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Commentary

Epilepsy Versus High Risk of Epilepsy in Autoimmune Encephalitis: An Essential Distinction

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Introduction

Terminology surrounding seizures related to autoimmune encephalitis (AE) has garnered increasing attention in recent years. In 2020, the International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce introduced the terms "acute symptomatic seizures secondary to autoimmune encephalitis" and "autoimmune-associated epilepsy" to distinguish conceptually whether seizures are due to a reversible provoking factor (i.e. immunotherapy-responsive neuroinflammation) or an enduring seizure predisposition (i.e. immunotherapy-resistant neuroinflammation and/or structural injury).[1] We introduced the modified term "autoimmune *encephalitis*-associated epilepsy" to make explicit that epilepsy is linked, either directly or indirectly, to encephalitis in all cases.[2] Recently, a practical definition of AE-associated epilepsy was proposed that has important therapeutic implications, because treatment of AE-associated epilepsy focuses on anti-seizure medications (ASMs) rather than immunotherapy.[3] This proposal advances the discussion of seizures related to AE. However, it equates epilepsy with *a high risk of* epilepsy, which are conceptually distinct. We highlight the importance of making this distinction to ensure optimal treatment of patients with seizures related to AE.

Epilepsy versus high risk of epilepsy: An essential distinction

The proposed practical definition of AE-associated epilepsy places substantial weight on an identified neural antibody, in keeping with evidence that seizure outcomes among groups of patients with AE can differ markedly depending on the target autoantigen. As per this proposed definition, patients who have seizures related to AE with antibodies against extracellular targets (e.g. anti-leucine-rich glioma-inactivated protein 1 [LGI1], anti-N-methyl-D-aspartate receptor [NMDAR]) are classified as acute symptomatic.[3] This is supported by studies showing that such patients often attain seizure freedom following immunotherapy, indicating that the majority have reversible antibody-mediated neuronal dysfunction. To account for uncommon patients with this subtype of AE who may initially have acute symptomatic seizures but go on to develop epilepsy, the authors proposed additional criteria that require persistent seizures following immunotherapy.[3] In contrast, all patients who have seizures related to AE with antibodies against intracellular targets (e.g. most high-risk paraneoplastic antibodies, anti-glutamic acid decarboxylase-65 [GAD65]) are classified as AE-associated epilepsy, with no requirement for persistent seizures following immunotherapy.[3] This is based on literature that such patients often do not attain seizure freedom following immunotherapy, indicating that the majority have immunotherapy-resistant neuroinflammation and/or structural injury causing an enduring seizure predisposition. The authors' rationale for automatically classifying all such patients as AE-associated epilepsy is that a diagnosis of epilepsy can be made in an individual if their seizure recurrence risk is >60%, while >80% of patients with this subtype of AE do not attain seizure freedom.[3,4] This reasoning incorrectly equates an individual having epilepsy, with a group having a high risk of epilepsy. The false equivalency results from an incomplete application of the practical definition of epilepsy.[4] As per this definition, diagnosing an individual with epilepsy does not simply require that they have a seizure recurrence risk of >60%; it requires that they have a seizure recurrence risk of >60% *following an unprovoked seizure,* with the term "unprovoked" implying the absence of an active, reversible provoking factor.[1,4] In order to apply this definition to a group, it thus follows that all individuals within that group – not simply most, but all individuals – should confidently be thought to have had at least one *unprovoked* seizure. As discussed below, this is not the case for all individuals with seizures who have antibodies against intracellular targets. While most develop an enduring seizure predisposition, a subset has seizures that appear to be caused by a reversible provoking factor: immunotherapy-responsive neuroinflammation.

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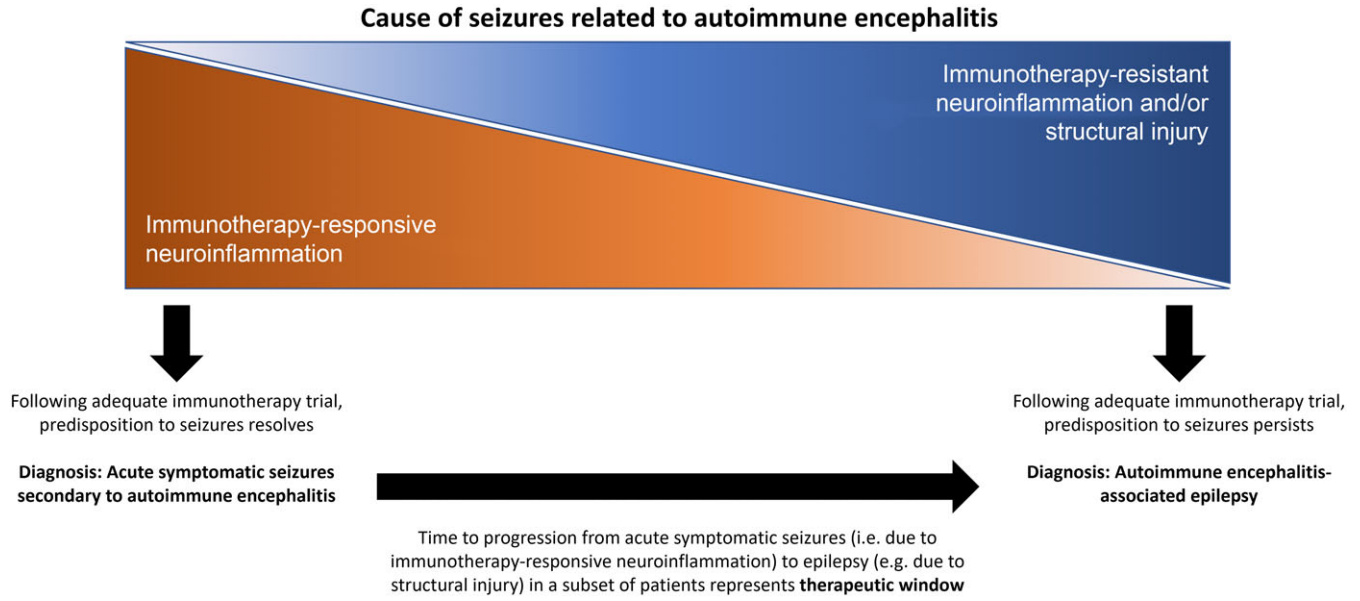

Figure 1: Cause of seizures related to autoimmune encephalitis. Diagram illustrating relative contribution of immunotherapy-responsive neuroinflammation and immunotherapy-resistant neuroinflammation and/or structural injury as the cause of seizures related to autoimmune encephalitis, in a given patient at a given point of time in their disease course. In a subset of patients, time to progression from acute symptomatic seizures (i.e. due to immunotherapy-responsive neuroinflammation) to epilepsy (e.g. due to structural injury) represents a therapeutic window, within which administration of immunotherapy can prevent the development of an enduring seizure predisposition.

Acute symptomatic seizures versus epilepsy related to AE: The discriminatory power of an adequate immunotherapy trial

Immunotherapy is an important treatment consideration for patients with AE, including those with antibodies against intracellular targets. The potential benefit of immunotherapy in such patients was highlighted in a recent study examining seizure outcomes in AE with high-risk paraneoplastic antibodies.[5] Fourteen of 31 (45%) surviving patients were seizure-free at last follow-up, all but one of whom received immunotherapy. The study authors hypothesized that, while the risk of AE-associated epilepsy is substantial in this group, a subset may have seizures that are caused by immunotherapy-responsive neuroinflammation. We agree with this and contend that if there is concern for a reversible, provoking factor (i.e. immunotherapy-responsive neuroinflammation) in an individual, then it would seem prudent to defer any determination of epilepsy until after appropriate treatment (i.e. an adequate immunotherapy trial) has been administered.[4] Deferring a diagnosis of epilepsy in this context does not preclude concomitant administration of ASMs; it simply reflects the uncertainty surrounding whether or not a reversible provoking factor is present.[4] This approach ensures that appropriate focus is placed on immunotherapy and that a potential therapeutic window (discussed below) is not missed. Yet, such deferral is at odds with the recent proposal to automatically classify all patients with antibodies against intracellular targets as AE-associated epilepsy. Using the example of antibodies against the intracellular antigen GAD65, the authors of this proposal assert that even patients who become seizure-free following early immunotherapy can still be considered to have "AE-associated epilepsy, responding to treatment."[3] Practically speaking, however, seizures that resolve following treatment intended to address a potentially reversible provoking factor (i.e. active neuroinflammation) would, in our view, be better characterized as acute symptomatic.

Conflicting perspectives on AE-associated epilepsy: Views from opposite ends of the therapeutic window?

Conflicting perspectives may relate to the different vantage points of clinicians treating patients in the acute and chronic settings. Recall that seizures related to AE can be thought of as due to immunotherapy-responsive neuroinflammation (causing acute symptomatic seizures), immunotherapy-resistant neuroinflammation, and/or structural injury (causing epilepsy). In a subset of patients, seizures may be due to immunotherapy-responsive neuroinflammation that, if left untreated, progresses to cause irreversible structural injury. This time to progression can be conceptualized as a therapeutic window, within which an adequate immunotherapy trial leads to seizure resolution and prevents development of epilepsy. This paradigm is illustrated in Figure 1. For patients who have seizures related to AE with antibodies against extracellular targets, this therapeutic window can be relatively long due to a protracted period of reversible antibody-mediated neuronal dysfunction; it often encompasses both patients with the classical syndrome of AE who present acutely, as well as those who present with seizures more chronically. Whether they are seen acutely in the inpatient setting or more chronically in the outpatient epilepsy clinic, such patients usually respond to an adequate immunotherapy trial. For this reason, there is little dispute over their general classification as having acute symptomatic seizures.

In contrast, for patients who have seizures related to AE with antibodies against intracellular targets, the therapeutic window can be relatively short due to a rapidly destructive T-cell-mediated process; it may encompass some patients who present acutely, but typically not those who present with seizures more chronically. Clinicians who encounter such patients acutely may be eager to administer immunotherapy because of the possibility that the patient is within the therapeutic window and will experience resolution of acute symptomatic seizures. An example would

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be acute presentations of AE with high-risk paraneoplastic antibodies, including unique phenotypes that might more often be immunotherapy-responsive such as adult-onset anti-Hu-associated extra-limbic encephalitis. Meanwhile, those who encounter such patients chronically in the outpatient epilepsy clinic, when they are almost certainly outside the therapeutic window and have a vanishingly small likelihood of seizures solely attributable to immunotherapy-responsive neuroinflammation, may understandably be unenthusiastic to administer immunotherapy due to high concern for futility and little doubt of epilepsy. Examples would include patients with high-risk paraneoplastic antibodies who are seen for chronic seizures following a more acute encephalitic presentation, as well as patients with anti-GAD65 who have chronic seizures for many years before the diagnosis is even made.

We acknowledge that the concept of a therapeutic window for seizures related to AE is a simplified one, and does not readily apply to patients with neuroinflammation that is resistant to currently available immunotherapies even at onset. Nonetheless, it may help to understand different perspectives of clinicians who encounter patients with seizures related to AE and motivate future collaborative development of practical definitions that are applicable across clinical settings.

Unanswered questions and future directions

Despite advancements in our understanding of seizures related to AE, creating practical definitions for AE-associated epilepsy remains challenging. As discussed herein, making the distinction between epilepsy and a high risk of epilepsy would be essential to such a definition. In patients with a subtype of AE that carries a high risk of epilepsy, an adequate immunotherapy trial can effectively assess for the possibility of a reversible provoking factor (i.e. immunotherapy-responsive neuroinflammation) causing acute symptomatic seizures. Yet, precise determination of what constitutes an "adequate" trial is often limited by the lack of highly sensitive and specific biomarkers to identify active, potentially immunotherapy-responsive neuroinflammation. The lack of such biomarkers also makes it difficult to ascertain if trialing immunotherapy is even appropriate in cases with high concern for futility, or if an attempt at an adequate immunotherapy trial has transitioned to ongoing immunotherapy for no adequate reason. Individualized clinical decision-making that incorporates useful, yet imperfect measures of active neuroinflammation (e.g. symptom trajectory, neuroimaging abnormalities, CSF pleocytosis, antibody status) and balances risks of immunotherapy thus remains paramount.

We have consciously chosen not to propose an alternative practical definition of AE-associated epilepsy; this is because we hold the view that tools to broadly yet accurately diagnose active neuroinflammation as a potential provoking factor in any individual with seizures who falls along the spectrum of AE, which would be integral to the successful development of such a definition, are lacking at present. This choice aligns with that of the ILAE Autoimmunity and Inflammation Taskforce, which also opted against proposing practical definitions due to the complexity of determining active neuroinflammation in AE, the breadth of potential clinical presentations across numerous autoantibodies, and the impact immunotherapy timing may have on the development of an enduring seizure predisposition.[1] Instead, they focused on developing conceptual definitions that now serve as a helpful framework with which to approach the diverse, dynamic presentations of patients with seizures related to AE. As our knowledge of diagnosing, monitoring, and treating active neuroinflammation improves, so too may our ability to successfully operationalize these conceptual definitions in the future.

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