Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Identifying Key Prognostic Indicators for Relapse and Chronic Epilepsy in Autoimmune Encephalitis: Insights from a Multicenter Retrospective Study

Qingwei Lai[1,*], Yue Chen[1,*], Wei Wang[2,*], Zhangxu Lian[3,*], Tengfei Liu[4], Chunmei Wen[5]

[1]Department of Neurology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, People's Republic of China; [2]Department of Neurology, Yancheng First People's Hospital, Yancheng, People's Republic of China; [3]Department of Neurology, Xuzhou Central Hospital, Xuzhou, People's Republic of China; [4]Department of Neurology, Xuzhou Mining Group General Hospital, Xuzhou, People's Republic of China; [5]Department of Neurology, Yancheng Third People's Hospital, Yancheng, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qingwei Lai, Department of Neurology, Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou, Jiangsu, 221002, People's Republic of China, Tel +8651685802193, Email lqw8696@163.com

Objective: The aims of this study were to investigate clinical factors associated with encephalitis relapse and chronic epilepsy development, and to evaluate the effectiveness of immunotherapy on encephalitis relapse.

Methods: Patients with autoimmune encephalitis diagnosed as positive for neuronal surface antibodies in five general hospitals were included. A minimum 12-month follow-up period was conducted, and binary logistic regression analysis was used to identify predictors of encephalitis relapse and chronic epilepsy development. Additionally, decision curve analysis (DCA) was employed to assess the clinical net benefit of predicting encephalitis relapse and chronic epilepsy.

Results: The study encompassed 65 patients with autoimmune encephalitis. The one-year relapse rate for encephalitis was 13.9%. The CASE score (P=0.045) was associated with encephalitis relapse, with subsequent immunotherapy proving beneficial in enhancing outcomes. Chronic epilepsy prevalence at one year was 26.2%, particularly higher among patients with positive LGI1 antibodies. Although adjustments in antiseizure medications were partially effective, 41.2% of patients developed drug-resistant epilepsy (DRE). DCA confirmed that the predictive models provided significant net clinical benefit in assessing the risk of encephalitis relapse and chronic epilepsy. Notably, the presence of diffuse cortical atrophy, medial temporal lobe atrophy, or cerebellar hemisphere atrophy was linked to relapsing encephalitis and chronic epilepsy.

Conclusion: Most cases of autoimmune encephalitis are effectively managed, however, a minority of patients experience relapse or chronic epilepsy. The CASE score and LGI1 antibodies are independent risk factors for encephalitis relapse and chronic epilepsy development, respectively. Immunotherapy remains beneficial for relapsing patients, yet a portion may progress to DRE. Individuals with relapses and chronic epilepsy are predisposed to the development of cortical, temporal lobe, and cerebellar atrophy.

Keywords: autoimmune encephalitis, relapse, chronic epilepsy, immunotherapy, prognosis

Introduction

Autoimmune encephalitis is an inflammatory brain disorder caused by antibodies targeting neuronal surface proteins, receptors, ion channels, or neuronal intracellular proteins.[1] It can also be triggered by antibodies against gangliosides, as seen in Bickerstaff brainstem encephalitis.[2] Common subtypes of neuronal surface antibodies include anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, leucine-rich glioma inactivated 1 (LGI1) protein, and gamma-aminobutyric acid B receptor (GABABR) antibodies. Typical symptoms comprise psychiatric behavioral abnormalities, seizures, cognitive impairments, autonomic dysfunction, and impaired consciousness.[3–5] While some patients face severe acute symptoms, the majority exhibit sustained functional improvement post immunotherapy.[6–8]

Received: 1 August 2024
Accepted: 15 December 2024
Published: 24 December 2024

Immunotherapy is generally effective in managing encephalitis and alleviating seizures, especially when administered early.[9,10] However, relapse rates range from 8–36.4% in anti-NMDAR encephalitis to 14–35% in anti-LGI1 encephalitis during long-term follow-up.[11–14] Moreover, up to 43.7% of patients may develop chronic epilepsy following acute autoimmune encephalitis remission.[15–18] The variability in relapse rates and the development of chronic epilepsy observed across studies suggests potential ethnic heterogeneity in autoimmune encephalitis. However, several factors could contribute to this variability, including differences in follow-up durations, the proportions of patients with specific antibodies, and the timing of immunotherapy initiation relative to disease onset. Delayed immunotherapy has been identified as an independent risk factor for increased relapse rates.[12,19] Different types of encephalitis have different probabilities of leading to chronic epilepsy development. For instance, anti-LGI1 and NMDAR antibodies are associated with a favorable prognosis in patients experiencing acute-phase seizures, indicating a higher likelihood of remission.[12,17] In contrast, GAD65 antibodies, paraneoplastic antibodies, and markers linked to Rasmussen's encephalitis are strongly correlated with the onset of chronic epilepsy and poorer prognosis.[20–24] Furthermore, in patients with autoimmune-associated epilepsy, structural factors such as hippocampal atrophy and multifocal cortical neuronal loss accompanied by gliosis in Rasmussen's encephalitis may also contribute to seizure activity.[25,26] Interictal epileptiform discharges or seizures captured on electroencephalogram during the acute phase heighten the chance of chronic epilepsy development.[17] Given the rarity of the disease and the limited available data, further research is required to identify additional risk factors. There is a notable scarcity of data regarding follow-up treatment options and outcomes for relapsed autoimmune encephalitis or chronic epilepsy. Moreover, significant attention should be given to the potential role of imaging biomarkers in predicting adverse outcomes in autoimmune encephalitis.

The objectives of this study were multiple: to determine the long-term prognosis of patients with autoimmune encephalitis, to explore clinical factors associated with encephalitis relapse and chronic epilepsy development, to evaluate the effectiveness of further immunotherapy in managing encephalitis relapse by mRS (modified Rankin scale) and CASE (Clinical Assessment Scale in Autoimmune Encephalitis) cases, and to assess the predictive capacity of imaging biomarkers in determining long-term outcomes.

Methods

Patients

This study involved the enrollment of patients diagnosed with autoimmune encephalitis who had been hospitalized at the Department of Neurology of the Affiliated Hospital of Xuzhou Medical University, Xuzhou Central Hospital, Xuzhou Mining Group General Hospital, Yancheng First People's Hospital, and Yancheng Third People's Hospital between March 2017 and December 2022. The definitive diagnosis was made by at least two neurologists following the diagnostic criteria for autoimmune encephalitis,[27] with positive neuronal surface antibodies detected in the cerebrospinal fluid (CSF) using cell-based assays. Exclusion criteria included patients with positive antibodies to other types of autoimmune encephalitis (neuronal intracellular antibody), combined CNS demyelination, neurological paraneoplastic tumours, associated autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis, desiccative syndrome), metabolic encephalopathies, hereditary diseases, epilepsy or traumatic brain injury (TBI) before the autoimmune encephalitis diagnosis, incomplete clinical data, and poor compliance. Data on enrolled patients encompassed demographic details, clinical features, seizure types, magnetic resonance imaging (MRI) findings, electroencephalography (EEG) characteristics, immunotherapy regimens, and instances of encephalitis relapse or chronic epilepsy emergence. The study received approval from the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL267-01), and all participants or their legal guardians provided informed consent. The study also complies with the Declaration of Helsinki.

EEG Protocol and Interpretation

We employed a standardized protocol for the acquisition and interpretation of EEG data throughout the study. EEG recordings were conducted using a minimum of 21 electrodes, adhering to the international 10–20 system, to ensure consistent electrode placement across all participating centers. Each EEG session lasted for a minimum of 12 hours. EEG

recording of the presence of epileptic waves (spike, sharp, spike-slow, spike-slow, etc), diffuse slow waves, and clinical seizures. The presence of these features was confirmed by two physicians holding professional certification in EEG from the China Association Against Epilepsy. Diffuse slow wave activity was defined as the presence of sustained slow waves (0.5–4 hz) that were prominent over multiple cortical regions.[28] The interpretation of diffuse slow wave activity was performed by experienced epileptologists who were blinded to the patients' clinical outcomes, ensuring unbiased analysis.

Definitions

Encephalitis relapse was defined as the recurrence of symptoms after a complete remission for at least 3 months or a significant worsening of symptoms following a previous stabilization.[18] Chronic epilepsy, also known as "autoimmune-associated epilepsy", was defined as the persistence of seizures in patients with autoimmune encephalitis without clear evidence of active inflammation, even after appropriate immunotherapy.[29] Delayed immunotherapy was characterized by a time interval exceeding 30 days between the onset of symptoms and the initiation of immunotherapy in patients.[17] Long-term immunotherapy included treatment with mycophenolate mofetil or azathioprine.

Assessment of Encephalitis Relapse and Chronic Epilepsy

Patients were followed up by their primary care physicians through outpatient visits or telephone interviews, with all physicians having undergone standardized specialized training prior to conducting follow-ups. The follow-up process also included the use of electronic medical record systems to ensure comprehensive and accurate data collection. Patients were assessed for encephalitis relapse or the development of chronic epilepsy. Follow-up was discontinued in cases of patient death or loss to follow-up.

Effectiveness of Further Immunotherapy in Relapsed Encephalitis

Patients experiencing a relapse of encephalitis underwent further immunotherapy, and their mRS and CASE scores were assessed at 3, 6, and 12 months post-treatment.

Analysis of Cranial Magnetic Resonance Imaging

Cranial MRI data were evaluated by a neurologist and an imaging specialist in a blinded fashion to assess for atrophy in the cerebral cortex, medial temporal lobe, and cerebellum among patients with autoimmune encephalitis. MRI scans were performed during the acute phase, at relapse, and at follow-up intervals of 3, 6, 9, and 12 months post-diagnosis of autoimmune encephalitis. Diffuse cortical atrophy (DCA) and medial temporal lobe atrophy (mTA) were evaluated using axial T1-weighted images on a scale from 0 to 3,[30,31] while cerebellar hemisphere atrophy (CHA) was assessed using sagittal T1-weighted images on a similar 0 to 3 scale.[32] During each assessment, patients' MRI scans were compared against standard reference images, with grades 2–3 indicating moderate to severe atrophy. Differences in atrophy levels in DCA, mTA, and CHA were compared between patients with relapsing versus non-relapsing encephalitis, as well as between those with chronic epilepsy and those without.

Statistical Analysis

Statistical analysis was conducted using SPSS23.0 software (IBM, Armonk, NY, USA) and R (version 3.4.2). The Mann–Whitney *U*-test, chi-squared test, or Fisher's exact test was employed to compare risk factors associated with encephalitis relapse or chronic epilepsy. Factors such as age at onset, diffuse slow waves, faciobrachial dystonic seizures (FBDS), multiple seizures daily/daily, CASE score, interictal epileptiform discharge, status epilepticus (SE), and LGI1 antibody were evaluated as associated risk factors. Binary logistic regression analysis was utilized to identify predictors of encephalitis relapse and chronic epilepsy. Internal validation was performed by bootstrap logistic regression analysis based on 1000 bootstrap samples. DCA was employed to assess the clinical net benefit of predicting encephalitis relapse and chronic epilepsy. A significance level of $P<0.05$ was considered statistically significant.

Results

Demographic Statistics and Clinical Characteristics

We screened 133 patients with suspected autoimmune encephalitis, excluding those with antibody negative encephalitis (n=52) and other types of antibody encephalitis (anti-GAD65, n=3; anti-GFAP, n=3; anti-AQP4, n=1). A total of 74 patients with autoimmune encephalitis (anti-NMDAR, n=27; anti-LGI1, n=26; anti-GABABR, n=11; anti-mGIuR5, n=4; anti-CASPR2, n=2; anti-AMPA1R, n=2; anti-IgLON5, n=1; anti-GlyR1,n=1) were included in this study, with 9 patients died during follow-up (anti-NMDAR, n=3; anti-LGI1, n=2; anti-GABABR, n=3; anti-mGIuR5, n=1) and 65 patients completing follow-up. The clinical characteristics of the patients are detailed in Table 1.

Table 1 Clinical Characteristics of the Patients

Characteristics	Anti-NMDAR (n=27)	Anti-LGI1 (n=26)	Anti-GABABR (n=11)	Other antibody (n=10)	*P*
Age at onset (range), y	27 (6–68)	63.5 (25–83)	65 (45–75)	61.5 (48–73)	0.000
Female	15 (55.6)	7 (26.9)	4 (36.3)	3 (30.0)	0.179
Delayed immunotherapy	6 (22.2)	14 (53.8)	9 (81.8)	4 (40.0)	0.005
≥2ASM	10 (37.0)	13 (50.0)	7 (63.6)	2 (20.0)	0.184
Presence of tumor	4 (14.8)	1 (3.8)	5 (45.4)	0 (0.0)	0.008
ICU admission	10 (37.0)	4 (15.3)	3 (27.2)	2 (20.0)	0.333
Any cognitive concerns, n (%)	22 (81.4)	21 (80.7)	9 (81.8)	10 (100.0)	0.565
Diffusion restriction (%)					
Cortex (%)	7 (25.9)	3 (11.5)	1 (9.1)	3 (30.0)	0.381
Subcortex/white matter (%)	4 (14.8)	0 (0)	0 (0)	1 (10.0)	0.140
Medial temporal cortex (%)	3 (11.1)	8 (30.7)	6 (54.5)	2 (20.0)	0.040
Infra-tentorium (%)	1 (3.7)	1 (3.8)	1 (9.1)	1 (10.0)	0.574
Video-EEG					
Diffuse slow wave	5 (18.5)	4 (15.3)	2 (18.1)	1 (10.0)	1.000
Interictal epileptiform discharge	11 (40.7)	21 (80.7)	10 (90.9)	4 (40.0)	0.001
Seizures captured	8 (29.6)	9 (34.6)	5 (45.5)	1 (10.0)	0.361
Initially treated with combined first-line IT, n (%)	19 (70.3)	18 (69.2)	6 (54.5)	4 (40.0)	0.318
Initially treated with long-term IT, n (%)	7 (25.9)	2 (7.6)	0 (0)	1 (10.0)	0.125
Initially treated with second-line IT, n (%)	7 (25.9)	1 (3.8)	1 (9.1)	1 (10.0)	0.110
Treated with long-term IT during course, n (%)	8 (29.6)	6 (23.1)	0 (0)	1 (10.0)	0.174
Treated with second-line IT during course, n (%)	8 (29.6)	2 (7.6)	1 (9.1)	0 (0.0)	0.062
Highest seizure frequency					
Multiple daily/daily	7 (25.9)	17 (65.3)	6 (54.5)	2 (20.0)	0.010
Weekly	3 (11.1)	5 (19.2)	5 (45.4)	1 (10.0)	0.104
Monthly	0 (0)	1 (3.8)	0 (0)	0 (0.0)	0.635

(*Continued*)

Table 1 (Continued).

Characteristics	Anti-NMDAR (n=27)	Anti-LGI1 (n=26)	Anti-GABABR (n=11)	Other antibody (n=10)	*P*
Type of seizure at onset, (%)					
FBDS	0 (0)	8 (30.8)	0 (0)	0 (0.0)	0.001
Focal seizures	15 (55.6)	19 (73.1)	6 (54.5)	4 (40.0)	0.277
SE	6 (22.2)	6 (23.0)	3 (27.3)	2 (20.0)	1.000
CASE scores M (P25,P75)	4 (3,8)	4 (3,6)	6 (4,7)	7 (3,9)	0.427

Abbreviations: ASM, antiseizure medication; ICU, intensive care unit; EEG, electroencephalography; IT, immunotherapy; FBDS, faciobrachial dystonic seizures; SE, status epilepticus; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

Among the 74 patients, 55 (74.3%) experienced acute symptomatic seizures. These seizures were observed in 62.9% (17/27) of those with anti-NMDAR encephalitis, 88.5% (23/26) with anti-LGI1 encephalitis, 100% (11/11) with anti-GABABR encephalitis, and 40% (4/10) with other antibody-positive encephalitis. Furthermore, status epilepticus occurred in 23.0% of patients with acute attacks (anti-NMDAR, n=6; anti-LGI1, n=6; anti-GABABR, n=3; anti-AMPA1R, n=1; anti-CASPR2, n=1). Notably, the onset of onset of anti-NMDA encephalitis was earlier than that of anti-LGI1 and anti-GABABR encephalitis. Compared to anti-NMDAR encephalitis, anti-GABABR encephalitis was more likely to involve the medial temporal cortex and was often associated with delayed immunotherapy. It also showed a higher incidence of malignancies, particularly small cell lung cancer (n=5), when compared to anti-LGI1 encephalitis. In contrast, anti-LGI1 encephalitis had a greater proportion of patients experiencing multiple daily seizures and interictal epileptiform discharges compared to those with anti-NMDAR encephalitis. Furthermore, FBDS developed in 8 patients (30.8%) with anti-LGI1 encephalitis, whereas no cases of FBDS were observed in either anti-GABABR or anti-NMDAR encephalitis patients.

Immunotherapy for Autoimmune Encephalitis and Antiseizure Drugs

Among the 74 patients, 94.6% received first-line immunotherapy (hormone, intravenous immunoglobulin (IVIG), plasmapheresis, alone or in combination). In addition, 47 patients (63.5%) were initially treated with a first-line combination therapy (anti-NMDAR, 19/27, 70.3%; anti-LGI1, 18/26, 69.2%; anti-GABABR, 6/11, 54.5%; anti-mGIuR5, 2/4, 50.0%; anti-AMPA1R, 1/2, 50.0%; anti-GlyR1, 1/1, 100.0%). Moreover, 10 patients (13.5%; anti-NMDAR, n=7; anti-LGI1, n=1; anti-GABABR, n=1; anti-GlyR1, n=1) initially received second-line immunotherapy (rituximab or cyclophosphamide), while 10 patients (13.5%; anti-NMDAR, n=7; anti-LGI1, n=2; anti-GlyR1, n=1) initially received long-term immunotherapy. Throughout the treatment course, 11 patients (14.9%; anti-NMDAR, n=8; anti-LGI1, n=2; anti-GABABR, n=1) were treated with second-line immunotherapy, and 15 patients (20.3%; anti-NMDAR, n=8; anti-LGI1, n=6; anti-GlyR1, n=1) received long-term immunotherapy. In addition, 53 patients (71.6%) were treated with one or more antiseizure drugs. Valproic acid (57.1%), levetiracetam (51.0%), oxcarbazepine (30.6%), pirempanel (8.2%), carbamazepine (8.2%), lamotrigine (6.1%), and topiramate (4.1%) were the most frequently used. Prior to immunotherapy during the acute phase, 71.4% of patients received anti-seizure medications that were ineffective in managing their seizures.

Predictors of Relapsing Encephalitis in Patients with Autoimmune Encephalitis

During the follow-up, 9 patients died, leaving 65 patients remaining in the study. Within this group, 9 patients experienced relapses (13.8%). The median time to relapse of encephalitis was 5.0 months (range 3–12.5 months). Patients with older age at onset (P=0.014), diffuse slow wave EEG (P=0.038), multiple seizures daily/daily (P=0.010), FBDS (P=0.031), and higher CASE score (P=0.011) were more likely to experience encephalitis relapse (Table 2).

Table 2 Comparison of Patients with and without Relapse of Encephalitis

Characteristics	Relapse (n=9)	No Relapse (n=56)	*P*
Female (%)	3 (33.3)	25 (44.6)	0.721
Age at onset (range), y	66 (6–72)	48 (9–77)	0.014
Delayed immunotherapy (%)	2 (22.2)	26 (46.4)	0.280
≥2ASM	5 (55.5)	22 (39.3)	0.472
ICU admission (%)	3 (33.3)	12 (21.4)	0.420
Any cognitive concerns, n (%)	7 (77.7)	47 (83.9)	0.642
Presence of tumor (%)	2 (22.2)	4 (7.1)	0.191
Diffusion restriction (%)			
Cortex (%)	2 (22.2)	11 (19.6)	1.000
Subcortex/white matter (%)	0 (0)	5 (8.9)	1.000
Medial temporal cortex (%)	4 (44.4)	13 (23.2)	0.225
Infra-tentorium (%)	0 (0)	4 (7.1)	1.000
Video-EEG			
Diffuse slow wave	4 (44.4)	7 (12.5)	0.038
Interictal epileptiform discharge	8 (88.8)	32 (57.1)	0.137
Seizures captured	2 (22.2)	16 (28.6)	1.000
Initially treated with combined first-line IT, n (%)	4 (44.4)	21 (37.5)	0.724
Initially treated with long-term IT, n (%)	2 (22.2)	6 (10.7)	0.305
Initially treated with second-line IT, n (%)	2 (22.2)	7 (12.5)	0.600
Treated with long-term IT during course, n (%)	4 (44.4)	10 (17.9)	0.091
Treated with second-line IT during course, n (%)	2 (22.2)	8 (14.3)	0.619
Highest seizure frequency, n (%)			
Multiple daily/daily	7 (77.8)	17 (33.9)	0.010
Weekly	1 (22.2)	13 (23.2)	0.670
Monthly	0 (0)	2 (3.6)	1.000
Type of seizure at onset, n (%)			
FBDS	3 (33.3)	3 (5.4)	0.031
Focal seizures	7 (77.8)	35 (62.5)	0.474
SE	4 (44.4)	10 (17.9)	0.091
Antibody subtype, n (%)			
NMDAR	2 (22.2)	22 (39.3)	0.466
LGI1	5 (55.5)	19 (33.9)	0.272
GABAB	2 (22.2)	6 (10.7)	0.305
CASE scores M (P25,P75)	7 (5,10.5)	4 (3,7)	0.011

Abbreviations: ASM, antiseizure medication; ICU, intensive care unit; EEG, electroencephalography; IT, immunotherapy; FBDS, faciobrachial dystonic seizures; SE, status epilepticus; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

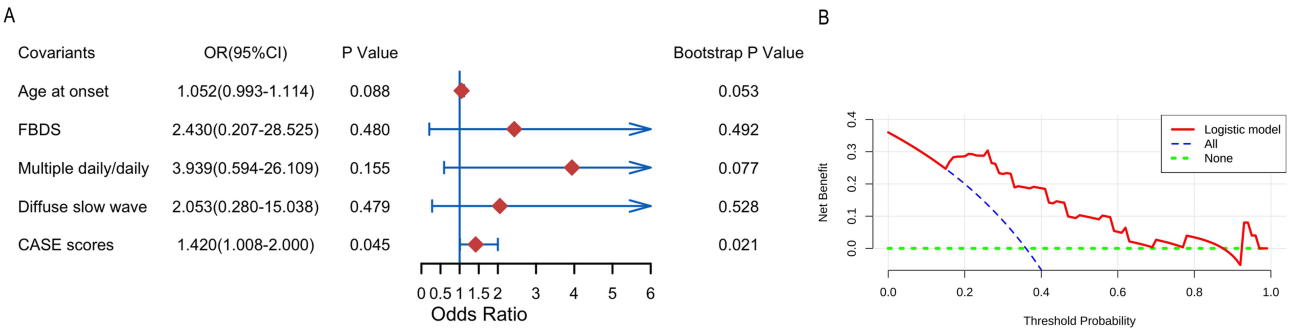

Figure 1 Elevated CASE scores represent independent predictors of patients' higher risk for encephalitis relapse. (**A**) Forest plots of the multivariate logistic regression analysis for the prediction of encephalitis relapse. A multivariate model was adjusted for age at onset, diffuse slow wave, multiple seizures daily/daily, FBDS, and CASE scores. (**B**) Decision curve analysis highlighted the clinical net benefit in the prediction of encephalitis relapse.
Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; FBDS, faciobrachial dystonic seizures; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

The multivariate logistic regression analysis was adjusted for CASE scores as well as age at onset, diffuse slow wave, FBDS and multiple daily/daily. Indeed, multivariate logistic regression analysis highlighted the independent significance of higher CASE scores in predicting relapse of encephalitis (OR 1.420, 95% CI 1.008–2.000, P=0.045, Figure 1A). Finally, DCA demonstrated that the predictive model provided a high net clinical benefit across a threshold probability range of 13% to 67% (Figure 1B).

Risk Factors of Chronic Epilepsy in Patients with Autoimmune Encephalitis

Among the 65 patients included in the study, 17 (26.2%) were identified as having chronic epilepsy. The median duration of chronic epilepsy was 8.0 months (range 6–12 months). Our analysis revealed that older age at onset (P=0.025), interictal epileptiform discharge (P=0.029), multiple seizures daily/daily (P<0.0001), FBDS (P=0.004), SE (P=0.037), presence of LGI1 antibody (P<0.0001), and higher CASE scores (P=0.031) were significantly associated with an increased risk of developing chronic epilepsy (Table 3). Conversely, patients with NMDAR encephalitis had a lower likelihood of developing chronic epilepsy (P=0.012, Table 3).

In a multivariate logistic regression analysis adjusting for LGI1 antibody, age at onset, FBDS, multiple seizures daily/daily, interictal epileptiform discharge, CASE scores, and SE, the independent predictive significance of LGI1 antibody in relation to chronic epilepsy was underlined (OR 43.734, 95% CI 3.332–573.990, P=0.004, Figure 2A). Finally, DCA demonstrated that the predictive model provided a substantial net clinical benefit across a threshold probability range of 7% to 88% (Figure 2B).

Table 3 Comparison of Patients with and without Chronic Epilepsy

Characteristics	Chronic Epilepsy (n=17)	No Chronic Epilepsy (n=48)	P
Female (%)	4 (23.5)	23 (47.9)	0.080
Age at onset (range), y	64 (6–76)	48.5 (9–77)	0.025
Delayed immunotherapy (%)	8 (47.1)	18 (37.5)	0.489
≥2ASM	8 (47.1)	19 (39.6)	0.591
ICU admission (%)	5 (29.4)	9 (18.8)	0.493
Any cognitive concerns, n (%)	13 (76.4)	41 (85.4)	0.458
Presence of tumor (%)	2 (11.7)	4 (8.3)	0.648

(*Continued*)

Table 3 (Continued).

Characteristics	Chronic Epilepsy (n=17)	No Chronic Epilepsy (n=48)	*P*
Diffusion restriction (%)			
Cortex (%)	3 (17.6)	9 (18.8)	1.000
Subcortex/white matter (%)	0 (0)	5 (10.4)	0.315
Medial temporal cortex (%)	6 (35.2)	10 (20.8)	0.326
Infra-tentorium (%)	1 (5.9)	3 (6.3)	1.000
Video-EEG			
Diffuse slow wave	5 (29.4)	6 (12.5)	0.138
Interictal epileptiform discharge	14 (82.3)	25 (52.1)	0.029
Seizures captured	8 (47.0)	10 (20.8)	0.058
Initially treated with combined first-line IT, n (%)	10 (58.8)	29 (60.4)	0.908
Initially treated with long-term IT, n (%)	1 (5.9)	7 (14.6)	0.669
Initially treated with second-line IT, n (%)	3 (17.6)	6 (12.5)	0.687
Treated with long-term IT during course, n (%)	5 (29.4)	9 (18.8)	0.493
Treated with second-line IT during course, n (%)	3 (17.6)	6 (12.5)	0.687
Highest seizure frequency			
Multiple daily/daily	13 (76.5)	13 (27.1)	0.000
Weekly	1 (5.9)	13 (27.1)	0.091
Monthly	1 (5.9)	1 (2.1)	0.458
Type of seizure at onset, (%)			
FBDS	5 (29.4)	1 (2.1)	0.004
Focal seizures	14 (82.4)	27 (56.3)	0.055
SE	7 (41.1)	7 (14.6)	0.037
Antibody subtype			
NMDAR	2 (11.8)	22 (45.8)	0.012
LGI1	14 (82.4)	10 (20.8)	0.000
GABABR	1 (5.9)	7 (14.6)	0.669
CASE scores [M (P25,P75)]	6 (5,8)	4 (3,7)	0.031

Abbreviations: ASM, antiseizure medication; ICU, intensive care unit; EEG, electroencephalography; IT, immunotherapy; FBDS, faciobrachial dystonic seizures; SE, status epilepticus; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

Follow-Up Treatment of Relapsing Encephalitis

Among the 9 patients with autoimmune encephalitis who experienced clinical relapse, 7 (77.8%) received further immunotherapy, including hormone therapy (n=7), IVIG (n=6), rituximab (n=3), and cyclophosphamide (n=2). However, 2 patients (28.6%) did not undergo further immunotherapy, with reasons given including the discovery of secondary pulmonary tuberculosis, the emergence of new lung cancer, and family members opting out of treatment.

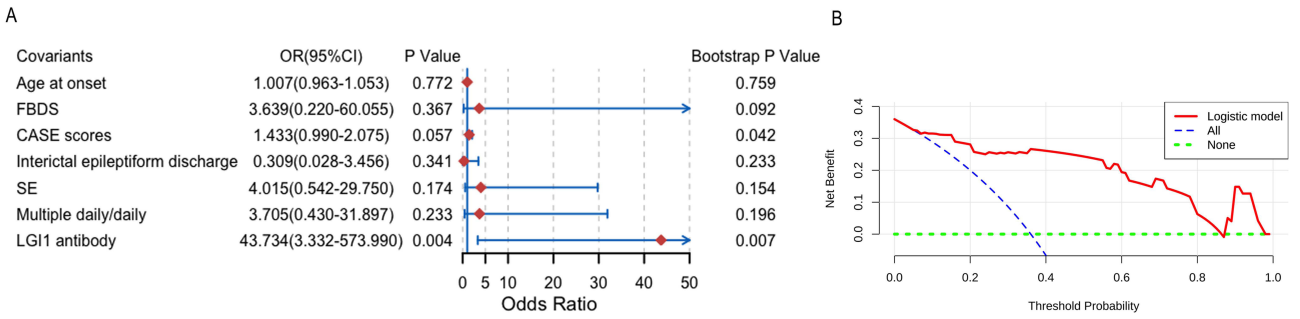

Figure 2 Positive LGI1 antibodies were independent predictors of patients' higher risk for chronic epilepsy. (**A**) Forest plots of the multivariate logistic regression analysis for the prediction of chronic epilepsy. A multivariate model was adjusted for age at onset, multiple seizures daily/daily, interictal epileptiform discharge, FBDS, CASE scores, SE, and LGI1 antibody. (**B**) Decision curve analysis highlighted the clinical net benefit in the prediction of chronic epilepsy.
Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; FBDS, faciobrachial dystonic seizures; CASE, Clinical Assessment Scale in Autoimmune Encephalitis; SE, status epilepticus.

We also evaluated the effect of immunotherapy post-relapsing encephalitis using CASE and mRS scores. Our findings showed that further immunotherapy reduced CASE scores at 3, 6 and 12 months post-encephalitis relapse ($P<0.05$, Figure 3A). Furthermore, further immunotherapy was associated with reduced mRS scores at 6 and 12 months among patients who experienced a relapse ($P<0.05$, Figure 3B). These results indicate the continued efficacy of immunotherapy in managing patients with relapsed encephalitis.

Follow-Up Treatment of Chronic Epilepsy

During the follow-up, 17 patients developed chronic epilepsy. After adjusting antiseizure medications, 10 patients (58.8%) achieved improved seizure control, whereas 7 patients (41.2%) developed drug-resistant epilepsy (DRE). The most commonly used antiseizure medications were sodium valproate (64.7%), oxcarbazepine (47.1%), levetiracetam (47.1%), lamotrigine (17.6%), and zonisamide (5.9%). The medical records indicated that antibody titers were documented for 14 patients with chronic epilepsy during follow-up. Among these, 12 patients tested negative for both CSF and serum antibodies. The remaining 2 patients showed negative CSF antibody results but positive serum antibody titers, specifically anti-NMDAR at 1:10 and anti-LGI1 at 1:10. Additionally, we identified 6 patients with DRE who received immunotherapeutic interventions, including corticosteroids (n=4) and IVIG (n=2). Among these patients, 4 experienced a reduction in seizure frequency of more than 50% compared to baseline, while the other 2 patients showed no significant changes in seizure frequency.

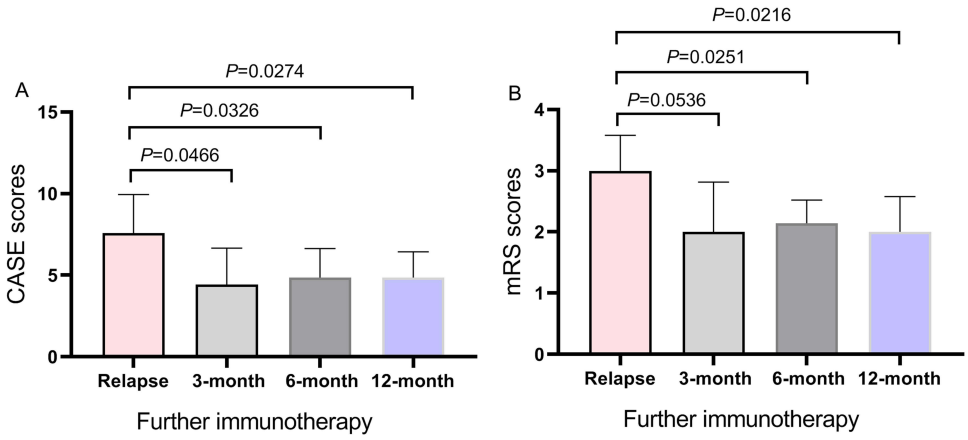

Figure 3 Further immunotherapy provided beneficial for encephalitis relapsing patients. (**A**) The evaluation of CASE scores at 3, 6 and 12 months post-encephalitis relapse. (**B**) The evaluation of mRS scores at 3, 6 and 12 months post-encephalitis relapse.
Abbreviations: CASE, Clinical Assessment Scale in Autoimmune Encephalitis; mRS, modified Rankin scale.

Imaging Evaluation of Relapsing Encephalitis

In patients with relapsing encephalitis, 7 patients (77.8%) had DCA, mTA and CHA. Of these, 6 patients (66.7%) developed DCA after a median of 3 (2–5.5) months, 3 patients (33.3%) developed mTA after 3 (2.5–4.5) months, and 5 patients (55.6%) developed CHA after 3 (2–5) months. Among patients without relapse, 10 patients (17.9%) showed DCA, mTA and CHA, including DCA (n=6, 10.7%), mTA (n=5, 8.9%) and CHA (n=1, 1.8%). Patients with relapsing encephalitis exhibited a higher likelihood of presenting with DCA, MTA, or CHA compared to those without relapse ($P<0.05$, Figure 4A and B). Moreover, patients demonstrating DCA, MTA, or CHA had higher mRS scores than those lacking encephalatrophy ($P<0.05$, Figure 4C), suggesting a potential role for these imaging findings as prognostic markers in autoimmune encephalitis.

Imaging Evaluation of Chronic Epilepsy

In patients with chronic epilepsy, 14 patients (82.4%) displayed DCA, mTA and CHA. Among these patients, 10 patients (58.8%) developed DCA after a median of 4 (2–7.5) months, 6 patients (35.3%) developed mTA after 3 (2.5–6) months, and 5 patients (29.4%) developed CHA after 4 (3–5.5) months. Conversely, only 3 patient (6.3%) without chronic epilepsy manifested DCA, mTA and CHA, including DCA (n=2, 4.2%), mTA (n=1, 2.1%) and CHA (n=1, 2.1%). Patients with chronic epilepsy exhibited a significantly higher likelihood of having DCA, mTA, or CHA compared to those without chronic epilepsy ($P<0.0001$, Figure 5A and B). These imaging characteristics could serve as valuable markers for predicting the development of chronic epilepsy.

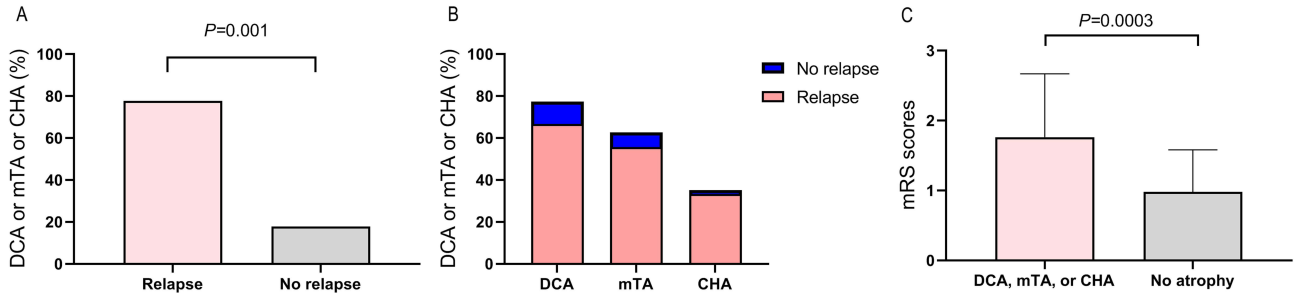

Figure 4 Patients with relapsing encephalitis are prone to encephalatrophy. (**A**) Proportion of DCA, mTA or CHA in patients with relapsing versus non-relapsing encephalitis. (**B**) Proportion of DCA, mTA or CHA in patients with relapsing versus non-relapsing encephalitis. (**C**) mRS scores for encephalatrophy (DCA, mTA or CHA) and without encephalatrophy.

Abbreviations: DCA, diffuse cortical atrophy; mTA, medial temporal lobe atrophy; CHA, cerebellar hemisphere atrophy.

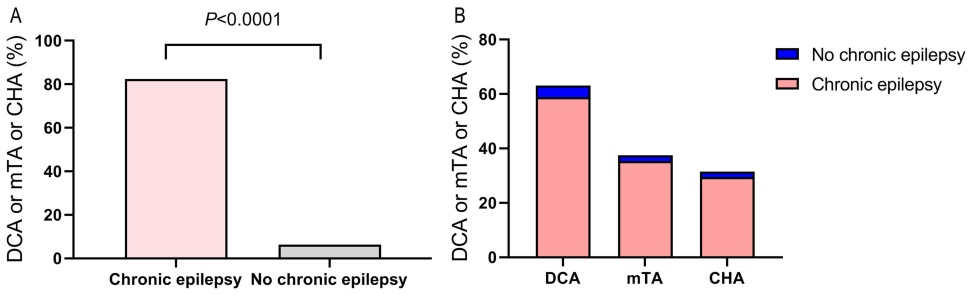

Figure 5 Patients with chronic epilepsy after encephalitis are prone to encephalatrophy. (**A**) Proportion of DCA, mTA or CHA in patients with and without chronic epilepsy. (**B**) Proportion of chronic epilepsy versus no chronic epilepsy in DCA, mTA or CHA.

Discussion

In this study, we conducted a comprehensive analysis of the clinical characteristics and prognostic factors associated with anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis. The findings from this multicenter study offer valuable insights into the prognosis of autoimmune encephalitis. Firstly, the one-year relapse rate for autoimmune encephalitis was 13.8%. A higher CASE score was indicative of a higher likelihood of encephalitis relapse. Secondly, the one-year incidence of chronic epilepsy was 26.2%, with patients with positive LGI1 antibodies showing a higher propensity for developing chronic epilepsy. Thirdly, subsequent immunotherapy demonstrated efficacy in enhancing the prognosis of relapsing encephalitis. Fourthly, adjustments in antiseizure medications exhibited partial efficacy in managing chronic epilepsy, although 41.2% of patients developed DRE. Fifthly, the emergence of diffuse cortical atrophy, medial temporal lobe atrophy, or cerebellar hemisphere atrophy correlated with recurrent encephalitis and chronic epilepsy, marking a poor prognosis and serving as potential imaging indicators for predicting encephalitis relapse and chronic epilepsy.

Numerous studies have indicated that the majority of patients with autoimmune encephalitis exhibit favorable outcomes following immunotherapy.[12,33,34] However, there remains a subset of patients who experience encephalitis relapse or progress to chronic epilepsy, significantly impacting both physical and mental well-being. Several studies have assessed the prognosis of relapsing encephalitis in autoimmune encephalitis patients with neuronal surface antibodies. Across these studies,[11–14] relapsing encephalitis rates ranged from 8% to 36.4%, with varying definitions of encephalitis relapse. In our present study, the data revealed a 13.8% relapse rate for autoimmune encephalitis, which fell in the scope of these studies. Within subgroups, the relapse rates for anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis were 8.3%, 20.8%, and 25.0%, respectively, without significant differences observed. Our observations indicated that patients with older onset age, EEG diffuse slow wave, multiple seizures daily/daily, FBDS, and elevated CASE scores were more predisposed to encephalitis relapse, consistent with prior research linking onset age to relapse risk and general prognosis.[35,36] Additionally, EEG slow wave activity > 50% and mRS scores at onset emerged as poor prognostic indicators.[37,38] While some studies have implicated delays in immunotherapy as a risk factor for relapse,[12,19] our study did not yield the same conclusion, possibly due to variations in antibody types and definitions of delayed treatment. Notably, our multivariate logistic regression analysis highlighted the significant predictive value of higher CASE scores in predicting encephalitis relapse. The CASE scoring system proved effective for the comprehensive assessment of Chinese autoimmune encephalitis patients,[39] showing a positive correlation with mRS scores.[39–41] Importantly, initial mRS scores significantly influenced prognosis.[38]

In a cohort of 65 patients who tested positive for neuronal surface antibodies, 26.2% were diagnosed with chronic epilepsy. The risk factors associated with the development of chronic epilepsy included older age at onset, multiple seizures daily/daily, FBDS, SE, interictal epileptiform discharge, presence of LGI1 antibodies, and higher CASE scores. Interestingly, patients with positive anti-NMDAR antibodies were found to have a lower likelihood of developing chronic epilepsy. Previous studies have reported a prevalence of chronic epilepsy in patients with positive neuronal cell surface antibody autoimmune encephalitis ranging from 0% to 43.7%,[12,16] although the definitions of chronic epilepsy varied between these studies. In our present study, we observed a chronic epilepsy incidence rate of 26.2%, falling within the range reported in the literature. One study identified uncontrollable seizures at onset and persistent interictal epileptic discharges as independent predictors of chronic epilepsy,[16] while another study found that patients with interictal epileptiform discharges or seizures recorded on EEG were more predisposed to developing chronic epilepsy.[17] In cases of anti-GABAR encephalitis, status epilepticus was correlated with seizure recurrence.[42] However, some studies had also suggested that a delay in immunotherapy was associated with persistent seizures.[17,18,43] Interestingly, in our patient cohort, we observed that a delay in immunotherapy initiation did not consistently predict the development of chronic epilepsy. Our multivariate logistic regression analysis underscored the significant predictive value of LGI1 antibodies in determining chronic epilepsy outcomes. Despite receiving active immunotherapy, 26.2% of patients in our cohort continued to experience persistent seizures, known as autoimmune-associated epilepsy.

In our multicenter study investigating risk factors for relapse and chronic epilepsy in autoimmune encephalitis, we found that delayed immunotherapy does not increase the risk of relapse and chronic epilepsy, contrary to previous findings. Several factors may contribute to this discrepancy. Firstly, the heterogeneity of autoimmune encephalitis subtypes and their varied responses to treatment could influence outcomes differently. In our cohort, it is possible that

patients with less aggressive forms of autoimmune encephalitis, who naturally have a more favorable prognosis, were overrepresented among those receiving delayed treatment, thereby skewing the results. Secondly, differences in study design, such as variations in the definition of "delayed" immunotherapy and the specific immunotherapeutic agents used, may account for the contrasting findings. Additionally, our study may have captured a subset of patients who, despite delayed treatment, received more intensive (first-line combination regimens) or prolonged therapy, which could mitigate the effects of the delay. Further research is needed to explore these factors and to determine whether specific patient characteristics or treatment regimens can explain the observed differences in outcomes related to the timing of immunotherapy.

In addition, our study provided evidence to support the efficacy of continued immunotherapy after a relapse of encephalitis. The data showed that continued immunotherapy resulted in reduced CASE and mRS scores at 6 and 12 months post-relapse, highlighting the continued effectiveness of immunotherapy in relapsed encephalitis cases. Previous research has shown that prolonged immunotherapy beyond 6 months in serum-negative patients with relapsing autoimmune encephalitis is associated with improved mRS and CASE scores.[44] The optimal duration of immunotherapy in relapsing encephalitis remains controversial, highlighting the importance of individualised assessment based on each patient's clinical presentation. Moreover, our study shed light on the management of autoimmune-associated epilepsy, revealing that 58.8% of patients experienced improved seizure control following adjustments to antiseizure medications, while 41.2% developed DRE. Furthermore, six patients with DRE received immunotherapeutic interventions, and notably, four of these patients experienced a reduction in seizure frequency of more than 50% compared to baseline. For patients with DRE, considering options such as surgical resection of epileptogenic foci or the implantation of neuroregulatory devices may be beneficial for achieving improved seizure management.[26,45]

The presence of DCA, CHA, or mTA in patients with autoimmune encephalitis was associated with a poor prognosis, potentially leading to relapsing encephalitis or chronic epilepsy. This observation underscores the importance of long-term cranial MRI monitoring for disease prognosis and treatment planning. Persistent or worsening DCA, CHA, or mTA despite active immunotherapy may indicate a less favorable prognosis. Numerous studies have demonstrated an association between abnormal brain MRI findings, including DCA, CHA, or mTA, and adverse clinical outcomes.[11,46–49] However, caution must be exercised regarding potential selection bias, as patients with poor outcomes may be more likely to undergo repeat MRI evaluations.

In our research, we emphasize the importance of controlling potential confounding factors, particularly the variability in treatment protocols across the different centers participating in this multicenter study. Variations in therapeutic approaches, including differences in immunotherapy regimens, selection of antiseizure medications, and timing of interventions, can significantly influence the clinical outcomes observed in patients with autoimmune encephalitis. To minimize these confounding effects, we selected five general hospitals renowned for their high standards of clinical care, each adhering strictly to established guidelines for the management of autoimmune encephalitis. Furthermore, Our analysis of data from these centers revealed no statistically significant differences in the usage proportions of first-line (either alone or in combination) and second-line immunotherapy agents, as well as the use of antiseizure drugs (either alone or in combination) or the timing of interventions. We encourage future studies to standardize treatment protocols to facilitate a more comprehensive assessment of their impact on the recurrence of encephalitis and the development of chronic epilepsy.

Given the identified risk factors for relapse and chronic epilepsy in autoimmune encephalitis, refining clinical management strategies is essential. Our study highlights CASE scores and anti-LGI1 antibodies as independent risk indicators for relapse and chronic epilepsy progression, respectively. Therefore, we recommend a stratified assessment approach at diagnosis, closely monitoring patients with higher CASE scores or positive LGI1 antibodies due to their elevated risk. For high-risk patients, personalized immunotherapy adjustments with early, aggressive interventions should be considered to reduce relapse and DRE development. Routine MRI scans should assess cortical, temporal lobe, and cerebellar atrophy in patients with relapse or chronic epilepsy histories, enabling timely interventions. Furthermore, enhancing patient education on relapse and chronic epilepsy risks and the importance of treatment adherence can improve outcomes and quality of life. Implementing these strategies can reduce relapse rates and chronic epilepsy incidence, ultimately improving patient outcomes.

Our study has several limitations. Firstly, despite recruiting patients from multiple centers, the sample size remained relatively modest, raising concerns about selection bias. Secondly, the relatively short follow-up duration may underestimate the rates of encephalitis relapse or chronic epilepsy, as patients who did not experience these outcomes during the study period could still manifest them in the future. Thirdly, while our study did not establish a clear association between immunotherapy and subsequent relapse or chronic epilepsy, this inconclusive finding could partly stem from a subset of patients not receiving immunotherapy, potentially compromising statistical power. Moreover, the limited number of patients receiving second-line immunotherapy highlights the need for further research to fully assess its impact on encephalitis relapse or chronic epilepsy. Fourthly, despite adjusting for various potential predictors in our multivariate model, residual confounders, such as concomitant cancer treatments, may still influence the analyses. Lastly, the limited number of cases of each autoimmune encephalitis subtype precluded conducting multivariate analyses to identify predictors of encephalitis relapse or chronic epilepsy.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

The present study was supported financially by Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy (KF-XY201904), Jiangsu Provincial Natural Science Foundation (BK20221221), Xuzhou Medical Science and Technology Innovation Project for Youths (XWKYHT20210582), and The Paired Assistance Scientific Research Project of Affiliated Hospital of Xuzhou Medical University (SHJDBF2024206).

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.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry*. 2021;92(7):757–768. doi:10.1136/jnnp-2020-325300
2. Lee SU, Kim HJ, Choi JY, et al. Expanding clinical spectrum of anti-GQ1b antibody syndrome: a review. *JAMA Neurol*. 2024;81(7):762–770. doi:10.1001/jamaneurol.2024.1123
3. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. *Physiol Rev*. 2017;97(2):839–887. doi:10.1152/physrev.00010.2016
4. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018;378(9):840–851. doi:10.1056/NEJMra1708712
5. 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
6. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12:157–165. doi:10.1016/S1474-4422(12)70310-1
7. Hoftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology*. 2013;81:1500–1506. doi:10.1212/WNL.0b013e3182a9585f
8. Harutyunyan G, Hauer L, Dunser MW, et al. Risk factors for intensive care unit admission in patients with autoimmune encephalitis. *Front Immunol*. 2017;8:835.
9. Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other in flammatory encephalitis. *Curr Opin Neurol*. 2017;30(3):345–353.
10. Dubey D, Britton J, McKeon A, et al. Randomized placebo-controlled trial of intravenous immunoglobulin in autoimmune LGI1/CASPR2 epilepsy. *Ann Neurol*. 2020;87(2):313–323. doi:10.1002/ana.25655
11. Feng J, Yang M, Cui D, et al. Recurrence of anti-N-methyl-D-aspartate receptor encephalitis: a cohort study in central China. *Front Neurol*. 2022;13:832634. doi:10.3389/fneur.2022.832634
12. Gong X, Chen C, Liu X, et al. Long-term functional outcomes and relapse of anti-NMDA receptor encephalitis: a cohort study in Western China. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e958.

13. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology*. 2016;87:1449–1456. doi:10.1212/WNL.0000000000003173
14. Guo K, Liu X, Lin J, et al. Clinical characteristics, long-term functional outcomes and relapse of anti-LGI1/Caspr2 encephalitis: a prospective cohort study in Western China. *Ther Adv Neurol Disord*. 2022;15:17562864211073203. doi:10.1177/17562864211073203
15. Shen CH, Fang GL, Yang F, et al. Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABAB R encephalitis. *Ann Clin Transl Neurol*. 2020;7(8):1392–1399. doi:10.1002/acn3.51137
16. 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;93:1194–1201. doi:10.1136/jnnp-2022-329195
17. Liu X, Guo K, Lin JF, et al. Long-term seizure outcomes in patients with autoimmune encephalitis: a prospective observational registry study update. *Epilepsia*. 2022;63(7):1812–1821.
18. Smith KM, Dubey D, Liebo GB, et al. Clinical course and features of seizures associated with LGI1-antibody encephalitis. *Neurology*. 2021;97(11): e1141–e1149.
19. Zhong R, Chen Q, Zhang X, et al. Relapses of anti-NMDAR, anti-GABABR and anti-LGI1 encephalitis: a retrospective cohort study. *Front Immunol*. 2022;13:918396. doi:10.3389/fimmu.2022.918396
20. Peltola J, Kulmala P, Isojärvi J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. *Neurology*. 2000;55 (1):46–50. doi:10.1212/WNL.55.1.46
21. Lilleker JB, Biswas V, Mohanraj R. Glutamic acid decarboxylase (GAD) antibodies in epilepsy: diagnostic yield and therapeutic implications. *Seizure*. 2014;23(8):598–602. doi:10.1016/j.seizure.2014.04.009
22. Malter MP, Frisch C, Zeitler H, et al. Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. *Seizure*. 2015;30:57–63. doi:10.1016/j.seizure.2015.05.017
23. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain*. 2004;127(Pt 8):1831–1844. doi:10.1093/brain/awh203
24. Varadkar S, Bien CG, Kruse CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol*. 2014;13 (2):195–205. doi:10.1016/S1474-4422(13)70260-6
25. Bien CG, Bauer J, Deckwerth TL, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. *Ann Neurol*. 2002;51(3):311–318. doi:10.1002/ana.10100
26. Carreño M, Bien CG, Asadi-Pooya AA, et al. Epilepsy surgery in drug resistant temporal lobe epilepsy associated with neuronal antibodies. *Epilepsy Res*. 2016;129:101–105. doi:10.1016/j.eplepsyres.2016.12.010
27. 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
28. Yildirim M, Konuskan B, Yalnizoglu D, et al. Electroencephalographic findings in anti-N-methyl-d-aspartate receptor encephalitis in children: a series of 12 patients. *Epilepsy Behav*. 2017;78:118–123. doi:10.1016/j.yebeh.2017.09.022
29. 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
30. Pasquier F, Leys D, Weerts JGE, et al. Inter-and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *Eur Neurol*. 1996;36:268–272. doi:10.1159/000117270
31. De Leon MJ, George AE, Golomb J, et al. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiol Aging*. 1997;18:1–11. doi:10.1016/S0197-4580(96)00213-8
32. Naka H, Ohshita T, Murata Y, et al. Characteristic MRI findings in multiple system atrophy: comparison of the three subtypes. *Neuroradiology*. 2002;44:204–209. doi:10.1007/s00234-001-0713-7
33. Xu X, Lu Q, Huang Y, et al. Anti-NMDAR encephalitis: a single-center, longitudinal study in China. *Neurol Neuroimmunol Neuroinflamm*. 2019;7 (1). doi:10.1212/NXI.0000000000000633
34. Zhao YY, Wang HX, Wang M, et al. Relapse factors of patients of anti-N-methyl-D-aspartate receptor encephalitis. *Acta Neurol Scand*. 2022;145 (4):434–441. doi:10.1111/ane.13568
35. Li TR, Zhang YD, Wang Q, et al. Clinical characteristics and long-term prognosis of anti-LGI1 encephalitis: a single-center cohort study in Beijing, China. *Front Neurol*. 2021;12:674368. doi:10.3389/fneur.2021.674368
36. Kong XY, Gong X, Li AQ, et al. Efficacy of immunotherapy and prognosis in anti-LGI1 encephalitis patients: a meta-analysis. *Ann Clin Transl Neurol*. 2023;10(9):1578–1589. doi:10.1002/acn3.51847
37. Wu Q, Xie QC, Liu L, et al. Factors influencing prognosis and relapse in patients with anti-N-methyl-D-aspartate receptor encephalitis. *Mult Scler Relat Dis*. 2023;74:104697. doi:10.1016/j.msard.2023.104697
38. Li HY, Qiao S, Cui CS, et al. Clinical features and outcomes of leucine-rich glioma-inactivated protein 1 and contactin protein-like 2 antibody-associated autoimmune encephalitis in a Chinese cohort. *J Clin Neurosci*. 2022;101:137–143. doi:10.1016/j.jocn.2022.05.007
39. Zhang YC, Tu E, Yao CX, et al. Validation of the clinical assessment scale in autoimmune encephalitis in Chinese patients. *Front Immunol*. 2021;12:796965. doi:10.3389/fimmu.2021.796965
40. Lim JA, Lee ST, Moon J, et al. Development of the clinical assessment scale in autoimmune encephalitis. *Ann Neurol*. 2019;85(3):352–358. doi:10.1002/ana.25421
41. Aboseif A, Li Y, Amin M, et al. Clinical determinants of longitudinal disability in LGI-1-IgG autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2023;11(1). doi:10.1212/NXI.0000000000200178
42. Huang Q, Ma MG, Wei X, et al. Characteristics of seizure and antiepileptic drug utilization in outpatients with autoimmune encephalitis. *Front Neurol*. 2018;9:1136. doi:10.3389/fneur.2018.01136
43. Chen SS, Zhang YF, Di Q, et al. Predictors and prognoses of epilepsy after anti-neuronal antibody-positive autoimmune encephalitis. *Seizure*. 2021;92:189–194. doi:10.1016/j.seizure.2021.09.007
44. Lee WJ, Lee HS, Kim DY, et al. Seronegative autoimmune encephalitis: clinical characteristics and factors associated with outcomes. *Brain*. 2022;145(10):3509–3521. doi:10.1093/brain/awac166
45. Chen B, Lundstrom BN, Crepeau AZ, et al. Brain responsive neurostimulation device safety and effectiveness in patients with drug-resistant autoimmune-associated epilepsy. *Epilepsy Res*. 2022;184:106974. doi:10.1016/j.eplepsyres.2022.106974

46. Lee WJ, Kwon YN, Kim B, et al. MOG antibody-associated encephalitis in adult: clinical phenotypes and outcomes. *J Neurol Neurosurg Psychiatry*. 2023;94(2):102–112. doi:10.1136/jnnp-2022-330074
47. Lei C, Chang X, Li H, et al. Abnormal brain MRI findings in anti-N-methyl-D-aspartate receptor encephalitis and correlation with outcomes. *Front Neurol*. 2022;13:834929. doi:10.3389/fneur.2022.834929
48. Lee WJ, Lee ST, Kim DY, et al. Disease progression and brain atrophy in NMDAR encephalitis: associated factor & clinical implication. *Ann Clin Transl Neurol*. 2022;9(7):912–924. doi:10.1002/acn3.51604
49. Zhao YY, Han B, Qin CH, et al. Brain magnetic resonance imaging predictors in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Clin Transl Neurol*. 2022;9(12):1974–1984. doi:10.1002/acn3.51690