**Intrathecal Production of MOG-IgG: Highlighting the Need for CSF Testing in Clinical Practice**

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Myelin oligodendrocyte glycoprotein antibody (Ab) associated disease (MOGAD) is now a well-recognised demyelinating disease. Despite the phenotypic overlap with both multiple sclerosis and aquaporin-4 (AQP4)-Ab neuromyelitis optica spectrum disorder (NMOSD), cumulative clinical and immunological evidence clearly discriminates between these conditions.

MOG is a membrane protein predominantly expressed on the surface of the myelin sheath. The location of MOG on the outer lamella support a pathogenic effect of the antibodies in vivo, but the mechanisms by which these antibodies cause disease have not been clearly established[1]. Pathological studies on the relationships between cellular and humoral immunity and demyelinating lesions were insufficient in MOGAD, and transfer of cross-reactive human MOG antibodies to rodents can only induce tissue alterations if large amount of antibodies are used compared to AQP4-Ab transfer models[2]. The presence of CD4+ T cells in lesions from patients with MOGAD,[3] as well as the fact that the antibody responses against protein targets evolve from B-T cell interactions[4], suggest that T cells also are important in the pathogenesis of the disease.

While some studies have reported a correlation between serum MOG-Ab titers and clinical relapse[5], a consistent relationship with disease activity has yet to emerge[6]. As only a portion of MOGAD patients have detectable antibodies in the CSF[7], and intrathecal oligoclonal bands and a positive IgG Index are also rare (accounting for less than 15%), the autoimmune induction is thought to occur outside of the CNS, in the peripheral immune system. This is further supported by the increased frequency of infectious prodrome, or recent vaccination, reported particularly in pediatrics.

In this current issue of *Neurology*, Akaishi et al[8] compare the Intrathecal production of disease specific antibody in 74/241 patients who presented with acute neurological episodes based on objective evidence of CNS lesions and had paired serum and CSF samples collected within 1 day of each other. The data reported reveal a clear difference between the two patient groups with 11/38 MOG-Ab patients and 0/36 AQP4-Ab patients uniquely positive in the CSF. Overall, the specific antibody quotient (a measure of the relative CSF abundance of an individual antibody) was more than 10 times higher for MOG-Abs than for AQP4-Abs. For patients with AQP4-Ab, there was a correlation between serum and CSF antibody level. However, for patients with MOG-Ab, no such relationship existed, with 80% of patients having higher CSF level than expected based on their serum level. The authors conclude that the majority of CSF MOG-Ab were intrathecally synthesized, whereas most CSF AQP4-Ab originate from the blood and were passively transferred into the CSF.

Interestingly, there were no correlations between the clinical phenotypes and intrathecal oligoclonal band positivity in both AQP4-Ab and MOG-Ab positive patients, but CSF level of MOG-IgG correlated with the CSF cell count ($\rho$ = 0.52, p = 0.0014), which was not seen in the AQP4-Ab group. Blood-brain barrier (BBB) compromise as shown by raised albumin quotients was seen in 75% of MOG-IgG-positive cases and 44% of AQP4-IgG-positive cases. This may suggest that systemic inflammation and blood brain barrier permeability may contribute to the differences in properties of B-cell trafficking and antibody production site between these diseases.

The biological significance of calculating intrathecal synthesis should be considered carefully. Using this approach, none of the patients demonstrated intrathecal synthesis for AQP4-IgG, contrasting previous studies demonstrating that AQP4-IgG-producing plasmablasts are found in the CNS or the intrathecal space and hence produce AQP4-IgG intrathecally[9]. In addition, the relative abundance of CNS target expression and turnover rate may impact on the level of free antibody available for measurement.

The high frequency of oligoclonal bands positivity and raised IgG seen in the MOGAD cohort compared to the published literature may raise concerns about selection bias and the applicability of the results to all patients with MOGAD. Furthermore, as stated by the authors the low patient numbers mean the data were insufficient to evaluate the clinical impact of intrathecal MOG-IgG and AQP4-IgG production on the clinical severity, relapse risk or prognosis of patients with these antibodies. Intrathecal antibody production could potentially explain the phenotypical variability seen in MOGAD in general and the increasing reports of MOGAD patients relapsing on rituximab treatment despite peripheral B cell depletion[10]. As CSF MOG-Ab and antibody indexes are not tested routinely as part of clinical care, the results of this study may suggest that testing for MOG-Ab should occur in both CSF and serum, whereas AQP4-Ab testing is higher yield in serum.

With explosion of research into molecular underpinnings of autoimmune disease and rationally-designed therapies to intensify or replace broader immunotherapy, better understanding of disease-specific pathobiological mechanisms is crucial. The current challenge when managing patients with antibody mediated CNS disorders is that the treatments used work by targeting the immune system peripherally with treatment responses focused on evaluating clinical activity in the CNS. Key consideration when treating patients are (i) BBB permeability (ii) the presence of intrathecal antibody production (iii) whether the treatment given can cross the BBB and reach the target site and (iii) time taken to achieve optimal treatment. As highlighted by Akaishi et al [REF] not only these factors are different for the different demyelinating diseases, but they may also vary within

individuals with the same disease. Further studies, particularly of these MOGAD patients with intrathecal MOG-IgG production and correlation with risk of relapse and treatment response, may provide insight to this complex disease.

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