Neuromyelitis optica spectrum disorder diagnostic criteria: Sensitivity and specificity are both important

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Although some of their characteristics overlap, neuromyelitis optica spectrum disorder (NMOSD) is distinct from multiple sclerosis (MS) in many clinical, laboratory, and neuroimaging features, including its strong association with a pathogenic autoantibody biomarker, AQP4-IgG.1 The specificity of AQP4-IgG was leveraged by its incorporation into revised diagnostic criteria in 2006.2 Subsequently, a number of additional clinical phenotypes and magnetic resonance imaging (MRI) patterns were noted to occur in AQP4-IgG-seropositive neuromyelitis optica (NMO) patients who fulfilled 2006 criteria. These presentations (notably, brain involvement and “NMO-typical” MRI lesion patterns) were proposed to be part of an umbrella term “NMO spectrum disorders” in 2007.3

In 2015, the International Panel for Neuromyelitis Optica Diagnosis (IPND) proposed consensus diagnostic criteria using the unified term NMOSD.4 The 2015 criteria effectively merged the 2006 and 2007 definitions by including all AQP4-IgG-seropositive patients and further defined an expanded array of clinical and MRI phenotypes. A category of NMOSD without AQP4-IgG was retained to identify the roughly one-third of clinical cases that do not have detectable serum AQP4-IgG. Early and accurate NMOSD diagnosis is important for treatment decision-making because AQP4-IgG-seropositive patients are at high risk for relapse (>60% in the first year) and MS disease-modifying therapies (especially interferon-beta and natalizumab) aggravate NMOSD regardless of AQP4-IgG serostatus.

In this issue, Hamid et al.5 present an analysis of the effects of diagnostic categorization by applying the 2006 NMO and 2015 NMOSD criteria to 176 subjects at an NMOSD specialty center in whom they diagnosed an inflammatory demyelinating central nervous system (CNS) syndrome suggestive of NMOSD and atypical for MS. In all, 63 (35.8%; 42 AQP4-IgG seropositive) had characteristics fulfilling the 2006 criteria. When 2015 IPND criteria were applied to the same cohort, 111 (63.1%; 81 seropositive) met criteria. All but nine of the incremental patients were AQP4-IgG seropositive and failed to meet 2006 criteria because they had not experienced both optic neuritis and myelitis. Hamid et al. conclude that application of the 2015 rather than 2006 criteria increased the diagnostic yield (sensitivity) by 76%. Another study demonstrated a similar increase (85%).6

Is the increase in sensitivity as impressive as it seems? Although not formally enshrined in diagnostic criteria, the 2007 concept of NMOSD had identified patients with recurrent optic neuritis, recurrent myelitis, and certain typical brain syndromes as NMOSD; such patients were treated with similar strategies as NMO patients who satisfied 2006 criteria. If one applies both the 2006 NMO definition and 2007 NMOSD concept (the latter includes only AQP4-IgG-seropositive cases), then 102 of 176 patients (58.0%) in Hamid et al.’s cohort would have been diagnosed NMO or NMOSD based on prevailing practice. The 2015 IPND criteria incrementally identified nine patients (all AQP4-IgG seronegative), an absolute increase in 5.1%; these cases experienced “combinations of clinical events” not satisfying 2006 criteria (brain stem plus either optic nerve or spinal cord or diencephalic plus spinal cord). A total of 50% of the AQP4-IgG-seronegative patients had myelin oligodendrocyte glycoprotein (MOG) autoantibodies.

Diagnostic criteria identify a collection of symptoms, signs, and tests that are used in routine clinical practice to provide care for individual patients. In contrast, classification criteria are standardized definitions that are meant to identify relatively uniform groups of patients for the purpose of clinical research. Diagnostic criteria must be broad (highly sensitive) in order to reflect disease heterogeneity yet maintain reasonable specificity; classification criteria require high specificity. The differentiation of criteria type is particularly

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important in the absence of a diagnostic standard, as is the case for most rheumatologic diseases.7

The distinction between criteria types is also relevant to MS and NMOSD. Although classification criteria are appropriate for MS because a single standard is lacking, AQP4-IgG may be a standard for NMOSD.8 Defining the disease based on AQP4-IgG seropositivity would identify a homogeneous patient cohort suitable for pathobiology studies and enhance the validity of therapeutic clinical trials at the expense of generalizability. However, restricting the diagnosis to AQP4-IgG-seropositive patients ignores the 30% of patients with otherwise typical NMOSD but who are AQP4-IgG seronegative. Such patients have a similar disease course and similar responses to preventive therapies as the seropositive patients.9 The Hamid report shows that a group of expert neurologists felt that 176 patients had a syndrome compatible with NMOSD (presumably with no better explanation), but only 63% could be diagnosed by 2015 criteria. The other 37% remain an important, likely heterogeneous, group of patients who lack a firm diagnosis, as recognized by others.10 Hamid and colleagues mention the following caveats: (1) some patients were MOG-IgG seropositive, a condition that overlaps clinically, but is likely a myelinopathy rather than an astrocytopathy,11 (2) some cases had suggestive clinical findings but lacked required “NMOSD-typical” MRI confirmation, (3) some had suggestive MRI findings without clinical correlate, and (4) AQP4-IgG-seronegative cases of recurrent isolated optic neuritis and recurrent longitudinal extensive transverse myelitis (LETM) are not included in the 2015 criteria, although many clinicians treat them as if they were AQP4 seropositive.

Beyond these possible explanations, how should the remaining gap in diagnostic criteria sensitivity be definitively addressed for AQP4-IgG-seronegative patients? We believe that ultimate validation of AQP4-IgG-seronegative cases as NMOSD will depend on systematic, prospective, and longitudinal studies (or analysis of retrospectively obtained follow-up data of a fully ascertained population) that examine a broad group of patients in whom NMOSD is reasonably suspected.4 The ultimate reference standard is continuing conformity to an NMOSD diagnosis and failure to exhibit signs, symptoms, or other findings of an alternative “mimic” condition.4 Evolution of the clinical course and MRI findings may fulfill NMOSD criteria over time or identify alternative diagnoses; this will allow estimation of criteria specificity, which is not evaluable from the Hamid study design. AQP4-IgG seroconversion rates should be examined. Immunopathological studies from biopsies or autopsies, when available, might arbitrate diagnosis in individual cases and serve to refine clinical and radiological disease patterns.12 The clinical spectrum, natural history, pathobiology, and response to treatment of MOG-IgG-associated NMOSD remains to be fully defined.

Future research may move us closer to an objective of biomarker-supported diagnosis that informs treatment decisions through understanding of underlying disease mechanisms. The ultimate goal is to have diagnostic criteria that individualize treatment yet account for all patients encountered in practice and that are both sensitive and specific. In the meantime, IPND consensus has achieved earlier, confident recognition of NMOSD diagnosis, so that early appropriate attack prevention is possible. Hamid and colleagues’ work highlights not only the utility of a more liberal and unified diagnostic criteria but also the work that remains to characterize AQP4-IgG-seronegative patients and assess the complete diagnostic properties of the 2015 IPND criteria.

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References


