

MOG CSF testing needs testing

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One of the most exciting developments in the field of antibody-associated neurological diseases has been the recognition, in contrast to many older studies that myelin oligodendrocyte glycoprotein (MOG) antibodies, measured appropriately, can be very helpful in discriminating between multiple sclerosis (MS) and other acute and relapsing demyelinating conditions which require different treatments¹. The most accurate methods to detect these clinically-relevant MOG antibodies (MOG-Ab) uses native myelin oligodendrocyte glycoprotein expressed on the surface of living cells as the substrate². Detection of the antibodies relies on binding of a secondary antibody, often a polyspecific anti-Ig (anti-IgG H&L) confirmed with an anti-IgG specific (anti-IgG Fc or anti-IgG1) secondary antibody. Antibodies to this uniquely mammalian protein are found in adults and children with optic neuritis, transverse myelitis, seizures or ADEM^{3,4} and, together with the aquaporin-4 antibodies (AQP4-Abs) found in neuromyelitis optica spectrum disorders (NMO-SD) they define people who are often very responsive to immunotherapy with good recovery⁵. However, a proportion are left with long-term, severe deficits from the onset attack; hence early accurate diagnostics are important to support treatment decisions^{6,7}. Serum taken at onset and before immunotherapy appears sufficient for MOG-Ab testing, but there have been no systematic studies looking at the possibility that some patients only have CSF antibodies.

In this issue of *NEUROLOGY*, Mariotto et al used a live cell based MOG assay, first published by co-authors from Innsbruck, and found CSF MOG-Ab in 8/13 (62%) people who were known to be MOG-Ab positive in their paired sera, while all 72 CSF samples from patients with neurodegenerative disease or MS were negative⁸. These data suggest that CSF testing is highly specific but only 62% sensitive. It was surprising, therefore, that the authors identified CSF MOG-Ab in 3/44 (7%) individuals with NMOSD or related disorders who were deemed negative for both MOG- and AQP4-

Abs in their paired sera⁹. These patients had clinical features typical of MOG-Ab disease such as optic neuritis, myelitis or poorly demarcated CNS lesions, and 2/3 responded rapidly to steroids as would be expected in patients with MOG-Abs. The patient, who failed to respond to steroids, had a partial response to PE and rituximab. Although the numbers of CSF-positive patients are few, these data suggest that CSF testing could be very useful in patients with negative serum MOG-Abs if the clinical features are highly suggestive.

One patient (#3, 21 year old male) had no previous episodes reported and a very high IgG-Fc MOG-Ab titre in the CSF (1:128) with marginal serum MOG-Abs (IgG-Fc 1:160). Clinically this patient was typically an ADEM and he made a complete recovery with steroids. It is difficult to explain why in an acute disorder, often associated with a preceding viral infection, the CSF MOG-Abs were at a similar level to those in the serum, since one might expect the serum levels to be much higher. By contrast, the two other patients (females aged 37 and 56) had had previous episodes, so the “onset” events were not the first. Moreover, Table 2 shows that they did have some MOG-Abs detected with the highly specific IgG-Fc detection, even though the titres (1:40) fell below the authors’ cut-off for MOG-Ab positivity (1:160). One could speculate that there are situations where the peripheral MOG-Ab response that initiated the first episodes had been suppressed, either by previous treatments or by endogenous immune regulatory mechanisms, while previously unrecognised B cell clone(s) had managed to persist in the brain and cause the positive CSF titres with subsequent relapse.

MOG IgG-Abs as measured in this study are present at a higher frequency in the healthy population than any other antibody that causes CNS disease, which is why the cut-off for positivity is set high (1:160)¹⁰. Using a similar substrate but different secondary antibody, a lower cut-off can be used which has led to some useful clinical associations such as the definition and prognosis of a non-MS disease course in children seropositive for MOG-Abs at first demyelination event¹.

Altogether the findings in this report raise questions. Would the results have been the same if they were tested earlier in the disease course? Could there be a different aetiological basis for CSF positive/serum negative patients? There are other aspects of MOG-IgG associated disease that require answers, some of which are now priorities: for how long do we treat MOG-IgG positive patients, do we treat children in a similar fashion to adults, and how can we predict relapsing patients. Currently we capture relapsing patients but cannot predict relapses, perhaps CSF evaluation at first episode will take us a step closer. Further prospective studies on pediatric as well as adult cohorts are a priority.

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Disclosures:

AV none of relevance. PW co-directs the Oxford Autoimmune Neurology Diagnostic Laboratory where MOG antibody testing is performed.