

Time to separate MOG-Ab-associated disease from AQP4-Ab-positive neuromyelitis optica spectrum disorder

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Antibodies (Abs) against conformational myelin oligodendrocyte glycoprotein (MOG) are a recently well-recognized cause of acquired demyelination. MOG-Abs have been frequently reported in children presenting with acute disseminated encephalomyelitis and optic neuritis but also in adults with neuromyelitis optica spectrum disorder (NMOSD) and its limited forms.¹ Although MOG-Abs were initially linked to a monophasic presentation,² longer follow-up times have shown an increasing number of patients with positive MOG-Abs and relapses.³ The clinical phenotype of patients with MOG-Ab-associated relapsing disease is different from that of patients with multiple sclerosis (MS) but overlaps that of patients with aquaporin 4 (AQP4)-Ab NMOSD.^{2,4,5} The presence of MOG-Abs is usually associated with better visual and motor outcomes than AQP4-Ab and quicker response to first-line treatments,¹ although a treatment-resistant group, who relapse on therapeutic doses of rituximab, has been reported.⁶

Earlier studies that looked at Abs to the linear epitopes of the denatured MOG protein using ELISA and Western blotting resulted in inconsistent results and positivity in patients with MS and healthy controls.⁷ In addition, even when the more appropriate cell-based assays were used, there were differences in the sensitivity and specificity, which depended on technical factors. The use of the full-length protein construct increases the sensitivity compared to the truncated form that lacks the intracellular domain, and the use of a better secondary Ab⁸ increases the specificity compared to some anti-human immunoglobulin G, which appears to cross react with immunoglobulin M as well.⁸

In this issue of *Neurology*®, Cobo-Calvo et al.⁹ report a large cohort of 197 adult patients with MOG-Abs retrospectively recruited from French referral centers for neuroinflammatory disorders. Of these 197 patients, 139 (70.6%) were diagnosed at presentation (after 2014, when the assay became available), and 58 (29.4%), who presented before 2014, were retrospectively diagnosed. In addition to describing the clinical, paraclinical, and outcomes in patients with MOG-Ab, the authors compared these patients to those with AQP4-Ab-positive NMOSD. As in previous reports and in contrast to patients with AQP4-Abs, MOG-Ab-positive patients were predominantly white (93%), without a female predominance, and had better outcomes. Optic neuritis was confirmed as the commonest presentation in nonpediatric MOG-Ab-positive patients.³ Nineteen percent of patients with MOG-Abs and abnormal brain MRI showed imaging features of predominantly cortical gray matter changes, which were also reported by others,¹⁰ and a clinical phenotype of encephalopathy, seizures, and headaches, together with focal leptomeningeal enhancement. This phenotype could be easily misdiagnosed as primary CNS vasculitis, with both management and treatment implications.

Approximately 45% of patients with MOG-Abs relapsed over the first 2 years, and this was not different in the incident vs the retrospective cohort. This is lower than in a nonincident cohort from Germany but similar to a UK incident cohort.³ There were no differences in the proportion of patients who attained Disability Status Scale score of 3.0 or visual acuity of 0.2 when relapsing patients were compared to monophasic patients, again confirming that most of the

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disability could be driven by the first attack.³ Among cases whose MOG-Ab titers were followed up, the titers were higher at relapse than in remission, but only 2 patients (18.2%) showed negative conversion, which is comparable to the UK study.³ With the use of a live cell-based assay, there were some trends in Ab titers, disease course, and immunosuppression, but the authors noted that on an individual-patient basis, these were not reliable enough to use in the clinical setting to manage patients.

The retrospective design, using nonstandardized imaging protocols and follow-up visits, along with nonrandomized treatment allocations, limits some conclusions, but the findings support, strengthen, and build on previous MOG-Ab studies. Although immunosuppressive agents are generally accepted as effective in preventing relapse in AQP4-Ab-positive NMOSD, the study design was not suitable to assess treatment response and relapse prevention in MOG-Ab-positive patients. Unanswered questions include the long-term risk of relapse in incident cases of MOG-Ab disease, including pediatric-onset cases, and the effect of early relapse prevention. In addition, in patients with relapsing disease, it is not clear what the optimum treatment regimens should be.

Despite the observed predilection for the optic nerve and the spinal cord,⁹ only 19% of patients fulfilled the International Panel for NMO Diagnosis 2015 criteria for NMOSD,¹¹ because those without AQP4-Abs have to fulfill more stringent conditions to be diagnosed with NMOSD such as having dissemination in space with at least one of these affecting a core location, with additional supporting MRI findings. As the authors note, this emphasizes the complexity of classifying patients on the basis of the clinical instead of a biological phenotype. Recent studies looking at the effect of MOG-Abs in both cell culture and mouse models reveal primary demyelination with loss of the microtubule cytoskeleton of oligodendrocytes, resulting in altered expression of axonal proteins. In contrast, AQP4-Ab is a primary astrocytopathy with secondary demyelination and complement activation.¹² With increased availability of biological treatment (monoclonal Abs) with specific mechanism of action, there is a risk that grouping patients by the clinical syndrome, rather than defining them on the basis of the mechanisms of their disease, may result in treatment failure and exposure to potentially serious side effect. There is now evidence that patients with MOG-Abs have a different disease course, suggesting that

they may differ in their response to some treatments compared to patients with AQP4-Abs. Therefore, the recent NMOSD criteria may need revision to take account MOG-Ab disease and its broadening phenotype.

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Disclosure

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