Finding NMO

OPEN

Richard Daneman

Correspondence to
Dr. Daneman:
rdaneman@ucsd.edu

Neurol Neuroimmunol Neuroinflamm
2017;4:e313; doi: 10.1212/NXI.0000000000000313

Neuromyelitis optica (NMO) is a severe inflammatory demyelinating disease with lesions found primarily in the spinal cord and optic nerve.[1,2] Although originally classified as a subtype of multiple sclerosis (MS), the finding of autoantibodies against the astrocyte water channel aquaporin-4 (AQ4) has defined this as a specific autoimmune disorder.[3] Important questions have arisen as to how AQ4 antibodies (NMO–immunoglobulin G [IgG]) lead to the neuropathology associated with NMO. One major thought is that NMO-IgG binding to AQ4 leads to complement-dependent lysis of astrocytes recruiting immune cells, including granulocytes and eosinophils, generating an inflammatory lesion.[4,5] Recently, however, 6 different types of histologically distinct lesions have been identified, some characterized by complement deposition (lesions 1, 2) and some lacking complement (lesions 4–6).[6] Therefore, a major question is how NMO-IgG causes lesion formation in the absence of complement.

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Takeshita et al.[7] aim to identify complement-independent pathways by which NMO-IgG cause lesion formation. They generated both static and flow-based in vitro brain–blood barrier co-culture models utilizing human brain microvascular endothelial cells and a human astrocyte cell line, either expressing AQ4 or not expressing AQ4. They identified that NMO-IgG increased endothelial cell permeability to dextran tracers with a corresponding decrease in Claudin 5 expression, suggesting that the paracellular tight junctions were disrupted. NMO-IgG also led to an increased inflammatory state of the endothelial cell layer, elevating CCL2 and CXCL8 expression and leukocyte migration across the monolayer. These results were mediated through astrocyte AQ4, as NMO-IgG had no effect on the co-cultures utilizing AQ4 negative astrocytes. They further demonstrated that NMO-IgG induced interleukin (IL)–6 expression by AQ4+ astrocytes, and IL-6 was sufficient to increase barrier permeability and the inflammatory state of the endothelial cells.

These data provide a potential mechanism for complement-independent lesion formation in patients with NMO: NMO-IgG binds to AQ4 on astrocyte endfeet, driving the production of IL-6, generating local BBB breakdown and neuroinflammation. This leads to several important questions about the pathogenesis and treatment of NMO. First, while this mechanism was discovered in vitro, it is not clear whether this same mechanism causes complement-independent lesion formation in patients with NMO. The testing of IL-6 blocking antibodies in NMO therapy may establish the role of IL-6-dependent mechanisms, including its possible role on Th17 differentiation in NMO,[8] and potentially help distinguish the significance of complement-independent lesion formation.

Another interesting question that arises is how this mechanism leads to neuropathology and symptomology. NMO has traditionally been described as a demyelinating disorder, yet both the mechanism described by Takeshita et al.[7] and the complement-dependent mechanism affect astrocytes and not myelin. One option is that NMO-IgG drives local BBB opening and inflammation, which would allow specific anti-myelin T cells or antibodies to enter the parenchyma and destroy myelin. A second possibility is that demyelination is a secondary bystander effect following a specific anti-astrocyte immune response likely destroying astrocyte buffering of glutamate leading to excitotoxic axonal and myelin damage. A final option is that demyelination is secondary to nonspecific IL-6-mediated BBB opening and neuroinflammation.

This study also leads to speculation about how different types of lesions can be formed within the same patient; specifically, how NMO-IgG could elicit complement-dependent astrocyte lysis in some locations but lead to astrocyte-derived IL-6-mediated BBB opening in others. One potential distinguishing feature may be the total amount of NMO-IgG in each lesion, with lower amounts leading to IL-6 production and greater amounts of antibody more likely

See article

From the Departments of Pharmacology and Neuroscience, University of California, San Diego.

Funding information and disclosures are provided at the end of the editorial. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by Neurology: Neuroimmunology and Neuroinflammation.

leading to complement-dependent lysis. Another possibility derives from an interesting finding by Takeshita et al.,[7] who found that addition of NMO-IgG to BBB co-culture flow models led to different immune cell populations crossing the endothelial barrier in different experimental replicates. Perhaps the stochastic recruitment of different immune cell populations determines the type of lesion formed. Because different lesions form within the same patient, the lesion-forming mechanism cannot be genetically encoded, but is likely due to the nature of the highly localized neuroinflammatory response.

It is also unclear how NMO-IgG antibody accesses astrocytes, given that these cells lie behind the BBB. Approximately 0.1% of the serum concentration of antibodies are able to enter the CNS parenchyma,[9] likely due to nonspecific uptake in pinocytotic vesicles, and thus a small amount of parenchymal access could stochastically lead to buildup of antibody in a discrete region, causing lesion formation when a threshold is reached for either IL-6 production or complement activation. Another option is that a second event is required to open the BBB, allowing access of the NMO-IgG. The second event could be environmental, such as hypoxia, or disease-related. Interestingly, Takeshita et al.[7] mention unpublished data that they have identified a second antibody in serum from patients with NMO that can disrupt the BBB, suggesting that this 2-hit model may indeed be the mechanism of lesion formation.

It is interesting to consider whether this IL-6-dependent mechanism is specific to NMO-IgG binding to astrocyte AQ4, or whether binding of any astrocyte-specific autoantibody would lead to IL-6-mediated neuroinflammation. A total of 10%–25% of patients with NMO do not have AQP4 antibodies,[2] suggesting that alternate mechanisms can indeed lead to lesion formation. Whether this is due to another anti-astrocyte antibody or represents a different disease mechanism remains unknown. Interestingly, antibodies against astrocyte K+ channels have been identified in 47% of patients with MS,[10] suggesting a role of anti-astrocyte antibodies in more widespread demyelinating disease. It remains a mystery as to what determines the spatial and temporal localization of lesions in patients with NMO. Astrocytes throughout the CNS express AQP4, and thus it is not apparent why NMO-IgG would lead to lesion formation only in the spinal cord and optic nerve, and not in gray matter or the brain. Identifying regional heterogeneity of astrocytes, and whether some are more primed to secrete IL-6, may shed important light on this question.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

R. Daneman has consulting agreements with Alector Pharmaceuticals and Inception. Go to Neurology.org/nn for full disclosure forms.

REFERENCES

1. Yang X, Ransom BR, Ma JF. The role of AQP4 in neuromyelitis optica: more answers, more questions. J Neuroimmunol 2016;298:63–70.
2. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805–815.
3. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106–2112.
4. Saadoun S, Waters P, Bell BA, Vincent A, Verkman AS, Papadopoulos MC. Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. Brain 2010; 133:349–361.
5. Hinson SR, Pittock SJ, Lucchinetti CF, et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. Neurology 2007;69: 2221–2231.
6. Misu T, Höftberger R, Fujihara K, et al. Presence of six different lesion types suggests diverse mechanisms of tissue injury in neuromyelitis optica. Acta Neuropathol 2013; 125:815–827.
7. Takeshita Y, Obermeier B, Cotleur AC, et al. Effects of neuromyelitis optica–IgG at the blood–brain barrier in vitro. Neurol Neuroimmunol Neuroinflamm 2017;4: e311. doi: 10.1212/NXI.0000000000000311.
8. Varrin-Doyer M, Spencer CM, Schulze-Topphoff U, et al. Aquaporin 4-specific T cells in neuromyelitis optica exhibit a Th17 bias and recognize *Clostridium* ABC transporter. Ann Neurol 2012;72:53–64.
9. Yu YJ, Zhang Y, Kenrick M, et al. Boosting brain uptake of a therapeutic antibody by reducing its affinity for a transcytosis target. Sci Transl Med 2011;3:84ra44.
10. Srivastava R, Aslam M, Kalluri SR, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. N Engl J Med 2012;367:115–123.