Pushing the boundaries of neuromyelitis optica

Does antibody make the disease?

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In just over a decade, neuromyelitis optica (NMO) has been transformed from an obscure, untreatable disorder that was often confused with multiple sclerosis (MS), or relegated to second-rank MS variant status, into a distinct nosologic entity with its own serologic marker and a wide range of as yet unproven, but universally deployed treatment options.[1,2] Such a remarkable change of fortune is due, in large measure, to the breakthrough discovery of serum aquaporin-4 immunoglobulin G antibody (AQP4-IgG) that is exquisitely specific to NMO.[3,4] The discovery of AQP4-IgG galvanized the field of NMO research and led to recognition of a much broader spectrum of clinical presentations seen in NMO than was previously appreciated.

In this issue of *Neurology*®, the International Panel for NMO Diagnosis (IPND) unveils the updated version of diagnostic criteria and introduces a unifying term for the disease: NMO spectrum disorders (NMOSD).[5] The new nomenclature subsumes the traditional opticospinal phenotype with the more restricted formes frustes of the disease and stratifies all NMOSD cases according to their AQP4-IgG serostatus. The IPND criteria for AQP4-IgG-seronegative NMOSD are broadly similar to the prior definition of NMO,[6] but allow for more latitude in the choice of core NMO syndromes. The most important novelty of the criteria relates to the AQP4-IgG-seropositive cases. The new criteria allow for diagnosis of NMOSD after just one clinical attack affecting just one CNS region if AQP4-IgG is present in serum and no alternative explanation is evident. The motivation for diagnosing seropositive patients early in the disease course is clear. Rate of disease recurrence after sentinel event is high in an AQP4-IgG-seropositive patient[7,8] and relapses tend to be severe. Given that long-term prognosis in NMO is almost exclusively due to sequelae of relapses, and that several MS disease-modifying drugs appear to be harmful in NMOSD, while appropriate immunotherapy is protective,[1,2] it would be highly desirable to identify and treat NMOSD after the first attack.

While the relaxation of diagnostic criteria proposed by the IPND is likely to increase chances for earlier treatment for many patients with NMOSD, it is not without risks, as can be illustrated with the following real-life example. A patient with monocular optic neuritis, no prior neurologic history, and nonspecific white matter lesions on MRI is referred to a tertiary MS center for treatment of NMOSD after her AQP4-IgG ELISA assay returns a positive result. This patient appears to meet IPND criteria for NMOSD, but is the diagnosis justified? To estimate the post-test probability of NMOSD diagnosis, we need to know local prevalence of NMOSD among patients with de novo monocular optic neuritis, as well as sensitivity and specificity of AQP4-IgG ELISA assay for NMOSD. Two recent studies furnish us with the requisite data. Prevalence of NMOSD among patients with monocular optic neuritis in the Western countries of 5.8%,[8] sensitivity of AQP4-IgG ELISA for NMOSD of 66.7%, and specificity of 98.7%[9] yield a positive likelihood ratio of 51.3 and post-test probability of NMOSD of 76.0%. We conclude that our AQP4-IgG seropositive patient with optic neuritis is likely to have NMOSD, but there is an almost 25% chance that she does not. Concerns about misclassification of NMOSD due to overreliance on serologic testing are not merely theoretical. False-positive rate of AQP4-IgG ELISA among 1,040 patients with bona fide MS was 0.5%.[10] While this rate may appear to be low, the false-positives could considerably inflate the size of NMOSD cohorts, which in the United States and Europe is estimated to comprise 1%–2% of patients with inflammatory demyelinating disorders of the CNS.

How is a clinician to avoid the pitfall of NMOSD misdiagnosis? The use of the more NMO-specific cell-based assays for AQP4-IgG, which are unfortunately not widely available, would help reduce the error rate, but would not entirely eliminate the problem.[10] The best antidote to diagnostic error is a thorough familiarity with the clinical and paraclinical features that increase or decrease pretest probability of NMOSD. To this end, the IPND investigators have incorporated in their review important findings that will help improve the accuracy of NMOSD

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diagnosis. Of special interest are the tables and figures accompanying the article, which are replete with clinical pearls. For example, the authors emphasize that onset-to-nadir time of less than 4 hours, or an inexorably progressive course, would be highly atypical for NMO myelitis. Medical history, as well, yields helpful clues: coexisting systemic lupus erythematosus, Sjögren syndrome, or myasthenia gravis increase confidence about NMOSD diagnosis, while extraneural sarcoidosis makes it less likely. A list of radiologic red flags will come in handy for anyone trying to decide whether the patient best fits under the MS or NMO rubric. Inferior temporal lobe, cortical, juxtacortical, U-shaped lesions, and Dawson fingers strongly favor MS. Radiologic features suggestive of NMO are discussed in table 3 and carefully chosen illustrative examples are shown in figure 1.

The neurologic community owes thanks to the IPND investigators for their efforts to clarify the boundaries of NMOSD and to formulate a research agenda for the future. Large-scale prospective validation and assessment strategies, as suggested by the Panel, will test the utility of the proposed criteria and lead to their refinement. The next decade of NMO research promises to be as exciting as the last.

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REFERENCES

1. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol 2014;261:1–16. doi: 10.1007/s00415-013-7169-7.
2. Wong E, Vishwanath VA, Kister I. Rituximab in neuromyelitis optica: a review of literature. World J Neurol 2015;5:39–46.
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. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202:473–477.
5. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177–189.
6. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–1489.
7. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. Ann Neurol 2006;59:566–569.
8. Jarius S, Frederikson J, Waters P, et al. Frequency and prognostic impact of antibodies to aquaporin-4 in patients with optic neuritis. J Neurol Sci 2010;298:158–162. doi: 10.1016/j.jns.2010.07.011.
9. Jarius S, Franciotta D, Paul F, et al. Testing for antibodies to human aquaporin-4 by ELISA: sensitivity, specificity, and direct comparison with immunohistochemistry. J Neurol Sci 2012;320:32–37.
10. Pittock SJ, Lennon VA, Bakshi N, et al. Seroprevalence of aquaporin-4-IgG in a northern California population representative cohort of multiple sclerosis. JAMA Neurol 2014;71:1433–1436.