



Autoimmune Epilepsy: Are We Seeing the Tip of the Iceberg . . . or the Whole Thing?

Autoimmune Epilepsy: Clinical Characteristics and Response to Immunotherapy.

Quek ML, Britton JW, McKeon A, So E, Lennon VA, Shin C, Klein CJ, Watson RE, Jr, Kotsenas AL, Lagerlund TD, Cascino GD, Worrell GA, Wirrell EC, Nickels KC, Aksamit AJ, Noe KH, Pittock SJ. *Arch Neurol* 2012;69:582–593.

OBJECTIVE: To describe clinical characteristics and immunotherapy responses in patients with autoimmune epilepsy. **DESIGN:** Observational, retrospective case series. **SETTING:** Mayo Clinic Health System. **PATIENTS:** Thirty-two patients with an exclusive ($n = 11$) or predominant ($n = 21$) seizure presentation in whom an autoimmune etiology was suspected (on the basis of neural autoantibody [91%], inflammatory cerebrospinal fluid [31%], or magnetic resonance imaging suggesting inflammation [63%]) were studied. All had partial seizures: 81% had failed treatment with 2 or more antiepileptic drugs and had daily seizures, and 38% had seizure semiologies that were multifocal or changed with time. Head magnetic resonance imaging was normal in 15 (47%) at onset. Electroencephalogram abnormalities included interictal epileptiform discharges in 20; electrographic seizures in 15; and focal slowing in 13. Neural autoantibodies included voltage-gated potassium channel complex in 56% (leucine-rich, glioma-inactivated 1 specific, 14; contactin-associated proteinlike 2 specific, 1); glutamic acid decarboxylase 65 in 22%; collapsin response mediator protein 5 in 6%; and Ma2, *N*-methyl-*D*-aspartate receptor, and ganglionic acetylcholine receptor in 1 patient each. **INTERVENTION:** Immunotherapy with intravenous methylprednisolone; intravenous immune globulin; and combinations of intravenous methylprednisolone, intravenous immune globulin, plasmapheresis, or cyclophosphamide. **MAIN OUTCOME MEASURE:** Seizure frequency. **RESULTS:** After a median interval of 17 months (range, 3–72 months), 22 of 27 (81%) reported improvement postimmunotherapy; 18 were seizure free. The median time from seizure onset to initiating immunotherapy was 4 months for responders and 22 months for nonresponders ($P < .05$). All voltage-gated potassium channel complex antibody-positive patients reported initial or lasting benefit ($P < .05$). One voltage-gated potassium channel complex antibody-positive patient was seizure free after thyroid cancer resection; another responded to antiepileptic drug change alone. **CONCLUSION:** When clinical and serological clues suggest an autoimmune basis for medically intractable epilepsy, early-initiated immunotherapy may improve seizure outcome.

Commentary

Neurologists are at once comfortable and uncomfortable with uncertainty: The first allows us to effectively care for patients despite incomplete knowledge, and the second drives us to new discoveries. Despite the use of sophisticated diagnostic tools, we lack a fundamental grasp of some basic facts about the epilepsies, including the cause of seizures in the majority of our patients.

Advances in neuroimaging have reduced the proportion of ‘unknown’ causes of epilepsy, and other disciplines—including genetics and immunology—are likely to reveal more. The ultimate size of the autoimmune segment is uncertain. Autoantibodies have had a recognized role for many years in the genesis of paraneoplastic limbic encephalitis, which frequently has seizures as a prominent feature. Other studies have suggested a role for autoantibodies in epilepsy outside of the bounds of paraneoplastic limbic encephalitis (1), but it has not been until

recently that more definite clues to a more expanded role of autoimmunity in epilepsy have been offered.

For example, in 2007, Bien and colleagues (2) retrospectively reported a series of patients with adult onset epilepsy and hippocampal sclerosis and found that features suggestive of an autoimmune etiology were common: A quarter had definite evidence of an autoimmune etiology and another quarter had suggestive features. They argued that immune mediated epilepsy may be more common than previously recognized.

Several approaches have been used to describe the scope and features of autoimmune epilepsy. Association studies have examined the prevalence of autoantibodies in patients with epilepsy—often refractory epilepsy—and compared them to healthy controls or patients with other neurological diseases (3, 4). Depending on the antibody and population studied, varying percentages of epilepsy patients have been discovered with the identified autoantibody and statistically distinguished from the prevalence of those antibodies in controls. Many patients did not fit the classic limbic encephalitis clinical profile, hinting at a broader spectrum of autoimmune mediated epilepsy. In general, these studies were not able to address



the pathogenicity of the identified antibodies. However, the fact that many of the antibodies studied were directed against ion channels or closely related epitopes brings a biological plausibility that the identified antibodies are pathogenic.

Other studies have strengthened the association by reporting cases or very small case series of patients with epilepsy and identified autoantibodies who responded to immunotherapy (5, 6). These reports are suggestive of a pathogenic role of the autoantibodies, although the numbers are small and the reports uncontrolled.

In the current study, Quek and colleagues from the Mayo Clinic make a sizable contribution to understanding the scope of autoimmune epilepsy (7). They approached the problem from the viewpoint of the clinician who is confronted with a patient with suspected autoimmune epilepsy. They reported a retrospective series of 32 patients seen over 5 years in both autoimmune neurological and epilepsy clinics. The sole or predominant presenting symptom was recurrent, uncontrolled seizures. These selected patients had a suspected autoimmune etiology on the basis of detected autoantibodies, inflammatory CSF (pleocytosis, elevated IgG) or an inflammatory pattern on MRI (increased T2 or DWI signal or gadolinium enhancement). They tested these patients for a wide range of paraneoplastic and nonparaneoplastic autoantibodies.

The group contained more women (59%) than men, as might be expected in autoimmune disease. The median age was 56 years. Autoantibodies were present in 91% (most with voltage gated potassium channel antibodies), 31% had inflammatory CSF, and 63% had identified inflammatory changes on MRI. The patients presented with refractory partial seizures; they were taking a median of 3 AEDs yet still experiencing frequent seizures (81% had daily seizures).

Twenty-seven of the 32 patients were treated for presumed autoimmune epilepsy with a range of immunotherapies—most commonly, IV methylprednisolone but also IVIG and combination therapies. Over a median 17 months of follow-up, 81% improved and 67% became seizure free; 44% within 12 weeks of starting immunotherapy. Median time from seizure onset to initiation of therapy was 4 months in responders and 22 months in nonresponders, suggesting a possible benefit of early treatment. Conventional AED changes were made throughout the course of the immunotherapy; this, or the natural history of the disorder, could have been responsible for some of the improved seizure control. Nonetheless, the results—especially the seizure-free rates in this highly refractory population—are striking and difficult to ignore. Importantly, about one-third of the patients did not have typical features of limbic encephalitis. The authors concluded that clinicians should maintain a high index of suspicion for autoimmune causes of epilepsy in patients with high seizure frequency, multifocality, AED resistance, personal or family history of autoimmunity, recent or past history of neoplasia, or antibody, imaging, or CSF findings suggestive of an inflammatory process. They cautioned that MRI and CSF studies were normal in half their patients, and these negative findings did not exclude an autoimmune etiology.

What is the scope of autoimmune epilepsy? This is a question without an easy answer. Prospective and population-based studies will be needed to better define the epidemiology of autoimmune epilepsy. In some cases, the role of auto-

immune antibodies could be overestimated, as in the early experience with GluR3 antibodies in Rasmussen's encephalitis. More often, the contribution of autoantibodies may have been underestimated. Better characterization of the spectrum of clinical signs associated with autoimmune epilepsy will help clarify its scope. For example, patients with anti-NMDA receptor antibodies may have a distinct syndrome of acute onset severe epilepsy, neuropsychiatric change, choreoathetoid movements, dysautonomia, and hypoventilation, but these features may define only a subset of patients who share this pathogenic mechanism. This classic presentation, often seen in a young woman with an ovarian teratoma, has been broadened to include patients of both genders and varying ages (8). Discovery of new autoantibodies may also expand the range of conditions considered to be autoimmune. Is it possible that patients with NORSE or FIRES are part of the autoimmune spectrum and harbor an as-yet unidentified autoantibody?

The study by Quek and colleagues is a major contribution to our understanding of the clinical and diagnostic findings in presumed autoimmune epilepsy. The patients were well characterized by extensive autoantibody and other diagnostic studies. The patients were all referred because of severe refractory epilepsy, and it is possible that a group of patients with milder autoimmune epilepsy were excluded. How large is the autoimmune epilepsy iceberg? Certainly bigger than most of us suspected a decade ago.

by David Spencer, MD

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