Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria

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Serum antibodies directed against myelin oligodendrocyte glycoprotein (MOG) are found in patients with acquired CNS demyelinating syndromes that are distinct from multiple sclerosis and aquaporin-4-seropositive neuromyelitis optica spectrum disorder. Based on an extensive literature review and a structured consensus process, we propose diagnostic criteria for MOG antibody-associated disease (MOGAD) in which the presence of MOG-IgG is a core criterion. According to our proposed criteria, MOGAD is typically associated with acute disseminated encephalomyelitis, optic neuritis, or transverse myelitis, and is less commonly associated with cerebral cortical encephalitis, brainstem presentations, or cerebellar presentations. MOGAD can present as either a monophasic or relapsing disease course, and MOG-IgG cell-based assays are important for diagnostic accuracy. Diagnoses such as multiple sclerosis need to be excluded, but not all patients with multiple sclerosis should undergo screening for MOG-IgG. These proposed diagnostic criteria require validation but have the potential to improve identification of individuals with MOGAD, which is essential to define long-term clinical outcomes, refine inclusion criteria for clinical trials, and identify predictors of a relapsing versus a monophasic disease course.

Introduction

The availability of cell-based assays for detection of serum autoantibodies directed against myelin oligodendrocyte glycoprotein (MOG) has increased in the past 10 years.[1,2] Some adults and children who have optic neuritis and longitudinally extensive transverse myelitis or who have been previously classified as having aquaporin-4 (AQP4)-seronegative neuromyelitis optica spectrum disorder (NMOSD) have now been identified as having serum MOG-IgG. Patients with MOG-IgG present with isolated optic neuritis or transverse myelitis, acute disseminated encephalomyelitis (ADEM), brainstem or cerebellar features, or cerebral cortical encephalitis.

Unlike multiple sclerosis and AQP4-IgG-seropositive NMOSD, in which multiple clinical attacks characterise relapsing forms of disease, individuals with MOG antibody-associated disease (MOGAD) can have either a monophasic or relapsing course.[3–6] Histopathological features of MOGAD differ from those of multiple sclerosis or NMOSD,[7,8] as do its imaging features, treatment responses, and outcomes. There is a clear need to establish formal consensus diagnostic criteria for MOGAD as a distinct entity.

Studies from multiple countries support MOGAD as a global disease affecting people of all ages. MOGAD incidence is 1·6–3·4 per million people per year, and prevalence is estimated at 20 per million (95% CI 11–34).[9,10] These numbers are expected to rise with increasing recognition and availability of testing, including identification of patients with mild disease, monophasic disease, and atypical presentations.

For multiple sclerosis[11] and NMOSD,[12] international criteria facilitate diagnosis, prognostication, and epidemiology, and guide disease-specific research and clinical trials. Several manuscripts have proposed recommendations for diagnosis of MOGAD[13–15] but formal, international consensus, diagnostic criteria have not been formulated. We convened an international panel of paediatric and adult neurologists, neuroimmunologists, and researchers to propose diagnostic criteria for MOGAD. These criteria are based on an extensive literature review of the clinical features and outcomes reported in paediatric and adult individuals with serum MOG-IgG, with careful consideration of methods used to detect such antibodies and by use of a structured consensus process (appendix p 16).

Clinical features of patients with MOG-IgG

Overview

The panel reviewed the clinical features of reported cohorts of patients with CNS demyelination and serological evidence of MOG-IgG. Figure 1 summarises frequencies of features at disease onset across different countries based on national studies including both paediatric and adult cohorts. Optic neuritis is by far the most common onset feature, particularly among adults, while ADEM with or without concomitant optic nerve involvement is the typical first manifestation in children, particularly before the age of 11 years.[5,16] Transverse myelitis is another common presentation.[4,16,20] Less common presentations include cerebral cortical encephalitis (often with seizures), brainstem and cerebellar demyelinating attacks, tumefactive brain lesions, cerebral monofocal and polyfocal CNS deficits associated with demyelinating lesions, cranial neuropathies, and progressive white matter damage (leukodystrophy-like pattern). In contrast to AQP4-IgG-seropositive NMOSD

and multiple sclerosis, no marked sex or racial predominance has emerged in populations with MOGAD.[4,9,16–18] A further difference compared with the chronic relapsing nature of AQP4-IgG-seropositive NMOSD and multiple sclerosis is that MOGAD can exist as either a monophasic illness or a relapsing disease.

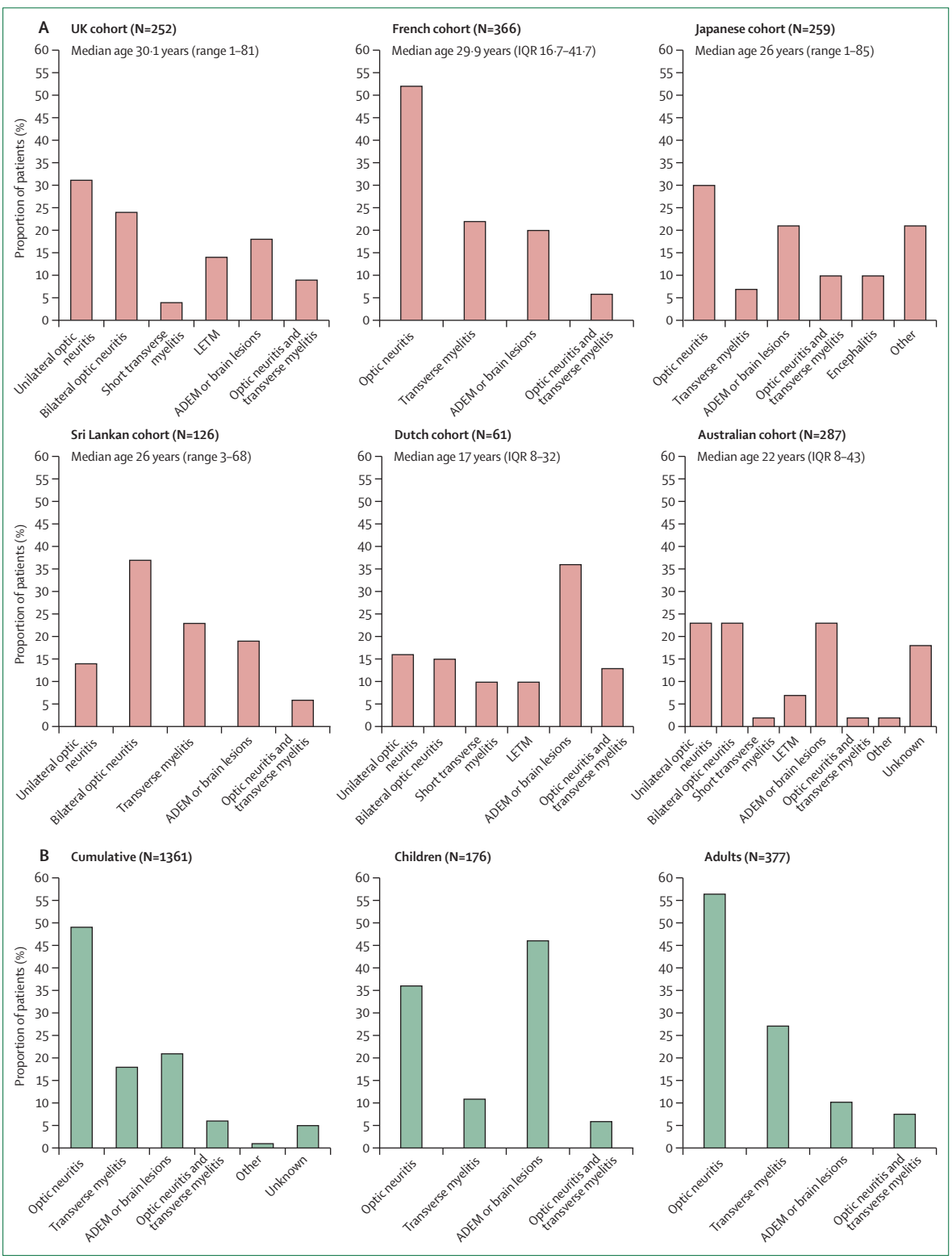

Figure 1: **Clinical features associated with MOG-IgG**
Clinical features at onset or during follow-up of patients with serum MOG-IgG from nationally-acquired cohorts are presented geographically, cumulatively, and by age (paediatric or adult).[4,9,16–19] (A) Clinical features at onset (UK, French, Sri Lankan, Dutch, and Australian cohorts) and over follow-up (Japanese cohort). The category ADEM or brain lesions (without ADEM) includes all patients presenting with signs of brain or brainstem involvement. (B) Clinical features at onset from the combined UK, French, Sri Lankan, Dutch, and Australian cohorts, and divided into paediatric and adult populations from studies where the frequency of clinical features was reported separately in these age groups (French, Sri-Lankan, and Dutch cohorts). A similar distribution of features at onset has been reported from multiple European centres.[20] Although truly national data have not been reported from China, a three-centre study of 16 paediatric and 34 adult patients with MOGAD also reported optic neuritis as the most frequent presenting feature in adults (71%).[21] Studies reporting paediatric-only or adult-only data are described in the main text. ADEM=acute disseminated encephalomyelitis. LETM=Longitudinally extensive transverse myelitis. MOG=myelin oligodendrocyte glycoprotein. MOGAD=MOG antibody associated disease.

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Optic neuritis and optic nerve involvement

Optic neuritis can be associated with central acuity loss, retro-orbital pain (described by some patients as a headache),[22] colour vision loss, and an afferent pupillary defect (which can be undetectable in people with bilateral or previous contralateral optic neuritis).[23] In patients with optic neuritis associated with serum MOG-IgG, optic disc swelling is commonly visible on fundoscopy (45–95%),[24,25] with moderate to severe oedema frequently reported.[25,26] Bilateral optic neuritis in adult and paediatric patients is common at onset and seems to be more frequent in MOGAD (31–58%)[20,24–27] than in optic neuritis associated with multiple sclerosis (less than 5%)[23] and AQP4-IgG-seropositive optic neuritis (13–37%; appendix pp 2–3).[23,27] Optic neuritis can occur in patients with MOG-IgG of all ages[20,24–27] and relapses are often unilateral.[20,24–29] Optic neuritis associated with MOG-IgG also occurs in association with ADEM and transverse myelitis.

Visual acuity loss, as measured using Snellen charts, is often worse than 6/60 at nadir, although milder vision loss can also occur.[4,20,24–26] Improvement in visual acuity often occurs rapidly, with recovery to full or near normal acuity following acute corticosteroid therapy.[4,6,18,23,24] Relapses can occur during corticosteroid weaning or shortly after cessation.[4,20,23,24,26,30] Electrophysiology, visual perimetry, and optical coherence tomography (OCT) have been used to quantify visual pathway damage and dysfunction in optic neuritis associated with MOG-IgG, but they are not diagnostically specific.[23] Despite similar amounts of neuroaxonal injury, as measured by OCT, patients with paediatric optic neuritis with MOG-IgG show better visual recovery than do adults.[31]

Overall, relapsing optic neuritis occurs in 30–50% of patients with MOG-IgG. The condition occurs commonly (but not exclusively) with three clinical scenarios: (1) paediatric patients who present initially with ADEM followed by recurrent optic neuritis; (2) adult or paediatric patients who initially present with optic neuritis and continue with further episodes of optic neuritis; and (3) adult and paediatric patients who present with NMOSD-like clinical features of concurrent optic neuritis and transverse myelitis at onset and then have relapses of optic neuritis.[4,5,20,23,24,26-29,31]

Typical funduscopic and MRI features of optic neuritis associated with MOG antibodies are shown in figure 2. Dedicated orbital fat-saturated images of the optic nerves with and without gadolinium are strongly encouraged to confirm the presence of optic nerve inflammation. We have outlined the key features that we determined best differentiate optic neuritis associated with MOG antibodies, multiple sclerosis, and AQP4-IgG seropositive NMOSD (table, appendix p 4). The presence or absence of optic nerve head swelling, lesion extent along the optic nerves, and involvement of perineural tissue are particularly important features. Most studies have focused on the incident optic neuritis attack, and thus imaging features of recurrent optic neuritis attacks are less well described.

Transverse myelitis and spinal cord involvement

Transverse myelitis in patients with MOG-IgG has clinical and imaging features that assist in differentiation from multiple sclerosis and AQP4-IgG seropositive NMOSD (table, figure 2, appendix p 5). Transverse myelitis in people with MOG-IgG can occur in isolation, as a component of ADEM, or concurrent with optic neuritis.[30,33,34] Clinical manifestations include sensory, motor, and sphincter disturbance.[30,33,34] The acute attack severity varies, but is typically moderate to severe at nadir (Expanded Disability Status Scale score >4) in 50% or more of patients with transverse myelitis and MOG-IgG antibodies.[35] Most patients experience good to excellent motor recovery,[30,33,34] but permanent bladder, bowel, or sexual dysfunction can occur.[4,30,33] Recurrent transverse myelitis episodes without demyelination elsewhere in the CNS are rare in patients with MOG-IgG antibodies.[36] Painful tonic spasms and severe neuropathic pain as an outcome is less common in patients with transverse myelitis with MOG-IgG, and is more representative of myelitis associated with AQP4-IgG-seropositive NMOSD.

Most patients with transverse myelitis associated with MOG-IgG have T2-hyperintense lesions on spinal MRI, although up to 10% of spinal MRI scans can be normal at onset.[37] People with MOG-IgG and attacks involving the brain or optic nerves can have clinically silent spinal cord lesions; conversely, clinically silent brain or optic nerve lesions can be detected in 33–50% patients with clinical transverse myelitis and MOG-IgG.[30,33,34] Acute transverse myelitis in patients with MOG-IgG is often longitudinally extensive (three or more vertebral segments in length in more than 60% of patients) on MRI, but shorter lesions also occur, and some people have multiple spinal cord lesions.[6,30,33,34] By contrast, a first attack of longitudinally extensive transverse myelitis rarely occurs in multiple sclerosis, and if multiple sclerosis is suspected, care should be taken to establish whether the appearance of a long lesion might represent coalescence of focal lesions.[38] In a study of more than 1000 patients with demyelination, only 11 (1·3%) of 863 patients with multiple sclerosis had involvement of the conus, compared with nine (6%) of 150 patients with AQP4 antibodies and seven (26%) of 27 patients with MOG antibodies.[39] Thickening and contrast enhancement of the dorsal nerve roots has been described in people with transverse myelitis and MOG-IgG.[40,41]

Most acute T2-hyperintense lesions in the spinal cord are centrally located on axial imaging (in 66–75% of patients with MOG-IgG), and can be restricted to the grey matter (as seen in 30–50% of patients), producing the H-sign.[30,33,42] However, 20–25% of spinal cord lesions in people with MOG-IgG do not involve spinal grey matter.[30] Contrast enhancement is seen in approximately 50% of patients with transverse myelitis and MOG-IgG,

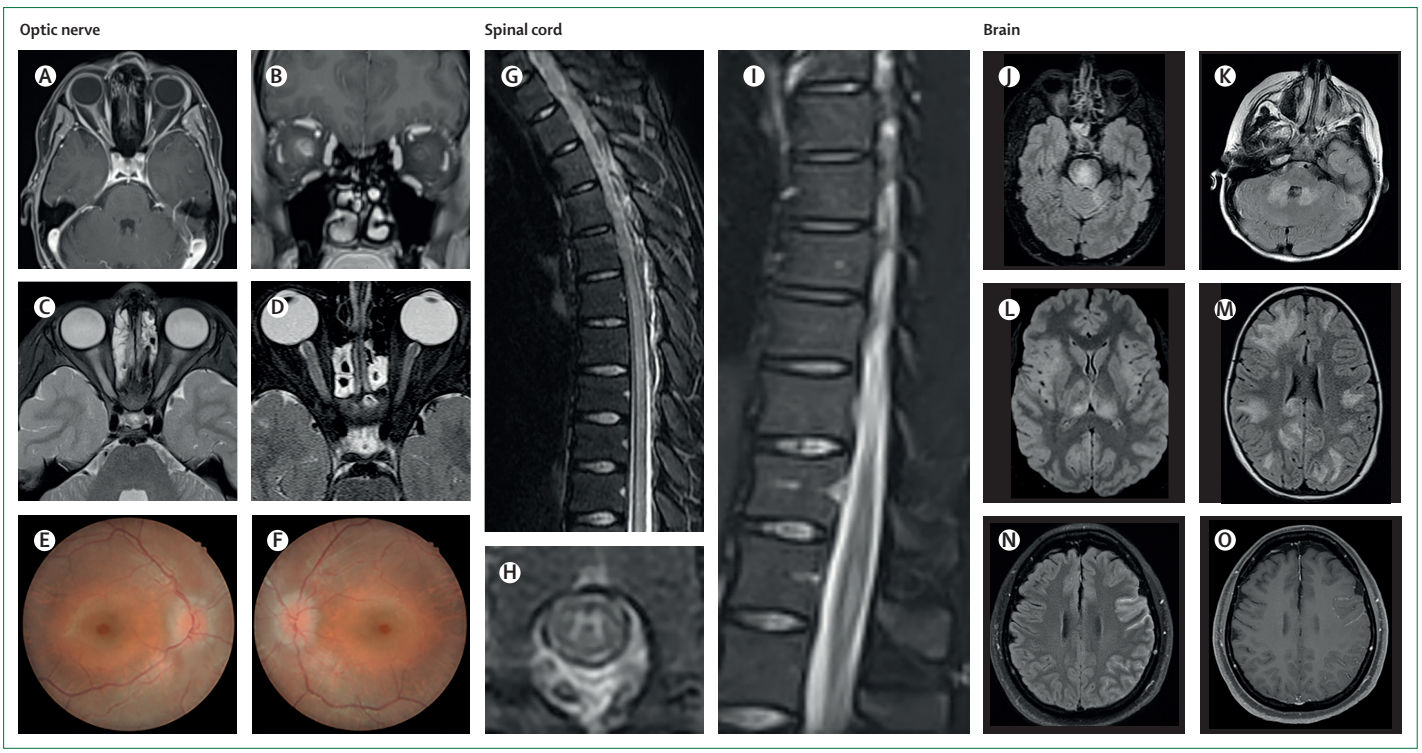

Figure 2: **Neuroimaging features of MOGAD**
MRI scans showing the features emphasised as being either common or unique to patients with MOGAD as delineated in figure 3. (A) Perineural optic sheath enhancement (with diffuse orbital fat involvement and optic nerve enhancement). (B) Right optic nerve swelling and enhancement (coronal view). (C) Bilateral longitudinally extensive optic nerve T2 hyperintensity. (D) Radiologically visible optic disc swelling. (E) Optic disc oedema on fundoscopy. (F) Optic disc oedema in the fellow eye of image (E). (G) Longitudinally extensive T2-hyperintense lesion in the thoracic spine. (H) Central spinal cord involvement with H sign. (I) Conus lesion. (J) T2-hyperintense pontine lesion. (K) Bilateral T2-hyperintense lesions of the middle cerebellar peduncles. (L) Bilateral T2-hyperintense cerebral lesions involving the thalami. (M) Large ill-defined T2-hyperintense lesions involving supratentorial white matter. (N) Cortical fluid attenuated inversion recovery hyperintensity with (O)associated leptomeningeal enhancement. E, F were reproduced from Ramanathan et al,[32] by permission of Elsevier. MOGAD=myelin oligodendrocyte glycoprotein antibody-associated disease.

and cauda equina and pial enhancement have been reported.[30,33,40,41] Most T2 lesions in the spinal cord resolve or reduce in size substantially at follow-up.[30,43] Spinal cord atrophy can occur in severe cases.[35,44,45] In contrast to multiple sclerosis, accumulation of silent spinal cord lesions between clinical attacks is very rare in MOGAD (0% of 110 follow-up spinal MRI scans in 81 patients).[46]

Brain and brainstem involvement

Involvement of the brain or brainstem in patients with MOG-IgG manifests as features of ADEM, cerebral cortical encephalitis, brainstem symptoms, or cerebellar symptoms, or as clinically silent brain or brainstem lesions in patients with clinical optic neuritis or transverse myelitis (table, figure 2, appendix pp 6–7). Brain MRI is normal at the time of a first attack of optic neuritis or transverse myelitis in only 8–16% of people subsequently diagnosed with multiple sclerosis,[47] but brain T2-hyperintense lesions are absent in 47–68%[3] of patients who have MOG-IgG (typically patients with optic neuritis or transverse myelitis).

Brain lesions in patients with MOG-IgG tend to be bilateral, ill-defined, and large, often with deep grey matter involvement. Classic multiple sclerosis lesions (small, ovoid T2-hyperintense lesions in the juxtacortical and periventricular white matter) and persistent T1-hypointense lesions are uncommon in patients with MOG-IgG.[48] In patients with MOG-IgG, the pons is frequently involved; large lesions in the middle cerebellar peduncle, when present, suggest MOG-IgG-associated demyelination, given that such lesions are rare in multiple sclerosis or AQP4-IgG-seropositive NMOSD.[48–50] Area postrema and midbrain involvement can associate with episodic but persistent (>48 h) nausea and vomiting in a small proportion of patients with brainstem lesions and MOG-IgG.[51,52] The appearance of brainstem lesions does not reliably distinguish patients with MOG-IgG from those with AQP4-IgG-seropositive NMOSD.[48,49] Tumefactive lesions can lead to life-threatening subfalcine and tentorial herniation.[53]

ADEM is the most prevalent clinical syndrome at presentation in children with MOG-IgG. MOG-IgG are detected in around 50% of paediatric patients with ADEM, but the frequency of MOG-IgG is lower in adult ADEM patients.[6,13,54] ADEM was the presenting syndrome in only 15 (5·6%) of 268 individuals with adult-onset demyelination with MOG-IgG.[16] Children with MOG-IgG and ADEM are typically younger than 10 years. Patients with MOG-IgG associated with optic neuritis, transverse myelitis, or brain lesions (without meeting the

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	MOGAD	AQP4-IgG seropositive NMOSD	Multiple sclerosis
Paediatric onset	Frequent	Extremely rare	Infrequent
Sex distribution	F=M	F>M	F>M (after puberty)
Disease course	Monophasic or relapsing	Most often relapsing	Relapsing, secondary progressive, or progressive from onset (adults only)
Optic nerve			
Initial visual acuity	Often severely impaired	Often severely impaired	Mild to moderately impaired
Initial recovery	Typically favourable	Risk for poor recovery	Typically favourable
MRI lesion characteristics	Frequently bilateral and anterior at onset, longitudinally extensive*, and involving the optic nerve sheath	Bilateral or unilateral at onset, often posterior, and frequently longitudinally extensive*; chiasmal and optic tract involvement might be present	Typically unilateral, anterior, short optic nerve lesions that do not involve the optic nerve sheath
Optic nerve head	Moderate to severe oedema is typical and can be associated with haemorrhage	Oedema and associated haemorrhages are less common than in MOGAD	Mild oedema can occur but severe oedema with haemorrhage is rarely seen
Spinal cord			
Initial deficits	Severe	Severe	Mild to moderate
Motor function	Excellent motor recovery after treatment	Risk for poor recovery or worsening motor impairment with relapses	Often good but risk for motor impairment during progressive phase of disease
Sphincter, bladder, and erectile function	Risk for residual sphincter and erectile impairment despite good motor recovery	Variable residual bladder impairment	Risk of bladder impairment during progressive phase of disease
Spinal cord MRI lesion characteristics	Single or multiple longitudinally extensive lesions, grey matter involvement leading to the H-sign and conus lesions are characteristic	Single longitudinally extensive lesion, which commonly involves entire transverse diameter of the cord and might have bright spotty lesion appearance; conus rarely involved	Often multiple focal cord lesions; often posterior and involving only a portion of the cross-sectional area of the cord; conus rarely involved
Brain			
Clinical presentation	Encephalopathy, seizures, focal deficits, and cerebral cortical encephalitis can occur	Area postrema symptoms, hiccups, hypersomnolence, or focal neurological deficits	Focal or polyfocal neurological deficits common; encephalopathy or seizures are rare
Brain MRI	Might be normal in optic neuritis or myelitis presentations	Might be normal in optic neuritis or myelitis presentations	Multifocal T2-hyperintense white matter lesions
Qualitative MRI lesion features	Fluffy or poorly demarcated T2 lesions; leukodystrophy-like pattern is rare	Multifocal T2 lesions most common in AQP4-rich regions; lesions can appear linear and along corticospinal tract or medulla	Ovoid or round, well demarcated T2 lesions; Dawson's fingers, S-shaped or U-fibre lesions; central venule sign; smouldering or slowly evolving lesions†
Typical MRI lesion locations	White matter, deep grey matter, middle cerebellar peduncle, large brainstem, and confluent cortical	Peri-third and peri-fourth ventricle, splenium of corpus callosum, internal capsule, and white matter	Periventricular and corpus callosum, juxtacortical, cortical, white matter, and infratentorial
MRI contrast enhancement pattern	Non-specific leptomeningeal around brainstem; unilateral or bilateral cortical (linear) leptomeningeal enhancement (with cerebral cortical encephalitis)	Patchy, cloud-like lesion enhancement pattern; pencil-thin pattern of the ependymal surface of lateral ventricles	Ovoid, ring, or open-ring lesion enhancement pattern
Resolution of T2-hyperintense lesions on MRI	Partial or complete resolution	Might be present	Complete resolution is infrequent
Silent MRI lesion accrual	Infrequent	Infrequent	Frequent
Residual T1-hypointense lesions	Extremely rare	Might be present	Frequent
Presence of oligoclonal bands in CSF but not serum	Infrequent	Infrequent	Extremely frequent

Frequencies were established through our literature review: extremely rare, <5%; infrequent, 5–20%; might be present, 21–50%; frequent, 51–80%; and extremely frequent, >80%. A more detailed comparison of optic neuritis (appendix p 4), transverse myelitis (appendix p 5), and brain involvement (appendix pp 6–7) in patients with MOG-IgG, those with AQP4-IgG seropositive NMOSD, and those with multiple sclerosis is in the appendix. NMOSD=neuromyelitis optica spectrum disorder. MOGAD=myelin oligodendrocyte glycoprotein antibody-associated disease. F=female. M=male. *Longitudinally extensive lesions of the optic nerve are defined as MRI signal (T1 gadolinium-enhancing or short tau inversion recovery or T2) involving >50% of the length of the optic nerve. †The limited available data indicate that smouldering lesions are absent in patients with MOGAD or AQP4-IgG seropositive NMOSD.[7]

Table 1: **Summary of the key features of MOGAD, AQP4-IgG NMOSD, and multiple sclerosis**

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criteria of ADEM)[55] typically present in adolescence. Children with ADEM and MOG-IgG are on average 2–3 years younger than children with seronegative ADEM.[6,16,56] An infectious episode (mainly respiratory) and fever frequently precede ADEM, particularly in children with ADEM and MOG-IgG (40–75% of patients).[13,57] Transverse myelitis and ataxia occur more commonly in patients with ADEM and MOG-IgG than in patients with ADEM who are seronegative.[58]

Complete or almost complete clinical and radiological resolution occurs in more than 70% of children with MOGAD associated with ADEM.[5,6,43,58] However, the outcome can be poor in rare cases of children who develop a leukodystrophy-like brain imaging pattern.[6,59] Relapses following ADEM occur more frequently in patients who are MOG-IgG seropositive (about 38%) than in people who are seronegative (around 3%),[6,60–62] and the time from onset to first relapse is variable (median

4·7 months, IQR 2·8–12·0, range 1–63).[6] Relapsing clinical attacks after ADEM include multiphasic disseminated encephalomyelitis (37–56%) and optic neuritis (21–36%), and some patients have features meeting criteria for AQP4-IgG seronegative NMOSD.[6,28,62–64]

Cerebral encephalitis, manifesting with fever, headache, reduced consciousness, seizures, or status epilepticus, also occurs in 6·7% (19 of 285) patients with MOG-IgG.[65–67] Cortical lesions in patients with MOG-IgG and seizures are more apparent with fluid attenuated inversion recovery (FLAIR) sequences. Such lesions are termed as FLAMES: FLAIR hyperintense lesions in anti-MOG encephalitis with seizures. Seizures can be focal or generalised. Symptoms of raised intracranial pressure can also occur and can be life-threatening.[53,68] Seizures might be the first manifestation, with more typical demyelinating presentations later in the disease course.[69] In addition to evaluation of serum MOG-IgG, testing for other neuroglial cell surface antibodies such as NMDA receptor antibodies (in CSF and serum) is also advised in children with features of autoimmune encephalitis, given that patients can have a dual antibody seropositivity either contemporaneously or sequentially (4–7·5% of patients with NMDA receptor encephalitis).[70]

Relapses in patients with MOG-IgG

The panel defined a relapse as being a new clinical attack occurring more than 30 days following onset of a previous attack. Relapses are more common in the first 6 months than later after the first attack. Relapses can occur within 2 months following oral corticosteroid therapy tapering or cessation.[4,24] Some patients have a cluster of early relapses whereas others have ongoing relapses beyond 12 months after onset.[71,72]

To remove the bias of overestimating the relapse risk based on inclusion of patients tested because of their relapses, some studies have focused on incident cohorts of patients confirmed to have MOG-IgG at the time of their first attack. Two studies that included mostly adults showed similar relapse risks: 16 (36%) of 44 patients with a median follow-up of 15·5 months and 37 (27%) of 139 patients with a median of 10·78 months.[3,4] Both cohorts showed the relapse risk was greatest over the first few months from the initial attack, but the follow-up duration was short. In two incident paediatric cohorts, 17–20% of the 200 patients confirmed to have MOG-IgG at the time of their first attack experienced relapsing disease over a median observation period of 1–7 years. The median time to first relapse was 11 months but some first relapses occurred several years after the incident attack.[5,6] In a UK study of 183 patients with MOG-IgG (68 paediatric onset and 115 adult onset)[73] followed for a median of 24·4 months (range 1·2–235·1 months), the 4-year risk of relapse was 31·7% and the 8-year risk was 36·3%.[73] Longitudinal observation of 13 adults with demyelination and MOG-IgG, none of whom was on chronic therapy and not all of whom were evaluated from onset, showed that 8 (62%) experienced relapses, some within the first 10 years after onset, although others had long intervals from onset to relapse (up to 46 years).[74]

A diagnostic hallmark for untreated relapsing multiple sclerosis is the silent accrual of lesions over time, which also portends future clinical attacks. This diagnostic and prognostic hallmark might not be equally applicable to patients with a first demyelinating attack associated with MOG-IgG. In a study with serial acquisition of brain MRI scans, clinically silent brain lesions occurred in a minority of children with MOG-IgG (14% of patients, 4% of all brain MRI scans). 44% of silent lesions were detected within 3 months of the first attack and 66% were detected within the first year with a low positive predictive validity (20%) for clinically relapsing disease.[75] In a study of 182 paediatric and adult patients with MOG-IgG imaged at various timepoints from onset of symptoms, accrual of silent brain lesions was also rare (4·1% of patients, 3·6% of brain MRI scans at follow-up). However, in this study, the presence of such lesions associated strongly with subsequent relapse.[46] In patients with first attacks of demyelination and MOG-IgG, the contribution over the first few years of either new MRI lesion formation or reduction in resolution of lesions to the risk of clinical relapses requires further study. The panel elected not to diagnose relapsing MOGAD on the basis of MRI alone and to restrict this term to patients with clinically relapsing disease. In contrast to patients with multiple sclerosis, progressive disease, with worsening of neurological deficits in the absence of clear new relapses, does not appear to occur in patients with demyelination associated with MOG-IgG, although this absence of relapse-free progression requires further study in cohorts with extended observation.[14,24,70,72,76]

Laboratory examinations

MOG-IgG testing

Serum is preferred specimen type for MOG-IgG testing (panel 1). Clotting factors in plasma can interfere with results (appendix pp 8–11, 16), while CSF testing is promising but requires further examination.[6,18,65,83]

The panel strongly endorses serum testing for patients with suspected MOGAD using cell-based assays that use full-length human MOG to detect MOG-IgG.[1,2,18,84,78] MOG-IgG are IgG1, and the panel recommends testing with IgG Fc, an IgG1 secondary antibody, or an IgG (heavy and light) secondary antibody if externally validated in-house assays are used.[1,28,77] Fixed cell-based assays are a reasonable alternative when live cell-based assay testing is unavailable, with the caveat that sensitivity and specificity of fixed cell-based assays are lower than cell-based assays.[1,78,84] However, antibody titres are often not consistently provided by testing centres (appendix p 8–11) and reproducibility between testing centres has not been systematically investigated for commercial cell-based assays.[85] ELISA is not recommended for MOG-IgG measurement owing to low sensitivity and specificity.[1,18,86]

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See Online for appendix

***Panel 1*: MOG-IgG isotypes and methodological considerations**

- Live cell-based assays quantified by flow cytometry or microscopy are the preferred methods to detect myelin oligodendrocyte glycoprotein (MOG) IgG in clinical settings (appendix pp 8–11, 17–18)
- Live cell-based assays offer the highest specificity; centres with established laboratory expertise most often use live cells expressing full length MOG, whereas commercial assays use fixed cells expressing full-length MOG
- The panel recommends testing for MOG-IgG with either an IgG Fc or IgG1-specific secondary antibody; use of an IgG (heavy and light) secondary antibody with externally validated in-house assays is also acceptable[18,77]
- All isotypes (IgG1, IgG2, IgG3, IgG4, IgM, and IgA) have been detected in patients with serum MOG-IgG[1,18,26,77–82] but further work on the clinical association of IgM, IgA, IgG2, IgG3, and IgG4 subclasses is needed to assess their use in clinical diagnostics
- Given that laboratories might not clarify whether they use live or fixed cell-based assays, the panel strongly urges clinicians requesting tests to inquire about the methods used for MOG-IgG detection
- Reporting of results (ie, titres, flow cytometry ratio, binary positive *vs* negative result, and test accreditations) varies according to geographical region (appendix pp 8–11, 17–18). To facilitate MOGAD diagnosis, the panel recommends that MOG-IgG test reports include qualitative results (ie negative, low positive, and clear positive); depending on cell-based assays and regions (appendix pp 8–11, 17–18), quantitative results (ie, titres or flow cytometry ratio) with reference values should also be included

Serum MOG-IgG reports should, in the opinion of the panel, at least include qualitative results (ie, negative, low positive, and clear positive), and semi-quantitative results (ie, titres, flow cytometry ratio, or visual scores). The panel proposes criteria for clear positive and low positive fixed and live cell-based assay results (appendix pp 8–11, 17–18). For live assays, we recommend that clear positives are defined as at least two doubling dilutions above the assay cutoff, or above the assay-specific titre cutoff, or flow-cytometry ratio cutoff (appendix pp 17–18). Fixed assays are considered clear positive by titres greater than or equal to 1:100. Fixed or live assay results are considered to be low positives if in the low range of the individual live assay (appendix pp 8–11, 17–18) or if titres are at least 1:10 and less than 1:100 for fixed cell-based assays. Quantitative results, titres, or flow cytometry ratios with reference values should be included in diagnostic reports for delineation of clear positive versus low positive results.

The rationale for emphasis on clear positivity versus low positivity was influenced by evidence that higher titres are more reproducible than lower titres.[87] An international, multicentre, blinded comparative study of seven live cell-based assays from four centres showed excellent interlaboratory agreement for clear positive results among most centres.[1] Low positive samples were more frequently discordant. The positive predictive value for clinical features consistent with MOGAD increased with increasing titre of MOG-IgG, and thus clear positives will have a higher positive predictive value.[87,88]

In three studies evaluating MOG-IgG titres in paired serum and CSF samples, only 61·5% (eight of 13),[89] 61·3% (19 of 31),[90] and 42·1% (48 of 114)[91] of MOG-IgG seropositive patients with clinical and MRI features of MOGAD also had positive CSF samples. These studies highlight the low sensitivity of MOG-IgG testing in CSF alone. However, in these investigations, a small number of patients with demyelinating disorders (three of 80, 13 of 262, and four of 118)[89–91] were positive for MOG-IgG in the CSF alone. Of these patients, three (100%) of three, ten (69%) of 13, and two (66%) of the three patients (of the four with CSF MOG-IgG), for whom clinical information was available, showed clinical features suggestive of MOGAD. Therefore, CSF testing for MOG-IgG can be used in selected circumstances to support the diagnosis of MOGAD in MOG-IgG seronegative patients with supporting clinical and MRI features (figure 2).

If detailed information (appendix pp 8–11) on a particular assay methods or titres is not provided, we recommend confirmation with a second independent test using, whenever possible, a live cell-based assay done in a laboratory with expertise in measuring MOG-IgG titres, ideally using serum obtained at initial presentation. We acknowledge that the choice of laboratory is often made at an institutional level and not all centres or clinicians can request testing at a different reference laboratory owing to issues of cost, shipping, and access.

Patients have the highest likelihood of MOG-IgG seropositivity when tested at the time of incident clinical attack. Ideally, testing should be done before the administration of corticosteroids, immunoglobulins, or apheresis, because these therapies can reduce serum MOG-IgG detection, as observed when testing for AQP4-IgG.[92] If initial serum MOG-IgG testing was negative but obtained after administration of acute therapies, then repeat testing is advised at least 3 months later (after a period of time sufficient for the effects of apheresis, in particular, to no longer be operative) or at the time of relapse.[20,93] MOG-IgG titres usually decline with time, but can remain positive for years, or become seronegative with or without immunotherapy. Seroconversion from negative to positive is extremely uncommon in patients with a negative test result at onset.[5,58]

Onset serum MOG-IgG titres do not have strong prognostic value for recovery or relapse.[16,83,94,95] Persistent MOG-IgG seropositivity is associated with an increased likelihood of having a relapse by a factor of 2–10,[5,6,49,71,94] particularly when the MOG-IgG titre remains high.[94] However, data to guide optimal timing of serial MOG-IgG testing and its interpretation are scarce. A standardised definition of persistence is required and the prognostic significance of persistent seropositivity requires prospective study.

General CSF testing

CSF pleocytosis, with white cell counts more than 5 per μL, occurs in over 50% of patients with a first demyelinating attack and MOG-IgG. Up to 12% of such patients have more than 100 white blood cells per

high-power field.[1,96] CSF pleocytosis is more likely during an attack than during remission and more frequent in patients who have ADEM or transverse myelitis than in patients who have optic neuritis.[1,96] CSF protein is elevated in 30% of patients with a first demyelinating attack and MOG-IgG, and does not allow discrimination of MOG-IgG-associated demyelination from other neuroinflammatory disorders.[1,54,89]

Intrathecally restricted CSF oligoclonal bands strongly favour a diagnosis of multiple sclerosis. However, oligoclonal bands are detected in up to 20% of patients with MOG-IgG (although they can be transient),[1,96] and their presence does not exclude a diagnosis of MOG-IgG antibody-associated demyelination. Measles, rubella, and varicella zoster CSF antibodies have been reported to be absent in patients with MOG-IgG[1,96] but very common in patients with multiple sclerosis. However, testing for the measles, rubella, and varicella zoster reaction is not universally available.

Coexistence of other antibodies or autoimmune disorders

Many laboratories run MOG-IgG and AQP4-IgG assays concurrently. Dual positivity is very rare, and when it occurs, the AQP4-IgG titres are nearly always high whereas the MOG-IgG titres are low.[97] The AQP4-IgG finding is the key diagnostic result given that dual-positive patients manifest with a clinical course consistent with AQP4-IgG-seropositive NMOSD.[97] If testing for AQP4-IgG and MOG-IgG is ordered independently, a positive serum test for AQP4-IgG in a person with optic neuritis, transverse myelitis, or other features consistent with NMOSD would strongly support a diagnosis of AQP4-IgG-seropositive NMOSD and testing for MOG-IgG would not be indicated. Patients presenting with features of NMOSD who are seronegative for AQP4-IgG should be tested for serum MOG-IgG.

Rarely, patients manifest with clinical features of demyelination associated with serum MOG-IgG followed or preceded by clinical anti-NMDA receptor encephalitis (termed MOGAD and anti-NMDA receptor encephalitis overlap syndrome).[98] Such patients have a history of episodes of encephalitis or demyelination, or can have concurrent serum MOG-IgG and CSF NMDA receptor antibodies and manifest with clinical features of anti-NMDA receptor encephalitis (with features including encephalopathy, psychosis, seizures, and dyskinesias) associated with white matter lesions and clinical features of CNS demyelination.

Considerations for the creation of MOGAD diagnostic criteria

Adults and children with an incident attack of acquired CNS demyelination require neurological examination, neuroimaging (dedicated orbital imaging, spinal cord MRI, and brain MRI), and laboratory investigations. Initial laboratory testing might include evaluation for CSF-restricted oligoclonal bands. Serum testing for MOG-IgG rests on the clinical presentation and imaging features. The panel unanimously agreed that serum evaluation for MOG-IgG should not be a screening test for all patients with incident demyelinating attacks (panel 2).

We have proposed diagnostic criteria for MOGAD (figure 3). Patients with one of the core clinical attack types and clear positive MOG-IgG test results in serum measured by fixed or live cell-based assay can be diagnosed with MOGAD. Patients with low positive serum MOG-IgG titres measured by fixed or live cell-based assay, patients with serum results reported as positive on fixed cell-based assay without titre, or seronegative patients with clear positive CSF MOG-IgG test results who present with one of the core clinical

Panel 2: Patient selection and positive predictive values for MOG-IgG testing

Key points

- Fundamental to the principles of myelin oligodendrocyte glycoprotein (MOG)-IgG testing is the selection, on the basis of clinical features, of individuals who are most appropriate to be tested to enhance positive predictive value (PPV) of the test—that is, the probability that individuals with a positive screening test truly have the disease: PPV=(sensitivity × prevalence) /[(sensitivity × prevalence) + (1−specificity) × (1−prevalence)], as emphasised previously.[14] PPV depends on the prevalence of MOG antibody-associated disease (MOGAD) in the population being tested but is useful to illustrate how the risk of a false positive MOG-IgG result can increase or decrease depending on what population is tested.
- MOG-IgG testing is not recommended for screening of all patients with CNS inflammatory demyelination. Caution is advised in interpretation of positive serum or CSF MOG-IgG results in patients with clinical or radiological features atypical for MOGAD, as false positives are more likely, particularly with low positive titres.

Caveats

- The frequency of MOG-IgG approaches 50% in children with optic neuritis or acute disseminated encephalomyelitis (particularly children younger than 11 years).[2,58] Screening these groups for MOG-IgG, where the pretest probability is high, would yield a high PPV and is recommended.
- The frequency of MOG-IgG in adults with optic neuritis is around 5%.[99] Universal screening of this group for MOG-IgG, where the pretest probability is moderate, would yield an intermediate PPV, so caution is recommended, and care with interpretation of positive results is needed.
- The frequency of MOG-IgG in adults with optic neuritis with severe optic disc oedema is substantially higher (around 39%)[47,99–101] than in adults with retrobulbar optic neuritis. Screening this group for MOG-IgG would yield a high PPV and is recommended. However, limiting preselection to patients with optic neuritis with disc oedema would exclude almost half the of the patients with optic neuritis who have MOG-IgG. Testing for MOG-IgG in patients with optic neuritis who also have longitudinally extensive optic nerve lesions, bilateral simultaneous optic nerve involvement, or perineuritic optic neuritis lesions on MRI will increase diagnostic yield without sacrificing PPV.[24,25,47,100,102,103]
- The frequency of MOG-IgG among adults with clinical, radiological, and CSF findings diagnostic of multiple sclerosis is 0·3–2·5%.[87,104,105] Thus, although fewer than 2·5% of patients with multiple sclerosis would test positive, the absolute number of false-positive results that would result from routine screening for MOG-IgG in adults with multiple sclerosis would be very high and is not recommended.[11]

Diagnosis of MOGAD (requires fulfilment of A, B, and C)			
(A) Core clinical demyelinating event	Optic neuritis* Myelitis† ADEM‡ Cerebral monofocal or polyfocal deficits§ Brainstem or cerebellar deficits¶ Cerebral cortical encephalitis often with seizures‖		
(B) Positive MOG-IgG test	Cell-based assay: serum**	Clear positive††	No additional supporting features required
		Low positive‡‡	• AQP4-IgG seronegative AND • ≥1 supporting clinical or MRI feature
		Positive without reported titre	
		Negative but CSF positive§§	
Supporting clinical or MRI features	Optic neuritis	• Bilateral simultaneous clinical involvement • Longitudinal optic nerve involvement (> 50% length of the optic nerve) • Perineural optic sheath enhancement • Optic disc oedema	
	Myelitis	• Longitudinally extensive myelitis • Central cord lesion or H-sign • Conus lesion	
	Brain, brainstem, or cerebral syndrome	• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter • Deep grey matter involvement • Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla • Cortical lesion with or without lesional and overlying meningeal enhancement	
(C) Exclusion of better diagnoses including multiple sclerosis¶¶			

Figure 3: **Proposed diagnostic criteria for MOGAD**
ADEM=acute disseminated encephalomyelitis. AQP4=aquaporin-4. MOG=myelin oligodendrocyte glycoprotein. MOGAD=MOG antibody-associated disease. *Optic neuritis is characterised by unilateral or bilateral reduced visual acuity that develops over hours to days and is often associated with retrobulbar orbital pain that is typically exacerbated with eye movement and accompanied by colour vision and visual field loss.[23] Diagnosis of optic neuritis can be supported by the presence of a T2-hyperintense signal in the optic nerve or chiasm, by enhancement of the optic nerve or chiasm with gadolinium, and by exclusion of clinical or radiographical evidence of an alternative compressive, infiltrative, or vascular process impacting the optic nerve or retina.[23] †Myelitis is typically characterised by acute disturbance in motor, sensory, sphincter, or erectile function in various combinations referable to the spinal cord that develops over hours to days.[105] The diagnosis of transverse myelitis is supported by MRI spinal cord T2 hyperintensity with or without gadolinium enhancement, by CSF inflammation, and by exclusion of a compressive or vascular disruption of the spinal cord. Spinal MRI sagittal T2 lesions in patients with MOG-IgG frequently extend three or more vertebral segments and often involve the conus and central grey matter (H-sign). ‡ADEM is defined by acute (worsening over hours to days) polyfocal neurological deficits with encephalopathy (alteration in level of consciousness, profound irritability, not related to postictal state) and by MRI features of multifocal T2 bright lesions often involving cerebral white and grey matter.[55] §Cerebral monofocal or polyfocal deficits develop over hours to days and are referable to one or more T2-hyperintense lesions (which might or might not be enhanced by gadolinium). T2-hyperintense lesions are often located in the middle cerebellar peduncle, peri-fourth ventricle, in supratentorial white matter, in juxtacortical or cortical in locations, and in deep grey nuclei. Periventricular lesions are less common than for multiple sclerosis. ¶Brainstem or cerebellar clinical deficits develop over hours to days and are associated with T2-hyperintense lesions in the brainstem or cerebellum, which might or might not enhance with gadolinium.[49] ‖Cerebral cortical encephalitis with seizures is associated with T2-hyperintense signal in the cortex often with enhancement of the overlying meninges in a patient with acute or subacute new onset seizures and evidence of cerebral irritation (encephalopathy, confusion, headache, or focal neurological deficits in addition to seizure).[67] **Serum testing is recommended for all patients being investigated for MOGAD. Testing both serum and CSF is not recommended for routine evaluation. CSF testing might be valuable in patients with clinical features suggestive of MOGAD but in whom serum testing was negative, particularly if confounded by apheresis or other therapeutic interventions. ††A live cell-based assay result by a standardised method that is a clear positive according to the individual assay cutoffs (appendix pp 8–11, 17–18) or a fixed cell-based assay result with a titre ≥1:100. ‡‡A live cell-based assay result by a standardised method that is a low positive according to the individual assay cutoffs (appendix pp 8–11, 17–18) or a fixed cell-based assay result with a titre ≥1:10 and <1:100. §§A positive CSF evaluation with a fixed or live cell-based assay by use of standardised methods. CSF contamination by blood should be viewed cautiously as a positive result in such samples could occur due to serum MOG-IgG. ¶¶Exclusion of no better explanation requires the expertise of the clinician. As an illustrative example, a patient with optic neuritis, MRI features meeting 2017 criteria for multiple sclerosis,[20] positive CSF oligoclonal bands, and low titre MOG-IgG would be more appropriately diagnosed with multiple sclerosis.[13] Conversely, a patient with bilateral optic neuritis associated with optic disc swelling and longitudinally extensive optic nerve involvement, with borderline CSF oligoclonal bands, with MRI lesions that involve the areas included in the dissemination in space criteria for multiple sclerosis but that are ill defined in character, and with clearly positive serum MOG-IgG titre, might technically meet 2017 criteria for multiple sclerosis but would be more appropriately diagnosed with MOGAD. Although most patients with multiple sclerosis will not have positive serum MOG-IgG, and most MOGAD patients do not meet the 2017 McDonald criteria for multiple sclerosis, some patients will meet both diagnostic criteria and the final diagnosis requires expertise and careful observation over time. We have compared features of MOGAD, multiple sclerosis, and AQP4-IgG-seropositive NMOSD (appendix pp 4–7) and outlined other conditions to consider in the differential diagnosis of MOGAD (appendix pp 12–15).

attack types are also required to have at least one of the supporting clinical or MRI features to be diagnosed with MOGAD. Patients should be diagnosed with MOGAD only after other diagnoses that better explain their features have been excluded.

Given that our proposed diagnostic criteria require the presence of MOG-IgG, the sensitivity of MOG-IgG testing cannot be assessed. It is therefore more relevant to consider the specificity of MOG-IgG testing and the importance of selecting appropriate patients to maximise

the positive predictive value of the diagnostic criteria (panel 2). Clear positive MOG-IgG titres are strongly associated with the clinical features proposed for MOGAD and distinguish such patients from those manifesting with clinical features and a disease course characteristic of AQP4-IgG-seropositive NMOSD or multiple sclerosis.[37] Low titres of MOG-IgG are less discriminatory and are encountered in patients with multiple sclerosis, other neurological diseases, and healthy individuals.[1,2,87,88] Although the frequency of MOG-IgG seropositivity in patients with clinically definite multiple sclerosis is between 0·3% and 2·5%,[1,84,87,88,94,105] universal testing for MOG-IgG of patients suspected to have multiple sclerosis will still yield a high number of false positive results and is strongly discouraged.[14] Although clear positive MOG-IgG titres are rarely found in controls, a positive result can be found in a person who does not have clinical features of MOGAD (particularly if MOG-IgG is included in broader diagnostic panels). A positive MOG-IgG titre alone would not meet our proposed criteria for MOGAD, and future studies are required to establish whether such individuals develop clinical MOGAD attacks at a later point (as has been found to occur in patients with AQP4-IgG-seropositive NMOSD whose serum revealed AQP4-IgG antibodies years before a clinical attack of optic neuritis or myelitis).[107]

The 2017 international McDonald criteria for multiple sclerosis advise caution in the application of those criteria for children younger than 11 years, owing to the rarity of multiple sclerosis in this age group and the concern that diagnoses other than multiple sclerosis are more likely.[11] Given that more than 50% of children aged younger than 11 years with acute CNS demyelination will have serum MOG-IgG at presentation, testing these patients is advised.

We acknowledge that some patients will present with clinical and imaging features consistent with MOGAD but will not have detectable MOG-IgG or will reside in world regions where reliable MOG-IgG testing is not available. Future studies will be needed to identify whether such patients follow a similar disease course as those who have MOGAD defined by the presence of MOG-IgG.

Critical to the diagnosis of MOGAD is the exclusion of a better diagnosis (appendix pp 12–15). Key red flags should prompt reconsideration of a diagnosis of MOGAD (panel 3).

Limitations

We acknowledge several limitations of this work. Prospective data were prioritised, although much of the data review relied on retrospective case series as these studies provided key longitudinal observational data. The available literature is enriched by more severe and relapsing patient populations. Radiology studies are heavily skewed towards imaging obtained during the incident attack and rarely include concurrent optic nerve, brain, and spinal cord imaging (mostly class II–IV evidence for diagnostic accuracy) or longitudinal evaluation. Our panel work focused on diagnosic criteria, rather than prognostic factors. Future studies are required to validate our proposed criteria, to evaluate factors that predict relapses, and to better define outcomes for people diagnosed with MOGAD.

Conclusions and future directions

Foremost among key areas for future research will be the validation of our proposed criteria in prospective paediatric and adult cohorts of patients with acquired CNS inflammatory demyelination. Our proposed criteria rest on the presence of MOG-IgG as a fundamental inclusion criterion, accompanied by clinical presentations identified as being associated with MOG-IgG. Our proposed criteria are inclusive of paediatric and adult patients, with the assertion that MOGAD is a single disease across the age spectrum, similar to what has been shown epidemiologically and pathobiologically for multiple sclerosis and AQP4-IgG-seropositive NMOSD. Given the fundamental nature of MOG-IgG detection for MOGAD diagnosis, comparative studies of MOG-IgG testing methods and development of international standards for assay methods and reporting will also be important.

Our proposed criteria should enable identification of consistent MOGAD cohorts for longitudinal studies, which will be crucial to determine whether relapsing MOGAD is a lifelong disease and whether patients with an initial monophasic course are at risk for relapse many years later. Better understanding of relapsing MOGAD is imperative, including identification of means to: predict at presentation the risk of relapses; establish the relevance of silent contrast-enhancing and non-contrast-enhancing new lesions of the optic nerves, brain, and spinal cord on disease course; and appreciate implications for disease chronicity when considering

***Panel 3*: Red flags against a diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease**

- Progressive neurological impairment in the absence of attacks
- Rapid worsening of clinical deficits from onset to nadir within minutes to hours
- No improvement following treatment with high-dose corticosteroids for an acute attack
- MRI findings of well circumscribed T2-hyperintense lesions in a pattern meeting dissemination in space criteria for multiple sclerosis, especially when accompanied by CSF oligoclonal bands and by the accrual over time of new silent T2-hyperintense focal lesions and retention of most previous T2-hyperintense lesions
- Lesion contrast enhancement that persists for 6 months or more.[43]

Search strategy and selection criteria

Literature searches were done by panel members in PubMed, MEDLINE, and Embase. An initial search on MEDLINE with search terms "myelin oligodendrocyte glycoprotein" and "MOG" identified 688 articles published between Jan 1, 2010, and Jan 31, 2021. Additional articles with focus on acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, or myelitis were identified by the members of the individual working groups. From this list, we excluded: articles not in English, as we wanted all panel members to be able to review all manuscripts; case reports and small cases series, unless they detailed rare but important data; and most review articles. Older, pivotal studies identified in other papers during our literature search were also included. 378 unique manuscripts were relevant: 204 articles identified by the serology working group, 111 by the brain and brainstem working group, 125 by the optic neuritis working group, and 76 by the transverse myelitis working group (some references were reviewed by more than one group). We also did a literature review of papers published relating to MOGAD during the period of our manuscript review. From Mar 1, 2022 to Oct 20, 2022 we identified several new review papers, which we decided not to cite in our current manuscript given the depth of data we provide in our supplementary materials that address the same points. We have not included isolated case reports and series that associate MOGAD with COVID-19, given that recent COVID-19 infection is not a contributory feature for diagnostic purposes and the high rate of COVID-19 infection at the community level, which renders determination of causality to MOGAD tenuous. We identified a few manuscripts discussing therapeutic approaches (no formal clinical trials), which we also do not feel should be included given that our manuscript does not address treatment.

relapses in the first few months as compared with persistent relapses over several years. Prospective studies with predefined imaging timepoints rather than imaging obtained only with clinical symptoms are required to assess subclinical disease activity. Prompt identification of patients with MOGAD destined for a chronic clinically relapsing disease course would expedite initiation of chronic immunomodulatory therapy, whereas expedited identification of patients likely to experience monophasic illness would avoid unnecessary immunosuppression. Enrolment in clinical trials of patients with MOGAD destined for monophasic disease would not only expose such patients to unnecessary immunosuppression, but also reduce the power to detect effective disease suppression for patients with chronic relapsing disease.

Serum and CSF cytokines, especially interleukin 6 (IL-6), and other biomarkers such as myelin basic protein, microtubule associated protein, tau, glial fibrillary acidic protein, and neurofilament light-chain might provide insight into MOGAD pathogenesis and severity; further studies are needed.[108–111] Specifically, given that elevated CSF IL-6 led to clinical trials and subsequent approval of anti-IL-6 receptor therapies for AQP4-IgG-seropositive NMOSD, confirmation of IL-6 elevation in the CSF of individuals with MOGAD has the potential to inform future therapies. MOGAD is a demyelinating disease, and thus elevations of myelin basic protein, rather than glial acid fibrillary protein (which is elevated in AQP4-IgG- seropositive NMOSD, an astrocytopathy) provides biological insight into disease-relevant tissue damage, whereas neurofilament-light chain concentrations might provide a more general index of disease severity irrespective of the cause.

MOGAD is conceptualised as a disorder driven by attack-specific clinical deficits and by the risk for stepwise (relapse-mediated) neurological impairments. An important challenge is the ability to quantify MOGAD-related neurological impairment. Permanent increase in disability might relate to relapse-mediated injury without recovery, as is seen in patients with AQP4-IgG-seropositive NMOSD. The progressive neurological deterioration that drives worsening disability independent of relapses in patients with multiple sclerosis does not appear to be operative in MOGAD. Patients with MOGAD do not seem to harbour the smouldering lesions that are associated with progressive neurological decline in multiple sclerosis.[7] Furthermore, pathological studies on animal models of demyelination mediated by MOG-IgG highlight that MOG protein is not expressed by oligodendrocyte precursor cells, which might be relevant for remyelination in patients with MOGAD.[11]

Tools that quantify visual impairment would be valuable in MOGAD, given the predilection for the optic nerve. The opticospinal impairment scale might prove useful in this regard.[112] Prospective longitudinal OCT studies might further inform our understanding of the effect of MOGAD on the optic pathway and differences between MOGAD, multiple sclerosis, and AQP4-IgG-seropositive NMOSD.[113]

In conclusion, we propose international expert consensus criteria for the diagnosis of MOGAD, with the intention that MOGAD will be identified as a distinct disease from AQP4-IgG-seropositive NMOSD and multiple sclerosis. We advocate testing for MOG-IgG in appropriate populations, and we caution against the testing of patients with clinical and radiological features typical of multiple sclerosis. We hope that these proposed criteria, when validated, will assist in optimising the design of clinical trials evaluating emerging new therapies and in developing targeted treatment and improved outcomes for patients with MOGAD.

Contributors

BB, JP, KF, HJK, JLB, FP, KR, RM, and SJP were members of the steering group. BB, JP, and KF drafted panel meeting agendas. BB led the Panel meetings. Panel members were all authors. BB drafted the manuscript with input from all panel members. JLB, SR, AB, KR, JSG, and FP formed the optic neuritis working group and were responsible for two supplementary tables (appendix p 2–4). JP, HJK, EPF, ST, RN, and DKS formed the transverse myelitis working group and created a supplementary table (appendix p 5). KF, RM, AS, LP, ST, BB, and CH were members of the brain and brainstem working group and were responsible for a supplementary table (appendix p 6–7). FB, PW, SJP, TC, and MR constituted the serology working group and created a supplementary figure and table (appendix pp 8–11, 17–18) and panels 1 and 2. ST designed a supplementary table (appendix pp 12–15) with input from all panel members. All panel members participated in virtual meetings and in the drafting, editing, and provision of final approval of the manuscript, figures, tables, and supplementary materials.

Declaration of interests

BB has or will potentially receive financial compensation for consultancy effort for Novartis, Roche, UCB, Horizon Therapeutics, Biogen, and Immunic Therapeutics for advice on clinical trial design. BB is funded by the National Multiple Sclerosis Society, National Institute of Health, and has been previously funded by the Canadian Multiple Sclerosis Society. JLB has received research grants from Novartis, Mallinckrodt Pharmaceuticals, Alexion, and the National Institutes of Health, license fees from a US patent (2014/0170140); consulting fees from Horizon Therapeutics, Alexion, BeiGene Chugai Pharmaceutical, Genentech, Genzyme, Mitsubishi-Tanabe Pharma, Reistone Biopharma, Roche, and AbbVie; and serves on Data Safety Monitoring Boards for Roche, Genentech, and Clene Nanomedicine. RM reports personal fees from Horizon Therapeutics, Alexion, Roche, and UCB and non-financial support from Horizon Therapeutics, Merck, Biogen, and Roche, outside the submitted work. HJK received a grant from the National Research Foundation of Korea and research support from Aprilbio and Eisai; received consultancy and speaker fees from Alexion, Aprilbio, Altos Biologics, Biogen, Celltrion, Daewoong, Eisai, GC Pharma, HanAll BioPharma, Handok, Horizon Therapeutics (formerly Viela Bio), Kolon Life Science, Mdimune, Merck Serono, Mitsubishi Tanabe Pharma, Novartis, Roche, Sanofi Genzyme, Teva-Handok, and UCB; and is a co-editor for the *Multiple Sclerosis Journal* and an associated editor for the *Journal of Clinical Neurology*. FB has received research funding from the National Health and Medical Research Council (Australia), Multiple Sclerosis Research Australia, New South Wales Health, Novartis, and the University of Sydney (Sydney, NSW, Australia). She has received speaker honoraria from Novartis, Biogen, Merck, and Limbic Neurology, and has been on advisory boards for Merck and Novartis. She works at the University of Sydney and at the Children's Hospital at Westmead, Westmead, New South Wales, Australia, which offers MOG-IgG testing. EPF has served on advisory boards for Alexion, Genentech, and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times and royalties from UpToDate for a topic on MOGAD. He was a site primary investigator in a randomised clinical trial on inebilizumab in neuromyelitis optica spectrum disorder run by Horizon Therapeutics. He is principal investigator on an RO1 on MOG-IgG disease. He works at Mayo Clinic, Rochester, MN,USA, which offers commercial MOG-IgG testing but he receives no royalties from such testing. SR has received research funding from the National Health and Medical Research Council (Australia), the Brain Foundation (Australia), the Royal Australasian College of Physicians, and the University of Sydney. She was supported by an National Health and Medicine Research Council Neil Hamilton Fairley Early Career Fellowship (APP1141169) and is currently supported by an NHMRC Emerging Leadership (EL2) Investigator Grant (APP2008339). She serves as a consultant on an advisory board for UCB and Limbic Neurology, and has been an invited speaker for Biogen, Limbic Neurology, and Excemed. PW has received research grants from Euroimmun AG, Commonwealth Serum Laboratories Behring and patent royalties for antibody testing (W02010046716A1). He is the co-director of the Oxford Autoimmune Neurology Diagnostic Laboratory (Oxford University, Oxford, UK) where MOG-IgG1 autoantibodies are tested and both he and the University of Oxford receive royalties (for antibody tests for LG11 and CASPR2, W02010046716A1). He has received honoraria or consulting fees from Biogen Idec, F Hoffmann La-Roche, Mereo BioPharma, Retrogenix, UBC, Euroimmun AG, University of British Columbia, and Alexion; and travel grants from the Guthy-Jackson Charitable Foundation. Work in the Oxford Autoimmune Neurology Diagnostic Laboratory is supported by the UK National Health Service Commissioning service for NMOSD. ST has received speaker and consulting fees from Biogen-Idec Argentina, Merck SA, Genzyme-Sanofi, Roche, Novartis Argentina, and Novartis Pharma. She serves as a consultant on an advisory board for Genentech-Roche. and Alexion Pharmaceuticals. JSG has grant or contract research support from the National Multiple Sclerosis Society, Biogen, and Octave Biosciences for work unrelated to the present project. She serves on a steering committee for a trial supported by Novartis. She has received speaker fees from Alexion and Bristol Myers Squibb, and served on an advisory board for Genentech. TC has received compensation for consulting from Biogen, Novartis Pharmaceuticals, Roche, Genentech, and Sanofi Genzyme. She has received research support from the National Institutes of Health, National Multiple Sclerosis Society, US Department of Defense, EMD Serono, Guthy-Jackson Charitable Foundation, I-Mab Biopharma, Mallinckrodt Pharmaceuticals, Novartis, Octave Bioscience, Roche Genentech, The Sumaira Foundation, and Tiziana Life Sciences. AUB has received grant support from Moore Foundation, Clinical and Trnaslational Awards Program, German Federal Ministry of Education and Research (BMBF). He has been named as inventor on several patents and patent applications describing multiple sclerosis serological biomarkers, drug targets for remyelination therapy, marker-less motor function analysis, and retinal image analysis methods. He serves on the Observational Study Monitoring Board for CAVS-MS. He is cofounder, board member, and currently serving as secretary treasurer of IMSVISUAL. He is cofounder and holds stocks of technology startups Motognosis GmbH and Nocturne GmbH. Motognosis GmbH develops and sells systems for assessing motor dysfunction in patients with neurological disorders. Nocturne GmbH offers analysis services for retinal optical coherence tomography. Both companies' products and services are relevant for neurology in general, but not specific to MOGAD. CH reports grant support from the Medical Research Council, Multiple Sclerosis Society, and Vasculitis UK. She serves as a consultant to Novartis, Biogen, Roche, UCB, Viela Bio, and Sanofi. She participated on an independent data safety monitoring board for the Wellcome Trust. RN reports grant support from Multiple Sclerosis Research Foundation (Netherlands). He has participated on a data safety monitoring board or advisory board for EXCEL study (neurofibromatosis). He is board member of the Dutch Pediatric Neurology Society. LP has received speaker honoraria and travel grants from Biogen, and has consulted for Biogen, Novartis, and Sanofi. Her university holds a patent for her invention: Live cell based assay for detection of autoantibodies for NMOSD and related disorders (Indian patent number 202141055841). MR is supported by research grants from the Austrian Science Fund (FWF project P32699), the Austrian Research Promotion Agency, Euroimmun, and Roche, and consulting fees and advisory board from Roche (to institution). MR works at the Clinical Department of the Medical University of Innsbruck (Innsbruck, Austria), which offers diagnostic testing for MOG-IgG and other autoantibodies. AS received personal compensation for consulting, serving on a scientific advisory board, speaking activities with Merck, Sanofi, Biogen, Roche, TEVA Pharmaceuticals, Novartis, Alexion, and Janssen. 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He has two patents issued (8889102; application 12-678350; Neuromyelitis Optica Autoantibodies as a Marker for Neoplasia; and 9891219B2; application 12-573942; Methods for Treating Neuromyelitis Optica [NMO] by Administration of Eculizumab to an individual that is Aquaporin-4 [AQP4]-IgG Autoantibody positive). SJP also has patents pending for IgGs to the

following proteins as biomarkers of autoimmune neurological disorders: septin-5, kelch-like protein 11, GFAP, PDE10A, and MAP1B. He works at Mayo Clinic, which offers commercial MOG-IgG testing. He receives no royalties from the sale of tests done at the neuroimmunology Laboratory at Mayo Clinic. KF serves as an advisor or on scientific advisory boards for Biogen, Mitsubishi Tanabe, Novartis, Chugai, Roche, Alexion, VielaBio/Horizon Therapeutics, UCB, Merck Biopharma, Japan Tobacco and Abbvie; has received funding for travel and speaker honoraria from Biogen, Eisai, Mitsubishi Tanabe, Novartis, Chugai, Roche, Alexion, VielaBio, Teijin, Asahi Kasei Medical, Merck, and Takeda; and has received the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Grants-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan. JP has received consulting fees from Merck, Novartis, Roche, Mitsubishi Tnabe Pharma, UCB, Alexion, Vitaccess, and Argenx, and MRI support from Medimmune, Merck, and Roche. She has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Merck, VielaBio, Roche and Alexion. She has participated on a data safety monitoring board or advisory board for Novartis, Roche, Argenx, UCB, Alexion, and Sanofi. She is member of the Charcot Foundation Board, Magnetic Resonance in Multiple Sclerosis steering committee, and National Health Service England Intravenous Immune Globulin Committee. She holds stock for AstraZeneca for a product that is not related to MOG-antibody associated disease. She has a patent for Diagnosing Multiple Sclerosis (application no PCT/GB2013/050285, final patent number 13704627.2–1408; client reference 4440; MS reference P37347WO; patent published Sept 13, 2021).

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