Do we need to measure specific antibodies in patients with limbic encephalitis?

Limbic encephalitis (LE) is an inflammatory brain disorder that predominantly involves the gray matter of the medial temporal lobes, resulting in mood and behavioral changes, seizures, and difficulty in forming new memories, often with retrograde memory loss. In most patients, the presence of an inflammatory process in the medial temporal lobes and hippocampi is visible on MRI fluid-attenuated inversion recovery (FLAIR) sequences and supported by demonstration of pleocytosis in the CSF. Nevertheless, several infections, systemic inflammatory diseases, and autoimmune mechanisms may lead to this syndrome (table). The recent descriptions of neuronal autoantibodies associated with LE have led to a dependency on antibody testing. However, many patients with autoimmune LE can be diagnosed on clinical grounds. This includes careful assessment of the syndrome and ancillary tests that are available in most institutions, such as routine CSF analysis with viral studies, brain MRJ, and EEG, which usually shows unilateral or bilateral temporal lobe epileptic discharges or slow activity (for a review on the clinical diagnosis of LE, see reference 1). There are few infectious agents that predominantly affect the medial temporal lobes, and most of the other potential causes of LE shown in the table can be excluded after a thorough clinical history and examination. Some symptoms may even suggest the immunologic subtype of LE (e.g., faciobrachial dystonic seizures and leucine-rich glioma-inactivated 1 [LG11] antibodies).

If the diagnosis of autoimmune LE can be established in many patients without antibody studies, what is the usefulness of antibody testing in this disorder? First, not all patients with autoimmune LE fulfill the strict clinically based criteria that were developed for cases in which antibody studies are not available. The demonstration of autoantibodies is particularly useful in patients with atypical features or who do not fulfill those criteria, such as cases with normal CSF or MRI findings. Second, the antibody findings assist in classifying LE in immunologic subtypes with different clinical implications. For example, while autoimmune LE with antibodies against intracellular antigens, such as glutamic acid decarboxylase or the paraneoplastic Hu, Ma2, or CRMP5 proteins, is often progressive, likely mediated by cytotoxic T-cell mechanisms and poorly responsive to treatment, LE with antibodies against neuronal cell surface proteins or receptors, such as LG11, CASPR2, AMPA, or GABAB receptors, is likely mediated by antibody-related mechanisms and frequently responds to immunotherapy and, if present, treatment of the tumor.

In the current issue of Neurology®, Drs. Do et al. describe 10 patients with IgG antibodies against adenylate kinase 5 (AK5), a cytoplasmic protein that has critical neuronal-specific metabolic functions. This disorder had been reported in 2007 in 2 patients with nonparaneoplastic LE refractory to treatment. The current 10 patients developed anterograde amnesia in less than 6 weeks, leading 7 patients to seek medical advice. Other symptoms included depression, disinhibition, aggressiveness, or confusion, and less frequently prosopagnosia. None of the patients had seizures, although one of the earlier patients developed generalized seizures. In many patients, the initial diagnostic consideration was Alzheimer disease, but the increased FLAIR-MRI signal in medial temporal lobes and lymphocytic pleocytosis redirected the diagnosis to LE. Only 1 of the 10 patients showed substantial clinical improvement despite 9 receiving first-line immunotherapy (steroids, plasma exchange, or IV immunoglobulin), and 5 rituximab or cyclophosphamide.

The limited improvement with immunotherapies is in line with other disorders associated with antibodies against intracellular antigens, as mentioned above. Indeed, the autopsy of one reported case showed extensive neuronal loss, microgliosis, and astrocytosis restricted to temporal cortex, hippocampi, insular cortex, and caustrum. The infiltrating lymphocytes were predominantly CD8 TIA-1 positive, confirming the presence of cytotoxic T-cell mechanisms. The origin of the antibodies in these patients is intriguing. They were all polyclonal and immunoglobulin G (IgG) 1, bound to more than one AK5 epitope, and found at high titers in both serum and CSF. The IgG index was raised, often with oligoclonal bands, consistent with a substantial

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intrathecal T-cell-dependent AK5-antibody (Ab) response, and there did not appear to be other brain-reactive antibodies, suggesting that the AK5-Abs were specifically linked to the primary cause. There was no evidence, however, that the antibodies bound to live neurons or directly caused the disease. These observations are similar to those in paraneoplastic disorders but do not appear to have a tumor, or other pathology in the periphery, and the raised CSF tau protein in 5/10 patients suggests a possible ongoing neuronal degeneration.

Based on the study of Drs. Do et al. and our own experience, AK5-Ab-associated encephalitis is infrequent; only 10 of 8,000 (0.125%) patients referred for antibody testing with possible autoimmune encephalitis had these antibodies. However, the authors mention that 2 of the 10 patients with AK5-Abs presented over a 6-month period, representing 4% (2/50) of patients with suspected autoimmune encephalitis in that period. These somewhat confusing numbers probably reflect the somewhat confusing numbers probably reflect the changing landscape of the disease. In the meantime, this study provides several useful messages: AK5-Abs associate with a rapidly progressive LE characterized by anterograde amnesia, medial temporal lobe MRI abnormalities, rare seizures, and limited response to immunotherapy, suggesting that prompt diagnosis and treatment strategies focused on cytotoxic T-cell mechanisms may improve the outcome of some of patients.

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**REFERENCES**


