Navigating Through the Recent Diagnostic Criteria for MOGAD: Challenges and Practicalities - *Ciccarelli O, Toosy AT, Thompson A, Hacohen Y*

International criteria for the diagnosis of myelin oligodendrocyte glycoprotein associated disease (MOGAD) were published in *The Lancet Neurology* on January 24th, 2023[1]. The criteria recommend that patients with a clinical event typically associated with MOG antibody (Ab) (optic neuritis, myelitis, ADEM, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, cortical encephalitis often with seizures) and clear positive serum MOG-Ab results can be diagnosed with MOGAD. A clear positive test is defined as MOG-Ab measured by fixed cell-based assay (CBA) with a titre ≥1:100 or live CBA with a standardised method (that is a clear positive according to the individual assay cutoffs). Patients with low positive serum MOG-Ab titres can be diagnosed with MOGAD if they possess at least one supporting clinical or MRI feature. In cases of optic neuritis and myelitis, the supporting features include bilateral simultaneous optic neuritis, longitudinally extensive spinal cord or optic nerve involvement or a conus lesion. Supporting features can also be applied to patients with positive MOG-Ab results without reported titres and patients with negative serum but positive cerebrospinal fluid (CSF) MOG-Ab. These diagnostic criteria require the exclusion of alternative diagnoses, including multiple sclerosis (MS).

These new diagnostic criteria represent a key step towards unifying and standardizing the definition of MOGAD. They were developed by a consensus of experts, and future studies should be able to test and validate them, and inform iterative refinements to future versions.

Some challenges may arise when implementing these criteria in clinical practice. These criteria were formulated to facilitate the diagnosis and prognosis of MOGAD and guide disease-specific research and clinical studies, but they were not developed to differentiate MOGAD from other neurological disorders[2] or to exclude MOGAD in patients presenting with an inflammatory demyelinating event[3]. The criteria stipulate that patients should be diagnosed with MOGAD after alternative diagnoses have been excluded, just as the McDonald criteria, including the 2017 version, recommend that, before diagnosing MS,

alternative diagnoses should be excluded[4]. This means there is potential discordance between these two criteria sets. This is compounded by the finding that around 0.3% of individuals with MS and 5% of people with optic neuritis have clear positive MOG-Abs.[5,6] As a result, the new MOGAD criteria raise several questions: Which criteria (MOGAD vs McDonald) should be applied in which order? Can MOGAD phenotypically resemble MS on clinical and paraclinical grounds? Is there a genuine MOGAD-MS overlap syndrome or does the positive MOG-Ab represent a type I error in MS in certain cases?

The new criteria are heavily dependent on the presence of Ab-positivity to diagnose MOGAD. However, the accuracies of MOG-Ab testing depend on the methodology used for antibody detection. Of note, false positivity, likely due to cross reactivity with MOG-IgM, occurs more frequently in MOG-Ab testing than in AQP4-Ab testing. To overcome some of these problems and increase specificity, research laboratories have used either higher thresholds for seropositivity or more specific secondary antibodies to IgG1 or IgG-Fcγ[7]. In a multicenter study MOG-Ab CBAs demonstrated excellent agreement for high seropositive and seronegative samples[7]. Patients with borderline or low MOG-Ab titers represent an undefined and diagnostically challenging group that include patients with low levels of true antibodies (as seen in other antibody-mediated conditions, such as myasthenia gravis[8]) and patients with false positive antibodies, due to methodological error.

The new criteria have additional implications. The dependence on the presence of MOG-Ab precludes the existence of 'seronegative' MOGAD'; however, cases have been reported of patients switching from a negative to a positive titre, and vice versa[9]. These observations reinforce the need to be guided by clinical judgment when interpreting antibody results. In particular, the age of the patient is important: MOG-Ab are seen in 30% of children with aquired inflammatory demyelination, suggesting that more frequent use of MOG-Ab testing in children is recommended. Thirdly, the 'core' clinical demyelinating events, which aid the diagnosis of MOGAD in the published MOGAD diagnostic criteria[1] (figure 3, panel A), include most presentations seen in MS. This weakens the recommendation not to test selectively in typical MS presentations. Finally, some aspects of the diagnostic criteria can be interpreted broadly, such as 'cerebral monofocal or polyfocal deficits'. Their accompanying supportive MRI features include 'ill-defined T2' hypertintense lesions in supratentorial and often

infratentorial white matter. These clinical and MRI criteria together can be met by patients with various neuroinflammatory disorders, other than MOGAD.

The MOGAD diagnostic criteria synthesize current international opinion and provide a platform to test scientific hypotheses. The new MOGAD criteria will also encourage laboratories to standardize methods across research and clinical sites, and to consider practicalities, including the sensitivity and specificity of the testing, when it needs to be repeated, how to minimize delays to obtain Ab test results that vary between clinical laboratories and the assays used (fixed, commercial, CBA methods provide quicker turn around times than live CBA) and the need to provide quantitative results (i.e., titres or flow cytometry ratio, with reference values) in addition to qualitative results (i.e., negative, low positive, positive Abs).

There are several ways to address the challenges mentioned above. Clinicians should use these criteria to inform their decisions in complex or equivocal situations, integrating elements from the medical history, clinical phenotype and physical examination, with results from MRI and laboratory studies when making a diagnosis of MOGAD. In clinical practice, it may be useful to look at the evolution of MRI lesions over time, since they can resolve completely in patients with MOGAD more frequently than in individuals with NMOSD or MS[10]. In addition, it may be sensible to establish that patients fulfil at least one supporting clinical or MRI feature for MOGAD before making this diagnosis, even in the presence of a high MOG-Ab titre. Ultimately, we believe it is important that consensus-based recommendations reconcile the potential conflicts between different sets of diagnostic criteria across multiple inflammatory demyelinating conditions. In the case of MS, there has been concerted international efforts to update the position with regard to differential diagnosis with a plan to cross-reference this initiative with the next iteration of the diagnostic criteria. Although challenging, this approach will improve utility in clinical practice and should also be considered in future revisions of the MOGAD criteria.

References

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