

Should we regularly check for autoimmune causes in patients with refractory epilepsy without other obvious causes?

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Autoimmune epilepsy exists when seizures are accompanied by evidence of autoimmune-mediated central nervous system inflammation (1). Seizures have long been known to occur as part of the spectrum of a variety of systemic autoimmune disorders, particularly systemic lupus erythematosus (2). More recently, an increasing number of 'autoimmune encephalitis' syndromes have been identified, with seizures either as the major manifestation, or accompanying other presentations such as psychiatric disorders (3).

Both intracellular (such as Hu and Ma) and surface antigens (for example GABAR or LGI1) may be antibody targets in autoimmune encephalitis (3). The former are more likely to be associated with tumors although NMDAR antibodies may be particularly associated with ovarian teratomata.

The overall incidence of autoimmune encephalitis is unknown. Surveys such as the California Encephalitis project may only test patients with specific symptoms or signs suggesting an immune etiology. For example, of 761 patients with encephalitis of unknown origin, only 47 were tested for NMDAR antibodies; 32 were positive (4). Twenty-one percent of patients in another survey had immune-mediated encephalitis (5). These patients, however, all had symptoms of acute encephalitis, rather than seizures alone. Other antibodies are much rarer. GABAB receptor antibodies were detected in seven of 3989 patients evaluated for autoimmune encephalopathy; five of them had small cell lung cancer (6). AMPA receptor antibodies were found in 1% of patients with suspected encephalitis/encephalopathy (7). In the Bethel Antibody laboratory from 2012-2014, 4.7% of 6893 patients with epilepsy had positive tests (NMDAR and GAD65 antibodies the most common) (8).

Some clinical features may suggest that autoimmune encephalitis should be considered as a potential seizure etiology (9). Some patients have signs or symptoms of 'limbic encephalitis' in addition to seizures, such as psychiatric manifestations or increased hippocampal signal. Other explanations such as bone marrow transplant-associated HHV6 encephalitis need to be excluded as well. Adults presenting with new-onset seizures, particularly if frequent or status epilepticus occurs, and there is no other explanation such as a tumor, should be considered for evaluation. Young women with a suspected ovarian teratoma and new-onset seizures should be tested for NMDA receptor antibodies. There are a few specific seizure syndromes, such as 'faciobrachial dystonic seizures,' that have been associated with autoimmune encephalitis due to LGI1 antibodies, as well as the 'extreme delta brush' EEG pattern in NMDAR encephalitis. CSF may show non-specific markers of 'inflammation.'

Although detection of some antibodies has high specificity for the diagnosis of autoimmune encephalitis, others have less certain implications, particularly when tiers are low. Treatment involves combinations of IVIG, plasmapheresis, and steroids as well as other drugs such as cyclophosphamide or rituximab that have serious potential toxicity. Moreover, controlled trial data are limited. These considerations suggest that testing all patients with seizures of uncertain etiology for possible autoimmune encephalitis may well lead to overdiagnosis and treatment, with increased adverse effects, as well as delay in furthering understanding of the best therapeutic approach.

Only patients whose signs and symptoms lead to reasonable suspicion of the diagnosis should be tested.

References

1. ILAE Revised Terminology for Organization of Seizures and Epilepsies 2011 - 2013 <http://www.ilae.org/visitors/centre/documents/OrganizationEpilepsy-overview.pdf> accessed 01.4.2016
2. Devinsky et al *Epilepsy Currents* 2013; 13: 62-8
3. Lancaster and Dalmau *Nat Rev neurol* 2012; 8: 380-90
4. Gable MS et al *Clin Infect Dis*. 2012 Apr;54(7):899-904
5. Granerod et al *Lancet Infect Dis* 2010 Dec;10(12):835-44
6. Jeffrey et al *Neurology*. 2013 Sep 3;81(10):882-7
7. Dogan Onugoren M, et al. *J Neurol Neurosurg Psychiatry* 2015;86:965–972.
8. Bien C. American Epilepsy Society December 2015.
9. Bien C. *Epilepsia* 2013;54 (Suppl 2):48