Merging Art with Science: A Detection Score for Autoimmune Epilepsy

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Antibodies Contributing to Focal Epilepsy Signs and Symptoms Score

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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 patients (3.4%) 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 anti–glutamic acid decarboxylase 65 (enzyme-linked immunosorbent assay concentrations >10,000IU/ml). Risk factors for AES were temporal magnetic resonance imaging hyperintensities (odds ratio [OR] = 255.3, 95% confidence interval [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 .95 and .92 in the validation cohort (n = 128). Assigning each factor 1 point, antibodies contributing to focal epilepsy signs and symptoms (ACES) score ≥ 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 ≥ 2) is useful to select patients requiring antibody testing.

Commentary

In the cusp of the 21st century, nearly two-thirds of the epilepsies were deemed to be “idiopathic.” Thanks to technological advances in genetics, neuroimaging, and laboratory testing, we are now able to pinpoint an underlying etiology far more frequently, allowing for diagnostic closure and targeted therapeutic interventions. The field of “autoimmune epilepsy” exemplifies that progress. Neurologists nowadays are vigilant to screen and treat for an autoimmune basis in patients with epilepsy who present with a more indolent course without an immediately apparent history of encephalitis.

In this manuscript, de Bruijn et al provide guidance on how to deal with this common scenario. Through a deep dive in the history and results of prior ancillary testing [Electroencephalography (EEG), Magnetic Resonance Imaging (MRI), and Cerebrospinal Fluid (CSF) analysis] of a large, prospectively collected, Dutch cohort of people with chronic, focal epilepsy of unknown etiology, they identified an inflammatory basis for patients. Two-thirds of patients had antibodies against anti-glutamic acid decarboxylase 65 (GAD65), with the rest interspersed against three neuronal surface antigens [anti–leucine-rich glioma inactivated 1 (anti-LGI1), anti–contactin-associated protein-like 2 (anti-CASPR2), and anti–N-methyl-D-aspartate receptors (anti-NMDAR)]. Certain parameters such as MRI hyperintensities in the temporal region, history of autoimmunity, cognitive, autonomic, behavioral, and speech problems were strongly associated with...
autoimmune epilepsy. These findings were validated in an external Czech cohort. By combining these predictors in unweighted fashion, an "antibodies contributing to focal epilepsy signs and symptoms" (ACES) score were created. An ACES score ≥2 had a sensitivity of 100% and a specificity of nearly 85% to detect an autoimmune etiology. Moreover, the ACES score performed better than the previously published APE/APE2 scores, particularly for patients with long disease duration and anti-GAD65 antibodies. Immuno-modulatory treatment resulted in seizure freedom in all patients with antibodies against neuronal surface antigens but provided noticeable reduction in seizure frequency in only half of the anti-GAD65 patients. Thanks to its rigorous design and execution, this study bears several advantages. The study population was referred prospectively to several academic centers and the derived score was validated in a different country increasing the generalizability of these findings. The patients were classified in definite, probable and possible autoimmune etiology based on well-defined criteria. Case record review on the majority of known symptoms and signs for an autoimmune etiology was thorough and patients were followed for one year. Extensive laboratory testing for autoantibodies was performed. Statistical analysis corrected for multiple comparisons and secondary analysis of combining the probable and possible patients with an autoimmune etiology with those without one was conducted to investigate the possibility of misclassification. A comprehensive but easy to use score was generated and compared in the same study cohort to previously published ones.

On the other hand, this investigation is not free of limitations, most of which are already acknowledged by the authors. Excluding patients with conventional etiologies of epilepsy prevented assessment of the prevalence of autoantibodies in the overall population and the creation of a score that could be applied to “all comers” in the epilepsy clinic. Symptoms and signs adjudication was based on interviewing rather than detailed neuropsychological (e.g., validated cognitive or psychiatric scales) or neurophysiological (e.g., polysomnograms or autonomic studies) testing, bearing the risk of recall bias. Given that CSF collection was available in a minority of patients only, laboratory testing was mostly based on serum samples using heterogeneous methodology. Only four types of autoantibodies were identified, and their prevalence did not allow for detailed subgroup analysis. In the interest of practicality, the generated score was unweighted despite the large differences in the adjusted odd ratios of the identified predictors. The study focused by and large on adult patients with temporal lobe epilepsy, particularly in the validation cohort. The available duration of follow up could not elucidate the longer-term risk for developing a systemic autoimmune disease or malignancy nor the longitudinal response to applied immunotherapy.

Nevertheless, this study provides solid scientific evidence and clinical direction. In line with prior investigations, it corroborates the inflammatory basis of a subset of chronic focal epilepsy without clear history of antecedent autoimmune encephalitis in much lower rates (<5%) than in new-onset cases (~10%) with and without clear history of antecedent autoimmune encephalitis (JNPN 2020), with GAD65 being the most detected culprit. It also validates the benefit of immunosuppression in carefully selected patients with a matching phenotype, no alternative etiology and high titers of well characterized autoantibodies, particularly those demonstrating intrathecal synthesis and targeting extracellular proteins. Foremost, it highlights the importance of the Neurologists' most vaunted skill, that of detailed history taking and thorough clinical examination. All patients with an identified autoimmune etiology in this study were referred as having focal epilepsy of presumed unknown etiology due to unrecognized signs of encephalitis. Perhaps the traditional emphasis on seizure control as the epicenter of an encounter in the epilepsy clinic in addition to the time constraints imposed by the ever-growing demands for clinical productivity in medical practice nowadays concealed this information from becoming immediately apparent. Admittedly, the complex interplay between chronic epilepsy and neuropsychiatric comorbidities, as well as the commonly encountered antiseizure medications adverse effects render the identification and differentiation of subtle cognitive, speech, psychiatric, sleep and autonomic disturbances challenging. At the end of the day though, it reminds us that “the future of neurology will be critically dependent on harmonizing the tensions between clinical skills and an overreliance on testing paradigms.”

Many questions regarding autoimmune epilepsy remain to be elucidated. It is unclear whether seizures themselves or chronic neuronal injury from genetic, infectious, traumatic, vascular, neoplastic, or degenerative causes can result in autoantibodies production. The plot further thickens when there is family or personal history of systemic autoimmunity. Hence, the exact course of action in antibody positive cases with a questionable phenotype or antibody negative cases with solid clinical suspicion for autoimmune epilepsy remains equivocal, particularly in the absence of randomized control immunomodulatory treatment trials or guidelines regarding surgical resections/ablations or neurostimulation approaches. Using such groups of patients with conventional epilepsy as controls in future studies may assist in establishing the pathogenic role of known and novel autoantibodies. Standardization of serum antibody testing, consistent inclusion of CSF sampling, expansion to new antibodies and longitudinal inclusion of alternative laboratory (e.g., cytokines), radiological (e.g., MR spectroscopy, positron emission tomography, and single-photon emission tomography) and neurophysiological (e.g., prolonged ambulatory EEG recordings and magnetoencephalography) biomarkers is anticipated to shed further light into the epidemiology, pathophysiology, diagnosis and treatment of these patients. Above all, we should be reminded that any polarization of physicians into technophiles who welcome and Luddites who dread the advent of biotechnological marvels is counter-productive and that the prowess of neurologists in merging the art and the science will always remain the touchstone of our practice.

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