The Search for Autoimmune-Associated Epilepsy Continues—Are We Getting Closer to Our Target?

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Clinical Features Which Predict Neuronal Surface Autoantibodies in New-Onset Focal Epilepsy: Implications for Immunotherapies

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Objective: To generate a score which clinically identifies surface-directed autoantibodies in adults with new-onset focal epilepsy and evaluate the value of immunotherapy in this clinical setting. Methods: Prospective clinical and autoantibody evaluations in a cohort of 219 consecutive patients with new-onset focal epilepsy. Results: A total of 10.5% (23/219) of people with new-onset focal epilepsy had detectable serum autoantibodies to known or novel cell surface antigenic targets. Nine of 23 with autoantibodies were diagnosed with encephalitis, by contrast to 0/196 without autoantibodies ($P < .0001$). Multivariate analysis identified 6 features which predicted autoantibody positivity (area under the curve = 0.83): age $\geq$54 years, ictal piloerection, lowered self-reported mood, reduced attention, magnetic resonance imaging limbic system changes, and the absence of conventional epilepsy risk factors. Eleven (79%) of 14 patients with detectable autoantibodies, but without encephalitis, showed excellent long-term outcomes (modified Rankin Score = 0) despite no immunotherapy. These outcomes were superior to those of immunotherapy-treated patients with confirmed autoantibody-mediated encephalitis ($P < .05$). Conclusions: Seizure semiology, cognitive and mood phenotypes, alongside inflammatory investigation findings, aid the identification of surface autoantibodies among unselected people with new-onset focal epilepsy. The excellent immunotherapy-independent outcomes of autoantibody-positive patients without encephalitis suggest immunotherapy administration should be guided by clinical features of encephalitis, rather than autoantibody positivity. Our findings suggest that, in this cohort, immunotherapy-responsive seizure syndromes with autoantibodies largely fall under the umbrella of autoimmune encephalitis.

Antibodies Contributing to Focal Epilepsy Signs and Symptoms Score.

de Bruijn M, Bastiaansen AEM, Mojzisova H, et al. *Ann Neurol.* 2021;89(4):698-710. doi:10.1002/ana.26013.

Objective: Diagnosing autoimmune encephalitis (AIE) is difficult in patients with less fulminant diseases such as epilepsy. However, recognition is important, as patients require immunotherapy. This study aims to identify antibodies in patients with focal epilepsy of unknown etiology and to create a score to preselect patients requiring testing. Methods: In this prospective, multicenter cohort study, adults with focal epilepsy of unknown etiology, without recognized AIE, were included, between December 2014 and December 2017, and followed for 1 year. Serum, and if available cerebrospinal fluid, were analyzed using different laboratory techniques. The ACES score was created using factors favoring an autoimmune etiology of seizures (AES), as determined by multivariate logistic regression. The model was externally validated and evaluated using the Concordance (C) statistic. Results: We included 582 patients, with median epilepsy duration of 8 years (interquartile range = 2-18). Twenty (3.4%) patients had AES, of whom 3 had anti-leucine-rich glioma inactivated 1, 3 had anti-contactin-associated protein-like 2, 1 had anti-*N*-methyl-D-aspartate receptor, and 13 had antiglutamic acid decarboxylase 65 (enzyme-linked immunosorbent assay concentrations >10 000 IU/mL). Risk factors for AES were temporal magnetic resonance imaging hyperintensities (odds ratio [OR] = 255.3, 95% CI = 19.6-3332.2, $P < .0001$), autoimmune diseases (OR = 13.31, 95% CI = 3.1-56.6, $P = .0005$), behavioral changes (OR = 12.3, 95% CI = 3.2-49.9, $P = .0003$), autonomic symptoms (OR = 13.3, 95% CI = 3.1-56.6, $P = .0005$), cognitive symptoms (OR = 30.6, 95% CI = 2.4-382.7, $P = .009$), and speech problems (OR = 9.6, 95% CI = 2.0-46.7, $P = .005$). The internally validated C-statistic was 0.95 and 0.92 in the validation cohort (n = 128). Assigning each factor 1 point, an antibodies contributing to focal epilepsy signs and symptoms (ACES) score $\geq$2 had a sensitivity of 100% to detect AES, and a specificity of

84.9%. Interpretation: Specific signs point toward AES in focal epilepsy of unknown etiology. The ACES score (cutoff $\geq$ 2) is useful to select patients requiring antibody testing.

Commentary

Diagnosing and treating an autoimmune cause of seizures remains a unique opportunity in the clinical practice of epilepsy to use truly anti-*epileptogenic* rather than anti-*seizure* therapies. How to best diagnose and treat autoimmune etiologies of seizures remains, however, incompletely understood. In the setting of acute symptomatic seizures secondary to autoimmune encephalitis, diagnostic criteria are available,[1] and early initiation of immune-targeted treatment is the standard of care.[2] The entity of autoimmune-associated epilepsy, recently distinguished from autoimmune encephalitis by the International League Against Epilepsy (ILAE), holds more unanswered questions.[3] McGinty et al[4] and de Bruijn et al[5] answer some, and raise many.

1. How frequent is autoimmune-associated epilepsy?

The literature on that question holds conflicting results. One study found antineuronal antibodies in a fifth of patients presenting with new-onset seizures or epilepsy of unknown cause,[6] while others, specifically investigating chronic temporal lobe epilepsy, found a much lower figure of around 5%.[7,8] Why? The inclusion of patients identified on the inpatient neurology ward and patients with new-onset seizures[6] may reflect a diagnosis of autoimmune encephalitis, not just autoimmune-associated epilepsy, which is the primary diagnostic dilemma. de Bruijn et al[5] explicitly aim to identify those with focal epilepsy of unknown cause, who do *not* have a clinical diagnosis of encephalitis but who may harbor antineuronal antibodies, and come to the conservative figure of 3.4% of patients being antibody positive, close to that of prior studies explicitly including only chronic epilepsy.[7,8] Meanwhile, McGinty et al[4] recruited patients with *new-onset* focal epilepsy, and identified about 3 times as many antibody positive patients (10.5%), but retrospectively found that about a third of these had a clinical diagnosis of encephalitis,[1] bringing the number of true *epilepsy* cases with positive antibodies to 5.8%. Therefore, if one only considers patients with epilepsy who do not have clinically suspected autoimmune encephalitis, about 5% of focal epilepsy of unknown cause is autoimmune.

2. Who should be considered for a diagnosis of autoimmune-associated epilepsy?

If only 1 in 20 patients harbors antineuronal antibodies, then testing all focal epilepsy of unknown cause for antineuronal antibodies may not be cost effective. McGinty et al propose a weighted score using older age, self-reported mood disturbance, limbic system lesions on magnetic resonance imaging (MRI), ictal piloerection as positive predictors of antibody positivity, and intact attention on cognitive testing and presence of epilepsy risk factors as negative predictors. de Bruijn et al[5] proposes a simpler score, in which 2 or more of comorbid autoimmune diseases, behavioral changes, cognitive symptoms, speech problems, autonomic symptoms, and MRI hyperintensities of the mesial temporal lobe, results in high sensitivity for positive antibodies. Since cognitive and psychiatric comorbidities are common in epilepsy clinical practice, an operationalized method of distinguishing the cognitive and psychiatric complaints between focal epilepsy with and without antibodies would have been welcome. Overall, both scores performed better at detecting *epilepsy* with antineuronal antibodies than the widely used antibody prevalence in epilepsy (APE) score,[6] which is likely better suited to detect acute symptomatic seizures secondary to autoimmune encephalitis.

3. Are antibodies the gold standard for diagnosis?

The assumption in both papers, and most of the literature, is that the detection of antineuronal antibodies in blood is the primary method of diagnosing autoimmune-associated epilepsy—its presence confirms the diagnosis, while its absence excludes it. Let us examine both aspects of this statement.

Do all antibody positive patients have autoimmune-associated epilepsy? The antibodies examined by de Bruijn et al[5] and McGinty et al have been extensively studied among healthy controls and are thought to be specific to autoimmune neurologic disorders. Although most studies investigating antineuronal antibodies in epilepsy have excluded patients with epilepsy of known cause, one study found that none of the 125 patients with a known etiology of seizures harbored antibodies.[9] But the interpretation of a positive test becomes gray with certain antibodies, such as glycine-receptor, or neuropil antibodies without a characterized antigen. Indeed, McGinty et al and de Bruijn et al take different approaches to interpreting these types of antibodies: the former include all positive tests in their autoimmune cohort, while the latter take a more conservative approach and categorize them as "possible" and "probable" autoimmune etiologies of seizures.

Conversely, can a patient with autoimmune-associated epilepsy be antibody negative? Seronegative autoimmune encephalitis can occur, and even has diagnostic criteria.[1] Similarly, the specificity of the scores proposed by McGinty et al and de Bruijn et al was not perfect. So there is a proportion of antibody negative epilepsy patients who have a similar phenotype to those with positive antibodies. In these studies, the lack of systematic cerebrospinal fluid testing, central to the workup of autoimmune encephalitis given the possibility of false seronegative results, may lead to underdiagnosis if only serum is investigated. But in clinical practice, there are also instances when both serum and cerebrospinal fluid testing yield negative results, in a patient with a "suspicious" phenotype. Do we then

need to choose between phenotype and antibody result for a definitive diagnosis?

Other medical fields use a combination of phenotypic characteristics and antibody markers to establish a diagnosis, for example, in rheumatologic disorders. Perhaps the "gold standard" lies in the combination of phenotypic characteristics with antibody markers.

4. Should we treat all patients with epilepsy and associated antibodies with immunotherapy?

In the context of autoimmune encephalitis, immunotherapy is the cornerstone of treatment. Is the same true with autoimmune-associated epilepsy? McGinty et al found that those with positive antibodies, but without a clinical diagnosis of encephalitis, had improved functional outcomes despite receiving no immunotherapy compared to their antibody positive counterparts who did receive immunotherapy. We do not know details on cognitive or seizure outcomes, and the ones who received immunotherapy may have been "sicker" at diagnosis, but this preliminary data calls into question the *need* for immunotherapy in all antibody positive patients that one might extrapolate from autoimmune encephalitis.[5] Further, response to immunotherapy in GAD65-positive epilepsy, which comprised the majority of the antibodies found in the de Bruijn cohort, is often poor.[10] Whether all antibody positive epilepsy patients need immunotherapy, and whether the specific mode of immunotherapy should be the same for autoimmune-associated epilepsy as for autoimmune encephalitis, remains unknown.

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Supplemental Material

Supplemental material for this article is available online.

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