EDITORIAL

Autoimmune Encephalitis Consensus Criteria

Lessons Learned From Real-World Practice

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Neurology: Clinical Practice 2023;13:e200155. doi:10.1212/CPJ.0000000000200155

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Autoimmune encephalitis (AE) encompasses a spectrum of neurologic disorders caused by brain inflammation, a subset of which is associated with autoantibodies to neuronal cell-surface antigens such as anti-N-methyl-d-aspartate (NMDA) receptor AE or anti-leucine-rich glioma-inactivated 1 (LGI1) AE.[1] Up to half of patients with AE, however, do not have abnormal neuronal or glial autoantibodies identified and are classified as having "seronegative" AE.[2] Clinical antibody testing can take several days to result, a time in which clinicians caring for patients with suspected AE may wish to initiate empiric immunosuppressive therapy. Antibody testing is also not readily accessible in some health care settings and, even when technically available, may require time-consuming advocacy with local clinical laboratories to justify relatively costly send-out testing. To add further complexity, some patients with immunoreactive (e.g., laboratory true-positive) antibodies do not have clinical AE, and over-reliance and misapplication of antibody testing were identified as important contributors to AE misdiagnosis in a 2023 multicenter analysis.[3]

To help clinicians navigate through the differential diagnosis of AE and identify patients with possible, probable, and definite AE, AE consensus criteria were published in 2016.[4] The criteria characterize possible AE based on the clinical phenotype of subacute (<3 months), rapidly progressive, short-term memory impairment; altered mental status; or psychiatric symptoms, with at least one additional feature of a new focal CNS finding, seizure (not explained by a previously identified seizure disorder), CSF pleocytosis, or MRI features of encephalitis, with additional levels of diagnostic confidence supported by antibody testing, EEG, elevated IgG index or oligoclonal bands on CSF examination, or brain biopsy.

In this article published in *Neurology® Clinical Practice*, Orozco and colleagues assessed how these 2016 AE consensus criteria applied to adults diagnosed with a range of autoimmune encephalopathies evaluated in a single-center autoimmune neurology specialty practice (Mayo Clinic) between 2006 and 2020.[5] The study excluded patients from the final analysis if they had a noninflammatory final diagnosis, an autoimmune condition without encephalopathy (such as isolated ataxias, myelopathies, or neuropathies), or a still uncertain diagnosis—in other words, the study included just patients with a clinic-based diagnosis of AE. Of 538 patients with AE, 361 (67%) met at least possible AE consensus criteria—61% definite AE, 5% probable, 28% possible, and 6% classified as Hashimoto encephalopathy. Just less than half of all AE patients—247 (46%)—were seronegative for an AE-specific neuronal or glial autoantibody (5% of seronegative patients had unclassified and possibly novel autoantibodies in CSF or serum by tissue immunofluorescence). Of patients with definite AE, 87% had AE-specific antibodies and the most common antibody-associated syndromes were anti-LGI1 encephalitis, anti-NMDA receptor encephalitis, and AE associated with high-titer glutamic acid decarboxylase 65 antibodies. The authors conclude that 2016 AE consensus criteria are moderately sensitive.

Of patients who did not meet consensus criteria for even possible AE but were diagnosed clinically with an AE, most had either an isolated seizure disorder with positive neuronal autoantibodies or brainstem encephalitis without cognitive impairment. Notably, while only a single patient with anti-NMDA receptor encephalitis did not meet at least possible consensus

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criteria for AE because of lack of a subacute onset, 34% of patients with anti-LGI1 encephalitis and 53% of patients with anti-GAD antibody–associated AE did not meet even possible AE criteria, primarily because of having an isolated seizure disorder without other clinical features of a broader AE syndrome.

While the 2016 AE consensus criteria carved out Bickerstaff brainstem encephalitis (associated with anti-GQ1b antibodies) as a discrete phenotypic entity, these data suggest that such a framing is too narrow to encompass the broader range of autoimmune brainstem encephalitis syndromes seen in real-world practice. Expanding AE criteria to define a more general syndrome of autoimmune brainstem encephalitis without cognitive impairment, as suggested by the study authors, would be very sensible.

Potentially expanding AE definitions to include isolated immune-mediated epilepsies associated with autoantibodies without other features of AE will require more nuance, however. In 2020, the International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce proposed that seizures in AE should be characterized as either "acute symptomatic seizures secondary to AE" resulting directly from active encephalitis (and more likely to be responsive to immunosuppression) or "autoimmune-associated epilepsy" as a downstream secondary consequence of structural injury from autoimmune encephalopathy but not necessarily from ongoing inflammation (and, therefore, less likely to benefit from immunosuppression).[6] Disease-specific revisions to AE criteria, such as for anti-LGI1 AE that spells out specific seizure semiology (e.g., faciobrachial dystonic seizures) characteristic of the syndrome, are likely to increase sensitivity without negatively affecting diagnostic accuracy. However, for isolated seizures associated with anti–GAD-65 or related antibodies, any expansion of AE consensus definitions would benefit from incorporating such distinctions in presumed seizure etiology with the goal of identifying patients most likely to respond to immunotherapy, acknowledging that this can be challenging in real time and empiric immunosuppression trials may be warranted.

AE consensus criteria necessitate "reasonable exclusion of alternative causes" as part of the clinical reasoning process. This is not a throw-away statement, particularly in the case of AE, but rather a plea and imperative for rigorous differential diagnosis and follow-up—the part of consensus criteria that keeps clinicians caring for patients with AE up at night. An important caveat to the analysis by Orozco et al. is that because the dataset only included true-positive cases, the study could not calculate the specificity nor analyze the frequency of misdiagnosis. Future studies that validate the specificity and diagnostic accuracy of the AE consensus criteria would be particularly valuable for the field.

In summary, the AE consensus criteria are very useful when applied in real-world clinical practice, but there is potential for improvement by incorporating a few additional disease-specific phenotypes that at least technically (if not sometimes clinically) fall through current cracks in AE classification.

Study Funding

The authors report no targeted funding.

Disclosure

J.M. Gelfand receives research support to his institution from Roche/Genentech and Vigil Neurosciences for clinical trials. He has received personal fees for consulting for the US Department of Health and Human Services in the Vaccine Injury Compensation Program. He serves without personal compensation on trial steering committees for Roche/Genentech, including related to autoimmune encephalitis. C.-Y. Guo has received compensation for medical consulting for EMD Serono, Genentech, and Horizon Therapeutics. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

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How to cite this article: Gelfand JM, Guo C.-Y. Autoimmune encephalitis consensus criteria: lessons learned from real-world practice. *Neurol Clin Pract.* 2023;13(3):e200155. doi: 10.1212/CPJ.0000000000200155.