Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Characteristics and Seizure Outcomes in Antibody-Positive Autoimmune Limbic Encephalitis

Hao Song[1,*], Sha Xu[1,*], Bing-Qing Du[1], Qi-Lun Lai[2], Meng-Ting Cai[1], Hong Li[3], Yin Hu[1], Yao Ding[1], Mei-Ping Ding[1], Yin-Xi Zhang[1], Chun-Hong Shen[1]

[1]Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310009, People's Republic of China; [2]Department of Neurology, Zhejiang Hospital, Hangzhou, 310013, People's Republic of China; [3]Department of Radiology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310009, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chun-Hong Shen; Yin-Xi Zhang, Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou, 310009, People's Republic of China, Email shen_neurology@zju.edu.cn; zyx-neurology@zju.edu.cn

Purpose: Autoimmune limbic encephalitis (ALE) often occurs with detectable neuronal antibodies, presenting with seizures as a prominent clinical manifestation. We aimed to investigate the clinical characteristics and seizure outcomes in a cohort with antibody-positive ALE.

Methods: We consecutively recruited patients with antibody-positive ALE and new-onset seizures between July 2014 and February 2024. Their demographic, clinical, and paraclinical characteristics, and treatment were collected. Seizure outcomes during follow-up were evaluated respectively, as well as the associated risk factors.

Results: Seventy-two patients were included, and the associated autoantibodies targeted the leucine-rich glioma-inactivated 1 (LGI1), gamma-aminobutyric acid type B receptor ($GABA_BR$), and glutamic acid decarboxylase 65 (GAD65). Secondarily generalized tonic-clonic seizures and focal non-motor seizures were the most prevalent seizure semiologies, and 28 (38.9%) patients exhibited multiple seizure types. Furthermore, among 54 patients with over two years of follow-up, 16 (29.6%) experienced intermittent seizures lasting for more than one year. Younger onset, specific antibodies, and multiple seizure types were correlated with the longer seizure duration (all $P < 0.05$). Six (11.1%) patients continued to have seizures even after two years of follow-up, comprising two with LGI1 and four with GAD65 antibodies. Female sex, younger onset, and specific antibody profiles were significantly associated with sustained seizures, indicating autoimmune-associated epilepsy (AAE, all $P < 0.05$).

Conclusion: In patients with antibody-positive ALE, seizure outcomes appeared to change over an extended follow-up period, particularly in those with LGI1 and $GABA_BR$ antibodies. Younger age at disease onset, female sex, and specific antibody profiles may be indicators of AAE.

Keywords: autoimmune limbic encephalitis, antibody, autoimmune-associated epilepsy, multiple seizure types

Introduction

Autoimmune limbic encephalitis (ALE) is an immune-mediated inflammatory brain disease characterized by acute or subacute development of seizures, memory impairment, and psychiatric disturbances, predominantly involving the mesial temporal lobe.[1] Currently, many patients with ALE have been identified with detectable neuronal autoantibodies, and some may have underlying tumors. In antibody-positive ALE, most antibodies target the neuronal cell surface antigens, such as leucine-rich glioma-inactivated 1 (LGI1), gamma-aminobutyric acid type B receptor ($GABA_BR$), and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR).[2] While others target neuronal intranuclear or cytoplasmic antigens, including glutamic acid decarboxylase 65 (GAD65), Hu, Ma2, amphiphysin, and CV2/collapsin response mediator protein 5.[3,4]

Received: 7 February 2025
Accepted: 23 May 2025
Published: 30 May 2025

As one of the prominent symptoms in antibody-positive ALE, seizures respond well to proper immunotherapy in most cases. Nevertheless, some patients may continue to experience seizures without any signs of encephalitis, which is known as autoimmune-associated epilepsy (AAE), with an undetermined risk rate.[4–6] Previous studies on ALE have indicated that nearly half of patients may develop AAE as a long-term sequela.[7,8] However, these studies were usually performed with limited sample sizes and mixed antibody-positive and antibody-negative cases, leading to an unclear profile of seizure outcomes in antibody-positive ALE. Prior research has also suggested that seizure outcomes may differ between the antibody-positive and antibody-negative groups.[9] Furthermore, the exact definition of AAE remains inconsistent across studies, and there is no universally accepted optimal observation period before diagnosing AAE. For instance, Geis et al suggested defining individuals who experienced seizures for more than one year as having AAE,[4] while Rada et al recently proposed that the observation period should be at least two years.[10]

Despite the increasing number of individuals afflicted with ALE in recent decades, comprehensive studies specifically focusing on antibody-positive ALE are lacking. Moreover, it remains unclear whether a longer follow-up period before assessment results in distinct seizure outcomes in patients with antibody-positive ALE, necessitating further evidence. Therefore, the current study aimed to delineate the clinical characteristics of patients with antibody-positive ALE and to identify seizure outcomes with different observation periods before diagnosing AAE and the potential risk factors.

Methods

Patients

This retrospective study recruited newly diagnosed patients with antibody-positive ALE and seizures from the ward of Second Affiliated Hospital, School of Medicine, Zhejiang University, between July 2014 and February 2024. The inclusion criteria were as follows: (1) diagnosis of ALE established based on the clinical approach proposed by Graus et al;[11] (2) patients with new-onset seizures in the acute stage; (3) positive autoantibodies in serum and/or cerebrospinal fluid (CSF) detected using a commercially available immunofluorescence kit (fixed cell-based assay). The exclusion criteria were as follows: (1) history of epilepsy, stroke, cerebral trauma, or other nervous system diseases before ALE onset; (2) presence of two or more autoantibodies; (3) loss to follow-up. The study was approved by the Ethics Committee of Second Affiliated Hospital School of Medicine Zhejiang University (approval number: 2024-LSY -0682). The Ethics Committee granted a consent waiver for our study given the retrospective observational nature of the research. All patient data were fully anonymized and stored securely to ensure confidentiality. Our study fully complies with the Declaration of Helsinki.

Information Collection

For each patient, clinical data including gender, onset age, disease duration, prodromal symptoms, clinical manifestations, seizure semiology, antibody types and titers, CSF analysis, magnetic resonance imaging (MRI), positron emission tomography (PET), and electroencephalogram (EEG) findings, anti-seizure medications (ASMs), and immunotherapy were collected. The modified Rankin Score (mRS) on admission was recorded as a metric for disease severity,[12] ranging from 0 to 6. After discharge, patients were evaluated by clinic visits at least once every three months in the first year and then every six months via clinical visits or telephone consultations after that. Follow-up information was collected and assessed, including clinical manifestations, paraclinical findings, treatment, and seizure outcomes. All the data were independently collected by two neurologists (HS and BQD) using a standardized protocol. Any discrepancies were resolved through rechecking and discussion to minimize bias.

Definition and Seizure Outcomes

Seizure semiology was categorized into four types: (1) secondarily generalized tonic-clonic seizure (sGTCS); (2) facio-brachial dystonic seizure (FBDS), a frequent tonic muscle contraction of the arm and face usually lasting 1–2 s;[13] (3) focal non-FBDS motor seizure; (4) focal non-motor seizure. The identification of seizure types was predominantly based on clinical descriptions provided by patients or witnesses. Meanwhile, some reports may not specify focal onset features, such as auras, head deviation, or other focal characteristics before the tonic-clonic phases, while others do. Therefore, it should

be noted that a subset of sGTCS could potentially be focal to bilateral tonic-clonic seizures (FBTCS). Multiple seizure types refer to two or more seizure types in a patient.[14] Status epileptics (SE) was defined based on the definition suggested by the International League Against Epilepsy (ILAE) in 2015.[15] Moreover, immunotherapy initiated > 1 month after disease onset was considered delayed immunotherapy.[16]

Seizure remission was defined as the achievement of a seizure-free state for more than six months at the last visit, irrespective of ongoing ASMs use. Otherwise, sustained seizure was defined. To elucidate the influence of observation duration on seizure outcomes, the study employed two distinct time points for analysis. If AAE was considered based on a minimum follow-up period of 1 year, patients were classified into: Group 1, sustained seizure ≤ 1 year, indicating the achievement of seizure remission within this period; Group 2: sustained seizure > 1 year. If AAE was considered based on a minimum follow-up period of 2 years, patients were classified as follows: Group 1, sustained seizure ≤ 2 year, indicating seizure remission within two years; Group 2, sustained seizure > 2 year. Furthermore, seizure episodes should be distinguished from a relapse of autoimmune encephalitis based on other clinical manifestations, antibody titers, MRI and EEG changes, CSF results, and/or PET scans. In cases where patients exhibited a relapse of encephalitis, seizure outcomes were evaluated from the time of the reinitiation of immunotherapy, considering that the present study focused specifically on the risk of AAE. Seizure outcomes were independently assessed by two neurologists (HS and CHS). In case of disagreement, the outcomes were adjudicated by another neurologist (YXZ).

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]), and categorical variables were presented as numbers and percentages. Comparisons between groups were performed using the Mann–Whitney *U*-test for continuous variables and either Pearson chi-square or Fisher's exact test for categorical variables. Factors with significantly different distributions were evaluated using multivariate logistic regression analysis, with odds ratio (OR) and 95% confidence interval (CI). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences software (version 22.0; IBM, Chicago, IL, USA).

Results

Patient Inclusion and Demographics

During the nine years, 79 patients with antibody-positive ALE were identified according to the criteria of Graus et al. Among them, 72 (91.1%) patients experienced seizures as a prominent symptom, while seven (8.9%) reported no new-onset seizures. As shown in Figure 1, a total of 72 patients with antibody-positive ALE and seizures (48 male, 66.7%) were finally enrolled, with a median onset age of 56 years (IQR: 45–63 and range: 19–76). The baseline demographics, clinical and paraclinical features, and treatment are summarized in Table 1.

Clinical Characteristics

In this study, the associated autoantibodies primarily targeted LGI1 (n = 42, 58.3%), $GABA_BR$ (n = 25, 34.7%), and GAD65 (n = 5, 6.9%). Prodromal symptoms are relatively rare. New-onset seizures were reported as the initial symptoms in 76.4% of patients, while cognitive impairment and psychiatric disturbances were observed in 9.7% and 4.2% of patients, respectively. Furthermore, sGTCS (n = 50, 69.4%) was the most common seizure type, followed by focal non-motor seizures (n = 34, 47.2%), FBDS (n = 12, 16.7%), and focal non-FBDS motor seizures (n = 8, 11.1%). Some patients exhibited multiple seizure types (n = 28, 38.9%), with sGTCS and focal non-motor seizure (14/28, 50.0%) as the most common combination. The primary symptoms of focal non-motor seizures include piloerection, déjà vu, hallucinations, paroxysmal feelings of fear, and epigastric sensation. In particular, piloerection was observed in 11/42 (26.2%) patients with LGI1 antibody and 1/5 (20.0%) patients with GAD65 antibody. Seizures occurred daily, weekly, or monthly in 54.2%, 27.8%, and 16.7% of patients. Furthermore, SE was recorded in 12/72 (16.7%) patients, including 10 cases with $GABA_BR$ antibodies and two with LGI1 antibodies. At baseline, the median mRS score was 3.0 (IQR: 3.0–4.0). Moreover, seven (9.7%) patients with $GABA_BR$ antibodies developed tumors involving small cell lung carcinoma in six cases and thymoma in one case.

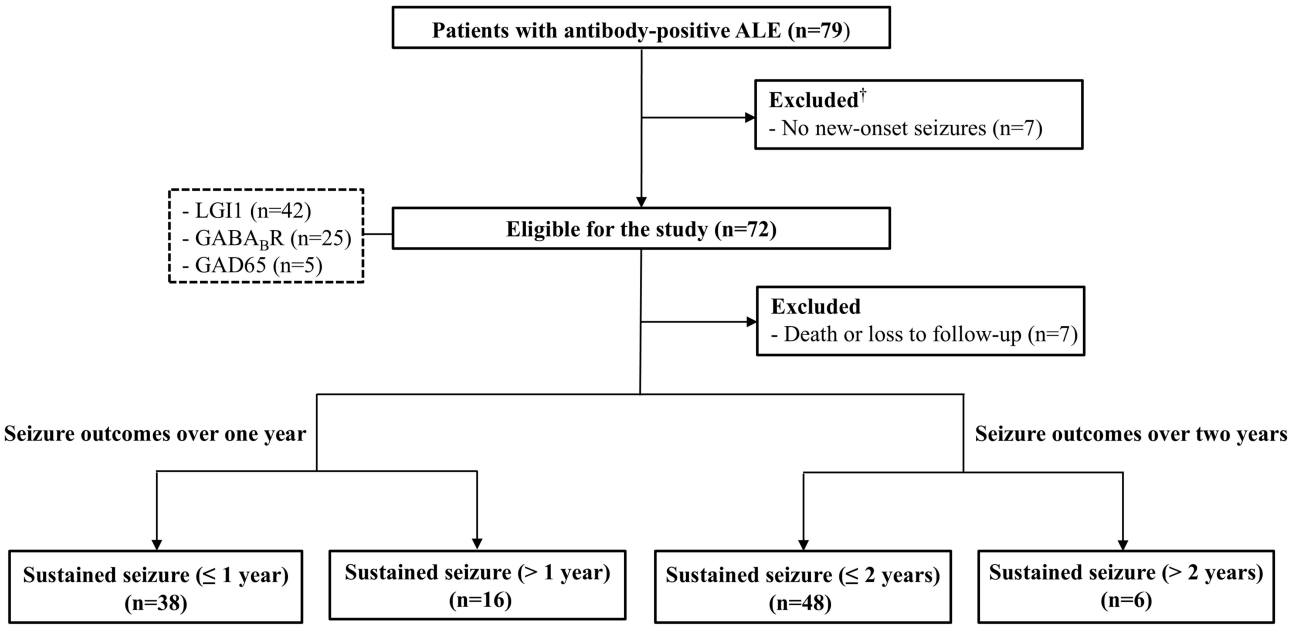

Figure 1 Flow chart of inclusion and exclusion criteria. †With LGI1 antibody (n = 4), Hu antibody (n = 1), amphiphysin antibody (n = 1), and CASPR2 antibody (n = 1).

Paraclinical Findings

Brain MRI revealed that 22/72 (30.6%) patients exhibited bilateral mesial temporal lobe fluid-attenuated inversion recovery hyperintensities, whereas 23/72 (31.9%) patients exhibited unilateral MRI changes. In the acute stage, 21 of the

Table 1 Demographic and Clinical Characteristics

Characteristics	Total (n=72)
Male, n (%)	48 (66.7)
Onset age, median (IQR), y	56 (45–63)
Antibody type, n (%)	
LGI1	42 (58.3)
GABA$_B$R	25 (34.7)
GAD65	5 (6.9)
Prodromal symptoms, n (%)	4 (5.6)
Initial symptoms, n (%)	
Seizures	55 (76.4)
Cognitive impairment	7 (9.7)
Psychiatric disturbances	3 (4.2)
Others (dizziness, muscle spasms, et al)	5 (6.9)
Seizure type, n (%)	
sGTCS	50 (69.4)
FBDS	12 (16.7)
Focal non-FBDS motor seizure	8 (11.1)
Focal non-motor seizure	34 (47.2)
Multiple seizure types, n (%)	28 (38.9)
Seizure frequency before immunotherapy, n (%)	
Daily	39 (54.2)
Weekly	20 (27.8)
Monthly	11 (15.3)

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n=72)
SE, n (%)	12 (16.7)
Tumor, n (%)	7 (9.7)
Hyponatremia, n (%)	26 (36.1)
ICU admission, n (%)	5 (6.9)
MRI, n (%)	
Bilateral medial temporal lobe FLAIR hyperintensities	22 (30.6)
Unilateral medial temporal lobe FLAIR hyperintensities	23 (31.9)
Normal or non-specific changes	27 (37.5)
Interictal EEG, n (%)	
Temporal IED	13/69 (18.8)
Temporal slow-wave activity	17/69 (24.6)
Normal or non-specific changes	44/69 (63.8)
CSF abnormality, n (%)	
Pleocytosis, >5/mm^3	27/70 (38.6)
Elevated protein, >0.45g/L	17/70 (24.3)
PET, abnormal metabolic changes in temporal lobes, n (%)	9/16 (56.2)
The mRS score, median (IQR)	3.0 (3.0–4.0)
≥3 ASMs, n (%)	18 (25.0)
Intravenous or intramuscular ASMs, n (%)	17 (23.6)
Delayed immunotherapy, n (%)	34 (47.2)
First-line immunotherapy, n (%)	71 (98.6)
Immunosuppressants therapy, n (%)	15 (20.8)

Abbreviations: ASM, anti-seizure medication; CSF, cerebrospinal fluid; d, days; EEG, electroencephalogram; FBDS, faciobrachial dystonic seizure; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, gamma-aminobutyric-acid B receptor; GAD65, glutamic acid decarboxylase 65; IED, interictal epileptiform discharge; ICU, intensive care unit; IQR, interquartile range; LGI1, leucine-rich glioma-inactivated protein 1; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; PET, positron emission tomography; SE, status epileptic; sGTCS, secondarily generalized tonic-clonic seizures.

69 patients with available EEGs underwent 24-h video-EEG (VEEG) recordings, whereas the remaining patients underwent routine EEG for 20 min. The EEG analysis indicated that 13/69 (18.8%) patients exhibited temporal interictal epileptiform discharge (IED), and 17/69 (24.6%) patients demonstrated focal temporal slow-wave activity. Moreover, VEEG revealed subclinical seizures in 5/25 (20.0%) patients, all of whom were diagnosed with anti-LGI1 encephalitis. Furthermore, CSF was collected from 70 patients when hospitalized, indicating pleocytosis in 27 (38.6%) patients and elevated protein in 17 (24.3%). Sixteen patients underwent PET scans, indicating that four (25.0%) patients exhibited focal hypermetabolism in the temporal lobes, and five (31.2%) exhibited hypometabolism.

ASM and Immunotherapy

In the acute stage, 67 (93.0%) patients with antibody-positive ALE and seizures received ASMs. Levetiracetam (n = 35, 48.6%) was the most frequently used ASM, followed by valproic acid (VPA; n = 32, 44.4%), oxcarbazepine/carbamazepine (OXC/CBZ; n = 25, 34.7%), lacosamide (n = 10, 13.9%), lamotrigine (n = 5, 6.9%), and clonazepam (n = 4, 5.6%). Among these, 18 (25.0%) patients received more than three ASMs, whereas 17 (23.6%) received intravenous or intramuscular ASMs, such as VPA, midazolam, and phenobarbital. Adverse effects such as rash were reported in 3/25 (12.0%) patients with anti-LGI1 encephalitis due to OXC/CBZ.

In addition to ASMs, 71 (98.6%) patients received first-line immunotherapy consisting of intravenous methylprednisolone, immunoglobulins, and plasma exchange alone or in combination. The median duration between disease onset and first-line immunotherapy was 26 days (IQR: 13–90). Moreover, six (8.3%) patients were prescribed second-line

immunotherapy (rituximab) during the acute phase, and nine (12.5%) patients received long-term maintenance treatments (mycophenolate mofetil, n = 6; tacrolimus, n = 2; rituximab, n = 2; cyclophosphamide, n = 2).

Sustained Seizures Beyond One year and Associated Risk Factors

At the last visit, the median follow-up duration of our cohort was 43.6 months (IQR: 30.4–77.6) after excluding seven cases due to death (uncontrolled seizures, n = 2; tumors, n = 2; pneumonia, n = 2; unknown reason, n = 1). Fifty-four patients were followed up for at least two years after immunotherapy, with a median period of 52.8 months (IQR: 34.9–83.0).

Among them, 38 patients achieved seizure remission within one year after immunotherapy. They were classified as the "sustained seizure ≤ 1 year" group, though 8/38 (21.0%) patients were still receiving ASMs at the last visit. The remaining 16 (29.6%) patients experienced intermittent seizures for more than one year (LGI1, n = 8; $GABA_BR$, n = 4; GAD65, n = 4), and were classified as the "sustained seizure > 1 year" group (Figure 2).

Comparisons between the two groups revealed that seizures occurring for more than one year were significantly correlated with younger onset ($P = 0.049$), specific antibody profiles ($P = 0.006$), and multiple seizure types ($P = 0.001$) (Table 2). From the perspective of antibody profiles, sustained seizures were observed in 8/35 (22.8%) patients with LGI antibody, 4/15 (26.7%) with $GABA_BR$ antibody, and 4/4 (100%) with GAD65 antibody. Multivariate logistic regression analysis, incorporating these factors, demonstrated a significant association between multiple seizure types and seizures duration lasting more than one year ($P = 0.005$, OR = 10.800, and 95% CI = 2.042–57.122).

Sustained Seizures Beyond Two years and Associated Risk Factors

Among the 16 patients who experienced intermittent seizures for more than one year, 10 achieved seizure remission within two years. This included six patients with LGI1 antibody and four with $GABA_BR$ antibody (Figure 2). Ultimately, six (11.1%) patients continued to have intermittent seizures for more than two years (LGI1, n = 2; $GABA_BR$, n = 0; and

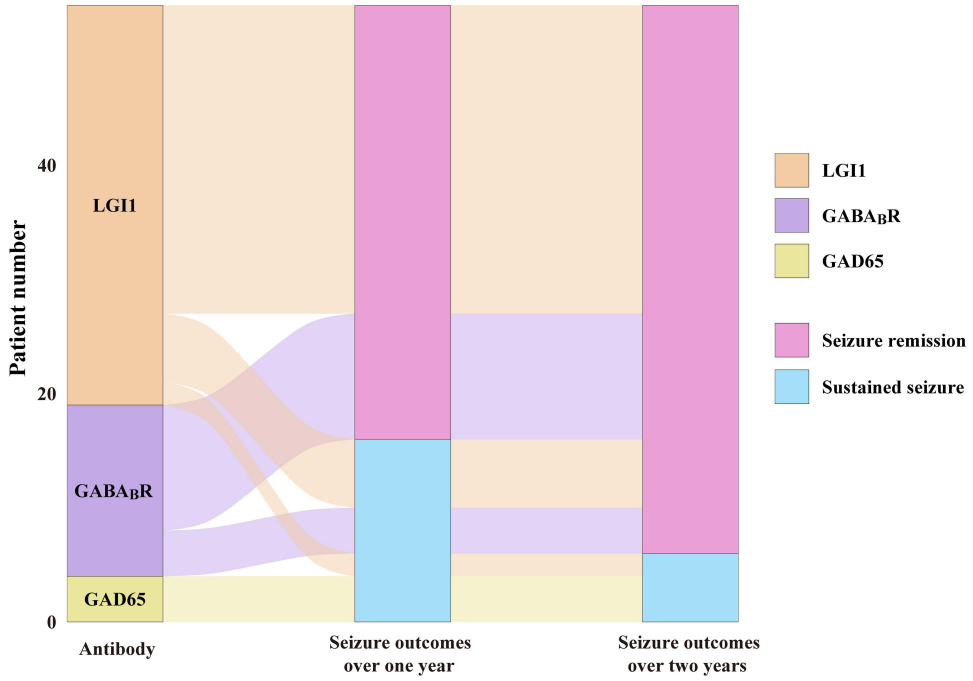

Figure 2 Sankey diagram of seizure outcomes in antibody-positive ALE. The diagram includes 54 patients who were followed up for more than two years. Among these patients, 16 exhibited sustained seizures lasting more than one year, who were classified into the "sustained seizures > 1 year" group (blue) while the remaining patients were classified into the "sustained seizure ≤ 1 year" group (pink). Of the 16 patients, 10 achieved seizure remission during the subsequent follow-up, and the remaining 6 continued to experience seizures beyond two years as the "sustained seizures > 2 year" group (blue). The others got seizure remission within two years and were categorized into the "sustained seizure ≤ 2 year" group (pink).

Abbreviations: ALE, autoimmune limbic encephalitis; $GABA_BR$, gamma-aminobutyric acid type B receptor; GAD65, glutamic acid decarboxylase 65; LGI1, leucine-rich glioma-inactivated 1.

Table 2 Risk Factors Associated with Different Seizure Outcomes

Characteristics	Sustained Seizure ≤ 1 year	Sustained Seizure > 1 year	*P*	Sustained Seizure ≤ 2 year	Sustained Seizure > 2 year	*P*
N	38	16	–	48	6	–
Male	27 (68.4)	9 (56.3)	0.392	34 (70.8)	1 (16.7)	0.030*
Onset age, median (IQR), y	56 (47–63)	50 (36–58)	0.049*	56 (47–63)	32 (24–44)	<0.001*
Antibody type			0.006*			<0.001*
LGI1	27 (71.1)	8 (50.0)		33 (68.8)	2 (28.6)	
$GABA_BR$	11 (28.2)	4 (25.0)		15 (30.6)	0 (0)	
GAD65	0 (0)	4 (25.0)		0 (0)	4 (57.1)	
Seizures as an initial symptom	29 (76.3)	13 (81.3)	0.968	37 (77.1)	5 (83.3)	1.000
sGTCS	26 (68.4)	11 (68.8)	0.981	34 (70.8)	3 (50.0)	0.569
Multiple seizure types	12 (31.6)	13 (81.3)	0.001*	21 (43.8)	4 (66.7)	0.531
Seizure frequency			0.323			0.944
Daily	25 (65.8)	7/15 (46.7)		28/47 (59.6)	4 (57.1)	
Weekly	6 (15.4)	5/15 (33.3)		10/47 (21/3)	1 (14.3)	
Monthly	7 (17.9)	3/15 (20.0)		9/47 (19.1)	2 (28.6)	
SE	6 (15.8)	2 (12.5)	1.000	8 (16.7)	0 (0)	0.575
ICU admission	3 (7.9)	1 (6.3)	1.000	4 (8.3)	0 (0)	1.000
MRI abnormality[#]	28 (73.7)	11 (68.8)	0.971	36 (75.0)	3 (50.0)	0.420
Temporal IED on EEG	5/37 (13.5)	3/15 (20.0)	0.870	6/47 (12.8)	2 (40.0)	0.164
CSF abnormality	17/36 (47.2)	5 (31.3)	0.282	21/46 (45.7)	1 (16.7)	0.362
The mRS score >2	33 (86.8)	13 (81.3)	0.913	42 (87.5)	4 (66.7)	0.213
≥3 ASMs	11 (28.9)	1 (6.3)	0.141	12 (25.0)	0 (0)	0.385
Delayed immunotherapy	19 (50.0)	10 (62.5)	0.400	24 (50.0)	5 (83.3)	0.267
Immunosuppressants therapy	7 (18.4)	7 (43.8)	0.110	10 (20.8)	4 (66.7)	0.055

Note: *$P<0.05$ [#]Medial temporal lobe FLAIR hyperintensities.

Abbreviations: ASM, anti-seizure medication; CSF, cerebrospinal fluid; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, gamma-aminobutyric-acid B receptor; GAD65, glutamic acid decarboxylase 65; ICU, intensive care unit; IED, interictal epileptiform discharge; IQR, interquartile range; LGI1, leucine-rich glioma-inactivated protein 1; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; SE, status epilepticus; sGTCS, secondarily generalized tonic-clonic seizures.

GAD65, n = 4), indicating the "sustained seizure > 2 year" group. The remaining 48 patients were classified as the "sustained seizure ≤ 2 year" group, of whom 14 (29.2%) were still taking ASMs at the last visit.

Female sex ($P = 0.030$), younger onset ($P < 0.001$), and specific antibody profiles ($P < 0.001$) were significantly associated with sustained seizures for more than two years (Table 2). However, multivariate analysis did not yield significant results. Regarding the antibody profiles, sustained seizures occurred in 2/35 (5.7%) of ALE with LGI antibody, 0/15 (0.0%) with $GABA_BR$ antibody, and 4/4 (100%) with GAD65 antibody. Notably, among two patients with anti-LGI1 encephalitis who experienced sustained seizures for over two years, both were females, with ages at disease onset of 35 and 48 years. These ages were much younger than the median onset age reported in previous research.[17]

Discussion

This study primarily described the seizure characteristics in a cohort of patients with antibody-positive ALE. Subsequently, we explored seizure outcomes and potential risk factors for sustained seizures at follow-up. Consistent with previous studies,[11,18] our findings demonstrated that the LGI1 antibody accounted for the highest proportion, followed by $GABA_BR$ and GAD65 antibodies. Symptomatic seizures were the most common initial symptoms with diverse semiology, including sGTCS, focal non-motor seizure, FBDS, and focal non-FBDS motor seizure. More than one-third of the patients exhibited multiple seizure types. Notably, we aimed to address a crucial knowledge gap by exploring the impact of different observation periods on seizure outcomes. The result demonstrated that a few ALE patients with LGI1 or $GABA_BR$ antibodies achieved terminal seizure remission between one and two years after immunotherapy initiation, suggesting a longer follow-up duration before diagnosing AAE is required. Furthermore,

female sex, younger onset, and specific antibody profiles were associated with sustained seizures lasting more than two years, indicating the development of AAE.

In the early stage of autoimmune encephalitis, patients may not present with a full-blown clinical picture. Therefore, a better knowledge of initial symptoms helps physicians promptly diagnose and treat. Compared to anti-NMDAR encephalitis, which typically manifests with psychiatric symptoms at onset,[19] patients with antibody-positive ALE experienced seizures as the most common symptom. In addition to the well-known sGTCS, focal non-motor seizure was considered another predominant seizure type, and it was less apparent and easy to ignore. Intriguingly, patients with LGI1 or GAD65 antibodies exhibit piloerection which seemed to be a distinct feature. Moreover, nearly 40% of the patients with antibody-positive ALE reported multiple seizure types, in accordance with the finding reported by Matricardi et al.[9] Seizures occurred daily or weekly in most cases; however, less frequent IEDs were observed on EEG recordings. Overall, although seizure characteristics were not highly specific, a thorough understanding of semiology was beneficial to identify seizures of autoimmune origin.[17]

Studies have been conducted to determine the risk of chronic epilepsy in autoimmune encephalitis over the last few years.[16,19–21] The results remained inconsistent to date, primarily due to the heterogeneous observation periods before diagnosing AAE in patients with ongoing seizures. As mentioned above, Geis et al suggested that seizures that persisted for more than one year after immunotherapy could be considered AAE.[4] However, Rada et al reported that it took more than 12 months for over half of the patients with antibody-positive autoimmune encephalitis to achieve seizure freedom in their cohort, and suggested that the follow-up duration should be extended to at least two years.[10,22] Another study defined chronic epilepsy as the presence of ongoing seizures in the last six months for patients with anti-LGI1 encephalitis who were followed up for at least two years.[23] The present study focused on patients with antibody-positive ALE who received proper immunotherapy in the acute stage. Interestingly, the findings revealed that 29.6% of the patients experienced intermittent seizures for more than one year, and only 11.1% experienced sustained seizures for more than two years. A few ALE patients with LGI1 or $GABA_BR$ antibodies achieved seizure remission within two years during an extended follow-up period. In contrast, the remaining patients with ongoing seizures appeared to have AAE. These findings suggested that seizures would require a longer period to resolve in some cases of ALE with neural surface antibodies, such as LGI1 or $GABA_BR$.[22] The immunological process may persist chronically and sustain the epileptic activity, as some studies have reported the positivity of serum antibodies for quite a long time.[22]

Previous studies have reported a higher incidence of AAE in patients with ALE compared to our cohort, which included both antibody-positive and antibody-negative ALE cases. A multicenter study recruited 25 pediatric patients with limbic encephalitis, and found about half of them experienced refractory seizures with a median follow-up period of two years.[7] Casciato et al indicated that 13/33 (39.4%) patients with ALE developed AAE, and those with the paucisymptomatic electro-clinical presentation were more likely to develop AAE.[8] This heterogeneity is reasonable, given that the pathogenesis of ALE may differ between antibody-positive and antibody-negative cases, despite similar structural changes. For instance, $GABA_BR$ antibodies may lead to neuronal dysfunction by functional blocking the target antigen, while LGI1 antibodies disrupt protein-protein interactions, thereby triggering downstream functional abnormalities.[4] Immunotherapy targeting antibodies could help restore most of these impaired functions. As for GAD65 antibodies, it remains uncertain whether they are pathogenic, yet a pathogenic effect of $CD8^+$ T cells and a regulatory effect of $CD4^+$ T cells have been identified in patients with GAD65 antibodies.[24] However, research on the pathogenesis of antibody-negative autoimmune encephalitis is quite limited. Previous studies have shown that patients with antibody-positive and -negative ALE exhibit varying levels of T and B cell activity, which may indicate different apoptotic neurodegeneration, astrogliosis, and microglial activation in the process of inflammation, autoimmunity, and epileptogenesis.[25–27] Overall, AAE may be associated with irreversible structural damage altering the neuronal networks or an ongoing inflammatory process that persists after the acute phase, or a combination of both, but the exact mechanism has not been fully elucidated.

Several potential factors, including younger onset, female sex, specific antibody profiles, and multiple seizure types, are indicative of sustained seizures for a longer period in antibody-positive ALE. Unsurprisingly, antibody profiles were strongly associated with long-term seizure outcomes. Research has demonstrated that patients with antibodies against intracellular antigens have a higher risk for AAE than those with antibodies against cell surface antigens.[4,28] Compared to

the probability of seizures occurring longer than one year, the risk for seizures occurring more than two years significantly decreased from 22.8% to 5.7% in anti-LGI1 encephalitis and 26.7% to 0.0% in anti-$GABA_B$ R encephalitis. However, all the patients with GAD65 antibody experienced persistent seizures for more than two years, indicating a significantly high rate of AAE in this group. Smith et al reported that chronic epilepsy occurred in 20.4% of patients with LGI1-antibody encephalitis despite aggressive immunotherapy.[23] Guery et al observed that 29% of patients developed drug-resistant epilepsy with a follow-up duration of at least 13 months.[29] Herein, patients with LGI1 antibody demonstrated a significantly lower risk for sustained seizures or AAE, and none of those with $GABA_B$ R antibody developed AAE, consistent with previous studies.[16,20] The heterogeneity could be attributed to several factors, such as population differences, inclusion criteria, and follow-up durations.

In addition to antibody types, younger age at disease onset and female sex were associated with a much longer seizure duration, indicating a propensity to develop AAE. The correlation between antibody types and younger age is an important concern,[30] as patients with anti-GAD65 were probably female and had a younger onset.[31,32] Although we did not perform a subgroup analysis based on antibody profiles, two patients with anti-LGI1 encephalitis who continued to experience intermittent seizures for over two years were both female and had a younger onset. This was consistent with the findings of Smith et al, who demonstrated that younger age at disease onset and female sex were associated with chronic epilepsy in anti-LGI1 encephalitis.[23] Therefore, confirming this phenomenon in future studies with larger sample sizes and multicenter prospective protocols is imperative.

In patients with antibody-positive ALE, multiple seizure types were associated with sustained seizures lasting more than one year, rather than a prognostic factor for AAE. The result highlighted the clinical significance of seizure semiology. It seemed to be consistent with our previous study, implying that patients with newly diagnosed epilepsy with multiple seizure types were less likely to achieve early seizure remission.[14] Multiple seizure types commonly present with a combination of focal non-motor seizures and sGTCS. It is well known that a history of GTCS coupled with focal seizures may be a negative predictor of seizure remission in temporal lobe epilepsy (TLE) with hippocampal sclerosis.[33] Multimodal MRI study by Chen et al indicated that sGTCS is associated with impaired integrity of the probabilistic hippocampal–thalamic pathway in TLE, reflecting a more widespread and abnormal epileptogenic network.[34] Consequently, multiple seizure types in antibody-positive ALE may indicate the involvement of widespread cortical brain regions in the acute phase, potentially contributing to a longer seizure duration. This was somewhat comparable to delay in immunotherapy which was frequently associated with late seizure remission rather than the development of chronic epilepsy.[23,29]

The study had several limitations. First, some patients were still receiving ASMs at their last visit, despite achieving long-term seizure remission. This may pose questions of whether they would experience seizure recurrence if ASMs discontinued, potentially leading to an underestimated AAE rate. Second, the sample size was relatively limited, especially in specific subtypes. Only five patients with GAD65 antibodies were included, and no patients with Hu, amphiphysin, or other antibodies were indeed identified according to Graus's criteria. It may raise concerns about whether the criteria used were too stringent. Third, our study did not include a comparison group of antibody-negative ALE patients due to the limited availability of well-characterized cases in the retrospective cohort. This omission restricts our ability to fully elucidate the distinct clinical characteristics and seizure outcomes between antibody-positive and antibody-negative ALE groups. Finally, the retrospective nature of the study may have introduced unavoidable bias. Future studies should be performed prospectively with a larger cohort and an extended follow-up period.

Conclusion

Our study highlighted the seizure characteristics in patients with antibody-positive ALE during the diagnostic workup. Importantly, seizure outcomes seemed to change over an extended follow-up period, especially in patients with LGI1 and $GABA_B$R antibodies. Younger age at disease onset, female sex, and specific antibody profiles may serve as potential indicators of AAE, underscoring the need for specific attention in these subgroups. However, further prospective research with a larger sample size is still needed to validate these results.

Abbreviations

ALE, Autoimmune limbic encephalitis; LGI1, leucine-rich glioma-inactivated 1; $GABA_BR$, gamma-aminobutyric acid type B receptor; GAD65, glutamic acid decarboxylase 65; AAE, autoimmune-associated epilepsy; AMPAR, alpha-amino -3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; EEG, electroencephalogram; ASM, anti-seizure medication; mRS, modified Rankin Score; sGTCS, secondarily generalized tonic-clonic seizures; FBDS, faciobrachial dystonic seizure; ILAE, International League Against Epilepsy; IQR, interquartile range; OR, odds ratio; CI, confidence interval; video-EEG, VEEG; IED, interictal epileptiform discharge; VPA, valproic acid; OXC, oxcarbazepine; CBZ, carbamazepine.

Data Sharing Statement

Anonymized data not published within this article will be made available upon reasonable request from any qualified investigator within 5 years after publication.

Ethical Approval and Informed Consent

The study was approved by the ethics committee of Second Affiliated Hospital School of Medicine Zhejiang University (approval number: 2024-LSY-0682). Patient consent was waived for this retrospective study.

Acknowledgments

We are grateful to all the participants in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Zhejiang Provincial Natural Science Foundation of China (grant number LQ23H090011 and LQ23H090004).

Disclosure

All authors declare that they have no competing interests in the study.

References

1. Budhram A, Leung A, Nicolle MW, Burneo JG. Diagnosing autoimmune limbic encephalitis. *CMAJ*. 2019;191(19):E529–E534. doi:10.1503/cmaj.181548
2. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018;378(9):840–851. doi:10.1056/NEJMra1708712
3. Vogrig A, Gigli GL, Nilo A, Pauletto G, Seizures VM. Epilepsy, and NORSE secondary to autoimmune encephalitis: a practical guide for clinicians. *Biomedicines*. 2023;11(1):44. doi:10.3390/biomedicines11010044
4. Geis C, Planagumà J, Carreño M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. *J Clin Invest*. 2019;129(3):926–940. doi:10.1172/JCI125178
5. Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: conceptual definitions. *Epilepsia*. 2020;61(7):1341–1351. doi:10.1111/epi.16571
6. Budhram A, Burneo JG. Acute symptomatic seizures, epilepsy, and autoimmune encephalitis: clarifying terminology in neural antibody-associated disease. *Epilepsia*. 2023;64(2):306–310. doi:10.1111/epi.17478
7. Sabanathan S, Abdel Mannan O, Mankad K, et al. Clinical features, investigations, and outcomes of pediatric limbic encephalitis: a multicenter study. *Ann Clin Transl Neurol*. 2022;9(1):67–78. doi:10.1002/acn3.51494
8. Casciato S, Morano A, Fattouch J, et al. Factors underlying the development of chronic temporal lobe epilepsy in autoimmune encephalitis. *J Neurol Sci*. 2019;396:102–107. doi:10.1016/j.jns.2018.10.026
9. Matricardi S, Casciato S, Bozzetti S, et al. Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy. *J Neurol Neurosurg Psychiatry*. 2022;93(11):1194–1201. doi:10.1136/jnnp-2022-329195

10. Rada A, Bien CG. What is autoimmune encephalitis-associated epilepsy? Proposal of a practical definition. *Epilepsia*. 2023;64(9):2249–2255. doi:10.1111/epi.17699
11. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391–404. doi:10.1016/S1474-4422(15)00401-9
12. Cai M, Lai Q, Zheng Y, et al. First-line immunotherapy of neuronal surface antibody-mediated autoimmune encephalitis: assessment of therapeutic effectiveness and cost-efficiency. *Mult Scler Relat Disord*. 2022;66:104071. doi:10.1016/j.msard.2022.104071
13. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis. *Neurology*. 2016;87(14):1449–1456. doi:10.1212/WNL.0000000000003173
14. Shen C, Du Y, Lu R, et al. Factors predictive of late remission in a cohort of Chinese patients with newly diagnosed epilepsy. *Seizure*. 2016;37:20–24. doi:10.1016/j.seizure.2016.02.007
15. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus-report of the ILAE task force on classification of status epilepticus. *Epilepsia*. 2015;56(10):1515–1523. doi:10.1111/epi.13121
16. Shen CH, Fang GL, Yang F, et al. Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis. *Ann Clin Transl Neurol*. 2020;7(8):1392–1399. doi:10.1002/acn3.51137
17. Kaaden T, Madlener M, Angstwurm K, et al. Seizure semiology in antibody-associated autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(6). doi:10.1212/NXI.0000000000200034
18. Chen B, Lopez Chiriboga AS, Sirven JI, Feyissa AM. Autoimmune encephalitis–related seizures and epilepsy: diagnostic and therapeutic approaches. *Mayo Clin Proc*. 2021;96(8):2029–2039. doi:10.1016/j.mayocp.2021.02.019
19. Liu X, Yan B, Wang R, et al. Seizure outcomes in patients with anti-NMDAR encephalitis: a follow-up study. *Epilepsia*. 2017;58(12):2104–2111. doi:10.1111/epi.13929
20. Liu X, Guo K, Lin J, et al. Long-term seizure outcomes in patients with autoimmune encephalitis: a prospective observational registry study update. *Epilepsia*. 2022;63(7):1812–1821. doi:10.1111/epi.17245
21. Lin N, Liu Q, Chen J, et al. Long-term seizure outcomes in patients with anti-Leucine-rich glioma-inactivated 1 encephalitis. *Epilepsy Behav*. 2021;122:108159. doi:10.1016/j.yebeh.2021.108159
22. Rada A, Birnbacher R, Gobbi C, et al. Seizures associated with antibodies against cell surface antigens are acute symptomatic and not indicative of epilepsy: insights from long-term data. *J Neurol*. 2021;268(3):1059–1069. doi:10.1007/s00415-020-10250-6
23. Smith KM, Dubey D, Liebo GB, Flanagan EP, Britton JW. clinical course and features of seizures associated with LGI1-antibody encephalitis. *Neurology*. 2021;97(11):e1141–e1149. doi:10.1212/WNL.0000000000012465
24. Dik A, Widman G, Schulte-Mecklenbeck A, et al. Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis. *Ann Clin Transl Neurol*. 2021;8(12):2289–2301. doi:10.1002/acn3.51486
25. Pitsch J, Loo KMJ, Gallus M, et al. CD8+ T-lymphocyte–driven limbic encephalitis results in temporal lobe epilepsy. *Ann Neurol*. 2021;89(4):666–685. doi:10.1002/ana.26000
26. Helmstaedter C, Hansen N, Leelaarporn P, et al. Specific B- and T-cell populations are associated with cognition in patients with epilepsy and antibody positive and negative suspected limbic encephalitis. *J Neurol*. 2021;268(2):455–466. doi:10.1007/s00415-020-10158-1
27. Langenbruch L, Bleß L, Schulte Mecklenbeck A, et al. Blood and cerebrospinal fluid immune cell profiles in patients with temporal lobe epilepsy of different etiologies. *Epilepsia*. 2020;61(10). doi:10.1111/epi.16688
28. Joubert B, Belbezier A, Haesebaert J, et al. Long-term outcomes in temporal lobe epilepsy with glutamate decarboxylase antibodies. *J Neurol*. 2020;267(7):2083–2089. doi:10.1007/s00415-020-09807-2
29. Guery D, Cousyn L, Navarro V, et al. Long-term evolution and prognostic factors of epilepsy in limbic encephalitis with LGI1 antibodies. *J Neurol*. 2022;269(9):5061–5069. doi:10.1007/s00415-022-11162-3
30. Cai MT, Zheng Y, Lai QL, et al. Phenotyping the late- and younger-onset neuronal surface antibody-mediated autoimmune encephalitis: a multicenter study. *Clin Exp Immunol*. 2023;211(1):78–83. doi:10.1093/cei/uxac117
31. Seifert-Held T, Eberhard K, Lechner C, et al. Functional recovery in autoimmune encephalitis: a prospective observational study. *Front Immunol*. 2021:12. 10.3389/fimmu.2021.641106.
32. Kunchok A, Mckeon A, Zekeridou A, et al. Autoimmune/paraneoplastic encephalitis antibody biomarkers: frequency, age, and sex associations. *Mayo Clin Proc*. 2022;97(3):547–559. doi:10.1016/j.mayocp.2021.07.023
33. Hemb M, Palmini A, Paglioli E, et al. An 18-year follow-up of seizure outcome after surgery for temporal lobe epilepsy and hippocampal sclerosis. *J Neurol Neurosurg Psychiatry*. 2013;84(7):800–805. doi:10.1136/jnnp-2012-304038
34. Chen C, Li H, Ding F, et al. Alterations in the hippocampal-thalamic pathway underlying secondarily generalized tonic–clonic seizures in mesial temporal lobe epilepsy: a diffusion tensor imaging study. *Epilepsia*. 2019;60(1):121–130. doi:10.1111/epi.14614