39. Chitnis T, Aaen G, Belman A, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. Brain 2020. Sep 1;143(9):2733-2741.
40. Cobo-Calvo A, Ruiz A, D'Indy H, et al. MOG antibody-related disorders: common features and uncommon presentations. J Neurol 2017;264:1945-1955.
41. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation 2016;13:279.

42. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nat Rev Neurol 2019;15:89-102.
43. Menge T, Lalive PH, von Budingen HC, Genain CP. Conformational epitopes of myelin oligodendrocyte glycoprotein are targets of potentially pathogenic antibody responses in multiple sclerosis. J Neuroinflammation 2011;8:161.
44. Mayer MC, Breithaupt C, Reindl M, et al. Distinction and temporal stability of conformational epitopes on myelin oligodendrocyte glycoprotein recognized by patients with different inflammatory central nervous system diseases. J Immunol 2013;191:3594-3604.
45. Marta CB, Oliver AR, Sweet RA, Pfeiffer SE, Ruddle NH. Pathogenic myelin oligodendrocyte glycoprotein antibodies recognize glycosylated epitopes and perturb oligodendrocyte physiology. Proc Natl Acad Sci U S A 2005;102:13992-13997.
46. Gaertner S, de Graaf KL, Greve B, Weissert R. Antibodies against glycosylated native MOG are elevated in patients with multiple sclerosis. Neurology 2004;63:2381-2383.
47. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm 2015;2:e89.
48. Waters PJ, Komorowski L, Woodhall M, et al. A multicenter comparison of MOG-IgG cell-based assays. Neurology 2019;92:e1250-e1255.
49. Tea F, Lopez JA, Ramanathan S, et al. Characterization of the human myelin oligodendrocyte glycoprotein antibody response in demyelination. Acta Neuropathol Commun 2019;7:145.
50. Kim Y, Hyun JW, Woodhall MR, et al. Refining cell-based assay to detect MOG-IgG in patients with central nervous system inflammatory diseases. Mult Scler Relat Disord 2020;40:101939.
51. Reindl M, Schanda K, Woodhall M, et al. International multicenter examination of MOG antibody assays. Neurol Neuroimmunol Neuroinflamm Feb 5;7(2):e674.
52. Waters P, Reindl M, Saiz A, et al. Multicentre comparison of a diagnostic assay: aquaporin-4 antibodies in neuromyelitis optica. J Neurol Neurosurg Psychiatry 2016;87:1005-1015.
53. Jarius S, Ruprecht K, Stellmann JP, et al. MOG-IgG in primary and secondary chronic progressive multiple sclerosis: a multicenter study of 200 patients and review of the literature. J Neuroinflammation 2018;15:88.
54. Jarius S, Lechner C, Wendel EM, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 2: Results from 108 lumbar punctures in 80 pediatric patients. J Neuroinflammation 2020;17:262.
55. Jarius S, Pellkofer H, Siebert N, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 1: Results from 163 lumbar punctures in 100 adult patients. J Neuroinflammation 2020;17:261.
56. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. J Neurol Neurosurg Psychiatry 2018;89:927-936.
57. Mariotto S, Gajofatto A, Batzu L, et al. Relevance of antibodies to myelin oligodendrocyte glycoprotein in CSF of seronegative cases. Neurology 2019;93:e1867-e1872.
58. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017;140:617-627.

59. Baumann M, Grams A, Djurdjevic T, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. J Neurol 2018;265:845-855.
60. Jurynczyk M, Tackley G, Kong Y, et al. Brain lesion distribution criteria distinguish MS from AQP4-antibody NMOSD and MOG-antibody disease. J Neurol Neurosurg Psychiatry 2017;88:132-136.
61. Hyun JW, Huh SY, Shin HJ, et al. Evaluation of brain lesion distribution criteria at disease onset in differentiating MS from NMOSD and MOG-IgG-associated encephalomyelitis. Mult Scler 2019;25:585-590.
62. Banks SA, Morris PP, Chen JJ, et al. Brainstem and cerebellar involvement in MOG-IgG-associated disorder versus aquaporin-4-IgG and MS. J Neurol Neurosurg Psychiatry 2020. Dec 28;jnnp-2020-325121.
63. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018;89:127-137.
64. Ogawa R, Nakashima I, Takahashi T, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. Neurol Neuroimmunol Neuroinflamm 2017;4:e322.
65. Hamid SHM, Whittam D, Saviour M, et al. Seizures and Encephalitis in Myelin Oligodendrocyte Glycoprotein IgG Disease vs Aquaporin 4 IgG Disease. JAMA Neurol 2018;75:65-71.
66. Ramanathan S, O'Grady G L, Malone S, et al. Isolated seizures during the first episode of relapsing myelin oligodendrocyte glycoprotein antibody-associated demyelination in children. Dev Med Child Neurol 2019 May;61(5):610-614.
67. Armangue T, Olive-Cirera G, Martinez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. Lancet Neurol 2020;19:234-246.
68. Narayan RN, Wang C, Sguigna P, Husari K, Greenberg B. Atypical Anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations. Mult Scler Relat Disord 2019;27:30-33.
69. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, Radiologic, and Prognostic Features of Myelitis Associated With Myelin Oligodendrocyte Glycoprotein Autoantibody. JAMA Neurol 2019 Mar 1;76(3):301-309.
70. Liu H, Zhou H, Wang J, et al. The prevalence and prognostic value of myelin oligodendrocyte glycoprotein antibody in adult optic neuritis. J Neurol Sci 2019;396:225-231.
71. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Positive Optic Neuritis: Clinical Characteristics, Radiologic Clues, and Outcome. Am J Ophthalmol 2018;195:8-15.
72. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Mult Scler 2016;22:470-482.
73. Oertel FC, Outteryck O, Knier B, et al. Optical coherence tomography in myelin-oligodendrocyte-glycoprotein antibody-seropositive patients: a longitudinal study. J Neuroinflammation 2019;16:154.
74. Oertel FC, Havla J, Roca-Fernandez A, et al. Retinal ganglion cell loss in neuromyelitis optica: a longitudinal study. J Neurol Neurosurg Psychiatry 2018;89:1259-1265.

75. Balk LJ, Cruz-Herranz A, Albrecht P, et al. Timing of retinal neuronal and axonal loss in MS: a longitudinal OCT study. J Neurol 2016;263:1323-1331.
76. Narayan RN, McCreary M, Conger D, Wang C, Greenberg BM. Unique characteristics of optical coherence tomography (OCT) results and visual acuity testing in myelin oligodendrocyte glycoprotein (MOG) antibody positive pediatric patients. Mult Scler Relat Disord 2019;28:86-90.
77. Ciron J, Cobo-Calvo A, Audoin B, et al. Frequency and characteristics of short versus longitudinally extensive myelitis in adults with MOG antibodies: A retrospective multicentric study. Mult Scler 2019:1352458519849511.
78. Martinez-Lapiscina EH, Arnow S, Wilson JA, et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurol 2016;15:574-584.
79. Gabilondo I, Martinez-Lapiscina EH, Fraga-Pumar E, et al. Dynamics of retinal injury after acute optic neuritis. Ann Neurol 2015;77:517-528.
80. Eyre M, Hameed A, Wright S, et al. Retinal nerve fibre layer thinning is associated with worse visual outcome after optic neuritis in children with a relapsing demyelinating syndrome. Dev Med Child Neurol 2018 Dec;60(12):1244-1250.
81. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016;13:280.
82. Bonnan M, Valentino R, Debeugny S, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. Journal of Neurology Neurosurgery and Psychiatry 2018;89:346-351.
83. Zhou J, Lu X, Zhang Y, et al. Follow-up study on Chinese children with relapsing MOG-IgG-associated central nervous system demyelination. Mult Scler Relat Disord 2019;28:4-10.
84. Chen JJ, Flanagan EP, Bhatti MT, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology 2020 Jul 14;95(2):e111-e120.
85. Cobo-Calvo A, Sepulveda M, Rollot F, et al. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. J Neuroinflammation 2019;16:134.
86. Durozard P, Rico A, Boutiere C, et al. Comparison of the Response to Rituximab between Myelin Oligodendrocyte Glycoprotein and Aquaporin-4 Antibody Diseases. Ann Neurol 2020;87:256-266.
87. Whittam DH, Cobo-Calvo A, Lopez-Chiriboga AS, et al. Treatment of MOG-IgG-associated disorder with rituximab: An international study of 121 patients. Mult Scler Relat Disord 2020;44:102251.
88. Saxena S, Lokhande H, Gombolay G, Raheja R, Rooney T, Chitnis T. Identification of TNFAIP3 as relapse biomarker and potential therapeutic target for MOG antibody associated diseases. Sci Rep 2020;10:12405.
89. Varrin-Doyer M, Shetty A, Spencer CM, et al. MOG transmembrane and cytoplasmic domains contain highly stimulatory T-cell epitopes in MS. Neurol Neuroimmunol Neuroinflamm 2014;1:e20.
90. Harding K, Williams O, Willis M, et al. Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. JAMA Neurol 2019;76:536-541.
91. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med 2019;381:2114-2124.

92. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 2019;394:1352-1363.
93. Linington C, Lassmann H. Antibody responses in chronic relapsing experimental allergic encephalomyelitis: correlation of serum demyelinating activity with antibody titre to the myelin/oligodendrocyte glycoprotein (MOG). J Neuroimmunol 1987;17:61-69.
94. Peschl P, Schanda K, Zeka B, et al. Human antibodies against the myelin oligodendrocyte glycoprotein can cause complement-dependent demyelination. J Neuroinflammation 2017;14:208.
95. Saadoun S, Waters P, Owens GP, Bennett JL, Vincent A, Papadopoulos MC. Neuromyelitis optica MOG-IgG causes reversible lesions in mouse brain. Acta Neuropathol Commun 2014;2:35.
96. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol Neuroimmunol Neuroinflamm 2014;1:e12.
97. Spadaro M, Winklmeier S, Beltran E, et al. Pathogenicity of human antibodies against myelin oligodendrocyte glycoprotein. Ann Neurol 2018 Aug;84(2):315-328.
98. Winklmeier S, Schluter M, Spadaro M, et al. Identification of circulating MOG-specific B cells in patients with MOG antibodies. Neurol Neuroimmunol Neuroinflamm 2019;6:625.
99. Spadaro M, Gerdes LA, Krumbholz M, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2016;3:e257.

Table 1 : Main clinical and paraclinical features in MOGAD

	Optic Neuritis	Transverse Myelitis	Acute Disseminated Encephalomyelitis
Clinical features	• Up to 80% of patients, either at onset or during the disease course [1,2] • Simultaneous bilateral involvement in up to 40%[1,3] • Average high contrast VA at nadir counting figures[3,4] • Optic nerve head swelling (papillitis)[3] • May have peripapillary haemorrhage[3] • More steroid responsive than in AQP4-Ab NMOSD and MS[3]	• Spinal cord involvement in 30% of episodes at onset and up to 50% during the disease course.[1,2] • Motor disability may be similar than AQP4-Ab NMOSD[5] • Urinary, bowel and erectile dysfunction are common[5] • More steroid responsive than AQP4-Ab NMOSD and MS	• Most frequent presentation in children [6–8] • Only in 5% of adult presentation [2,9] • Seizures at onset observed in up to 40% of children with ADEM [7,10] • Higher risk of post-ADEM epilepsy [8,10]
Imaging	• Extensive T2 and gadolinium enhancing lesion in the optic nerve and/or chiasm, more evident on orbit MRI [11] • Predominates in the anterior parts of the nerve but may extend to the optic chiasm[11] • Perineural gadolinium enhancement[12] • OCT peripapillary RNFL thinning frequent but clinical-radiological paradox (despite severe atrophy of RNFL- VA is preserved)[13,14] • Attack related RNFL thinning with temporal predominance [14] • Microcystic macular in 24%[15]	• Initially described as LETM but short myelitis in up to 40%.[5,16] • Involvement of the conus medullaris[5] • Abnormalities confined to grey matter (sagittal line and axial H sign) and nerve roots.[5] • Less frequent gadolinium enhancement than AQP4-Ab NMOSD and MS.[5] • Initial spinal cord MRI negative in 10% of patients. [17] • Complete resolution at follow-up scan.[5]	• Large, hazy and poorly demarcated asymmetrical bilateral lesions. [7,18,19] • Deep grey matter involvement, most commonly affecting the thalamus. [20,21] • Lesions may be highly enhancing[21] • Corpus callosum, brainstem and cerebellum involved. [2] • Frequently associated to spinal cord involvement • Complete resolution at follow-up scan[7,22]
CSF	• rare OCB (<10%) – frequent mild lymphocytic pleocytosis[1,2]	• rare OCB (<10%) – frequent mild lymphocytic pleocytosis [1,2]	• rare OCB (<10%) – frequent mild lymphocytic pleocytosis[1,2]
Risk of relapse and outcome	• Patients <45 years at higher risk of relapse, compared to older ones [2] • Permanent visual impairment (VA <20/100) rare at 2 years[1,2,23] • Reversible visual dysfunction was derived from the first episode in up to 75% [2] • Progressive thinning of the pRNFL (but not of the combined ganglion cell and inner plexiform layer) may be observed in absence of new clinical attacks.[24]	• Good or full recovery from the onset attack in 60%. [16] • Younger patients were more likely to have a complete recovery from the onset attack. [9] • Around 20% of patients reached a permeant motor disability at 2 years (DSS>3). [1] • In patients who reached DSS 3.0 and DSS 6.0, irreversible motor disability was explained by disability at onset attack in 68.4% and 87.5% of patients, respectively.[1] • Permanent bowel, bladder and erectile dysfunction are frequent despite good motor recovery[5]	• Up to 50% of children will relapse following ADEM[7] • Phenotype at relapse may be MDEM, ADEM-O[18,25]N • A proportion of children will have a single relapse within 3month of first episode • Behavioural and cognitive problems may occur following ADEM and are more common in relapsing group (up to 50%)[8,26] • Up to 10% (predominantly very young children) can develop a "leukodystrophy-like" phenotype with large confluent highly enhancing lesions and significant brain atrophy over time.[27]

Abbreviations; ON: optic neuritis; TM: transverse myelitis; ADEM: acute disseminated encephalomyelitis; AQP4: aquaporin-4; MS: multiple sclerosis; RNFL: retinal nerve fiber layer; LETM: longitudinally extensive transverse myelitis; OCB: oligoclonal bands; VA: visual acuity; DSS: disability status scale; MDEM: multiple disseminated encephalomyelitis; NMOSD: neuromyelitis optica spectrum disorder

- Patients with MOGAD may have more uncommon phenotypes; 1) Isolated brainstem involvement in 7% and 30% of adult and children, respectively (postrema syndrome is rare);[1,28,29] 2) Cortical (unilateral or bilateral) encephalitis with or without white matter involvement;[1,7,30–32] 3) Cranial neuropathies or mixed central and peripheral syndromes; [33,34] 4) Features of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERs);[35,36] 6) Pseudotumor cerebri-like, associating bilateral papillitis to elevated cerebrospinal fluid opening pressure.[37]

For references see supplementary material pp 2-5.

Table 2 Demographic, clinical and laboratory differences according to age at disease onset in MOGAD

	Children			**Adults**			
Age-groups[33, 38]	**< 10 years**	**10-17 years**	**All children**	**18-39 years**	**40-59 years**	**≥ 60 years**	**All adults**
Female:male ratio[33, 38]	Similar	Similar	Similar	Slightly favours female	Slightly favours female	Slightly favours female	Slightly favours female
Onset phenotype, %[8, 28, 36, 37] †Optic neuritis Myelitis Brainstem †ADEM	 20-30 15-20 <10 50-60	 50-60 15-20 <10 20-30	 20-60 15-20 <10 20-60	 50-65 20-40 <10 <8	 50-65 20-40 <10 <8	 50-70 20-40 <10 <8	 50-70 20-40 <10 <8
Patients relapsing at 2 years, %[8, 15, 33]	-	-	40	-	-	-	40-44
††Risk of relapse[38]	very low	low	low	modera te	moderate	very low	modera te
ARR, mean (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
‡VA disability, % (reaching VA 0.2)[38]	<10	<10	<10	<10	10-20	10-20	<20
Bladder/bowel/erectile dysfunction[33]	-	-	20	-	-	-	28-46

Abbreviations; ADEM, acute disseminated encephalomyelitis; ARR, annualized relapse risk; SD, standard deviation; VA, visual acuity; ref cat, reference category; CSF, cerebrospinal fluid. Annualized relapse rates (ARRs) was calculated as number of relapses/year pre-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.

†Patients aged <5 years-old initiated with ON in 10.5% and with ADEM phenotype in 68% of cases.

††Age group <10 years-old is the reference category. 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

‡Reported motor and visual acuity disability are based on cohort of patients with a median follow-up between 2 and 4 years.

No data as evalable on the risk of relapse and Bladder/bowel/erectile dysfunction stratified to the different age group. We have therefor included a reference for all children and all adults. Refrain from drawing definitive conclusions regarding visual acuity disability and bladder/bowel and erectile dysfunction in children due to probable recall bias.

PANEL : Proposed Immunopathology of MOGAD

- Human MOG-Ab are typically of the IgG1 isotype[42]
- The hypothesis of their pathogenic potency was derived from a monoclonal mouse antibody against MOG (8-18C5), established several decades ago[93]
- The transfer of this monoclonal Ab to rodents that already have complement-dependent EAE enhances demyelination[94].
- Studies looking at the effect of MOG-Ab both *in vivo* and *in vitro* reveal primary demyelination[95] with loss of the microtubule cytoskeleton of oligodendrocytes, resulting in altered expression of axonal proteins[96].
- The presence of CD4+ T cells in lesions from MOGAD patients, and recent data from rat models, suggest that T cells are important in the pathogenesis of the disease[10, 97]
- Recently, MOG-specific B cells were identified in the peripheral blood from patients with MOGAD[98]

Figure 1: Proposed model for immunopathology of MOGAD and treatment strategies

1A: The trigger for MOG-Ab production is yet unknown, but the auto-immune induction is thought to occur outside the CNS, in the peripheral immune system. Although post-infection autoimmunity has been raised as a likely mechanism for trigger no disease-specific pathogens have been identified. A number of mechanisms for post-infectious auto-immunity have been discussed, either in isolation or in combination, including molecular mimicry, bystander activation, epitope spreading, B-cell receptor mediated co-capture of antigens and polyclonal activation of B cells.

1B: Apart from MOG-Ab and MOG-Ab specific producing cells (B cell[98], plasmablasts and plasma cells), antigen-specific T follicular helper (Tfh) cells are also probably involved. Indeed, as human MOG-Ab are mainly of IgG1 phenotype, Tfh are required for differentiating B cell into MOG-Ab-producing plasma cells.

1C. Then, B cell, plasma cell and auto-antibodies need to cross the blood brain barrier to interact with their autoantigen, and mediate their pathogenic effects. One can speculate that MOG-Ab may get into the CNS when the blood-brain barrier is damaged, or via endothelial FcR.

1D**.** Once into the CNS, MOG-specific antibodies presumably bind MOG expressed on myelin where they lead to myelin injury and subsequent demyelination[56, 97]. In parallel, MOG-Ab and plasma cells may also enhance activation of cognate MOG-specific CD4+ T cells or MBP-specific T cells and macrophages (Mϕ) in the CNS[99] Indeed, there is an increase of pro-inflammatory cytokines such as IL-6, IL-17, G-CSF and TNFalpha as well as B cell cyto-

/chemokines (BAFF, APRIL, CXCL13 and CCL19) described in the CSF of MOGAD patients[56]

MOGAD= Myelin oligodendrocyte-IgG1 associated disease; Tfh= T folliculat helper cell; FcR= FC receptor; Mϕ= macrophages; G-CSF= granulocyte colony stimulating factor, TNF= tumor necrosis factor; CSF= cerebrospinal fluid