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Seizure characteristics, treatment, and outcome in autoimmune synaptic encephalitis: A long-term study

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ABSTRACT

Objectives: The objective of this study was to report seizure characteristics, long-term outcome, and potential factors associated with persistent seizures in patients with autoimmune synaptic encephalitis (ASE).
Method: Clinical data and courses of 52 patients with ASE who presented with seizures at the Department of Neurology of the First Hospital of Jilin University from January 2015 to August 2017 were reviewed. Seizure outcomes were assessed with a median follow-up duration of 30 months (8–40 months).
Results: Most patients (71.2%) presented with seizure at initial consultation; focal to bilateral tonic–clonic seizures (50.0%) were the most common type. The temporal lobe (73.5%) was the prominent region of seizure origin, which was incident with hippocampal lesions on magnetic resonance imaging (MRI) in 62.1% of the patients. Status epilepticus, subclinical seizures, and nonepileptic events were observed in 28.9%, 36.8%, and 28.9% of the patients, respectively. Twenty-seven out of the 43 followed-up patients (62.8%) exhibited seizure remission after initial immunotherapy. Others (37.2%) developed persistent seizures to different extents. Six out of 9 patients experienced additional seizure freedom because of antiepileptic drugs (AEDs); however, the seizures of the other three patients, with serious conditions, showed poor response. Patients with anti-*N*-methyl-D-aspartate receptor antibodies had a lower risk of developing persistent seizures than those with anti-leucine-rich glioma-inactivated 1 (LGI1) or anti-γ-aminobutyric acid receptor type B receptor ($GABA_BR$) antibodies ($P = 0.001$).
Conclusions: A complex of clinical and subclinical seizures, and nonepileptic events characterize ASE. Patients with anti-LGI1 or anti-$GABA_BR$ antibodies have a higher risk of developing persistent seizures; AEDs are suitable for achieving additional seizure freedom, but not for patients with serious conditions. A few patients present with super-refractory epilepsy despite multiple treatments.

1. Introduction

Autoimmune synaptic encephalitis (ASE) is a type of limbic encephalitis characterized by positive antibodies targeting extracellular antigens in the cerebrospinal fluid (CSF) or serum [1]. Target antigens are receptors or proteins that have critical roles in synaptic transmission and regulation of nerve excitability, including the *N*-methyl-D-aspartate receptor (NMDAR), γ-aminobutyric acid receptor type B receptor ($GABA_BR$), and leucine-rich glioma-inactivated 1 (LGI1) [2]. Seizures are a prominent feature of ASE, and occur in the acute phase of the disease and later during disease progression [3]. Current studies have reported that seizure manifestation is diverse, including tonic/tonic–clonic seizures, faciobrachial dystonic seizures (FBDS), automatisms, vocalizations, sensory events, and status epilepticus (SE) [4–6]. Immunoglobulins or steroids are currently the current valid treatment options for patients with ASE; however, 20–30% of the patients are at risk of developing persistent seizures [7]. The underlying mechanism and potential predictors of persistent seizures are unclear. In addition, data regarding the effectiveness of antiepileptic drugs (AEDs) or repeated immunotherapy for persistent seizure control are lacking.

In this study, we systematically investigated the seizure characteristics of patients with ASE based on both clinical symptoms and long-term video electroencephalogram (EEG) recording because in these patients, substantial seizure insults can present with merely clinical manifestations and some spontaneous activities can also be detected as nonepileptic events. Moreover, we analyzed the potential risk factors of the patients who developed persistent seizures, and assessed the effectiveness of AEDs and repeated immunotherapy in achieving additional seizure freedom based on a long-term follow-up.

Abbreviations: ASE, autoimmune synaptic encephalitis; CSF, cerebrospinal fluid; $GABA_BR$, γ-aminobutyric acid receptor type B receptor; LGI1, leucine-rich glioma-inactivated 1; SE, status epilepticus; AEDs, antiepileptic drugs; EEG, electroencephalogram; FBDS, faciobrachial dystonic seizures; NCSE, nonconvulsive status epilepticus; NMDAR, *N*-methyl-D-aspartate receptor; IQR, interquartile range.

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2. Materials and methods

2.1. Participants

The patients in our study were recruited from the Department of Neurology of the First Hospital of Jilin University between January 2015 and August 2017, with the following inclusion criteria: (1) acute or subacute onset symptoms of encephalitis; (2) seizure occurrence in acute or subacute phase of the disease; (3) positive test results for antibodies against NMDAR, LGI-1, or $GABA_BR$ in the CSF; and (4) immunotherapy as initial treatment, including corticosteroids, immunoglobulin, or a combination of both. Exclusion criteria included the following: (1) patients with other factors that may influence seizure outcome, such as history of epilepsy, brain tumors, or cerebral trauma; (2) patients with coexisting antibodies, such as Hu, Yo, CV2, Ri, Ma2, PCA2, ANNA3, and other autoimmune antibodies to cell-surface antigens; and (3) patients with incomplete clinical data. This study was approved by the Ethics Committee of the First Hospital of Jilin University. Written informed consent to participate was obtained from the patients or their next of kin.

2.2. Clinical information

Clinical information was obtained from electronic medical records and personal interviews, including seizure semiology, symptoms, underlying tumor, the type of AEDs, CSF tests, and brain magnetic resonance imaging (MRI) and EEG findings. Patients' seizure outcome and additional therapy were followed up every 3 months by telephonic interview and/or clinic visits after discharge. According to the 2017 guidelines of the International League Against Epilepsy, we classified seizures into focal motor/nonmotor onset seizures with or without awareness, focal to bilateral tonic–clonic seizures, and generalized onset seizures [8]. We defined SE as prolonged seizure activity or recurrent seizures without full recovery of consciousness between episodes for more than 5 min [9]. We also analyzed nonconvulsive status epilepticus (NCSE) by monitoring long-term video EEGs. Baseline seizure frequency was categorized as daily (more than one seizure per day), weekly (more than one seizure per week but not daily), monthly (more than one seizure per month but not weekly), or single seizure. For CSF tests, leukocytosis was defined as white blood cell count $>8 \times 10^6$/L. Protein concentration exceeding 0.45 g/L was defined as abnormal elevation.

2.3. Statistical analysis

Continuous data are described as mean (range) or median (interquartile range [IQR]), and categorical data are shown as counts (percentages). We compared the difference between the two groups using Student's *t*-test for continuous variables and Pearson's chi-squared or Fisher's exact test for categorical variables. All analyses were performed using SPSS software (version 18.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Seizure characteristics

From January 2015 to August 2017, our center diagnosed ASE in 73 patients, 58 of whom presented with at least one seizure in the acute or subacute phase of the disease. The incidence of seizures in ASE was 79.5%. We recruited 52 eligible patients in our cohort, excluding 6 with incomplete clinical data.

The mean age at seizure onset was 46 years (range, 17–73 years), and 23 (44.2%) patients were women. The median number of days between seizure onset and disease onset was 8 days (IQR, 4–10), except for 37 (71.2%) patients with seizure as the initial symptom. At seizure presentation, nearly 85% of the patients had focal onset seizures with or without awareness, in which the focal to bilateral tonic–clonic seizures was the most common type (50.0%). Moreover, generalized onset seizures were observed in 15.4% of the patients; FBDS (19.2%) was only found in patients with anti-LGI1 antibodies. The seizures had both motor (88.5%) and nonmotor onset (11.5%, included sensory seizures [vestibular sensations], cognitive seizures, and behavioral arrest). Regrading basal seizure frequency, 26 (50.0%) patients manifested with weekly seizures; 18 (34.6%) had daily seizures, and 5 (9.6%) had monthly seizures; SE was observed in 15 (28.8%) patients, including convulsive SE in 8 (15.4%) and nonconvulsive SE in 7 (13.5%). Other accompanying symptoms were cognitive dysfunction, psychiatric disorders, and abnormal movements, which were found in 50.0%, 69.2%, and 57.7% cases, respectively. All patients (52) underwent brain MRI; 29 out of 52 (55.8%) patients showed abnormal hyperintense signals in T2-weighted imaging/fluid-attenuated inversion recovery, among which the proportions of patients exhibiting multifocal and isolated unilateral lesions were similar. The lesioned regions were as follows: the hippocampus (62.1%, 18/29), temporal lobe (37.9%, 11/29), frontal lobe (17.2%, 5/29), insular cortex (13.8%, 4/29), parietal lobe (13.8%, 4/29), thalamus (10.3%, 3/29), and cingulate gyrus (3.4%, 1/29). The detailed seizure semiology and results of complementary studies have been summarized in Table 1.

3.2. EEG monitoring findings

All the 52 patients underwent EEG monitoring, the average duration for which was 22.9 (range, 8–24) h. We reviewed three aspects of the EEG findings: background activity, interictal abnormal waves, and spontaneous events. Notably, we first observed EEG burst suppression and lateralized periodic discharges in patients with ASE. Interictal epileptic discharges were observed in 28 (53.8%) patients. While 38 (73.1%)

Table 1
Seizure semiology of ASE with neuronal cell surface antibodies (n = 52).

Characteristics	n (%)
Age at seizure onset (years), mean (range)	46 (17–73)
Sex (female)	23 (44.2)
Duration between first symptom and seizure onset	
Seizure as first presenting symptom	37 (71.2)
If not, duration (days), median (interquartile range)	8 (4–10)
Presenting symptoms	
Cognitive disorders	26 (50)
Psychiatric disorders	36 (69.2)
Movement disorders	30 (57.7)
Tumors	9 (17.3)
Seizure classification	
Focal to bilateral tonic–clonic seizures	26 (50.0)
Focal motor seizures	12 (23.1)
Focal nonmotor seizures	6 (11.5)
Generalized onset seizures	8 (15.4)
Faciobrachial dystonic seizures	10 (19.2)
Status epilepticus	
Convulsive status epilepticus	8 (15.4)
Nonconvulsive status epilepticus	7 (13.5)
Baseline seizure frequency	
Daily	18 (34.6)
Weekly	26 (50)
Monthly	5 (9.6)
Single seizure	3 (5.8)
Complementary studies	
MRI abnormal hyperintense in T2-weighted imaging/FLAIR	29 (55.8)
CSF WBC counts (10^6/L), mean (range)	32 (1–208)
CSF protein level (g/L), mean (range)	0.45 (0.19–1.06)
CSF neuronal autoantibody type	
NMDAR	17 (32.7)
LGI1	17 (33.7)
$GABA_BR$	18 (34.6)

Note: ASE, autoimmune synaptic encephalitis; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; CSF, cerebrospinal fluid; WBC, white blood cell; NMDAR, *N*-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; $GABA_BR$, γ-aminobutyric acid receptor type B.

patients were monitored for spontaneous activity, not all spontaneous events were epileptic. Eleven out of the 38 (28.9%) patients showed nonepileptic events; all of these 11 patients presented with movement disorders: 4 demonstrated only nonepileptic events, and 7 exhibited epileptic events mixed with nonepileptic ones. Among the 34 patients with seizure activity documented by EEG, we identified 20 (52.6%, 20/38) with clinical seizures alone, 11 (28.9%, 11/38) with subclinical seizures alone, and the remaining 3 (7.9%, 3/38) with both. The origins of seizure activities were as follows (26 unilateral and 8 multifocal origins): the temporal lobe (73.5%), frontal lobe (20.6%), and hemisphere (8.8%). Others locations of origin were the parietal, central, or posterior regions of the brain, accounting for 11.8% of the patients in total. The summary of the EEG information is shown in Table 2.

3.3. Seizure outcomes

We performed a continuous follow-up (8–40 months) after discharge, which was terminated when patients died. In total, we included 43 patients in our seizure outcome study, excluding 2 patients who died of respiratory failure during the acute phase of the disease, 3 who discontinued initial immunotherapy, and 4 who were lost during the extended follow-up.

Of the 43 patients, 27 (62.8%) experienced seizure remission upon completion of initial immunotherapy (immunoglobulins, steroids, or combination of both), including 13 with anti-NMDAR antibodies, 8 with anti-LGI1 antibodies, and 6 with anti-$GABA_BR$ antibodies. The duration of seizure remission was 1–3 months from disease onset, and the patients never experienced another seizure until the end of follow-up. Although 22 out of 27 patients received AEDs concurrent with immunotherapy, only 3 patients continued receiving them for >6 months. The remaining 16 (37.2%) patients developed persistent seizures and experienced varying degrees of seizure episodes during the follow-up. Statistical analysis (Table 3) revealed that related factors included age at seizure onset, SE in acute phase, high protein level in the CSF, and neuronal antibody type ($P < 0.05$).

Among the 16 patients who developed persistent seizures, 6 (37.5%) experienced a short-term seizure remission; the median duration was 4.8 months (range, 1–10 months) after discharge. These patients could not be considered as exhibiting disease relapse, as they did not present with other encephalitis symptoms except seizure attacks. Moreover, 9 out of the 16 patients received subsequent therapeutics for persistent seizure control. Six patients experienced additional seizure freedom because of AED adjustment, which accounted for 66.7% (6/9). The other 3 patients underwent alternative immunotherapy, as performed for serious conditions: one patient with anti-$GABA_BR$ antibodies experienced seizure freedom after 3 additional rounds of immunotherapy combined with levetiracetam, with the duration from disease onset being 20 months; another patient with anti-$GABA_BR$ antibodies exhibited >50% seizure reduction after additional immunotherapy, but discontinued AEDs after discharge; one patient with anti-LGI1 antibodies showed super-refractory epilepsy and continued to experience frequent episodes after 2 additional rounds of immunotherapy combined with 3 AEDs.

Table 2
EEG studies of ASE with neuronal surface antibodies (n = 52).

EEG findings	n (%)
Absence of PDR	15 (28.8)
Background activity	
α-dominated rhythm	41 (78.8)
δ-/θ-dominated rhythm	6 (11.5)
Mixed rhythm with low amplitude	4 (7.7)
Burst suppression	1 (1.9)
Interictal abnormal waves	
IEDs	28 (53.8)
LPDs	1 (1.9)
EDB	4 (7.7)
Lateralized RDA	6 (11.5)
Absence of sleep features	11 (21.2)
EEG-documented spontaneous activity (n = 38)	
Clinical seizures	23 (60.5)
Subclinical seizures	14 (36.8)
Nonepileptic events	11 (28.9)
EEG-documented seizure origins (n = 34)	
Temporal lobe	25 (73.5)
Frontal lobe	7 (20.6)
Others	7 (20.6)

Note: EEG, electroencephalography; PDR, posterior dominant rhythm; IEDs, interictal epileptic discharges; LPDs, lateralized periodic discharges; EDB, extreme delta brush; RDA, rhythmic delta activity.

Table 3
Statistical analysis of risk factors for patients who developed persistent seizures after initial immunotherapy.

	Short-term seizures (n = 27)	Persistent seizures (n = 16)	P-value
Age (years)	41 (18–73)	58 (38–68)	<0.001
Sex (female)	11 (40.7)	8 (50.0)	0.555
Interval before starting initial treatment (days)	31 (7–160)	48 (8–180)	0.308
Seizure as initial symptom	18 (66.7)	13 (81.3)	0.303
Absence of α-dominated rhythm	3 (11.1)	3 (18.8)	0.655
IEDs	12 (44.4)	10 (62.5)	0.252
SE	4 (14.8)	9 (56.3)	0.004
Abnormal MRI findings	14 (51.9)	10 (62.5)	0.497
CSF tests			
Hing protein level	7 (25.9)	9 (56.3)	0.047
Leukocytosis	17 (63.0)	9 (56.3)	0.663
Therapy selection			0.138
IVIG alone	2 (7.4)	4 (25.0)	
Corticosteroids alone	6 (22.2)	1 (6.3)	
Combination	19 (70.4)	11 (68.8)	
Neuronal antibody type			0.001
NMDAR	13 (48.1)	0	
LGI1	8 (29.6)	7 (43.8)	
$GABA_BR$	6 (22.2)	9 (56.3)	

Note: IEDs, interictal epileptic discharges; SE, status epilepticus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IVIG, Intravenous immunoglobulin; NMDAR, *N*-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; $GABA_BR$, γ-aminobutyric acid receptor type B.

4. Discussion

The pathogenic mechanisms of seizure in ASE are yet to be elucidated. The activation of B cells, and their subsequent proliferation and differentiation into plasma cells and reactive memory B cells play an important role in the production of autoantibodies [10]. Existing antibodies can interfere with the normal function of ion channels or synaptic transmission through receptor internalization and crosslinking [11]. Recently, Nibber et al. reported that anti-$GABA_BR$ antibodies could reduce the duration of the active (up) states of the intrinsic oscillations and spike rates in cortical networks, based on whole-cell patch-clamp recording [12]. These factors may disturb the balance between excitation and inhibition in the central nervous system, resulting in recurrent seizure episodes.

In our cohort, 79.5% of the patients manifested with new-onset seizures, which is similar to the previously reported incidences of 88% and 80.7% in patients with ASE [4,13,14], but higher than the 50% incidence reported in patients with neuronal intracellular antibodies [15]. Based on the retrospective review of seizure semiology in our study, we can conclude that focal onset acute seizures with high episode frequency are a feature of ASE-associated epilepsy. Although we found 15.4% of the patients to exhibit generalized onset seizures, several of these could have focal onset; since we did not capture the seizure attacks during EEG monitoring except in case of one patient, we only assessed them based on the onset manifestation. The EEG recordings

in our study captured multiple discharge origins, with predominant onset in the temporal lobe (73.5%), which was consistent with the incidence of hippocampal lesions (62.1%) found on brain MRI. Therefore, most cases of ASE-associated epilepsy can be categorized as temporal lobe epilepsy. This may also explain the diverse manifestation of seizures reported in previous studies.

Our study also showed that seizure was the initial symptom in the majority of the patients; however, a subtle distinction existed among the patients in terms of different antibody types. In our study, nearly all the patients (94.4% [17/18]) with anti-$GABA_BR$ antibodies presented with seizure as their first symptom, whereas the incidence of seizure at initial consultation was lower in patients with anti-NMDAR and anti-LGI1 antibodies (58.3% [10/17]). This clinical feature was consistent with the findings of previous studies which demonstrated that seizures often occur after psychiatric disorder or memory deficits in anti-NMDAR and anti-LGI1 antibody encephalitis [4,16]. Although seizures always occurred in the acute stage of the disease, it is noteworthy that a minority of patients presented with late-onset seizures. In this study, the 2 patients who exhibited cognitive disorders at the beginning experienced their first seizure 30 and 45 days after disease onset, respectively. In particular patients, the duration could be even longer. Muehlebner et al. [17] have reported the case of a 15-year-old girl with memory loss at the beginning who exhibited a generalized tonic–clonic seizure after 6 months of disease onset.

Seizure manifestation was of multiple forms in patients with ASE. In our cohort, the majority of patients manifested with motor seizures, 19.2% of the patients exhibited FBDS, which was only observed in anti-LGI1 antibody encephalitis. Nonmotor seizures were presented with cognitive seizures, behavioral arrest, and sensory seizures (vestibular sensations) in 6 patients in our study. This seizure semiology is in agreement with previous studies [18]. Notably, we found that spontaneous activities change their manifestation in different stages of the disease. For instance, in several patients with anti-LGI1 antibodies, tonic–clonic seizures followed FBDS; in some cases, FBDS disappeared with disease progression and was instead replaced by other types of motor seizures. In addition, we also observed that the form of focal motor seizures could change in patients with both anti-NMDAR and anti-LGI1 antibodies, but seldom in patients with anti-$GABA_BR$ antibodies. Therefore, we propose that anti-$GABA_BR$ antibody encephalitis involves a relatively unitary seizure manifestation. However, it was noticeable that several of the changed spontaneous activities were revealed to be nonepileptic events by EEG recording. These nonepileptic events were associated with movement disorders, and were very similar to seizure attacks, such as spontaneous bilateral or unilateral motor activities, repeated speech, and groping behavior. Instead, there were also 2 patients in our study who presented with nonepileptic events but the subsequent changed form of spontaneous activities was found to be epileptic seizure. Taken together, the results emphasize that thorough examination should be performed to avoid unsuitable treatment.

A previous study reported that numerous subclinical seizures, denoted as subtle or clinically unrecognized seizures apparent only on EEG, are observed in patients with anti-LGI1 antibodies [19]. In our study, we found this type of seizure to also be common in patients with anti-NMDAR or anti-$GABA_BR$ antibodies, observed in 36.8% of the patients with ASE. This is considerably higher than the 5.3% incidence rate previously reported in 742 patients with epilepsy [20]. The different incidence rate in this study may indicate that subclinical seizures are a feature of ASE-associated epilepsy. Importantly, it is necessary to recognize these seizures accurately and in good time, as they are strongly associated with cognitive impairments [21]. Kanazawa et al. have reported the case of a patient with antivoltage-gated potassium channel complex antibodies who exhibited memory impairment that persisted over two years, and finally was found to exhibit subclinical seizure patterns in EEG; his memory was greatly improved and normal EEG patterns were restored after prednisolone administration [22]. However, the extent of relationship between subclinical seizures and memory disorders in ASE still needs further study. Nevertheless, the need for repeated long-term EEG monitoring should be highlighted in the identification and treatment of ASE. Recently, autoimmune encephalitis has been recognized as the cause of unknown SE based on a multicenter cohort study [23]. We only identified patients with SE based on EEG recordings; thus, the incidence (28.9%) reported in this study may be lower than those reported in other studies. Further, we found that CSE and NCSE occupied approximately equal proportions in our study; NCSE can be manifested with mental disorders, occasionally mimicking coma, which was observed in our study. Therefore, there may be confusion regarding the limbic symptoms of ASE.

Here, we analyzed the EEG characteristics of patients with ASE. The incidence of interictal epileptic discharges was 53.8%, including 4 cases with extreme delta brush, which all involved patients with anti-NMDAR antibodies, 6 (11.5%) with continuous slow waves, and 34 (65.4%) with documented seizure activities on EEG. These EEG features are consistent with the findings of previous studies [18,24]. In addition, for the first time, we found burst suppression and lateralized periodic discharges in ASE. Other than seizure assessment, EEG also plays a role in the recognition of ASE. A recent study by Limotai et al. reported that poorly sustained posterior dominant rhythm, which was significantly intermixed with low- to high-amplitude theta or delta activity or both, has predictive value for the early diagnosis of ASE, particularly in patients with anti-NMDAR antibodies [25].

The first-line immunotherapy used in our study included the following: immunoglobulin (0.4 g/kg/d for 5 days); methylprednisolone (1000, 500, 250, and 120 mg/d for 3 days each); prednisone tablets, with the dose starting at 60 mg/d, decreased by 5 mg every week; or a combination of these. A total of 43 patients were included in our follow-up study; 27 (62.8%) patients exhibited seizure remission after initial immunotherapy (within 3 months of discharge), the remaining 16 (37.2%) patients developed persistent seizures of varying degrees. The success rate of immunotherapy varies across previous studies, such as 50%, 36%, and 75.6% in the studies by Byun et al., Feyissa et al., and Sarkis et al. [3,26,27]. These differences may be attributed to the duration of immunotherapy, the spectrum of antibodies tested in each study, or differences in the follow-up period. During the long-term continuous follow-up, we found that patients with seizure remission after initial immunotherapy did not require long-term AEDs because many discontinued receiving the drugs after a short time and did not experience seizures again. This may be because the seizures were a result of neuroinflammation activated by environmental factors, such as viral infection [28]; once the excessive immunoreaction was suppressed, and the activator was absent, clinical symptoms would also disappear. Moreover, persistent seizures may result from ongoing inflammatory processes that persist after the acute phase of encephalitis, or from the irreversible changes that alter neuronal networks and persist after the inflammatory process resolves [7].

We found that target autoantigen was a significant risk factor for patients who developed persistent seizures ($P = 0.001$). None of the patients with anti-NMDAR antibodies developed persistent seizures in our cohort, whereas the rates in patients with anti-LGI1 and anti-$GABA_BR$ antibodies were high, 46.7% (7/15) and 64.3% (9/14), respectively. This is consistent with the findings of a previous study by Dalmau et al., which had reported that anti-NMDAR encephalitis rarely develops to chronic seizures [29]. One potential mechanism for the development of epilepsy is that the inflammation results in cortical changes, especially hippocampal sclerosis. Previous studies have indicated that more than half the patients with antivoltage-gated potassium channel complex or anti-$GABA_BR$ antibodies develop medial temporal or hippocampal sclerosis, based on long-term follow-up MRI [30,31]. In addition, several large studies have shown that MRI abnormalities are infrequent in patients with anti-NMDAR antibodies [6]. These observations support our findings. Although we found that older age at onset and acute SE are also related to poor prognosis, we speculate that these two factors may

be influenced by neuronal antibody type. Previous studies and our data show that patients with anti-NMDAR antibodies were predominantly young, and SE is always observed in patients with anti-$GABA_BR$ antibodies [3,32]. In addition, for the first time, we observed that high CSF protein levels are related to poor seizure outcome, potentially because of severe destruction of the blood–brain barrier. However, the P value, although below the threshold of significance, was not sufficiently low; therefore, a large-scale sample study is needed to further examine this association. In summary, we propose that seizure outcome in anti-NMDAR encephalitis is better than that in the other two types of ASE.

Although AEDs alone always show low effectiveness for seizure control in ASE, several patients could benefit from these drugs after immunotherapy failure [33]. Feyissa et al. also reported that AEDs with sodium channel-blocking properties resulted in seizure freedom in a few cases [26]. This is consistent with our findings. In the present study, 6 out of the 9 patients who received subsequent therapy experienced additional seizure freedom because of AED administration or adjustment. The seizures of the remaining 3 patients, with serious conditions, showed drug resistance. Repeated immunotherapy was performed for these patients, and the seizures in 2 of the patients were responsive, although the recovery duration was very long; the other patient developed super-refractory epilepsy. This indicates that seizure outcome in several patients who continue to experience serious seizure attacks after initial treatment could worsen further; therefore, a more complex therapy is necessary in such cases. In addition, one should not be biased toward AED administration for patients with ASE, especially for controlling persistent seizures. Other therapies, such as rituximab, immunoadsorption, or plasma exchange, have recently been reported to be successful for additional seizure control; however, large-scale and long-term studies are still lacking [3,34].

Our study has several limitations. First, the number of patients included in our cohort was relatively small, and the study predominantly used descriptive statistics. In the future, a larger cohort size should be used, and independent risk factors should be analyzed using logistic regression. Second, the seizure outcomes were determined based on verbal reports by patients or their next of kin, and therefore, nonmotor seizures may have been overlooked. Third, patients with seizure remission after completion of initial immunotherapy were identified by clinical symptoms, and long-term EEG information and follow-up MRI for these patients were lacking.

5. Conclusion

The seizure manifestation of ASE is diverse and variable. Repeated long-term EEG monitoring is required for better understanding of seizure semiology and timely treatment. The patients with anti-LGI1 and anti-$GABA_BR$ antibodies had a higher risk of developing persistent seizures than those with anti-NMDAR antibodies; therefore, for these patients, the effects of AED withdrawal should be carefully considered. Furthermore, AEDs are suitable for achieving additional seizure freedom for patients with failed initial treatment. However, the seizure outcome of patients who continued to experience serious residual seizure attacks was poor; therefore, we suggest a comprehensive therapy for these patients.

Disclosure statement

The authors have no conflicts of interest to declare.

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