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Should We Measure CSF Complement Levels in Patients With MOGAD?

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Aquaporin-4 (AQP4) IgG seropositive neuromyelitis optica (NMO) is an autoimmune astrocytopathy that leads to secondary demyelination.[1] Complement deposition is a hallmark feature of NMO lesions,[1] and treatment with anti-C5 monoclonal antibodies dramatically reduces NMO relapses.[2] Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) is a neuroinflammatory syndrome characterized by IgG targeting MOG, a protein present on the outer surface of oligodendrocytes.[3,4] Currently, our understanding of MOGAD immunopathology is more limited, and no therapies are approved to prevent disease attacks. The CNS inflammatory lesions in MOGAD are characterized by a predominance of $CD4^+$ T cells.[5-7] Yet, reports on the extent of complement deposition have varied.[5-7] Thus, it is unknown whether MOGAD pathology, like NMO, universally requires complement-mediated damage.

In a simplified view, the complement cascade involves a sequence of protein cleavage steps that can be activated after antibody binding to a target antigen. The early parts of the cascade generate the fragments C3a and C5a that may promote recruitment of immune cells into a tissue, among other proinflammatory functions.[1,4] The terminal stages of the complement cascade form the membrane attack complex (MAC), composed of the factors C5b-9 that create a pore in target cell membranes, leading to cell death in a process called complement-dependent cytotoxicity.[4,8] AQP4 and MOG-specific antibodies can induce complement-dependent cytotoxicity of cells expressing their respective target antigens in vitro, but whether this occurs in vivo in MOGAD is less clear.[9]

In this issue of *Neurology: Neuroimmunology and Neuroinflammation®*, Kaneko et al.[8] report on the levels of complement proteins in CSF from persons with NMO, MOGAD, MS, and noninflammatory neurologic diseases. It is important to note that CSF samples were obtained during attacks before the initiation of immune-suppressing medications. The authors made 3 key observations. First, they found that C3a and C5a are increased in the CSF of both MOGAD and NMO compared with MS. Second, C3a and C5a levels were not significantly different between MOGAD and NMO. Surprisingly, the terminal MAC components (C5b-9) were dramatically lower in MOGAD compared with NMO, indicating complement-dependent cytotoxicity is typically less prominent in MOGAD. Third, after stratifying the MOGAD cohort by the Expanded Disability Status Scale, the authors, nevertheless, found that patients with more severe disease during attacks and at follow-up had higher levels of CSF C5b-9 than those with milder disease. These data suggest that the heterogeneity in MOGAD severity may be associated with the degree of MAC-mediated complement-dependent cytotoxicity.

Collectively, the reported findings raise important questions about MOGAD pathologic mechanisms, including whether C3a and C5a are important for immune cell recruitment or other pathogenic functions in MOGAD, even if there is no participation of downstream MAC-mediated complement-dependent cytotoxicity. The authors also question whether higher expression of the complement inhibitory protein CD59 on oligodendrocytes compared with astrocytic end-feet, the primary target in NMO,[10] may contribute to differences in complement-

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dependent cytotoxicity between MOGAD and NMO.[8] If direct complement-mediated damage is reduced in MOGAD, one might ask whether this difference contributes to the better functional recovery that may occur in some MOGAD cases compared with NMO.[3]

While the authors' new findings are exciting, their study had some limitations. The main limitation was the small sample size. In addition, the study did not include pediatric-onset MOGAD cases. The adult patients who were included had low rates of optic neuritis, which is another common clinical presentation of MOGAD. Thus, it is unknown whether the CSF complement activation patterns observed are also representative of MOGAD in children and in patients with optic neuritis.

If replication studies with larger cohorts validate these provocative findings, one could envisage future studies to determine whether measuring CSF complement levels could predict prognosis in patients with MOGAD. In addition, these results question whether complement inhibition may be beneficial to prevent neurologic deterioration in severe MOGAD cases. In summary, the article by Kaneko et al. advances our knowledge of the humoral aspects of MOGAD immunopathology. Understanding these fundamental immunopathogenic mechanisms in MOGAD may improve the management of this condition.

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