Epilepsy Currents
2023, Vol. 23(5) 286-288

DOI: 10.1177/15357597231175009
journals.sagepub.com/home/epi
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Is There a Continuum Between Acute Symptomatic Seizures Secondary to Autoimmune Encephalitis and Autoimmune-Associated Epilepsy?

Seizure Underreporting in LGI1 and CASPR2 Antibody Encephalitis

Baumgartner T, Pitsch J, Olaciregui-Dague K, Hoppe C, Racz A, Rüber T, Becker A, von Wrede R, Surges R. *Epilepsia*. 2022;63(9): e100-e105. doi:10.1111/epi.17338. PMID: 35735209

Patients with anti-leucine-rich glioma-inactivated1 protein (LGI1) or anti-contactin-associated protein 2 (CASPR2) antibody encephalitis typically present with frequent epileptic seizures. The seizures generally respond well to immunosuppressive therapy, and the long-term seizure outcome seems to be favorable. Consequentially, diagnosing acute symptomatic seizures secondary to autoimmune encephalitis instead of autoimmune epilepsy was proposed. However, published data on long-term seizure outcomes in CASPR2 and LGI1 antibody encephalitis are mostly based on patient reports, and seizure underreporting is a recognized issue. Clinical records from our tertiary epilepsy center were screened retrospectively for patients with LGI1 and CASPR2 antibody encephalitis who reported seizure freedom for at least 3 months and received video-electroencephalography (EEG) for >24 h at follow-up visits. Twenty (LGI1, n = 15; CASPR2, n = 5) of 32 patients with LGI1 (n = 24) and CASPR2 (n = 8) antibody encephalitis fulfilled these criteria. We recorded focal aware and impaired awareness seizures in four of these patients (20%) with reported seizure-free intervals ranging from 3 to 27 months. Our results question the favorable seizure outcome in patients with CASPR2 and LGI1 antibody encephalitis and suggest that the proportion of patients who have persistent seizures may be greater. Our findings underline the importance of prolonged video-EEG telemetry in this population.

Commentary

The autoimmune encephalitides are rare and still a cause for much debate regarding biomarkers, diagnosis, treatment, and prognosis. In these conditions, neural antibodies are associated with a variety of symptoms, including impaired memory and cognition, seizures, movement disorders, psychiatric symptoms, and more. Seizures are a frequent manifestation in certain forms of autoimmune encephalitis, and in some cases may be the most severe symptom, progressing to status epilepticus and increasing morbidity. However, differing seizure types, frequency, severity, and responses to treatment, are still being understood, in part because autoimmune encephalitis can be caused by different antibodies, and the overall prevalence is very low. As such, studies of a particular type of autoimmune encephalitis often have only a handful of patients.

In the setting of seizures associated with encephalitis, the recognition of an autoimmune etiology is important as it can guide treatment toward the use of immunotherapy and not only anti-seizure medication (ASM). However, this understanding is not enough. The International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce proposed 2 conceptual definitions to help understand and better manage patients with seizures associated with autoimmune encephalitis: "acute symptomatic seizures secondary to autoimmune encephalitis" and "autoimmune-associated epilepsy."[1] Acute symptomatic seizures secondary to autoimmune encephalitis refers to seizures occurring during the active phase of the autoimmune encephalitis. Seizures in this setting often respond to immunotherapy and other symptoms of encephalitis typically improve simultaneously with this treatment. Examples of acute symptomatic seizures secondary to autoimmune encephalitis include NMDAR, $GABA_BR$, LGI1, and CASPR2 antibody encephalitis. On the other hand, patients with autoimmune-associated epilepsy tend to have seizures that linger long after the acute phase of the encephalitis has resolved. These seizures may be chronic and resistant to immunotherapy and ASMs. Some examples include GAD65, onconeural protein antibodies, and Rasmussen encephalitis.

In patients with anti-LGI1 antibody encephalitis, the pathognomonic ASM-resistant tonic or tonic-dystonic motor spasms[2,3] commonly referred to as faciobrachial dystonic seizures[4] disappear within 30 days of starting immunotherapy in

at least half of cases.[5] Other studies have reported that a large majority of these patients become seizure-free and are off ASMs 2 years after the acute encephalitis.[6] Such findings are well aligned with the definition of "acute symptomatic seizures secondary to autoimmune encephalitis." However, encephalitis relapses can occur. These relapses may be manifested by a recurrence of psychiatric and memory problems, often accompanied by seizure recurrence.[6] The ILAE Autoimmunity and Inflammation Taskforce suggests that labeling "acute symptomatic seizures" in the setting of encephalitis recurrence would still be appropriate, if the judgment of the clinician "suggests that seizures occurring in the relapse remain potentially reversible." But what if the seizures never really went away? What if this is not a "recurrence" but simply delayed recognition of an ongoing symptom? And how does one know that the encephalitis ever really went away?

Baumgartner and colleagues noted that the studies reporting good outcomes in patients who had been diagnosed with LGI1 and CASPR2 antibody encephalitis were mainly based on patient-reported seizure activity. As such, they sought to evaluate the video-EEG studies obtained in their patients who self-reported being seizure-free for at least 3 months. Interestingly, these authors discovered underreporting of seizures in patients with LGI1 and CASPR2 antibody encephalitis, leading them to question the presumption of "favorable seizure outcome" in patients with these forms of voltage-gated potassium channel (VGKC) complex autoimmune encephalitis.[7] In this study, they included patients (1) with previous positive results for anti-LGI1 antibodies and/or anti-CASPR2 antibodies, (2) who fulfilled criteria for autoimmune limbic encephalitis, (3) who reported seizure-freedom for at least 3 months, and (4) who had at least 24 hours of video-EEG during the seizure-free period. From a group of 32 patients with LGI1 and CASPR2 antibody encephalitis, 20 patients fulfilled the above criteria. Patients who did not have video-EEG in the seizure-free period, those who were still having seizures and those lost to follow-up were excluded.

Among the 20 eligible patients (15 LGI1 and 5 CASPR2), the period of active seizures around the time of diagnosis of encephalitis lasted 1 to 96 months (average 21.3 +/- 22.39). The period of reported seizure-freedom at last follow-up ranged from 3 months to 76 months (average 24.2 +/- 20.91). All patients received first-line immunosuppressive therapy at the time of diagnosis and were taking ASMs at the time of last video-EEG. Out of the 20 patients who reported seizure-freedom, 4 (20%) were found to be having seizures as determined by 24 to 48 hours of video-EEG. These patients did not have any other signs of encephalitis relapse. There was no decline in neuropsychological performance or behavioral changes. There were no new seizure types and the imaging studies had not shown any changes. Two of the 4 patients with seizures during video-EEG were having focal impaired awareness seizures (FIAS) and were unaware of them. The other 2 patients were having focal aware seizures, but one did not interpret the symptoms as seizure and the other had "habitual auras." The specific ASMs taken by the patients at the time of video-EEG were not described, information that would have been interesting to know in this cohort given that focal temporal lobe seizures in patients diagnosed with VGKC-complex autoimmune encephalitis may respond well to sodium channel blockers or acetazolamide, and poorly or not at all to other classes of ASM.[8,9]

There are several reasons for seizure underreporting, especially in patients with FIAS. An older study of patients admitted to an epilepsy monitoring unit showed that only 44% of FIAS were recognized by patients, possibly due to retrograde amnesia.[10] Furthermore, seizures may be interpreted as something else (panic attacks, anxiety, disorientation, etc). In addition to underreporting clinical seizures, patients with anti-LGI1 encephalitis may also have frequent subclinical temporal lobe seizures. In a study of 9 patients with LGI1 antibody encephalitis, 5 (56%) had subclinical temporal lobe seizures identified during routine EEG recordings that included hyperventilation.[11] All seizures had unilateral onset, although patients would have seizures arising independently from both temporal lobes. Although these subclinical seizures were present early in a few patients, in others they were discovered 6 to 14 months after initial symptoms, suggesting an ongoing epileptic dysfunction.

Baumgartner et al's study was retrospective and some limitations were inevitable. For instance, patients included had video-EEG to determine whether or not to stop ASM. As such, some patients elected not to undergo the study and stay on medication regardless of their need. In addition, immunosuppressive therapy was not standardized, and neither were the timing of follow-up visits nor the choices of ASMs, the latter particularly relevant for these 2 types of autoimmune encephalitis, as mentioned above. Finally, antibody titres are not reported from around the time the last video-EEG recordings were done.

Despite those shortcomings, this is a very important study as it challenges the notion that LGI1 and CASPR2 antibody encephalitis are generally associated with good seizure outcome, so long as the conditions are recognized early and treated with immunotherapy.[12] Furthermore, the results provide good evidence that the lines between "acute symptomatic seizures secondary to autoimmune encephalitis," "acute symptomatic seizures secondary to autoimmune encephalitis *recurrence*, or *persistence*," and "autoimmune-associated epilepsy" are blurred. One can probably diagnose an episode of recurrent encephalitis if it is associated with recurrence of non-seizure symptoms, such as neurocognitive decline and behavioral changes. But if those nonseizure symptoms are absent and the patient is found to still have clinical or subclinical seizures, are those caused by a recurrence of the encephalitis, a persistence of the encephalitis, or are they now a chronic post-encephalitic symptom, to be classified as "autoimmune-associated epilepsy"? With the tools we currently have at hand, is it possible to know?

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Acknowledgments

The author wishes to thank Dr Richard Wennberg for his thoughtful review and comments to this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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