Autoimmune encephalitis in the age of neuronal surface antigens

Since anti-NMDA receptor (NMDAR) encephalitis was first described almost a decade ago, the family of disorders associated with antibodies against neuronal surface antigens is one of the most rapidly expanding categories of neurologic disease. With this growth comes a paradigm shift in neurology—autoimmune encephalitis has evolved from an often vaguely defined clinical syndrome to a group of precisely delineated disorders associated with specific autoantibodies.

Forms of autoimmune encephalitis, even those associated with long-established neuronal autoantibodies, are now identified as having distinct subtypes likely caused by distinct pathogenic antibodies directed to neuronal surface antigens. For example, some patients with GAD65 antibodies harbor likely disease-causing antibodies against glycine receptors or GABA receptors, and the encephalitides associated with voltage-gated potassium channel (VGKC) antibodies are now subdivided into multiple unique disorders with antibodies against potassium channel associated proteins, such as leucine-rich glioma-inactivated 1 (LGI1) and Caspr2. A more precise understanding of these previously nebulous conditions may lead to important changes in clinical diagnosis and treatment. In this month’s issue of Neurology® van Sonderen et al. report a nationwide study of the incidence and clinical features of anti-LGI1 encephalitis, providing a comprehensive view of this recently defined form of autoimmune encephalitis.

The authors report a current annual incidence of anti-LGI1 encephalitis in the Netherlands of 0.83 cases per million. Although still rare, this incidence marks a steep rise in recognition of the disorder, with a nearly 4-fold increase over the known annual incidence in the preceding 3 years. As the authors point out, this incidence places anti-LGI1 encephalitis in the same ranks as Creutzfeldt-Jakob disease or Lambert-Eaton myasthenic syndrome, both well-known and clinically important disorders. Furthermore, anti-LGI1 encephalitis is almost certainly still underdiagnosed. It is likely that many potential autoimmune encephalitis patients, particularly those with atypical or mild presentations, are never even tested for the disorder. Additionally, given the low sensitivity of CSF testing alone (only a 53% detection rate in this study), diagnosis may be missed if a serum sample is not also evaluated. Therefore, as awareness of this disorder increases, the known incidence will likely rise.

As neurologists increasingly make a specific diagnosis of anti-LGI1 encephalitis, how might clinical practice change?

First, by defining the clinical syndrome more precisely, we can begin to recognize symptom sets in need of specific management, and start to delineate specific approaches to this management. For example, establishment of anti-NMDAR encephalitis as a distinct clinical syndrome has led to work describing its associated particular psychiatric features, with the goal of rationally targeted psychopharmacologic therapies. Similarly, definition of the movement disorder in patients with anti-NMDAR encephalitis has led to successful treatment of some patients with tetrabenazine. Likewise, in anti-LGI1 encephalitis, approximately half of patients have an unusual seizure type, termed faciobrachial dystonic seizures. These seizures may lack ictal EEG findings, leading to underrecognition and undertreatment. Knowledge that a patient has anti-LGI1 encephalitis may facilitate prompt appreciation and management of such seizures.

Second, an emerging story is that specific forms of autoimmune encephalitis may have distinct responses to immunotherapy. Here, the authors report an 80% initial efficacy for first-line immunotherapy (corticosteroids alone, IV immunoglobulin alone, or corticosteroids plus IV immunoglobulin or plasma exchange). A similar marked responsiveness to first-line therapy, particularly corticosteroids, has been reported for anti-LGI1 encephalitis. Although it is difficult to compare across modalities, this initial response rate appears more robust than that reported for anti-NMDAR encephalitis, approximately 50% by 1 month after first-line therapies.

In contrast, there may be persistent neurocognitive deficits even in those anti-LGI1 patients who have made substantial recoveries. In the current study, neuropsychological assessment, obtained for a subset of patients, showed disturbed spatial recognition memory. Malter et al. recently evaluated neurocognitive outcomes...
following corticosteroid therapy in patients with limbic encephalitis and VGKC complex–related antibodies. In this small study, the presence of anti-LGI1 antibodies was associated with both hippocampal atrophy and greater memory impairment, as compared to those patients with anti-Caspr2 or undifferentiated anti-VGKC antibodies. Therefore, long-term improved cognition for patients with anti-VGKC encephalitis associated with LGI1 antibodies may call for more aggressive immunotherapies. Taken together, these studies suggest immunotherapy for autoimmune encephalitis may not be a one size fits all situation, and appropriate treatment may depend on the autoantibody type.

Over the last decade, the shift to precision autoimmune neurology has had paradoxical effects on clinical practice. When there is a defined autoantibody, neurologists are increasingly more comfortable with aggressive immunotherapy. In the past, without detection of pathogenic autoantibodies, such approaches were infrequently employed and difficult to justify both clinically and financially. Yet, at the same time, when a definite autoantibody is not found, there is often reluctance to clinically diagnose and treat autoimmune encephalitis. Even in this era of acknowledged surface autoantibodies, there are many forms of autoimmune encephalitis that cannot be proven with laboratory testing, yet deserve at least a trial of immunotherapy. It is important to remember that many cases of autoimmune encephalitis likely still fall into the category of antibody-negative, with pathology caused by as yet unidentified autoantibodies.

As the understanding of autoimmune encephalitis grows with the characterization of specific autoantibodies responsible for distinct pathologies, treatment strategies and patient outcomes will improve. The current study adds to our understanding of anti-LGI1 encephalitis; as the world of autoimmune encephalitis continues to become more nuanced, the reported information will help treating neurologists determine the clinical import of anti-LGI1 antibodies, thereby refining treatment decisions in this new autoantibody era.

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**REFERENCES**