MOG encephalomyelitis

International recommendations on diagnosis and antibody testing

Jarius, S.; Paul, F.; Aktas, O.; Asgari, N.; Dale, R. C.; de Seze, J.; Franciotta, D.; Fujihara, K.; Jacob, A.; Kim, H. J.; Kleiter, I.; Kümpfel, T.; Levy, M.; Palace, J.; Ruprecht, K.; Saiz, A.; Trebst, C.; Weinshenker, B. G.; Wildemann, B.

Published in:
Journal of Neuroinflammation

DOI:
10.1186/s12974-018-1144-2

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

Document license
CC BY

Citation for published version (APA):
Jarius, S., Paul, F., Aktas, O., Asgari, N., Dale, R. C., de Seze, J., ... Wildemann, B. (2018). MOG encephalomyelitis: International recommendations on diagnosis and antibody testing. Journal of Neuroinflammation, 15, [134]. https://doi.org/10.1186/s12974-018-1144-2

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 28. Apr. 2019
MOG encephalomyelitis: international recommendations on diagnosis and antibody testing

S. Jarius1*, F. Paul2,3,4, O. Aktas5, N. Asgari6, R. C. Dale7, J. de Seze8, D. Franciotta9, K. Fujihara10, A. Jacob11, H. J. Kim12, I. Kleiter13, T. Kümpfel14, M. Levy15, J. Palace16, K. Ruprecht4, A. Saiz17, C. Trebst18, B. G. Weinshenker19 and B. Wildemann1*

Abstract

Over the past few years, new-generation cell-based assays have demonstrated a robust association of autoantibodies to full-length human myelin oligodendrocyte glycoprotein (MOG-IgG) with (mostly recurrent) optic neuritis, myelitis and brainstem encephalitis, as well as with acute disseminated encephalomyelitis (ADEM)-like presentations. Most experts now consider MOG-IgG-associated encephalomyelitis (MOG-EM) a disease entity in its own right, immunopathogenetically distinct from both classic multiple sclerosis (MS) and aquaporin-4 (AQP4)-IgG-positive neuromyelitis optica spectrum disorders (NMOSD). Owing to a substantial overlap in clinicoradiological presentation, MOG-EM was often unwittingly misdiagnosed as MS in the past. Accordingly, increasing numbers of patients with suspected or established MS are currently being tested for MOG-IgG. However, screening of large unselected cohorts for rare biomarkers can significantly reduce the positive predictive value of a test. To lessen the hazard of overdiagnosing MOG-EM, which may lead to inappropriate treatment, more selective criteria for MOG-IgG testing are urgently needed. In this paper, we propose indications for MOG-IgG testing based on expert consensus. In addition, we give a list of conditions atypical for MOG-EM (“red flags”) that should prompt physicians to challenge a positive MOG-IgG test result. Finally, we provide recommendations regarding assay methodology, specimen sampling and data interpretation.

Keywords: Myelin oligodendrocyte glycoprotein (MOG) antibodies, Consensus recommendations, Diagnosis, Antibody testing, Multiple sclerosis (MS), Neuromyelitis optica spectrum disorders (NMOSD), Optic neuritis (ON), Myelitis

Background

Over the past few years, the role of immunoglobulin G serum antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) in patients with inflammatory CNS demyelination has been revisited. While antibodies to MOG were originally thought to be involved in multiple sclerosis (MS), based on results from enzyme-linked immunosorbent assays employing linearized or denatured MOG peptides as antigen, more recent studies using new-generation cell-based assays have demonstrated a robust association of antibodies to full-length, conformationally intact human MOG protein with (mostly recurrent) optic neuritis (ON), myelitis and brainstem encephalitis, as well as with acute disseminated encephalomyelitis (ADEM)-like presentations, rather than with classic MS [1–11].

Based on evidence from (a) immunological studies suggesting a direct pathogenic impact of MOG-IgG, (b) neuropathological studies demonstrating discrete histopathological features, (c) serological studies reporting a lack of aquaporin-4 (AQP4)-IgG in almost all MOG-IgG-positive patients, and (d) cohort studies suggesting differences in clinical and paraclinical presentation, treatment response and prognosis, MOG-IgG is now considered to denote a disease entity in its own right, distinct from classic MS and from AQP4-IgG-positive neuromyelitis optica spectrum disorders (NMOSD), which is now often referred to as MOG-IgG-associated encephalomyelitis (MOG-EM) [11–13].
Importantly, however, MOG-EM and MS show a relevant phenotypic, i.e., clinical as well as radiological, overlap [3, 14]; like MS, MOG-EM follows a relapsing course in most cases [3, 6], at least in adults, and 33 and 15% of adult patients with MOG-EM meet McDonald's and Barkhof’s criteria for MS, respectively, at least once over the course of disease [3, 14]. Accordingly, many patients with MOG-EM were falsely classified as having MS in the past [3, 4]. However, such misclassification has potential therapeutic implications: (a) similar to what has been observed in AQP4-IgG-positive NMOSD, some drugs approved for MS might be ineffective or even harmful in MOG-EM owing to differences in immunopathogenesis [3, 4, 15–17]; (b) MOG-EM is associated with a high risk of flare-ups after cessation of steroid treatment for acute attacks and may thus require close monitoring and careful steroid tapering [3, 18–22]; and (c) patients positive for MOG-IgG might be particularly responsive to antibody-depleting treatments for acute attacks such as plasma exchange or immunoadsorption [3, 4, 9, 14, 23, 24], to B cell-targeted long-term therapies such as rituximab, to treatment with intravenous immunoglobulins (IVIG) (especially in children [25]), and to immunosuppressive treatments [3, 6, 14, 25, 26]. Therefore, increasing numbers of patients with suspected or established MS are currently being screened for MOG-IgG.

However, screening of large unselected populations for rare biomarkers generally decreases the positive predictive value of diagnostic tests by increasing the rate of false-positive results [27, 28]. Even if assays with high specificity (≥99%) are used, true-positive (TP) results can easily be outnumbered by false-positive (FP) results if the prevalence of a marker is low and the number of samples tested is high. This also applies to MOG-IgG testing. Based on a hypothetical prevalence of 1% genuinely MOG-IgG-positive cases among all patients currently diagnosed with MS, testing of 100,000 patients with an almost flawless, 99% specific and 100% sensitive assay would result in an unacceptable ratio of 990 FP results to 1000 TP results. Therefore, unscreened testing of all patients with suspected or established MS for MOG-IgG should be discouraged and more specific criteria for MOG-IgG testing are urgently needed.

In this paper, we propose for the first time indications for MOG-IgG testing based on expert consensus. In addition, we give a list of conditions considered atypical for MOG-EM (“red flags”) that should prompt physicians to challenge the validity of a positive MOG-IgG test result. Finally, we provide recommendations regarding assay methodology, specimen sampling, and data interpretation.

**Methods**

PubMed was searched for articles published between February 2007 and February 2017 using the following search term: ("myelin oligodendrocyte glycoprotein" OR MOG) AND (antibody OR antibodies OR IgG). All articles identified by this means were reviewed by a core group of physicians (S.J., B.W., F.P., K.R.) for clinical and paraclinical findings that have been frequently reported in association with MOG-IgG seropositivity in patients with CNS demyelination and which, therefore, may justify MOG-IgG testing, as well as for potential “red flags”, i.e., conditions that are typically found in inflammatory disorders of the CNS but have been reported to be absent or very rare in MOG-IgG-positive patients and thus may indicate diagnoses other than MOG-EM. Based on core group consensus, a first set of recommendations was formulated and then circulated to a broader panel of experts in the field from Australia, Denmark, France, Germany, Italy, Japan, South Korea, Spain, UK, and the USA for discussion and refinement. Panel members were invited by the core group based on eminence and previous contributions to the field. Based on several rounds of core group-led peer-to-peer discussions of the individual recommendations with all individual members of the panel, a final set of evidence- as well as eminence-based recommendations was drawn up to which all members gave their approval. All recommendations given here should be considered as expert consensus.

**Recommendations on MOG-IgG testing**

In Table 1, we propose indications for MOG-IgG testing based on clinical and paraclinical findings that are typical of MOG-EM and/or atypical for MS and were considered by the panel members to be associated with pre-test odds high enough to justify MOG-IgG testing or that demand MOG-IgG testing because of potentially significant therapeutic consequences of a positive test result according to expert consensus. These recommendations apply to all patients with suspected CNS demyelination of putative autoimmune etiology and an either monophasic or relapsing disease course. Given the very low pre-test probability [29], we recommend against general MOG-IgG testing in patients with a progressive disease course. In Table 2, we give a number of case vignettes of patients considered to be at high risk of MOG-EM to illustrate the broad spectrum of symptoms associated with that syndrome and the practical feasibility and relevance of the proposed criteria. In Table 3, we give a number of recommendations regarding assay selection, specimen sampling, and data interpretation. Finally, Table 4 lists conditions (“red flags”) that we believe are atypical for MOG-EM and should thus prompt physicians to challenge a positive MOG-IgG test result and seek a better explanation for the patients’ clinical and paraclinical findings.

In practice, many patients diagnosed with AQP4-IgG-negative NMOSD according to the IPND 2015 criteria...
Table 1 Recommended indications for MOG-IgG testing in patients presenting with acute CNS demyelinization of putative autoimmune etiology

1. Monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, encephalitis, or any combination thereof,
and
2. Radiological or, only in patients with a history of optic neuritis, electrophysiological (VEP) findings compatible with CNS demyelination, and
3. At least one of the following findings:

MRI:
- a. Longitudinally extensive spinal cord lesion (≥3 VS, contiguous) on MRI (so-called LETM)\(^b\)
- b. Longitudinally extensive spinal cord atrophy (≥3 VS, contiguous) on MRI in patients with a history compatible with acute myelitis\(^a\)
- c. Conus medullaris lesions, especially if present at onset\(^c\)
- d. Longitudinally extensive optic nerve lesion (e.g., >1/2 of the length of the pre-chiasmal optic nerve, T2 or T1/Gd)\(^d\)
- e. Perioptic Gd enhancement during acute ON\(^f\)
- f. Normal supratentorial MRI in patients with acute ON, myelitis and/or brainstem encephalitis
- g. Brain MRI abnormal but no lesion adjacent to a lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion and no Dawson’s finger-like or juxtaocular U fiber lesion (Matthews-Jurynczuk criteria\(^i\))
- h. Large, confluent T2 brain lesions suggestive of ADEM

Fundoscopy:
- i. Prominent papilledema/papillitis/optic disc swelling during acute ON

CSF:
- j. Neutrophilic CSF pleocytosis\(^j\) or CSF WCC > 50/\(μl\)\(^n\)
- k. No CSF-restricted OCB as detected by IEF at first or any follow-up examination\(^p\) (applies to continental European patients only)

Histopathology:
- l. Primary demyelination with intralesional complement and IgG deposits

m. Previous diagnosis of “pattern II MS”\(^j\)

Clinical findings:
- n. Simultaneous bilateral acute ON
- o. Unusually high ON frequency or disease mainly characterized by recurrent ON
- p. Particularly severe or frequent episodes of acute myelitis or brainstem encephalitis
- q. Permanent sphincter and/or erectile disorder after myelitis
- r. Patients diagnosed with “ADEM,” “recurrent ADEM,” “multiphasic ADEM”\(^a\), or “ADEM-ON”
- s. Acute respiratory insufficiency, disturbance of consciousness, behavioral changes, or epileptic seizures (radiological signs of demyelination required)
- t. Disease started within 4 days to ~4 weeks after vaccination
- u. Otherwise unexplained intractable nausea and vomiting or intractable hiccups (compatible with area postrema syndrome)\(^a\)
- v. Co-existing teratoma and NMDAR encephalitis (low evidence)\(^a\)

Treatment
- x. Frequent flare-ups after IVMP, or steroid-dependent symptoms\(^l\) (including CRION)
- y. Clear increase in relapse rate following treatment with IFN-beta or natalizumab in patients with MS (low evidence)

Note that these recommendations are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in young children need not to be as rigorous as in adults, since MOG-EM is thought to be significantly more frequent among young children with acquired demyelinating disease (up to 70%; frequency declining with age) than among their adult counterparts (≤1% in Western countries; probably ≤5% in Japan and other Asian countries because of lower MS prevalence), which reduces as the risks attached to antibody screening outlined in the Introduction.

Abbreviations: ADEM acute disseminated encephalomyelitis, ADEM-ON ADEM with recurrent ON, AQP4 aquaporin-4, CNS central nervous system, CRION chronic relapsing inflammatory optic neuropathy, CSF cerebrospinal fluid, EM encephalomyelitis, Gd gadolinium, IA immunoadsorption, IgG immunoglobulin G, IVMP intravenous methylprednisolone, LE left eye, LETM longitudinally extensive transverse myelitis, MOG myelin oligodendrocyte glycoprotein, MRI magnetic resonance imaging, MS multiple sclerosis, NMDAR N-methyl-D-aspartate receptor, NMO neuromyelitis optica, OCB oligoclonal IgG bands, ON optic neuritis, PEX plasma exchange, RE right eye, RMS relapsing-remitting MS, VEP visual evoked potentials, VS vertebral segments, WCC white cell count

*If costs play a role and disease is stable: test AQP4-IgG and MOG-IgG in parallel
\(^b\)LETM is common both in MOG-EM and in AQP4-NMOSD, but rarely if ever occurs in MS; as a caveat, however, non-contiguous lesions may mimic LETM in some patients with MS. N.B.: Short lesions do not per se exclude MOG-EM. MRI shows short lesions at least once over the disease course in around 44–52% of all MOG-EM patients [3, 39] and around 15% of all AQP4-NMOSD patients [40]. Lesion length may also depend on MRI timing issues, with shorter lesions detected if costs play no role: test AQP4-IgG and MOG-IgG in parallel

\(^c\)Note that these recommendations are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in young children need not to be as rigorous as in adults, since MOG-EM is thought to be significantly more frequent among young children with acquired demyelinating disease (up to 70%; frequency declining with age) than among their adult counterparts (≤1% in Western countries; probably ≤5% in Japan and other Asian countries because of lower MS prevalence), which reduces as the risks attached to antibody screening outlined in the Introduction.

**Clinical findings**
- a. Longitudinally extensive spinal cord lesion (≥3 VS, contiguous) on MRI in patients with a history compatible with acute myelitis
- b. Longitudinally extensive spinal cord atrophy (≥3 VS, contiguous) on MRI in patients with a history compatible with acute myelitis
- c. Conus medullaris lesions, especially if present at onset
- d. Longitudinally extensive optic nerve lesion (e.g., >1/2 of the length of the pre-chiasmal optic nerve, T2 or T1/Gd)
- e. Perioptic Gd enhancement during acute ON
- f. Normal supratentorial MRI in patients with acute ON, myelitis and/or brainstem encephalitis
- g. Brain MRI abnormal but no lesion adjacent to a lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion and no Dawson’s finger-like or juxtaocular U fiber lesion (Matthews-Jurynczuk criteria)
- h. Large, confluent T2 brain lesions suggestive of ADEM

**Fundoscopy**
- i. Prominent papilledema/papillitis/optic disc swelling during acute ON

**CSF**
- j. Neutrophilic CSF pleocytosis or CSF WCC > 50/μl
- k. No CSF-restricted OCB as detected by IEF at first or any follow-up examination (applies to continental European patients only)

**Histopathology**
- l. Primary demyelination with intralesional complement and IgG deposits

**Clinical findings**
- m. Previous diagnosis of “pattern II MS”

**Treatment**
- n. Frequent flare-ups after IVMP, or steroid-dependent symptoms (including CRION)
- o. Clear increase in relapse rate following treatment with IFN-beta or natalizumab in patients with MS (low evidence)
Table 1 (Continued)

1Positive in ≥ 90% of RRMS patients [37, 36, 50]. By contrast, ovoid/round lesions adjacent to a lateral ventricle, lesions adjacent to a lateral ventricle in association with a temporal lobe lesion, and Dawson’s finger-type lesions were absent in 21/21 (100%) MOG-IgG-positive patients in a mixed adult (n = 15) and pediatric (n = 6) cohort [36, 37] and juxtacortical U fiber lesions in 20/21 (95.2%). Recently, a lack of Dawson’s finger-type lesions in MOG-IgG-positive patients has been confirmed in an exclusively pediatric cohort (absent in 68/69 [98.6%]; the only patient positive for Dawson’s finger lesions had typical MS and was negative for MOG-IgG at re-testing); U fiber lesions were absent in 65/69 (94.2%) MOG-IgG-positive pediatric patients in the same study [41].

2Present at least once in 64% of patients with pleocytosis [3] (median 22% of all white cells; range 3–69%) but typically absent in MS. N.B.: Neutrophilic pleocytosis is also frequently found in AQP4-IgG-negative NMOSD [51].

3Observed in 43% (14/36) of MOG-IgG-positive patients with pleocytosis (peak values) [3], but only rarely in patients with MS (≤ 2% according to [52]): 1/71 patient ≥ 15 years of age (range 15–29) in [53].

4Oligoclonal bands (OCB) have been reported in up to 98% of patients with MS in central and Northern Europe [53] but only in around 12–13% of patients with MOG-EM in two recent Central European studies [3, 54].

5These criteria (e.g., patients with recurrent bilateral non-longitudinal ON without chiasm involvement plus non-NMOSD-typical brain lesions, those with severe and recurrent non-longitudinal extensive myelitis, and those with ADEM-like presentation with severe brain and brainstem involvement but no area postrema lesion) [61].

6Recent, though preliminary, reports suggest that MOG-EM and NMDAR encephalitis may occasionally co-exist [61] or may be misdiagnosed with another condition. Additional testing for NMDAR antibodies is highly recommended in patients with teratoma and neurological symptoms [80].

Table 2 Casen vignettes of patients at risk of MOG-IgG seropositivity (examples)

Example 1: 35-year-old woman presenting with bilateral acute ON. Develops transient blindness; fundoscopy shows papillodema; lumbar puncture reveals lymphomonocytic pleocytosis with 10% neutrophils and negative OCBs; brain MRI shows perioptic Gd enhancement but is otherwise normal; flaring up of symptoms after tapering of oral steroids; later recurrent ON attacks, stabilization with rituximab.

Example 2: 40-year-old woman with two attacks of acute, OCB-negative myelitis. Spine MRI shows an isolated short spinal cord lesion at first attack and abnormal but no Dawson’s finger-type lesion, no juxtacortical U fibre lesion, and no lesion adjacent to a lateral ventricle that is ovoid or associated with an inferior temporal lobe lesion [36, 37, 50]; flaring up of myelitis symptoms after discontinuation of intravenous steroid treatment, good response to PEX.

Example 3: Young man with a previous diagnosis of ‘OCB-negative RRMS’. Predominantly ON and myelitis attacks; conus with severe erectile and sphincter disturbance after first myelitis; longitudinally extensive optic nerve lesion with involvement of the optic chiasm; increase in relapse rate under treatment with interferon-beta but stabilization with rituximab.

Example 4: 42-year-old woman presenting with incomplete, painful tetraparesis. Previous diagnosis of RRMS with positive OCB; spinal cord MRI reveals a contiguous lesion extending from C3 to T1; negative serology for AQP4-IgG.

Example 5: ADEM-like presentation with large white matter lesions and disturbance of consciousness, brainstem lesions, and involvement of the entire spinal cord in a 25-year-old woman; onset 3 weeks after vaccination.

Example 6: Simultaneous unilateral ON and LETM extending into the brainstem in a 39-year-old man. CSF pleocytosis (90 white cells/μL) with 5% neutrophils; no CSF–restricted OCB; negative AQP4-IgG serostatus.

Example 7: Young woman presenting with recurrent and steroid-dependent isolated ON, previously classified as CRION; normal brain MRI.

Example 8: Young man with acute encephalitis and seizures. MRI reveals large cortical/subcortical white matter lesions not involving the inferior temporal lobe; good response to steroids; negative for typical viral and autoimmune causes of encephalitis.

Abbreviations: ADEM acute disseminated encephalomyelitis, AQP4 aquaporin-4, CRION chronic relapsing inflammatory optic neuropathy, CSF cerebrospinal fluid, EM encephalomyelitis, Gd gadolinium, IgG immunoglobulin G, LETM longitudinally extensive transverse myelitis, MOG myelin oligodendrocyte glycoprotein, MRI magnetic resonance tomography, MS multiple sclerosis, ON optic neuritis, RRMS relapsing-remitting MS.
negative test for MOG-IgG would be a prerequisite for MOG-IgG testing. (5) Finally, but less importantly, using NMOSD criteria for diagnosing MOG-EM would, in addition to resulting in a substantial loss in sensitivity and specificity, also be confusing to non-experts, given that AQP4-IgG-positive NMOSD and MOG-EM are distinct diseases with different target antigens (AQP4 vs. MOG), pathophysiology (astrocytopathy vs. primary demyelination), and clinical spectra.

Alternatively, should we restrict MOG-IgG testing to patients with AQP4-IgG-negative NMO according to Wingerchuk’s 2006 criteria [31]? This would again result in a substantial loss of patients at high risk of MOG-EM, since those criteria require a history of both ON and myelitis and would thus be inappropriate. Of note, MOG-IgG testing in patients with seronegative NMO according to the 2006 criteria is already covered by our recommendation to test all patients with LETM for MOG-IgG (see Table 1), since the 2006 criteria strictly require a history of LETM in patients negative for AQP4-IgG.

Instead, we propose to base the indication for MOG-IgG testing in patients with suspected CNS demyelination on the presence of specific clinical and paraclinical findings that are considered typical for MOG-EM and/or atypical for conventional MS (see Table 1). During the consensus-finding process, concerns were raised regarding inclusion of the following treatment-related indications for MOG-IgG testing in Table 1:
a. Particularly good response to antibody-depleting therapies (plasma exchange [PEX], immunoadsorption [IA])
b. Particularly good response to B cell-depleting therapies (rituximab, ocrelizumab, ofatumumab) but relapse immediately after re-occurrence of B cells

It was argued by some members of the panel that good responses to PEX, IA, or B cell depletion have also been observed in conventional MS. However, consensus was achieved that if present in addition to any of the indications listed in Table 1, good response to antibody or B cell-depleting treatments or IVIG further increases the pre-test likelihood of MOG-EM and thus supports the decision to test for MOG-IgG.

Taking into account that MOG-IgG serum concentrations depend on disease activity (with higher concentrations during acute attacks) and treatment status (with lower concentrations while on immunosuppression) as well as on assay sensitivity, we recommend re-testing patients during acute attacks or during treatment-free intervals and/or in a second cell-based assay if MOG-IgG was negative at first examination but MOG-EM is still suspected based on the list of indications given in Table 1 [3].

Only sparse data are available on the usefulness of regular monitoring of antibody titers in individual patients known to be positive for MOG-IgG. Median MOG-IgG titers have indeed been shown to be significantly higher during relapse than during remission [2], making regular MOG-IgG testing a potentially promising method for predicting attacks and monitoring treatment efficacy. However, there are several limitations: While titers > 1:2560 were found only during acute attacks in a recent study using a live cell-based assay [2], some patients still had relatively low titers during acute attacks and others had relatively high titers during remission, suggesting that additional factors such as blood–CSF barrier damage, T cell activation, antibody affinity, or complement-activating activity may be involved, with no general cut-off value for relapse induction [2]. In addition, treatment effects could

Table 4 “Red flags”: conditions that should prompt physicians to challenge a positive test result (consider re-testing the patient, ideally using an alternative, i.e., methodologically different cell-based assay; in case of doubt, consider seeking expert advice from a specialized center)

| Disease course | MRI | CSF | Serology | Others |
|----------------|------|------|----------|--------|
| Chronic progressive disease (very rare in MOG-IgG-positive patients [3]), including SPMS (especially SPMS without relapses) and PPMS<sup>a</sup> | Lesion adjacent to a lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion, or Dawson’s finger-type lesion | Bi- or trispecific MRZ reaction<sup>b</sup> (consider MS) | MOG-IgG levels at or just barely above the assay-specific cut-off<sup>c</sup>, especially (but not exclusively) if clinical picture is atypical | Clinical or paraclinical findings suggesting diagnoses other than MOG-EM, NMOSD or MS (e.g., neurotuberculosis, neuroborreliosis, neurophthils, neuromyelitis optica, Behçet syndrome, Babesiosis, subacute combined degeneration of the spinal cord, Leber’s hereditary optic neuropathy, vasculitis, CNS lymphoma, glialoma or glioblastoma cerebri, paraneoplastic neurological disorders<sup>d</sup>, PRES, PML, and evidence for CNS infection<sup>e</sup>) |
| Sudden onset of symptoms, e.g., < 4 h from onset to maximum (consider ischemic cause), or continuous worsening of symptoms over weeks (consider tumor, sarcoidosis, etc.) | Active brain MRI over time with silent increase in lesion burden between relapses (limited evidence) | Positive MOG-IgM and/or MOG-IgA result with negative MOG-IgG (clinical significance unknown) | MOG-IgG positivity in the CSF but not in the serum<sup>d</sup> (MOG-IgG is typically produced extrathecally) | Combined central and peripheral demyelination<sup>f</sup> (MOG is not expressed in the peripheral nervous system)<sup>g</sup> |

Notes:
- Just one borderline MOG-IgG result found among 290 patients with PPMS (<i>n</i> = 174) or SPMS (<i>n</i> = 116) in a recent study [29].
- Measles (M), rubella (R), and zoster (Z) reaction: Intrathecal synthesis against at least two of these three viral agents (i.e., against M + R, M + Z, R + Z, or M + R + Z); part of the polyspecific, intrathalamic humoral immune reaction in MS; present in around 70% of MS patients but not at all, or only very rarely, in MOG- or AQP4-IgG-positive patients (MOG-EM: 0/11; NMO: 1/42; “ADEM”: 1/26) [3, 70, 71].
- Except in patients who were previously positive at levels clearly above the cut-off, in which case low-titer results may reflect true (spontaneous or treatment-related) decline in antibody levels.
- May be valid in the rare instances in which co-existing serum autoantibodies hamper serum analysis but not CSF analysis (false-negative serum test).
- If confirmed in a second assay and IPND criteria for NMOSD are met, co-existence of MOG-EM and AQP4-NMOSD must be assumed.
- Note, however, that preliminary reports suggest occasional co-incidence of MOG-EM and NMDAR encephalitis [61]; in such patients teratoma needs to be excluded [60].
- Note that CSF findings in MOG-EM (as well as in AQP4-NMOSD) may mimic CNS infection with neutrophil pleocytosis, impaired blood-CSF barrier function, and a lack of CSF-restricted oligoclonal bands [3, 40, 51]. White cell counts in MOG-EM ranged between 6 and 306 cells/µl (median 33; quartile range 13–125) in a recent European study [2]; WCC ≥ 100 cells/µl were present at least once in 9/32 (28.1%) patients; neutrophil granulocytes were present at least once in 9/14 (64.3%) patients with pleocytosis and available data (median 22% of all white cells; range 3–69%).

Abbreviations: ADEM, acute disseminated encephalomyelitis; EM, encephalomyelitis; Ig, immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; MRZ, measles, rubella and zoster virus; MS, multiple sclerosis; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; PPMS, secondary progressive MS; SPMS, secondary progressive MS; WCC, white cell count.

<sup>a</sup>May be true positive in the rare cases in which MOG-EM and unrelated peripheral neuropathy of other cause co-exist.
play a role. Finally, intervals sufficient to detect imminent attacks in time have not yet been defined. Based on experience from studies on AQP4-IgG-positive NMOSD, in which serum antibody levels rise only very shortly before an attack [32], very close testing intervals may be required, which would make monitoring both expensive and challenging from a practical point of view. Accordingly, no general recommendation for regular monitoring of MOG-IgG titers for relapse prediction or treatment monitoring can currently be made.

Of note, some patients have been reported in whom MOG-IgG disappeared over time [2, 33–35]. Interestingly, many of these patients had monophasic disease. By contrast, MOG-IgG was detectable at the last follow-up in all patients (n = 18) with a relapsing disease course and available follow-up samples (mean interval 33 months since first testing; maximum follow-up period 10 years) in a recent study [2]. Disappearance of MOG-IgG after the initial attack might thus have prognostic implications, and re-testing of MOG-IgG-positive patients 6–12 months after the first attack might therefore be useful. However, there are some limitations: Most of the reported monophasic patients were children or juveniles, and most had ADEM. Moreover, no long-term data were provided for most cases. This is important, since titers may fall below cut-off temporarily following treatment with steroids, plasma exchange, or immunosuppressants (or even spontaneously) and rise again at a later disease stage; accordingly, (transient) seroconversion has also been observed in a few patients with relapsing disease [2, 14, 33]. It would therefore be challenging to base long-term treatment decisions solely on whether MOG-IgG disappears or not after a first attack. If long-term treatment with immunosuppressants or oral steroids is abandoned because of conversion to seronegativity, close monitoring of the patient’s MOG-IgG serostatus is highly recommended to confirm seronegativity in the long-term course. Before making a diagnosis of “monophasic” MOG-EM and thus a decision against long-term treatment, one should also take into account that the interval between first and second attack in relapsing MOG-EM varies considerably among patients, with the second clinical attack occurring only after an interval of several years in some cases [3].

**Diagnostic criteria for MOG-EM**

There is an unmet need for diagnostic criteria for MOG-EM. However, no specific clinical or radiological findings (except for the general requirement of a demyelinating CNS lesion) have yet been identified that are present in all MOG-IgG-positive patients and which would thus represent a diagnostic sine qua non. A lack of Dawson’s finger lesions and ovoid/round lesions on brain MRI have been proposed to be typical for MOG-EM, but this awaits confirmation in independent and larger cohorts [36, 37]. We propose that for the time being MOG-EM should be diagnosed in all patients who meet all of the following criteria:

1. Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes
2. MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination
3. Seropositivity for MOG-IgG as detected by means of a cell-based assay employing full-length human MOG as target antigen

In patients with conditions considered “red flags” as defined in Table 4 and in whom MOG-IgG has not yet been confirmed in a second (and third if necessary), methodologically different cell-based assay, a diagnosis of “possible MOG-EM” should be made, especially in the context of clinical studies and treatment trials.

**Limitations and caveats**

It is a limitation that all recommendations given here are necessarily based on expert consensus, owing to a lack of systematic and prospective studies. Moreover, as a general caveat, it should be stressed that before a diagnosis of MOG-EM is made, all available information, including clinical, radiological, electrophysiological, and laboratory data, need to be taken into account, and differential diagnoses, some of which are listed in Table 4, need to be excluded. Most of the information given in a previous consensus paper on differential diagnosis in MS [38] is also pertinent to MOG-EM. Finally, while the criteria proposed here can certainly help in identifying pediatric patients at high risk of being positive for MOG-IgG, they are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in children do not need to be as rigorous as in adults, since MOG-IgG is thought to be much more common in children with acquired demyelinating disease (up to 70% depending on age) than in their adult counterparts (≤ 1% in Western countries; probably ≤ 5% in Japan and other Asian countries because of lower MS prevalence). In consequence, the risk of an unfavorable ratio of FP to TP results outlined above is lower in children. While ADEM is the predominant clinical association in young children, in older children with MOG antibodies there is a shift towards presentation with ON, myelitis, and/or brainstem symptoms [11].

**Conclusion**

Here, we give for the first time indications for MOG-IgG testing and propose preliminary criteria for the diagnosis of MOG-EM. While we believe that our recommendations are highly timely considering the large
numbers of patients currently being tested, we are well aware that they reflect current knowledge in an evolving field and may need to be adjusted when new clinical and paraclinical data emerge and novel and optimized assays become available.

Abbreviations

ADEM: Acute disseminated encephalomyelitis; ADEM-ON: ADEM with ON; AQP4: Aquaporin-4; CNS: Central nervous system; CRION: Chronic relapsing inflammatory optic neuropathy; CSF: Cerebrospinal fluid; EM: Encephalomyelitis; Gd: Gadolinium; IA: Immunoadsorption; Iga: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IVMP: Intravenous methylprednisolone; LETM: Longitudinally extensive transverse myelitis; MDG: Myelin oligodendrocyte glycoprotein; MRI: Magnetic resonance imaging; MRZ: Measles, rubella and zoster virus; MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMO-MS: NMO spectrum disorder; OB: Optic neuritis; PEX: Plasma exchange; PML: Progressive multifocal leukoencephalopathy; PPMS: Primary progressive MS; PRES: Posterior reversible encephalopathy syndrome; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS; VEP: Visual evoked potentials; VS: Vertebral segments; WCC: White cell count

Acknowledgements

BW is grateful to the Dietmar Hopp Stiftung and to Merck Serono for funding research on MOG-IgG. AS is supported by La Marató de TV3 (20141830). We acknowledge financial support by Deutsche Forschungsgemeinschaft within the funding programme Open Access Publishing, by the Baden-Württemberg Ministry of Science, Research and the Arts and by Ruprecht-Karls-Universität Heidelberg.

Funding

The work of BW was supported by the Dietmar Hopp Foundation; Merck Serono; German Federal Ministry of Education and Research (Competence Network Multiple Sclerosis); Deutsche Forschungsgemeinschaft (funding programme Open Access Publishing); Baden-Württemberg Ministry of Science, Research and the Arts; and Ruprecht-Karls-Universität Heidelberg. The funding sources had no role in study conception or design, data collection, analysis, or interpretation, or any other aspect pertinent to the article. None of the authors has been paid to write this article by a pharmaceutical company or other agency. The corresponding authors have final responsibility for the decision to submit for publication.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Authors’ contributions

SJ and BW conceived the project. SJ collected and analyzed the data and wrote the first draft. All authors were involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Competing interests

OA has received grants by the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF) (KWKNS; for NEMOS); NationNMO FKZ 01GI1602), speaking fees and travel grants by Bayer, Biogen, Genzyme, MedImmune, Merck, Novartis, Roche, Sanofi, and Teva. DF received one honorarium for a presentation from Biogen not related to the present paper. KF serves on the advisory boards for Bayer Schering Pharma, Biogen Idec, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Alexion Pharmaceuticals, and MedImmune; has received travel funding and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Eisai Inc., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Astellas Pharma Inc., Takeda Pharmaceutical Company Limited, Asahi Kasei Medical Co., Daiichi Sankyo, and Nihon Pharmaceutical; is on the editorial board for Clinical and Experimental Neuroimmunology; is an advisory board member for Sri Lanka Journal of Neurology; and received research support from Bayer Schering Pharma, Biogen Idec: Japan, Asahi Kasei Medical, The Chemo-Sero-Therapeutic Research Institute, Teva Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Nihon Pharmaceutical, Genzyme Japan, Ministry of Education, Science and Technology of Japan, and Ministry of Health, Welfare and Labor of Japan. AI is supported by the NHS National Specialised Commissioning Group for NMO and has been a consultant for Shire, Alexion, Terumo-BCT and Chugai pharmaceuticals and has received research funding from Biogen and Alexion pharmaceuticals.

HUK has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Teva-Handok, and UCB; received a grant from the Ministry of Science, ICT & Future Planning; and accepted research funding from Genzyme, Kael-GemVax, Merck Serona, Teva-Handok, and UCB; serves on a steering committee for MedImmune; is a co-editor for the Multiple Sclerosis Journal – Experimental, Translational, and Clinical, and an associated editor for the Journal of Clinical Neurology. IK has received honoraria for consultancy or lectures and travel reimbursement from Bayer Health Care, Biogen Idec, Chugai, Novartis, Shire and Roche and grant support from Biogen Idec, Novartis, Chugai and Diamed.

TK has received travel expenses and personal compensations from Bayer Healthcare, Teva Pharma, Merck-Serono, Novartis, Sanofi Genzyme and Biogen-Idec as well as grant support from Chugai Pharma and Novartis. ML receives support from Quest Diagnostics.

JP has received support for scientific meetings and honoraria for advisory work from Merck Serono, ABIDE, Biogen Idec, Novartis, Alexion, MedImmune, Teva, Chugai Pharma and Bayer Schering, and unrestricted grants from Merck Serono, Novartis, Biogen Idec, and Bayer Schering. Grants from the MS Society, GMS, NIH and Guthy- Jackson Foundation for research studies. She runs a nationally commissioned service for neuromyelitis optica and congenital myasthenia. FP has received honoraria and research support from Alexion, Bayer, Biogen, Chugai, MerckSerono, Novartis, Genzyme, MedImmune, Shire, Teva, and serves on scientific advisory boards for Alexion, MedImmune and Novartis. He has received funding from Deutsche Forschungsgemeinschaft (DFG Exc 257), German Federal Ministry for Education and Research (Competence Network Multiple Sclerosis), Guthy Jackson Charitable Foundation, EU Framework Program 7, National Multiple Sclerosis Society of the USA. KR has received research support from the German Federal Ministry of Education and Research (BMBF/KNNS, Competence Network Multiple Sclerosis) and Novartis as well as travel grants or speaking fees from the Guthy Jackson Charitable Foundation, Bayer Healthcare, Chugai Idec, Merck Serono, sanofi-aventis/Genzyme, Teva Pharmaceuticals, and Novartis. AS is supported by La Marató de TV3 (20141830).

CT has received honoraria for consultation and expert testimony from Bayer Vital GmbH, Biogen Idec/GmbH, Genzyme GmbH and Novartis Pharmaceuticals. None of this interfered with the current report.

BGW receives royalties from RSR Ltd., Oxford University, Hospices Civil de Lyon, and MWZ Labor PD Dr. Vollmann und Kollegen GbR for a patent of NMO-IgG as a diagnostic test for NMO and related disorders. He receives personal compensation for serving as a member of an adjudication committee for clinical trials in NMO being conducted by MedImmune and Alexion pharmaceutical companies. He is a consultant for Calabrius Biosciences regarding a clinical trial for NMO. He receives personal compensation for serving on a data safety monitoring board for Novartis for clinical trials in MS.

The work of BW was supported by research grants from the Dietmar Hopp Foundation, from Merck Serono and from the German Federal Ministry of Education and Research (Competence Network Multiple Sclerosis). SJ, NA, RCD, and JDS declare that they have no competing interests.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

1Molecular Neuroimmunology Group, Department of Neurology, University Hospital Heidelberg, Im Neuenheimer Feld 350, 69120 Heidelberg, Germany.
2NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin,
and Berlin Institute of Health, Berlin, Germany. 12Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany. 13Department of Neurology, University of Southern Denmark, Odense, Denmark. 14Children’s Hospital at Westmead, University of Sydney, Sydney, Australia. 15Department of Neurology, Hôpital de Hautepierre, Strasbourg Cedex, France. 16HRCs, National Neurological Institute C. Mondino, Pavia, Italy. 17Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine, Sendai, Japan. 18The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool, UK. 19Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, South Korea. 20Department of Neurology, University of Düsseldorf, Düsseldorf, Germany. 21Institute of Clinical Neuroimmunology, Ludwig Maximilian University, Munich, Germany. 22Department of Neurology, Johns Hopkins Hospital, Cleveland, USA. 23Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK. 24Service of Neurology, Hospital Clinic, and Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Barcelona, Spain. 25Department of Neurology, Hannover Medical School, Hanover, Germany. 26Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Received: 16 January 2018 Accepted: 2 April 2018

Published online: 03 May 2018

References

1. Jarius S, Di Pauli F, Kuenz B, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. J Neuroinflammation. 2011;8:148.

2. Jarius S, Ruprecht K, Borisov N, Asgari N, Pitarokoili K, Pache F, Stich O, Beume LA, Hummert MW, 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;13:27.

3. Jarius S, Ruprecht K, Borisov N, Asgari N, Pitarokoili K, Pache F, Stich O, Beume LA, Hummert MW, 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.

4. Jarius S, Kienle R, Ruprecht K, Asgari N, Pitarokoili K, Borisov N, Stich O, Beume LA, Hummert MW, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: brainstem involvement - frequency, presentation and outcome. J Neuroinflammation. 2016;13:281.

5. Pache F, Zimmermann H, Mikolajczak J, Schumacher S, Lacheta A, Oerel FC, Bellmann-Strobl J, Jarius S, Wildemann B, Reindl M, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: allergic systemic visual damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients. J Neuroinflammation. 2016;13:282.

6. Sepulveda M, Armangue T, Martinez-Hernandez E, Arribarbe G, Sala-Valls N, Sabater L, Tejelo N, Mldagia L, Arino H, Peschl P, et al. Clinical spectrum associated with MOG autoreactivity in adults: significance of sharing rodent MOG epitopes. J Neurol. 2016;263:1349-60.

7. Kitiet J, Waters P, Woodhall M, Leite MJ, Munchson A, George J, Kuker W, Chadrat V, Vincent A, Palace J. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. JAMA Neurol. 2014;71:276-83.

8. Sato DK, Callegaro D, Lina-Peixoto MA, Waters PJ, De Haidar Jorge FM, Takahashi T, Nakashima I, Apostollos-Pereira SL, Talm N, Simen RF, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology. 2014;82:474-81.

9. Kitiet J, Woodhall M, Waters P, Leite MJ, Devenney E, Craig J, Palace J, Vincent A. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology. 2012;79:1279-73.

10. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev. 2016;15:307-24.

11. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol. 2017;30:295-301.
...