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1. Blümcke, Ingmar, et al. "Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy." *Epileptic Disorders* 21.2 (2019): 129-140.

# Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions

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## Abstract

Seizures are a well-recognized and often prominent manifestation of autoimmune encephalitic syndromes. Progress in detection of pathogenic neural autoantibodies has led to increased awareness of autoimmune causes of seizures. Clinical studies of patients with these autoantibodies have improved our understanding of the seizure characteristics, treatments, and seizure prognosis in these disorders. The International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce proposes conceptual definitions for two main diagnostic entities: (a) acute symptomatic seizures secondary to autoimmune encephalitis, and (b) autoimmune-associated epilepsy, the latter of which suggests an enduring predisposition to seizures. Such a distinction is relevant when discussing the pathophysiology, treatment, prognosis, and social consequences of these disorders. We discuss the role of biomarkers in the application of these conceptual definitions and illustrate their use in patients cared for by members of the task force.

## KEYWORDS

autoimmune encephalitis, autoimmune epilepsy, classification, seizures

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## 1 | INTRODUCTION

Seizures are a common manifestation in encephalitis due to immune causes. In addition, administrative database research has shown patients with systemic autoimmune disorders to be at increased risk of seizures.<sup>1</sup> The term “autoimmune epilepsy” was initially suggested as a concept in 2002 in recognition of an emerging body of evidence suggesting the importance of autoimmune mechanisms in a subset of patients with “epilepsy.”<sup>2</sup> Use of the term “autoimmune epilepsy” has increased in the last decade in publications involving cohorts of patients with intractable seizures of unusual seizure frequency and manifestations, in which the cause was determined to be autoimmune encephalitis.<sup>3–4</sup> The often definitive response to immunotherapy observed in these patients emphasized the importance for neurologists to consider a diagnosis of autoimmune encephalitis when encountering patients with similar features.<sup>5</sup> The proliferation of the use of the term “autoimmune epilepsy,” however, has led to criticism hinging on the long-held important distinction between the concepts of epilepsy and seizures. There have also been calls to eliminate the term entirely once a diagnosis of encephalitis is established, given the term's emphasis on the seizures occurring in these disorders at the expense of other important neurologic manifestations in these patients.

In the most recent International League Against Epilepsy (ILAE) Definitions and Classifications guideline, the category of “immune etiology” was introduced alongside structural, genetic, infectious, and metabolic etiologies.<sup>6</sup> In the commenting paragraph of this publication, the Classification Commission explicitly refers to autoimmune encephalitides characterized by antibodies against the *N*-methyl-D-aspartate receptor (NMDAR) or leucine-rich glioma inactivated 1 (LGI1) as representative of “immune etiology.” “Immune etiology” was deemed to have particular value given that it identifies a group of patients who may benefit from etiology-targeted therapies distinct from those used in epilepsy due to other etiology categories.

Use of the word “epilepsy” in the context of autoimmune encephalitis has been challenged, with these concerns articulated in a recent publication.<sup>7</sup> The authors highlighted that many patients with encephalitis associated with autoantibodies against surface antigens achieve complete seizure freedom after treatment, and that in many, antiseizure medications (ASMs) can eventually be discontinued. Such features are counter to the concept of epilepsy as a condition defined by an *enduring* predisposition to unprovoked seizures.<sup>8,9</sup> In those who no longer need life-long ASMs, the authors argued that the term epilepsy is inappropriate and potentially harmful given the social stigma and restrictions associated with chronic epilepsy. The authors suggested use of the term “autoimmune seizure disorder” rather than epilepsy in reference to the seizures that occur in these diseases.

Clearly, there is a need to standardize the terminology used in reference to seizures occurring in the context of

### Key Points

- We support using the term “acute symptomatic seizures secondary to autoimmune encephalitis” to refer to seizures occurring in the setting of the active phase of immune-mediated encephalitis.
- We suggest the term “autoimmune-associated epilepsy” to refer to chronic seizures determined to be secondary to autoimmune brain diseases.
- Autoimmune-associated epilepsy may stem from ongoing brain autoimmunity and also from associated structural brain abnormalities.
- The distinction between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy has clinical and therapeutic implications.

autoimmune brain diseases. Great effort has been made by the ILAE to clarify the terminology most appropriate to be used in the care of seizures and epilepsy. One important distinction has been the differentiation of acute symptomatic seizures from epilepsy.<sup>8–10</sup> In the present article, the ILAE Autoimmunity and Inflammation Taskforce proposes conceptual definitions to be used in reference to seizures occurring in autoimmune disorders, in order to align with current ILAE definitions and concepts. We then illustrate the application of these definitions to cases seen by the authors.

## 2 | DEFINITIONS

### 2.1 | Acute symptomatic seizures secondary to autoimmune encephalitis

Evidence is accumulating that certain antibodies to neural surface antigens have a direct effect on neural function.<sup>11</sup> This has prompted treatments aimed at downregulating and removing these antibodies in the treatment of these conditions. In addition, early response to immunotherapy in some antibody-mediated encephalitides (eg, LGI1)<sup>12,13</sup> suggests that immunological mechanisms beyond those caused directly by antibody binding are likely at work as well. Indeed, the majority of such patients are reported to achieve a marked reduction or elimination of seizures with immune-targeted therapy, in parallel with resolution of other symptoms of autoimmune encephalitis. In one study of NMDAR-antibody encephalitis, of the 88 patients with seizures during the encephalitic illness, more than 80% became seizure-free after 6 months, and no patients had seizures 24 months after disease onset. Thirty-eight percent of the cases stopped ASMs as



early as 3 months after onset and still remained seizure-free.<sup>14</sup> An even more rapid effect of immunotherapy is observed in patients with LGI1 antibodies, with 51% of patients showing cessation of faciobrachial dystonic seizures (FBDS) within 30 days after starting immunotherapy.<sup>12</sup> In another study of LGI1-antibody encephalitis, of the 21 patients with follow-up greater than 2 years, 86% were seizure-free for  $\geq 1$  year at most recent follow-up, and 72% were not taking ASMs.<sup>15</sup> The same group reported that 89% of 110 patients with antibodies against the NMDAR, LGI1, or  $\gamma$ -aminobutyric acid-B receptor (GABA<sub>B</sub>R) achieved seizure freedom, with a median follow-up of 27 months (interquartile range [IQR] 15–49).<sup>13,16</sup> Of the 98 patients who reached seizure freedom (with or without immunotherapy), 76 (86%) successfully discontinued ASMs without seizure recurrence at last follow-up. Nine of 12 patients still on ASMs had a follow-up of greater than 12 months (personal communication by Dr de Bruijn). Only one patient (with LGI1-antibodies) was said to have progressed to epilepsy, whereas the remaining ones who never achieved seizure freedom died of the encephalitis.

Relapses, often accompanied by seizure recurrence, have been described with many autoantibodies, including NMDAR-, GABA<sub>B</sub>R-, LGI1-, and contactin-associated protein-like 2 (CASPR2)-antibody encephalitis. The relapse rate in autoimmune encephalitis ranges from 15% to 35%, depending on the antibody.<sup>15,17–19</sup> The overall presence of seizures in such a patient beyond what is usually implied by use of the term “acute,” presents some challenges in use of the term “acute symptomatic seizures.” However, it would still be appropriate to conceptualize such situations as a recurrence of “acute symptomatic seizures” rather than epilepsy if the judgment of the clinician suggests that the seizures occurring in the relapse remain potentially reversible.

In reference to current ILAE terminology, seizures in the context of autoimmune encephalitis at initial or relapsing presentations are best conceptualized as acute symptomatic seizures instead of epilepsy, despite the seizures sometimes taking weeks or even months to resolve. For such patients, the taskforce suggests the term “acute symptomatic seizures secondary to autoimmune encephalitis.” With this term, there is an understanding that there is a specific entity causing the seizures. The term implies the need to discover the underlying entity and indicates that the seizures are a consequence of an autoimmune disorder.

### 2.1.1 | Autoimmune-associated epilepsy

In contrast to patients with acute symptomatic seizures, some patients with immune-mediated brain diseases have seizures that become chronic and prove resistant to both ASMs and immunotherapy. This may occur more frequently in those with antibodies targeting glutamic acid decarboxylase (GAD)

65,<sup>20–22</sup> onconeural protein antibodies (eg, Hu, Ma2, collapsing response mediator protein 5/CV2),<sup>23</sup> and in Rasmussen encephalitis.<sup>24</sup> In these conditions, evidence suggests that cytotoxic T cells play a more prominent role in pathogenesis, resulting in neural death, and that the neural autoantibodies are present more as a by-product of the immune response rather than playing a direct pathogenic role.<sup>25–27</sup> In this context, the persistence of seizures despite immunotherapy suggests an enduring predisposition, thus fitting the current conceptual definition of epilepsy. In addition, the low rates of seizure freedom in these conditions suggest that their risk of further seizures over the next 10 years is very high. Thus, in these conditions, the conceptual and practical definitions of epilepsy are fulfilled.<sup>8,9</sup>

Further questions remain as to an etiological characterization in these cases. The term “autoimmune epilepsy” implies that the etiology is purely autoimmune. However, a structural etiology may also exist in these patients, for example, hippocampal atrophy, or multifocal cortical cell loss with gliosis as in Rasmussen encephalitis.<sup>27,28</sup> We propose the term “autoimmune-associated epilepsy,” to highlight that immune factors, postencephalitic structural injury, or a combination (as in case 3) may be contributing to the chronic predisposition to seizures in these patients. The use of the term “autoimmune epilepsy” implies that an active inflammatory response is present, and suggests that immunotherapy should be considered as the primary treatment. However, immune-altering therapy is often ineffective in these patients. The less definite term “autoimmune-associated epilepsy” permits consideration that non-immune factors, such as structural, are also present, and may be playing a role in seizure production. This concept allows the clinician to continue to treat the epilepsy by conventional means or even to address identified structural causes with epilepsy surgery in well-selected cases.<sup>28</sup>

Let us consider the arguments for both frameworks in the context of autoimmune-associated epilepsy, noting that “immune” and “structural” etiologies can coexist in the same patient and both likely play a role in seizure production. Certain observations support the concept of “structural (postencephalitic) epilepsy.”<sup>29</sup> T-cell-mediated encephalitides lead to a loss of neurons and gliosis, as has been demonstrated in the setting of Rasmussen encephalitis and its associated hemispheric tissue destruction.<sup>24,27</sup> In addition, histopathological investigations of tissue obtained after epilepsy surgery among patients with neural antibodies show varying degrees of neural loss, including hippocampal sclerosis.<sup>28</sup> However, not all patients with antibody-mediated encephalitis have MRI or histopathological evidence of brain atrophy. Indeed, structural injury leading to epilepsy after encephalitis may be microscopic and not always visible on imaging.

Other arguments support the concept of “immune-mediated epilepsy.” First, structural brain injury is not always

sufficient to cause epilepsy. Indeed, hippocampal atrophy is a frequent consequence of LGI1-antibody encephalitis, but its presence does not necessarily lead to epilepsy according to preliminary longitudinal studies.<sup>15,30,31</sup> Second, even in late stages of Rasmussen encephalitis, there may still be minimal T-cell inflammation present.<sup>32,33</sup> Similarly, although there is no evidence for a direct role of antibodies in the pathogenicity of GAD65 and onconeural antibodies or consistent response to immunotherapy, there is often histopathological evidence of inflammation in such patients on epilepsy surgery or brain biopsy.<sup>25,28</sup> One may postulate that T-cell-mediated inflammation may lead to an enduring alteration in the brain conducive to spontaneous seizures in such patients.<sup>34</sup>

2.2 | Discussion of definitions

We propose to conceptually distinguish acute symptomatic seizures as a manifestation of active autoimmune encephalitis and autoimmune-associated epilepsy (Table 1).

Why have epileptologists not consistently made this distinction? After an inciting brain injury such as stroke or head trauma, acute symptomatic seizures are generally restricted to the first 7 days of acute injury.<sup>10</sup> The term “acute” fits easily in the timeframe of seizures occurring in the immediate aftermath of a well-defined insult such as stroke or trauma, but its use is more difficult in seizures due to autoimmune encephalitis, in which onset of the illness is sometimes uncertain, and in which seizures may be present for weeks or months prior to diagnosis and successful treatment. However, according to the ILAE definition of “acute symptomatic seizures,” there are no specific time parameters for use of the term, only a requirement that seizures occur in proximity with an “active phase” of an underlying condition. In fact,

in this terminology-consensus article, “autoimmune diseases” are specifically mentioned as an example of a situation in which the term might be used.<sup>10</sup> The determination of active disease in autoimmune encephalitis generally stems from a combination of laboratory (eg, elevated titers of antibodies to surface antigens, cerebrospinal fluid [CSF], and imaging markers of inflammation) and clinical evidence of active encephalitis. Unfortunately, we cannot recommend a strict operational time definition for these disorders given the wide spectrum in clinical presentation, which can vary according to the particular associated antibody and timing of immune-targeted therapy.

Early acute symptomatic seizures may be responsive to immunotherapy, but in patients with autoimmune-associated epilepsy, the seizures are typically not immunotherapy-responsive.<sup>22</sup> In such cases, there is precedence for use of the term epilepsy in patients experiencing recurrent seizures following other types of brain injury in which seizures continue beyond a timeframe that can be considered the active phase. Examples include the epilepsies following traumatic brain injury and stroke.

The role of biomarkers, both in predicting progression to epilepsy after acute symptomatic seizures, and in distinguishing between “structural” or “immune” etiology in the chronic epilepsy phase, will be instrumental to the development of practical definitions and in determining future treatment directions. The specific antibody and type of encephalitis in question serve as useful prognostic biomarkers early in the disease: for example, autoimmune encephalitis with acute symptomatic seizures has a good chance of eventual remission when due to LGI1 and NMDAR antibodies. However, the presence of other antibodies (eg, GAD65 and onconeural) and Rasmussen encephalitis are associated with a grimmer prognosis and development of chronic epilepsy. It remains unknown which of these terms is most applicable to

TABLE 1 Acute symptomatic seizures secondary to autoimmune encephalitis versus autoimmune-associated epilepsy

	Acute symptomatic seizures secondary to autoimmune encephalitis	Autoimmune-associated epilepsy
Underlying antibodies or conditions	Antibodies against certain surface antigens (NMDAR, LGI1, CASPR2, GABABR, GABAAR, mGluR5, DPPX, AMPAR) and intracellular antigens (onconeural, GAD65)	Antibodies against intracellular antigens (onconeural, GAD65) Rasmussen encephalitis Persistent epilepsy after acute autoimmune encephalitis
Hypothesized pathophysiology	Antibody-mediated ictogenesis	Epileptogenesis due to structural postencephalitic pathology and/or ongoing T-cell-mediated brain inflammation
Therapy	Immunotherapy Antiseizure medications (usually ineffective in isolation)	Antiseizure medications (often ineffective) Epilepsy surgery (usually with incomplete response) Immunotherapy (usually with poor response)
Outcome	Seizures usually terminate with remission of encephalitis. Potential for antiseizure medication discontinuation Potential enduring cognitive deficits.	Pharmacoresistant focal epilepsy common Potential enduring cognitive deficits

less common antibodies due to more limited data, for example, those related to GABA<sub>A</sub>R,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor, or glial fibrillary acidic protein (GFAP). Cases of seronegative autoimmune encephalitis pose even greater difficulty.

### 2.2.1 | Features aiding the identification of acute symptomatic seizures and epilepsy

Acute symptomatic seizures secondary to autoimmune encephalitis are generally more straightforward to diagnose than autoimmune-associated epilepsy. Various tools and criteria can be used to help identify patients with autoimmune encephalitis.<sup>5,35</sup> Here we summarize key clinical characteristics relevant to seizures in the context of autoimmune encephalitis.

#### *Clinical characteristics*

The clinical features of acute symptomatic seizures secondary to autoimmune encephalitis have recently been reviewed.<sup>36</sup> Seizures are usually resistant to ASMs early in the course<sup>3,37–39</sup> and status epilepticus at presentation can also occur.<sup>40,41</sup> The syndrome of FBDS is highly suggestive of LGI1 encephalitis.<sup>12,42,43</sup> Other notable focal aware seizure types associated with LGI1 antibodies include thermal, sensory, and pilomotor seizures; however, these can also be seen in other limbic encephalitis and nonencephalitic forms of limbic focal seizures.<sup>15,44–46</sup> Paroxysmal dizziness spells are uncommon yet characteristic in LGI1-antibody encephalitis, which may represent vertiginous seizures.<sup>47</sup> In grouped cohorts of patients representing a variety of antibody types, the following seizure characteristics have been reported in contrast to focal seizures due to other causes: multiple seizure types, high seizure frequency,<sup>45,48</sup> short seizure duration,<sup>48</sup> relative lack of postictal confusion,<sup>48</sup> perisylvian semiology (eg, multimodal auras, facial clonic seizures, sensory aphasia),<sup>49,50</sup> and a proclivity for bilateral tonic-clonic seizures to occur nocturnally.<sup>48</sup> Finally, these patients usually lack other typical epilepsy risk factors, such as febrile seizures or family history of epilepsy.<sup>50</sup>

Status epilepticus may occur early in the disease course. Status epilepticus at presentation is particularly common in GABA<sub>B</sub>R and GABA<sub>A</sub>R antibody encephalitis.<sup>51–54</sup> One large retrospective cohort study identified an autoimmune cause in one-third of new-onset status epilepticus cases in which antibody testing was performed (many patients were excluded because no testing was done). Of note, antibodies of unclear clinical significance were included.<sup>55</sup> Another prospective cohort study identified an autoimmune cause in one fourth of a cohort with status epilepticus.<sup>56</sup>

Cognitive and behavioral dysfunction commonly accompany acute symptomatic seizures secondary to autoimmune

encephalitis, ranging from episodic memory loss<sup>30</sup> to complex presentations of concomitant involvement of mood, psychosis, and catatonia, as seen in NMDAR-antibody encephalitis.<sup>57,58</sup> Dysautonomia and movement disorders, such as orofacial dyskinesias, are also characteristic of NMDAR-antibody encephalitis,<sup>58</sup> which may be misdiagnosed initially as seizures.<sup>59</sup> A viral prodrome may precede the onset of autoimmune encephalitis. The clearest example of this is herpes simplex virus encephalitis, in which NMDAR-antibody encephalitis may occur a few weeks after initial resolution.<sup>60</sup> A prior history of malignancy, particularly in the range of a few years prior to seizure onset, suggests the possibility of paraneoplastic encephalitis.<sup>35</sup> Finally, a personal or family history of systemic autoimmune disorders may be a risk factor.<sup>3</sup>

#### *Ancillary testing*

Although neuroimaging may be negative, particularly in NMDAR encephalitis, there are several imaging findings suggestive of autoimmune encephalitis, including classic medial temporal fluid-attenuated inversion recovery (FLAIR) hyperintensities,<sup>5,61,62</sup> and multifocal gray and/or white matter FLAIR hyperintensities<sup>62,63</sup> in the acute phase. Gadolinium enhancement and diffusion restriction may also accompany FLAIR hyperintensities.<sup>64</sup> In children with myelin oligodendrocyte glycoprotein (MOG) antibodies presenting with seizures, nonspecific isolated white matter lesions may be seen without other imaging features of acute disseminated encephalomyelitis and may herald typical autoimmune encephalomyelitis by months to years.<sup>65</sup> Cerebral spinal fluid (CSF) findings suggestive of inflammation, such as pleocytosis, elevated protein or IgG index, and the presence of oligoclonal bands, help to support an autoimmune cause when present, but are absent in up to 60% of cases, especially in LGI1-antibody associated seizures, including FBDS.<sup>66,67</sup>

Electroencephalography (EEG) abnormalities are commonly present in autoimmune encephalitis; however, normal EEG does not rule out the diagnosis. Generalized rhythmic delta activity,<sup>68</sup> with or without superimposed beta activity (“extreme delta brush”), is characteristic of NMDAR-antibody encephalitis<sup>69</sup>; however, EEG findings are otherwise not specific to autoimmune encephalitis in general. FBDS typically can have no EEG correlate, or can be associated with subtle findings of generalized electrodecrement with contralateral frontal slow<sup>70</sup> or infraslow activity identified with use of broadband recordings not typically employed in routine clinical evaluation.<sup>71</sup> Finally, LGI1-antibody encephalitis may alternatively be associated with multiple daily brief temporal lobe seizures.<sup>45,72</sup>

The more challenging diagnostic dilemma is the identification of autoimmune-associated epilepsy in which definitive clinical features of encephalitis are lacking. For example, GAD65 antibodies can be associated with chronic epilepsy in the absence of a prior history of limbic encephalitis.<sup>73</sup>

Seizure characteristics observed in autoimmune encephalitis, summarized earlier, should be investigated in cohorts without other features of encephalitis to improve our understanding of the phenotype of autoimmune-associated epilepsy.

We next illustrate use of our proposed conceptual definitions of acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy through discussion of representative cases seen by the authors.

### 3 | ILLUSTRATIVE CASES

#### 3.1 | Case 1

A 13-year-old previously healthy girl presented with three episodes of altered responsiveness and head deviation of 1 minute duration. EEG demonstrated right temporal slowing and sharp waves. Brain magnetic resonance imaging (MRI) was normal. After starting daily clobazam, seizures resolved. Over the following week, she developed altered behavior, agitation, repetitive and paranoid language, and disrupted speech. She had increased tone, dystonic posturing, and repetitive stereotypical mouth movements with pouting and associated sustained blepharoclonus. A dose of risperidone was associated with worsening of her tone and rigidity and a rise in creatine kinase. CSF studies revealed lymphocytic pleocytosis (22 lymphocytes/ $\mu$ l), and positive CSF NMDAR antibodies. No teratoma was identified. Despite intravenous pulse methylprednisolone 1 g for 3 days and plasma exchange, 5 cycles over 10 days, she deteriorated and required intensive care admission for 2 weeks for management of agitation, repetitive stereotyped movements, and autonomic dysregulation. Over the ensuing 12 weeks, she slowly improved and at discharge was ambulatory, and was vocalizing with limited speech. At 2 years follow-up she was back at school and her academic function was adequate, but she had residual inattention, impulse control issues, and mild emotional dysregulation. She had no further seizures, and ASM therapy was discontinued after 6 months.

*Classification:* Acute symptomatic seizures secondary to autoimmune encephalitis. Specific etiology - NMDAR encephalitis.

*Discussion:* In this case of NMDAR-antibody encephalitis, focal unaware seizures with motor signs occurred in the acute phase of the illness. They resolved after immunotherapy and ASMs were successfully discontinued. Hence, use of the term epilepsy would not be appropriate.

#### 3.2 | Case 2

A previously well 62-year-old man dropped a number of cups of tea while at home. His wife noticed that each was

associated with a very brief jerk of his arm, often synchronous with a spasm of his ipsilateral hemiface. His general practitioner observed one in clinic, which lasted around 2 seconds, and referred him to neurology. While awaiting the neurology appointment, these attacks increased in frequency to occur 10 times per day. Some were preceded by the sensation of a warm feeling rushing up his chest, others accompanied by a transient sense of disorientation, and others with no associated symptoms. Throughout this period, he was able to maintain an executive job and did not develop amnesia, behavioral alterations, or personality changes. When he arrived at his neurology appointment, around 3 months later, he was having 30 attacks each day, and these were clinically diagnosed as FBDS. In addition, he had developed independent episodes with a warm feeling rushing up his body, associated with piloerection, which were occurring five times per day. Six FBDS were observed in clinic, two with disrupted consciousness, and an underlying LGI1-antibody was suspected on clinical grounds. He was commenced on intravenous methylprednisolone (500 mg per day for 5 days), and, after day 3, the attacks ceased. Brain MRI, routine CSF examination, and routine EEG were all normal. A week later, serum for LGI1-antibodies was positive (titer 1:1000). Oral corticosteroids were successfully tapered over 1 year, and he never required a conventional ASM.

*Classification:* Acute symptomatic seizures secondary to autoimmune encephalitis. Specific etiology - LGI1 antibody encephalitis.

*Discussion:* In this case, several focal seizure semiologies, including autonomic and thermal sensations in addition to FBDS, were present in this patient with LGI1 antibodies. The seizures resolved with immunomodulation, and no ASMs were required.<sup>12</sup> Full diagnostic criteria for autoimmune encephalitis were not met in this patient given the lack of other neurologic features of encephalitis and negative imaging and normal CSF. However, given the characteristic presentation, it was determined that encephalitis due to LGI1 antibodies was present on clinical grounds. Given the lack of need for ASMs and eventual resolution with immunotherapy, a diagnosis of epilepsy would not be appropriate.

#### 3.3 | Case 3

A 23-year-old man with a history of a febrile seizure at age 4, presented with attacks of déjà-vu and panic. These were diagnosed as anxiety attacks and treated with psychotherapy, venlafaxine, and mirtazapine. At age 29, three bilateral tonic-clonic seizures occurred without a clear warning; however, on one occasion, he had experienced exceptionally many déjà-vu and panic sensations on the same day. Brain MRI showed T2 signal hyperintensity in the right amygdala. The déjà-vu and panic sensations were interpreted as focal aware seizures,



and he was diagnosed with focal epilepsy. Levetiracetam was started. The frequency of focal aware seizures decreased from daily to weekly. Subsequently, at age 30, a testicular seminoma was detected and surgically treated. He reported cognitive impairment, but extensive neuropsychological testing revealed a performance within the normal range or above average. Screening instruments for depression and anxiety were negative. EEG was notable for independent left and right temporal slowing, right temporal sharp waves, and right temporal seizures. Standard CSF studies were normal; but Ma2 antibodies were identified both in serum and CSF. Neither changes in AED therapy nor tumor removal or subsequent steroid and azathioprine therapy improved his condition. Upon most recent follow-up (at age 32), video-EEG, neuropsychological testing, and brain MRI were unchanged. He was evaluated with bilateral limbic depth electrodes and then underwent a right temporal lobectomy. Histopathology revealed the presence of hippocampal sclerosis type 3 and inflammatory infiltrates consistent with encephalitis. The first follow-up visit is still pending.

**Classification:** Autoimmune-associated epilepsy. Specific etiologies: immune (paraneoplastic Ma2 antibody limbic encephalitis), and structural (hippocampal sclerosis).

**Discussion:** This patient presented with chronic focal aware and focal to bilateral tonic-clonic seizures, with semiology and EEG consistent with focal epilepsy, likely of temporal origin. The testicular cancer and the amygdala T2 hyperintensity suggest a paraneoplastic cause, confirmed by the presence of Ma2 autoantibodies in serum and CSF. The enduring predisposition to seizures despite adequate treatment of the underlying malignancy and immunotherapy indicate that the diagnosis of epilepsy is appropriate. The histopathological findings demonstrate a case of autoimmune-associated epilepsy with both immune and structural etiologies in the same patient.

### 3.4 | Case 4

A 60-year-old woman was referred for evaluation of drug-resistant seizures and mental status changes. One year prior to her neurologic illness she was diagnosed with type 1 diabetes, without a preceding diabetes history. Her neurologic illness began 10 months prior to referral, with subacute onset of memory loss, unsteadiness, weight loss, and paroxysmal spells of anxiety, light-headedness, palpitations, heavy breathing, and unresponsive staring. She subsequently developed confusion, losing the ability to multi-task, and began experiencing episodes of auditory hallucinosis described as a “wind-roaring” noise. These events occurred several times daily, each lasting 1-2 minutes.

Five months prior to referral she experienced a bilateral tonic-clonic seizure. Her sodium was markedly low, at

112 mEq/L. Brain MRI showed FLAIR hyperintensity in the bilateral hippocampi, orbitofrontal cortical gyri, and hypothalamus. EEG showed right central spikes, left temporal spikes, and right frontal seizures. Spinal fluid examination showed 11 nucleated cells/hpf, protein 27 mg/dL (within normal range), a normal IgG index, and negative viral serologies and PCR. CTs of the chest, abdomen and pelvis were unremarkable. A serum paraneoplastic antibody panel was negative. Seizures continued, despite treatment with levetiracetam, phenytoin, and oxcarbazepine (which was initiated after resolution of the hyponatremia).

On neurologic examination, the patient was disoriented, stating the year as 15 years prior to the actual date, and place as being her home doctor's office 300 miles away. She ruminated over upcoming responsibilities that did not exist. There was no aphasia. Her gait was mildly ataxic. EEG monitoring showed multiple subclinical and clinical right fronto-temporal seizures. A serum GAD65 antibody was positive at 556 nmol/L (normal range  $\leq 0.02$  nmol/L). Thyroperoxidase antibodies were also elevated, but to a lesser extent (74.9 IU/ml, normal  $\leq 9$  IU/ml). A repeat CSF examination showed 2 nucleated cells, mildly increased protein (48 mg/dL), mildly elevated CSF IgG index (1.0, normal = 0.85), 5 oligoclonal bands (normal  $<4$ ), and a GAD65 antibody concentration of 102 nmol/L (normal  $\leq 0.02$  nmol/L).

Treatment with 1 g methylprednisolone, i.v., daily for 3 days followed by weekly infusions led to a brief improvement in seizure frequency, but seizures recurred within 2 weeks, and there was no response to 60 mg oral prednisone daily. Intravenous immunoglobulin (IVIg) was ineffective. Subsequent trials of intravenous cyclophosphamide 0.8 g/m<sup>2</sup> monthly for 6 months and rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks were also ineffective. A re-trial of intravenous methylprednisolone was ineffective 9 months after the initial trial. Lacosamide was substituted for oxcarbazepine, with minimal benefit. A trial of a moderate dose of diazepam (10 mg twice daily) was associated with some improvement in seizure frequency, but also sedation. At her most recent clinic visit (8 years after her initial appointment), the patient continues to have daily brief focal seizures with and without impaired awareness, and has severe anterograde and partial retrograde amnesia. A follow-up MRI of the brain showed diffuse atrophy, including bilateral hippocampal atrophy with increased T2 signal abnormalities.

**Classification:** Autoimmune-associated epilepsy. Specific etiologies: immune (GAD65 antibody-associated limbic encephalitis), and structural (hippocampal atrophy).

**Discussion:** The onset of seizures in this patient is accompanied by features consistent with autoimmune encephalitis at onset (cognitive disturbance, MRI findings of encephalitis, CSF lymphocytic pleocytosis, and oligoclonal bands). However, the seizures have continued well beyond resolution of the acute encephalitis and have become enduring.



Therefore, the diagnosis of epilepsy applies. The lack of response to immunotherapy and ASMs is typical of epilepsy seen in association with high titer GAD65 antibodies. The initial CSF and imaging abnormalities suggest an immune etiology at the outset. Similarly to case 3, the presence of bilateral hippocampal atrophy supports the concurrence of a structural etiology for her epilepsy.

### 3.5 | Case 5

A 32-year-old man, with prior history of herpes labialis, developed fever and nausea, followed by a 2-minute bilateral tonic-clonic seizure. He was admitted and continued to have bilateral tonic-clonic seizures daily as well as focal impaired awareness seizures multiple times daily, despite treatment with levetiracetam, lacosamide, and phenobarbital. Subsequent phenytoin and valproic acid trials were unsuccessful. Over the course of 1 week, he developed right-sided focal aware seizures with motor signs (face, arm, and leg). EEG revealed frequent clinical and subclinical seizures of left temporal origin. Brain MRI was unremarkable. He had an elevated CSF white cell count of 13/ $\mu$ L. Multiple infectious etiologies, including herpes encephalitis, were excluded. Empiric intravenous antiviral and antibacterial therapies were ineffective. Neural autoantibody testing of serum and CSF was negative, including GAD65 antibody. Upon treatment with intravenous methylprednisolone corticosteroids and IVIg over 6 weeks the patient had marked and sustained improvement in seizure frequency. Bilateral convulsive and focal impaired awareness seizures ceased, although he continued to experience occasional episodes of facial twitching. Serum autoantibody testing was repeated, and GAD65 antibody was detected at a low value (0.23 nmol/L; normal range  $\leq 0.02$  nmol/L).

**Classification:** Acute symptomatic seizures, secondary to autoimmune encephalitis. Specific etiology – probable seronegative autoimmune encephalitis.

**Discussion:** This acute presentation of focal aware seizures with motor signs with a viral prodrome, high frequency of seizures, and refractoriness to multiple ASMs is characteristic of acute symptomatic seizures resulting from an underlying encephalitis that is potentially autoimmune in origin. An autoimmune cause is supported by the presence of CSF lymphocytic pleocytosis. However, the patient does not completely satisfy published criteria of “autoantibody-negative but probable autoimmune encephalitis” given the lack of brain MRI findings consistent with encephalitis.<sup>5</sup> The absence of autoantibodies does not singularly exclude a diagnosis of autoimmune seizures, and should not singularly deter a course of immunotherapy, which was effective in this case. Autoimmune neurologic disorders due to GAD65 antibodies are typically associated with titers  $>20$  nmol/L.

The appearance of low-titer GAD65 antibodies is not of diagnostic significance in this case, and is likely a false positive secondary to a donor effect from treatment with IVIg therapy, given the 2%–8% prevalence of low titer GAD65 in the general population.<sup>74,75</sup> If the focal motor seizures continue to be present for a significant period after completion of immunotherapy, a diagnosis of autoimmune-associated epilepsy would be appropriate.

## 4 | SUMMARY

Acute symptomatic seizures can result from autoimmune brain disease, and affected patients may present to an epileptologist before the underlying etiology is determined. We propose the term “acute symptomatic seizures secondary to autoimmune encephalitis” in reference to seizures occurring during the active phase of autoimmune encephalitis. In contrast, when seizures persist despite adequate trials of immunotherapy and in the absence of clear evidence of active inflammation, we propose the term autoimmune-associated epilepsy. The clinical, therapeutic, and prognostic differences between these entities justify the use of separate terms. The epilepsy in such cases may result from immune-mediated structural brain injury, ongoing active autoimmune brain disease, or both. Autoimmune-associated epilepsy can occur in the setting of high titer GAD65-antibody positivity, onconeural antibodies, and in Rasmussen encephalitis. This term would also be applicable to those few patients who continue to experience continued seizures after resolution of the acute phase of autoimmune encephalitis.

We recommend that the current classification of epilepsies<sup>6</sup> be further refined to clarify the conceptual differences between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy, given the pathophysiological, prognostic, therapeutic, and social differences in these entities. Improvements in diagnosis and prognostication in the future with novel clinical biomarkers perhaps will allow this distinction earlier in the clinical course in affected patients.

## ACKNOWLEDGEMENT

The authors are grateful to the International League Against Epilepsy for its support. The authors also thank Prof. Josep Dalmau for critical discussion and input in the development of this manuscript.

## CONFLICT OF INTEREST

Claude Steriade has received honoraria from UCB, and receives NYU salary support for consulting work on behalf of the Epilepsy Study Consortium for SK Life Sciences, Engage, and Xenon. Claude Steriade receives research

support from FACES (Finding A Cure for Epilepsy and Seizures) and the American Epilepsy Society. Jeffrey Britton has consulted for UCB and has conducted research without personal payment with GW Pharmaceuticals and Grifols. Sarosh Irani is supported by the Wellcome Trust (104079/Z/14/Z), the UCB-Oxford University Alliance, BMA Research Grants-Vera Down grant (2013) and Margaret Temple (2017), Epilepsy Research UK (P1201), and by the Fulbright UK-US commission (MS-SOCIETY research AWARD). The research was funded/supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC; The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health). Sarosh Irani is a coapplicant and receives royalties on patent application WO/210/046716 (UK patent no., PCT/GB2009/051441) entitled "Neurological Autoimmune Disorders." The patent has been licensed to Euroimmun AG for the development of assays for LGII and other VGKC-complex antibodies. Christian Bien obtained honoraria for speaking engagements from UCB (Monheim, Germany), Desitin (Hamburg, Germany), and Euroimmun (Lübeck, Germany). He receives research support from Deutsche Forschungsgemeinschaft (German Research Council, Bonn, Germany) and Gerd-Altenhof-Stiftung (Deutsches Stiftungs-Zentrum, Essen, Germany). The remaining authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**How to cite this article:** Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia*. 2020;61:1341–1351. <https://doi.org/10.1111/epi.16571>