

Are aquaporin antibody titers useful outcome measures for neuromyelitis optica spectrum disorders?

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Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory demyelinating disease of the CNS, characterized by an increased risk for severe relapses.¹ Most patients with NMOSD (>70%) are seropositive for pathogenic antibodies against the aquaporin-4 (AQP4-Ab) water channel. Recently, several randomized controlled trials have demonstrated clinical effectiveness of immunosuppressive agents in AQP4-Ab positive NMOSD.² However, a potential biomarker of NMOSD activity that could be measured serially and predicted relapses would assist clinicians in their selection of patients for immunotherapies. A few small observational studies have suggested changes in AQP4-Ab titers as a potential biomarker of NMOSD activity.^{3,4}

In this issue of *Neurology*[®] *Neuroimmunology & Neuroinflammation*, Jitrapaikulsan et al.⁵ provided Class II evidence that neither AQP4-Ab titers nor complement-mediated cell killing has any significant prognostic or predictive utility in NMOSD. The authors have analyzed 336 serial serum samples from 82 AQP4-Ab seropositive patients taken preattack, at attack onset, or at remission. AQP4-Ab titers were not significantly changed between the preattack, attack, or remission samples or in those of individual patients during their disease course. Furthermore, maintenance immunotherapy did not significantly affect AQP4-Ab titers. Similarly, the ability of AQP4-Ab for complement-mediated killing in vitro was not influenced by disease activity or treatment. Differences to previous reports reporting conflicting results could be explained by the substantially larger number of patients and samples in this study.

However, the current study of Jitrapaikulsan et al. also had a number of potential limitations, such as its retrospective design, with samples having been collected many years before study (3–14 years), the effect of acute attack immunotherapies given before collection of attack sera, and the experimental setup using 10-fold dilution for titrations.

Previous studies on the utility of serum levels of autoantibodies in other neurologic autoimmune diseases have shown differential results. In myasthenia gravis, serum titers of acetylcholine receptor antibodies generally vary widely between patients and do not predict disease severity.⁶ By contrast, CSF and, to a lesser degree, serum antibody titers against the NMDA receptor have been associated with a poor outcome in NMDA receptor encephalitis.⁷ There is also conflicting evidence regarding the usefulness of serum antibody titers against the myelin oligodendrocyte glycoprotein (MOG-Ab) which are also present in a subset of AQP4-Ab seronegative NMOSD patients. Some studies have indicated that the clinical recovery or a monophasic disease course is associated with transient MOG-Ab titers, whereas other studies have not been able to confirm these findings.⁸ To summarize, there is controversial evidence about the value of serial serum antibody titers for monitoring disease activity in neurologic autoimmune diseases, which also applies to various other autoantibodies. Possible explanations for these disappointing findings are as follows: first, the limited ability of peripheral blood antibody levels to reflect the situation in the target organ (e.g., the CNS); second, pathogenic

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autoantibodies are known to be bound to their target antigens and may therefore not be detectable in the periphery; and finally, in autoimmune encephalitis, CSF autoantibodies levels could be of higher clinical relevance than those found in the serum.^{7,9}

Therefore, distinct peripheral blood biomarkers such as neurofilament-light or glial fibrillary acid protein are urgently needed and currently under investigation for their prognostic role and their use as therapeutic biomarkers in NMOSD.¹⁰

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