Journal Pre-proof

Autoimmune-associated Epilepsy – a challenging concept

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Please cite this article as: Nico Melzer , Felix Rosenow , Autoimmune-associated Epilepsy – a challenging concept, *Seizure: European Journal of Epilepsy* (2024), doi: https://doi.org/10.1016/j.seizure.2024.05.017

Highlights

- It is important to distinguish acute provoked seizures due to autoimmune encephalitis from chronic unprovoked seizures due to autoimmune-associated epilepsy.

- Currently it is hardly possible in an individual AIE/ALE/RE patient to separate acute provoked seizures from chronic unprovoked seizures due to limitations in determining seizure outcomes, unclear time courses, potential causal interactions between both seizure origins, compartmentalized immune-inflammation, and a lack of licensed drugs to reliably resolve immune-inflammation in the brain parenchyma.

- This makes it hard to decide when to terminate ASMs and to counsel the individual patient regarding driving abilities and other behavioral restrictions and recommendations.

- Studies are urgently needed to define clinical and paraclinical biomarkers in a hypothesis-free, data-driven approach reliably predicting (or not) the development of AAE and the cognitive and behavioral outcome in the due course of an individual patient´s disease.

- These studies should be experimentally validated in suitable animal models.

Focused Review – Seizure – ALOE Special Issue

Autoimmune-associated Epilepsy – a challenging concept

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Words: 1222 words excluding the abstract, title page, and references.

Abstract: 236 words

References: 35

Display items: 0

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Abstract

The current International League Against Epilepsy (ILAE) definition and classification guidelines for the first time introduced the category of immune-mediated focal epilepsy in addition to structural, genetic, infectious, and metabolic aetiologies. Moreover, the ILAE Autoimmunity and Inflammation Taskforce recently provided a conceptual framework for the distinction between acute "provoked" seizures in the acute phase of autoimmune encephalitis from chronic "unprovoked" seizures due to autoimmune-associated epilepsy. The first category predominately applies to those autoimmune encephalitis patients with autoantibodies against cell surface neural antigens, in whom autoantibodies are assumed to exert a direct ictogenic effect without overt structural damage. These patients do not exhibit enduring predisposition to seizures after the "acute phase" encephalitis, and thus do not fulfil the definition of epilepsy. The second category applies to those autoimmune encephalitis patients with autoantibodies against intracellular neural antigens and Rasmussen's encephalitis, in whom T cells are assumed to cause epileptogenic effects through immune-inflammation and overt structural damage. These patients do exhibit enduring predisposition to seizures after the "acute phase" of encephalitis and thus fulfil the definition of epilepsy. AAE may result from both, ongoing brain autoimmunity and associated structural brain damage according to the current ILAE definition and classification guideline. We here discuss the shortcomings and defaults of this concept and suggest an unbiased translationally validated and data-driven approach to predict in an individual encephalitis patient the propensity to develop (or not) AAE and the cognitive and behavioural outcome.

1. **Introduction**

Seizures and epilepsy are a common clinical manifestation of autoimmune encephalitis (AIE; [1, 2]) especially autoimmune limbic encephalitis (ALE; [3, 4]), predominantly affecting mesial temporal structures such as the amygdala and the anterior part of the hippocampus.

In 2016 initial consensus criteria regarding the diagnosis of possible, probable, and definite AIE were established [1] and have recently been validated, independently [2]. In this framework, we suggested the restriction of MRI phenotypes to the mesial temporal lobe structures to define possible, probable, and definite ALE [3, 4], especially to facilitate the investigation of neurocognitive symptoms of the disorder as well as seizure semiology and outcome [5]. Importantly, the diagnosis can be established also in the absence of distinct autoantibodies in serum and CSF [1, 2] underlying the existence of seronegative probably T

cell-mediated ALE [6-8]. Using these criteria, approximately 50% of all patients in a tertiary epilepsy centre did not exhibit autoantibodies [3, 4], while presenting with a rather strong seizure phenotype with limited response to anti-seizure medication (ASM) and immunotherapy.

These and similar findings in other cohorts posed the question what factors may drive epileptogenesis i.e. the transition of the affected the neural network from acute immune-inflammation-driven to chronic immune-inflammation independent hyperexcitability and dysfunction in AIE and especially in ALE [9, 10].

2. Acute provoked seizures and chronic unprovoked seizures in autoimmune (limbic) encephalitis

Following the introduction of the concept by experts in the field [11], the current International League Against Epilepsy (ILAE) definition and classification guidelines for the first time introduced the category of immune-mediated focal epilepsy in addition to structural, genetic, infectious, and metabolic aetiologies [12, 13]. Moreover, the ILAE Autoimmunity and Inflammation Taskforce recently provided a conceptual framework for the distinction between acute "provoked" seizures in the acute phase of AIE/ALE from chronic "unprovoked" seizures due to autoimmune-associated epilepsy (AAE) [14]. The first category predominately applies to those AIE/ALE patients with autoantibodies against cell surface neural antigens, in whom autoantibodies are assumed to exert a direct ictogenic effect without overt structural damage. These patients do not exhibit *enduring* predisposition to seizures after the "acute phase of AIE/ALE", and thus do not fulfil the definition of epilepsy [15]. The second category applies to those AIE/ALE patients with autoantibodies against intracellular neural antigens and Rasmussen's encephalitis (RE, [16]), in whom T cells are assumed to cause epileptogenic effects through immune-inflammation and overt structural damage. These patients do exhibit *enduring* predisposition to seizures after the "acute phase of AIE/ALE/RE" and thus fulfil the definition of epilepsy [15]. The authors point out that AAE may result from both, ongoing brain autoimmunity and associated structural brain damage according to the current ILAE definition and classification guideline [12-14].

First of all, it is important to distinguish acute provoked seizures due to autoimmune encephalitis from chronic unprovoked seizures due to autoimmune-associated epilepsy. However, the current concept has several shortcomings and defaults with strong consequences for clinical counselling and treatment of affected patients:

(i)   It is still unclear – especially in an individual ALE patient with seizures originating from affected mesial temporal lobe structures – whether assumed clinical seizure

freedom indeed corresponds also to electroencephalographic seizure freedom (seizure underreporting; [17]). Thus, the *enduring* predisposition to seizures *per se* is hard to assess reliably due to clinical seizure underreporting [17]. Moreover, restrictions in recording duration and invasiveness of current EEG techniques pose another source of inaccuracy to reliably assess seizure outcomes [17]. Regular use of long-term (video-)EEG recording during the disease course would aid to improve the diagnostic accuracy.

(ii)   The time course of the "acute phase of AIE/ALE/RE" is very poorly or even undefined [14], and there are no reliable biomarkers for this period. Moreover, while an acute phase may be clinically recognized in RE and AIE/ALE with autoantibodies against cell surface neural antigens such as anti-NMDAR, anti-LGI1, or anti-CASPR2 encephalitis, it may virtually be absent in patients with anti-GAD65 AIE/ALE.

(iii)   Nothing is said about the large number of patients with seronegative AIE/ALE [3, 4]. Giving the histopathological evidence for a T cell-mediated pathology in these cases [6-8], they may have a higher likelihood of developing AAE but are not covered by the proposed conceptual definitions [14].

(iv)   There are also AIE/ALE patients with autoantibodies against cell surface neural antigens, who also exhibit strong parenchymal T cell responses [18-21], rendering their predisposition of AAE fully unclear according to the proposed conceptual definitions [14].

(v)   A large proportion of AIE/ALE patients with autoantibodies against cell surface neural antigens develop persistent brain atrophy even when immune-inflammation appears to have resolved [22].

(vi)   As pointed out above, in AAE immune effector mechanisms may still be present, while immune-mediated structural brain damage already occurred that may or may not be visible on MRI [14] i.e. there is no MRI criterion to reliably distinguish seizures from epilepsy in AIE/ALE.

(vii)   Uncontrolled seizures in the acute phase of AIE/ALE (and not the cellular localization of the target antigen of autoantibodies) have recently been identified as a major risk factor of developing AAE [23, 24].

(viii) Moreover, it is fully unclear whether parenchymal immune-inflammation is ever fully resolved given the persistence of tissue resident memory T cells and activated microglia also for decades of pharmacoresistant focal epilepsy [25]. These cells have been shown to drive compartmentalized parenchymal immune-inflammation in the brain [26, 27].

(ix)   Moreover, the criterion of a response of a cessation of seizures following immunotherapy as reflecting their acute provoked origin and the absence of structural brain damage as opposed to their chronic unprovoked nature due to structural brain damage is even more inappropriate given the fact that there are no drugs licensed based on larger phase III randomized controlled trials to treat AIE/ALE. So, a lack of a clinical response to immunotherapy is not suitable to conclude of resolution of immune-inflammation given the unknown efficacy of currently used drugs and compartmentalized immune-inflammation in the brain.

Current concepts of epileptogenesis refer to the fact that a previously normal neural network after or during a certain pathological stimulus that may or may not by itself induce acute symptomatic seizures (such as stroke, brain tumours, traumatic brain injury, or encephalitis) becomes persistently hyperexcitable independent of the continuous impact of the precipitating pathogenic factor [9, 10]. This is likely an active process of neural network adaptation, and it is likely not the structural damage itself that drives seizures and epilepsy [9, 10].

These concepts of epileptogenesis can be experimentally tested in suitable animal models and then be transferred to humans. We recently established a model of primary T cell-driven ALE resulting in hippocampal sclerosis (HS) [7, 8], which goes along with early activated astrogliosis and microglia activation and acute high-frequency seizures. This turns into hippocampal sclerosis (HS) with astrogliosis and microglia activation with persisting chronic low-frequency seizures [7, 8]. This model is ideally suited to study T cell-driven epileptogenesis experimentally and provide hints how to identify and monitor this process in patients.

Conclusion

Currently, it is hardly possible in an individual AIE/ALE/RE patient to separate acute provoked seizures from chronic unprovoked seizures (epilepsy) due to limitations in determining seizure outcomes unclear time courses, potential causal interactions between both seizure origins, compartmentalized immune-inflammation and a lack of licensed drugs to resolve immune-inflammation in the brain parenchyma. This makes it hard to decide when to terminate ASMs and to counsel the individual patient regarding driving abilities and other behavioural restrictions and recommendations.

Thus, studies are urgently needed to define clinical and paraclinical (MRI [28-30], EEG [31-35], serum or cerebrospinal fluid (CSF) [36, 37]) biomarkers in a hypothesis-free data-driven approach reliably predicting (or not) the development of AAE and the cognitive and behavioural outcome in the due cause of an individual patient´s disease [28-30]. These studies should be experimentally validated in suitable animal models.

Declaration of Competing Interest

Acknowledgements

Funding

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