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RESEARCH ARTICLE

Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis

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Abstract

Background: Accumulating data have suggested seizures occur frequently in patients with neuronal surface antibody-mediated autoimmune encephalitis. We aimed to evaluate seizure outcomes and potential factors associated with the development of epilepsy in patients with anti-N-methyl-D-aspartate receptor (NMDAR), anti-leucine-rich glioma-inactivated 1 (LGI1), and anti-gamma-aminobutyric-acid B receptor ($GABA_BR$) encephalitis. **Methods**: Patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis were prospectively recruited from 2014 to June 2019, with a median follow-up period of 30.5 months (range 8–67 months). Seizure outcomes were assessed and risk factors of epilepsy were analyzed. **Results**: A total of 119 patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis were included, and 83 (69.7%) of them developed new-onset seizures. By the end of follow-up, 17 (21.3%) of 80 patients had seizure relapses after intermittent seizure remission or exhibited uncontrolled seizure episodes, contributing to epilepsy. Immunotherapy delay and interictal epileptic discharges (IEDs) were identified to be associated with the development of epilepsy in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis, particularly anti-NMDAR encephalitis. Furthermore, multivariate logistic regression analysis demonstrated that immunotherapy delay was an independent predictor for epilepsy. **Conclusion**: Our study suggested that immunotherapy delay and IEDs were associated with the development of epilepsy in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis. Early diagnosis and treatment were required, and particular consideration should be given to patients with these risk factors.

Introduction

In the last decade, autoimmune encephalitis (AIE) is increasingly recognized as a large proportion of encephalitis,[1] particularly AIE with antibodies against neuronal cell-surface proteins, such as N-methyl-D-aspartate receptor (NMDAR) antibodies, leucine-rich glioma-inactivated 1 (LGI1) antibodies, and gamma-aminobutyric-acid B receptor ($GABA_BR$) antibodies.[2–5] This form of encephalitis presents with multifaceted presentation of seizures, behavioral changes, memory deficits, and other neurologic dysfunctions.

It is frequently considered that encephalitis associated with seizures and autoantibodies is autoimmune epilepsy, which is inaccurate and may have led to overuse of the term "autoimmune epilepsy" and antiepileptic drugs (AEDs) prescription.[6] In fact, studies have found that the probability of seizure occurrence after the acute phase is not much high in AIE patients who reported seizures.[7,8] Titulaer et al.'s study also indicated that seizures in AIE tend to resolve faster and more frequently after immunotherapy, suggesting AEDs could be considered as add-on treatment, unlike in epilepsy.[9] Thus, it is of great interest to find out potential factors predictive of seizure outcomes and identify the duration of AEDs use in AIE patients. For those patients who are likely to have persistent seizure freedom after acute symptomatic seizures,

AEDs could be tapered off early. Instead, for those with high risk of developing to chronic epilepsy or refractory epilepsy, long-term AEDs use should be recommended.[10] To the best of our knowledge, previous studies always focused on seizure outcomes after the acute stage (mostly the first 3 months) in AIE, but the data evaluating the exact probability of developing epilepsy and its potential risk factors were lacking.

As seizures occur most frequently in AIE with NMDAR, LGI1, and $GABA_BR$ antibodies, we are aiming to delineate the patterns of seizure outcomes in these patients, and identify potential factors predisposing to the development of epilepsy.

Methods

Patients and study design

The prospective, observational study was performed at a tertiary hospital which served a population of approximately 3,500,000 each year. Newly diagnosed hospitalized patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis were consecutively identified between 2014 and June 2019, according to the diagnostic criteria established in 2016.[11] Antibodies were detected in serum or cerebrospinal fluid (CSF) with cell-based assay. Whole-body PET/ CT, ultrasonographic scan, chest and abdomen CT with contrast, pelvis MRI or other methods were applied for tumor screening. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) or video-EEG (VEEG) monitoring were conducted in all the patients with seizures. The exclusion criteria includes: (1) patients with laboratory evidence of infectious encephalitis, for example, viral, bacteria, mycobacterium tuberculosis, parasitic, or fungal; (2) patients diagnosed with epilepsy, stroke, cerebral trauma, and/ or other nervous system disease prior to the onset of encephalitis; (3) patients with coexisting antibodies, such as anti-contactin-associated protein 2 (CASPR2) antibody, myelin oligodendrocyte glycoprotein (MOG) antibody, aquaporin 4 (AQP4) antibody, and other antibodies.

For each eligible case, the following data were collected from medical records and nursing records: patient demographics, age at onset, clinical manifestations, seizure frequency, types of seizures, underlying malignancy, complete CSF and serum findings, interictal EEG, MRI findings, AEDs and immunotherapy. Seizure outcomes, AEDs utilization and chronic immunotherapy use were followed up every 3 months by telephonic interview and/ or clinic visits after discharge. The decisions about the duration of AEDs use and the choice of chronic immunotherapy were based on physicians' experience. Follow-up was discontinued when the patient was dead or lost to follow-up. Each patient was followed up for at least 8 months. When seizure relapsed after intermittent seizure remission, patients would receive a detailed evaluation including neurological symptoms except seizures, physical examination, antibody titer change, imaging and CSF evidences. Our study was approved by the ethics committee of the Second Affiliated Hospital School of Medicine Zhejiang University.

Definitions

For patients with anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis who presented with symptomatic seizures, the acute stage is defined as the first 6 months after the onset of encephalitis symptoms. Status epilepticus (SE) is defined as continuous seizure activity lasting longer than 5 min or recurrent seizures without regaining consciousness between episodes for more than 5 min.[12,13] Seizure remission is defined as a period of uninterrupted seizure freedom lasting six months or longer. According to the definition of epilepsy established by the International League Against Epilepsy in 2014, epilepsy is identified with two unprovoked seizures occurring >24 h apart, or one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.[14] We defined patients with early withdrawal of AEDs as the subjects who stopped AEDs within 6 months of AEDs utilization. In addition, if an immunotherapy was started 28 days later after the disease onset, it was considered as a delayed immunotherapy.[9]

Statistical analysis

Student's *t*-test or non-parametric method of Kruskal–Wallis test were used for comparisons of the continuous variables. Risk factors between groups were tested with two-tailed chi-square or Fisher's exact tests. Factors with significantly different distribution were further assessed by multivariate logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were calculated. The P value of <0.05 was considered as statistically significant. All the analyses were performed with SPSS 22.0 software.

Results

Patient and seizure characteristics

A total of 119 patients were included in our study, after excluding four patients with co-existing antibodies (one patient with LGI1 and CASPR2 antibodies, one with NMDAR and $GABA_BR$ antibodies, one with NMDAR and

AQP4 antibodies, one with NMDAR and MOG antibodies). It comprised of 85 anti-NMDAR encephalitis patients, 21 anti-LGI1 encephalitis patients, and 13 anti-$GABA_BR$ encephalitis patients. Among these cases, 69.7% ($N = 83$) patients reported new-onset seizures at acute stage (NMDAR: 52; LGI1: 18; $GABA_BR$: 13), while 30.3% had no acute seizures. At follow-up, one patient with anti-NMDAR encephalitis and two with anti-$GABA_BR$ encephalitis deceased and were excluded from the following analysis. Figure 1 shows a flow diagram of included patients.

Compared to patients without seizures, no significant difference was found in age at onset, gender and MRI findings among those with seizures ($P > 0.05$). Patients with seizures seemed to require admission into intensive care unit (ICU) more frequently (6/80, 12.5%; 0/36, 0%), however, the difference was non-significant. Among the 80 AIE patients (44 males; 36 females) with seizures, the median age at onset was 30.5 years (range 14–71 years), and the median follow-up was 30.5 months (range 8–67 months). Most patients presented with tonic-clonic seizures, while faciobrachial dystonic seizure (FBDS) were only exhibited in patients with LGI1 antibodies. Seventy-three (91.3%) of 80 patients presented with more than one seizure episode, and 23 (28.8%) patients exhibited SE during the acute stage. MRI abnormalities at onset were identified in 27 (33.8%) patients with mesial temporal lobes and brain cortex involvement. Interictal epileptic discharges (IEDs) were detected in 14 (17.5%) patients while slow wave or normal findings were reported in the remaining cases. Notably, whole-body PET/ CT were applied in 15 (18.8%) patients for detection of tumors, and ultrasonographic scanning, chest and abdominal CT with contrast, pelvis MRI and other methods were used in the remaining patients for tumor screening. Consequently, tumors were reported in five patients without any related symptoms, including three anti-NMDAR encephalitis patients with teratoma and two anti-$GABA_BR$ encephalitis patients with lung cancer.

All the patients with seizures were prescribed with AEDs to control seizures. Twenty-nine (36.3%) of these patients received single AED, 21 (26.3%) patients received two AEDs, whereas 30 (37.5%) were treated with more than two AEDs. Levetiracetam was the most commonly prescribed AED (59/80, 73.8%), followed by valproate (35/80, 43.8%), and oxcarbazepine (23/80, 28.8%). During our follow-up, 21 patients stopped AEDs within 6 months. With regards to immunotherapy, most patients ($N = 69$, 86.3%) were treated with combined immunotherapy of pulsed methylprednisolone and intravenous immunoglobulin (IVIG), and the others received either methylprednisolone or IVIG alone. Three patients were prescribed with rituximab and one patient underwent plasma exchange in addition to the steroids or IVIG. After the acute stage, seven patients received long-term chronic immunotherapy, including azathioprine and mycophenolate mofetil. Five patients with teratoma or lung cancer underwent treatment for the tumors (surgery, chemotherapy, or radiotherapy). The treatment delay between disease onset and the start of immunotherapy were found in 26 (32.5%) patients, particularly in anti-LGI1 encephalitis ($N = 11$, 61.1%) patients.

Patterns of seizure outcomes

Seizure outcomes over time were evaluated in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$

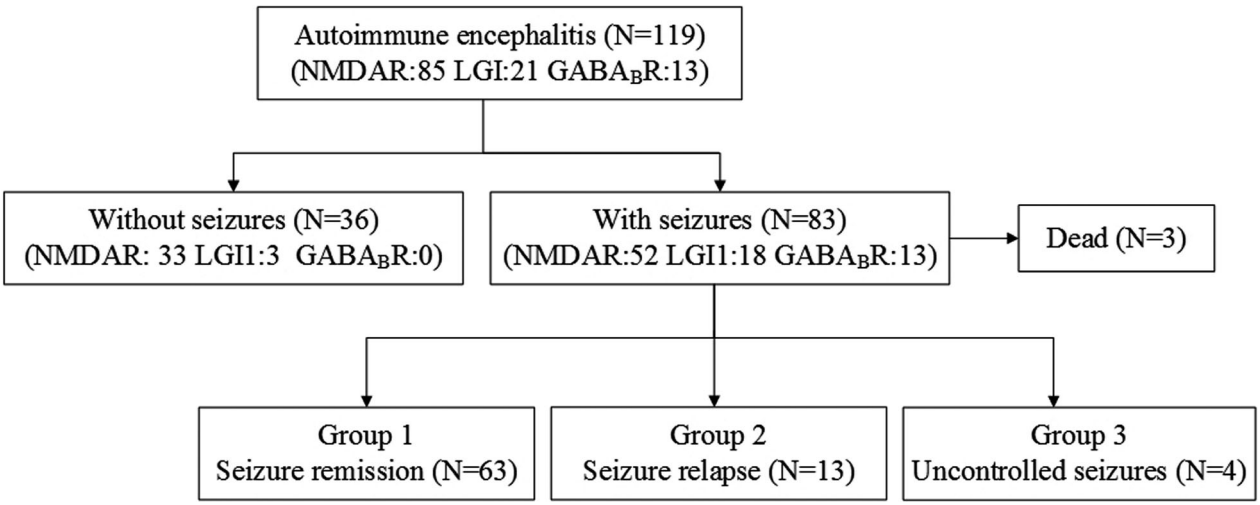

Figure 1. A flow diagram of included patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis. Abbreviations: $GABA_BR$, gamma-aminobutyric-acid B receptor; LGI1, leucine-rich glioma-inactivated 1; NMDAR, N-methyl-D-aspartate receptor.

encephalitis, and no new-onset seizures were reported after the acute stage. All the patients with seizures at disease onset were categorized into three groups (Fig. 1). Group 1 were those with sustained seizure remission by the end of follow-up ($N = 63$). Of these 63 cases, 57 achieved persistent seizure remission within three months after disease onset, the remaining six patients achieved seizure remissions within 6 months. Those six patients may present with seizure attacks for a quite long period due to treatment delay, severe autoimmune process, or experienced new-onset seizures after three months of earlier symptoms without any treatments, which meant they were probably within their first disease episode. Thus, they were still categorized into Group 1. Group 2 were those with seizure relapse after intermittent seizure remission ($N = 13$). All theses seizure relapses were not considered as encephalitis relapse, based on the assessment of neurological symptoms, physical examination, antibody titer change, imaging and CSF evidences. Of these 13 patients, most cases experienced one or several seizure relapses with subsequent seizure remission by AEDs switching or dosage adjustment. Group 3 were those patients who had uncontrolled seizure episodes without seizure remission ($N = 4$), Notably, they were followed up with the period of more than 18 months, and all the patients experienced at least one episode of seizure every month. According to the definition of epilepsy, 17 (21.3%) patients from group 2 and 3 were considered to develop epilepsy, who were our particular concerns.

Among 51 patients with anti-NMDAR encephalitis, 10 (19.6%) of them didn't achieve persistent seizure remission and developed to epilepsy. As for anti-LGI1 and anti-$GABA_BR$ encephalitis, 5 (27.8%) and 2 (18.2%) patients had developed to epilepsy, respectively.

Potential factors associated with epilepsy

Demographics and clinical characteristics of patients with anti-NMDAR, anti-LGI1 or anti-$GABA_BR$ encephalitis were provided in Table 1. Among 17 patients who developed epilepsy, 12 (70.6%) of them received delayed immunotherapy and 6 (35.3%) of them presented epileptiform discharges on interictal EEG. As noted in Table 1, patients with immunotherapy delay ($P = 0.000$) or IEDs ($P = 0.030$) had a higher risk of epilepsy. No significant association were observed between the development of epilepsy and age at onset, sex, frequency of seizures, tumor, MRI abnormality, types of autoantibodies, number of AEDs, chronic immunotherapy and early withdraw of AEDs ($P > 0.05$). In multivariate analysis, immunotherapy delay was independently associated with epilepsy (OR 7.69, 95% CI 2.26–26.10; $P = 0.001$).

According to different patterns of seizure outcomes, clinical characteristics in subgroups with anti-NMDAR, anti-LGI1, or anti-$GABA_BR$ encephalitis were shown in Tables 2 and 3. In anti-NMDAR encephalitis, subgroup analysis also revealed a significant correlation between the

Table 1. Clinical characteristics and potential factors associated with seizure outcomes.

	Total ($N = 80$)	Sustained seizure remission ($N = 63$)	Seizure relapse or uncontrolled seizures ($N = 17$)	*P* value
Age at onset (years)	36.4 ± 17.2	36.4 ± 16.5	36.4 ± 20.1	0.991
Sex				
Female	36 (45.0)	29 (46.0)	7 (41.2)	
Male	44 (55.0)	34 (54.0)	10 (58.8)	0.721
Frequency of acute seizures				
Once	7 (8.8)	6 (9.5)	1 (5.9)	
Repeated	73 (91.2)	57 (90.5)	16 (94.1)	1.000
Status epilepticus				
Yes	23 (28.8)	17 (27.0)	6 (35.3)	
No	57 (71.2)	46 (73.0)	11 (64.7)	0.502
Tumor				
Yes	5 (6.3)	4 (6.3)	1 (5.9)	
No	75 (93.7)	59 (93.7)	16 (94.1)	1.000
Interictal EEG findings				
Epileptiform discharges	14 (17.5)	8 (12.7)	6 (35.3)	
Slow waves or normal	66 (82.5)	55 (87.3)	11 (64.7)	0.030*
MRI abnormality				
Abnormal	27 (33.8)	19 (30.2)	8 (47.1)	
Normal	53 (66.2)	44 (69.8)	9 (52.9)	0.191
Immunotherapy delay				
Yes	26 (32.5)	14 (22.2)	12 (70.6)	
No	54 (67.5)	49 (77.8)	5 (29.4)	0.000*
Antibodies				
NMDAR	51 (63.8)	41 (65.1)	10 (58.8)	
LGI 1	18 (22.5)	13 (20.6)	5 (29.4)	
$GABA_BR$	11 (13.7)	9 (14.3)	2 (11.8)	0.740
Number of AEDs				
≥2 kinds	51 (63.8)	38 (60.3)	13 (76.5)	
1 kind	29 (36.2)	25 (39.7)	4 (23.5)	0.266
Chronic immunotherapy				
Yes	7 (8.8)	6 (9.5)	1 (5.9)	
No	73 (91.2)	57 (90.5)	16 (94.1)	1.000
Early withdraw of AEDs				
Yes	21 (26.3)	18 (28.6)	3 (17.6)	
No	59 (73.7)	45 (71.4)	14 (82.4)	0.537

Abbreviations: AED, antiepileptic drug; EEG, electroencephalograph; $GABA_BR$, gamma-aminobutyric-acid B receptor; LGI1, leucine-rich glioma-inactivated 1; NMDAR, N-methyl-D-aspartate receptor.

*$P < 0.05$; Age at onset presented as mean ± standard deviation; other data presented as *n* (%).

development of epilepsy and immunotherapy delay ($P = 0.007$), IEDs ($P = 0.038$). Multivariate analysis showed that immunotherapy delay (OR 8.71, 95% CI 1.69–44.90; $P = 0.010$) was the unique predictor. In anti-LGI1 encephalitis (Table 3), patients with immunotherapy delay were predisposed to develop epilepsy, however, no significant difference was found ($P = 0.101$). Besides, there was no significant association between the development of epilepsy and age at onset, sex, frequency of seizures, tumor, IEDs, MRI abnormality, autoantibodies, number of AEDs, chronic immunotherapy and early withdraw of AEDs ($P > 0.05$). As for patients with anti-$GABA_BR$ encephalitis, no significant relationship was observed either, probably due to the limited sample size.

Discussion

In our current study, about 70% patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis presented with new-onset seizures at the acute stage. During a median follow-up of 30.5 months, 21.3% patients had developed epilepsy. Our study suggested that immunotherapy delay and IEDs tended to be predictive of autoimmune epilepsy in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis. Particularly, early withdrawal of AEDs was not associated with the development of epilepsy.

Epidemiology researches have shown the prevalence and incidence of autoimmune encephalitis is comparable to infectious encephalitis and its detection is increasing over time.[15] As seizure was one of the core symptoms of AIE, it is vital to distinguish "acute seizures" from "autoimmune epilepsy," which was defined as the "epilepsy" resulted directly from an immune disorder.[16,17] According to the definition of epilepsy mentioned above, our data showed that 21.3% patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis may contribute to autoimmune epilepsy, and patients with anti-NMDA encephalitis described the similar probability. The proportion was in keeping with Liu et al.'s study,[7] in which 109 cases with anti-NMDAR encephalitis were enrolled, showing more than 80% of the whole cohort with acute seizures had their last seizure within 6 months from disease onset. Another study demonstrated that 37.2% patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis developed persistent seizures to different extents and the remaining experienced seizure remission during the follow-up.[18] However, this study did not provide the definition of persistent seizures and seizure remission, probably leading to the overestimation of epilepsy risk.[18] In addition, Casciato et al.'s study had reported a much higher percentage of 40% developed chronic epilepsy in limbic encephalitis with anti-voltage-gated potassium channel (LGI-1 and CASPR2), anti-NMDAR, anti-SOX1, anti-Ri, anti-Hu and anti-glutamic acid decarboxylase antibodies.[10] This could be explained by different samples. It is well known that encephalitis with antibodies against neuronal intracellular antigens (e.g. anti-glutamic acid decarboxylase antibodies, anti-SOX1, anti-Ri, anti-Hu) were more likely to have poor seizure outcomes.[19,20]

The identification of predisposing factors for epilepsy will be beneficial to develop alternative interventions to

Table 2. Clinical characteristics and potential factors associated with seizure outcomes in patients with anti-NMDAR encephalitis.

	Total ($N = 51$)	Sustained seizure remission ($N = 41$)	Seizure relapse or uncontrolled seizures ($N = 10$)	*P* value
Age at onset (years)	27.2 ± 10.4	27.9 ± 9.8	24.2 ± 12.5	0.722
Sex				
Female	30 (58.8)	25 (61.0)	5 (10.0)	
Male	21 (41.2)	16 (39.0)	5 (10.0)	0.722
Frequency of acute seizures				
Once	5 (9.8)	5 (12.2)	0 (0.0)	
Repeated	46 (90.2)	36 (87.8)	10 (100.0)	0.569
Status epilepticus				
Yes	14 (27.5)	9 (22.0)	5 (10.0)	
No	37 (72.5)	32 (78.0)	5 (10.0)	0.113
Tumor				
Yes	3 (5.9)	2 (4.9)	1 (10.0)	
No	48 (94.1)	39 (95.1)	9 (90.0)	0.488
Interictal EEG findings				
Epileptiform discharges	8 (15.7)	4 (9.8)	4 (40.0)	
Slow waves or normal	43 (84.3)	37 (90.2)	6 (60.0)	0.038*
MRI abnormality				
Abnormal	15 (29.4)	11 (26.8)	4 (40.0)	
Normal	36 (70.6)	30 (73.2)	6 (60.0)	0.454
Immunotherapy delay				
Yes	12 (23.5)	6 (14.6)	6 (60.0)	
No	39 (76.5)	35 (85.4)	4 (40.0)	0.007*
Number of AEDs				
≥2 kinds	36 (70.6)	27 (65.9)	9 (90.0)	
1 kind	15 (29.4)	14 (34.1)	1 (10.0)	0.246
Chronic immunotherapy				
Yes	6 (11.8)	5 (12.2)	1 (10.0)	
No	45 (88.2)	36 (87.8)	9 (90.0)	1.000
Early withdraw of AEDs				
Yes	15 (29.4)	13 (31.7)	2 (20.0)	
No	36 (70.6)	28 (68.3)	8 (80.0)	0.703

Abbreviations: AED, antiepileptic drug; EEG, electroencephalograph; NMDAR, N-methyl-D-aspartate receptor.
*$P < 0.05$; Age at onset presented as mean ± standard deviation; other data presented as *n* (%).

Table 3. Clinical characteristics and potential factors associated with seizure outcomes in patients with anti-LGI1 and $GABA_BR$ encephalitis.

	LGI1 (*N* = 18)			$GABA_BR$ (*N* = 11)		
	Sustained seizure remission (*N* = 13)	Seizure relapse or uncontrolled seizures (*N* = 5)	*P* value	Sustained seizure remission (*N* = 9)	Seizure relapse or uncontrolled seizures (*N* = 2)	*P* value
Age at onset (years)	52.2 ± 15.5	52.2 ± 18.7	0.996	52.6 ± 14.0	57.5 ± 5.0	0.646
Sex						
Female	2 (15.4)	2 (40.0)		2 (22.2)	0 (0.0)	
Male	11 (84.6)	3 (60.0)	0.533	7 (77.8)	2 (100.0)	1.000
Frequency of acute seizures						
Once	1 (7.7)	0 (0.0)		0 (0.0)	1 (50.0)	
Repeated	12 (92.3)	5 (100.0)	1.000	9 (100.0)	1 (50.0)	0.182
Status epilepticus						
Yes	5 (38.5)	1 (20.0)		3 (33.3)	0 (0.0)	
No	8 (61.5)	4 (80.0)	0.615	6 (66.7)	2 (100.0)	1.000
Tumor						
Yes	0 (0.0)	0 (0.0)		2 (22.2)	0 (0.0)	
No	13 (100.0)	5 (100.0)	–	7 (77.8)	2 (100.0)	1.000
Interictal EEG findings						
Epileptiform discharges	3 (23.1)	2 (40.0)		1 (11.1)	0 (0.0)	
Slow waves or normal	10 (76.9)	3 (60.0)	0.583	8 (88.9)	2 (100.0)	1.000
MRI abnormality						
Abnormal	4 (30.8)	3 (60.0)		4 (44.4)	1 (50.0)	
Normal	9 (69.2)	2 (40.0)	0.326	5 (55.6)	1 (50.0)	1.000
Immunotherapy delay						
Yes	6 (46.2)	5 (100.0)		2 (22.2)	1 (50.0)	
No	7 (53.8)	0 (0.0)	0.101	7 (77.8)	1 (50.0)	0.491
Number of AEDs						
≥2 kinds	6 (46.2)	3 (60.0)		5 (55.6)	1 (50.0)	
1 kind	7 (53.8)	2 (40.0)	1.000	4 (44.4)	1 (50.0)	1.000
Chronic immunotherapy						
Yes	1 (7.7)	0 (0.0)		0 (0.0)	0 (0.0)	
No	12 (92.3)	5 (100.0)	1.000	9 (100.0)	2 (100.0)	–
Early withdraw of AEDs						
Yes	4 (30.8)	0 (0.0)		1 (11.1)	1 (50.0)	
No	9 (69.2)	5 (100.0)	0.278	8 (88.9)	1 (50.0)	0.345

Age at onset presented as mean ± standard deviation; other data presented as *n* (%).

Abbreviations: AED, antiepileptic drug; EEG, electroencephalograph; $GABA_BR$, gamma-aminobutyric-acid B receptor; LGI1, leucine-rich glioma-inactivated 1.

prevent from autoimmune epilepsy, and determine the comprehensive therapy for seizures and encephalitis at follow-up. IEDs and immunotherapy delay were proved to be the prognostic factors for epilepsy in patients with anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis, particularly in those with anti-NMDAR encephalitis. The exact mechanism had not been elucidated clearly. One of the possible mechanisms was the intrinsic disease severity. It could be affected by a predetermined, complex interaction between underlying autoimmune pathology, reflecting the patterns of seizure outcomes and IEDs. Besides, repeated seizures have been shown to produce neuronal loss and mossy fiber sprouting in the hippocampus, which in turn can reinforce their production forming excitatory recurrent circuits, and increase the possibility of IEDs.[21,22] Previous literature on epilepsy have also suggested IEDs may predict unfavorable seizure outcomes and refractory epilepsy.[23,24] As for immunotherapy delay, one of the main causes was atypical and insidious symptoms, for example, symptomatic seizures occurred as the unique presentation in several patients with AIE, particularly in anti-LGI1 encephalitis. To date, there were fewer studies reporting the relationship between immunotherapy delay and the development of epilepsy in neuronal surface antibody-mediated autoimmune encephalitis. Thompson et al.'s study has revealed that time to cessation of FBDS was significantly affected by the number of months to treatment with immunotherapy according to the follow-up data from 103 patients with LGI encephalitis at 12, 24, and 48 months. In our study, we failed to

find the significant relationship between immunotherapy delay and the development of epilepsy in the subgroup patients with LGI encephalitis, which could be probably explained by the limited sample size.[25] A retrospective study by Casciato et al.[10] has demonstrated that delay in diagnosis was related with the development of chronic temporal lobe epilepsy in limbic encephalitis, but the sample size was relatively small and the term "immunotherapy delay" was not defined. Another two studies done by Dubey et al.[6,26] revealed that patients with autoimmune epilepsy initiated on immunomodulatory therapy at early stage might have favorable seizure outcomes. Both studies have defined favorable seizure outcomes as >50% reduction in seizure frequency, but not the development of epilepsy which was focused on in our study. However, given that better seizure outcomes were achieved after early initiation of immunotherapy, it was reasonable that treatment delay might lead to more seizure attacks and aggravate the autoimmune process, resulting in the evolvement of epilepsy.

Previous studies have noted that there is no significant difference in seizure relapse rate between groups with early withdrawal and late withdrawal of AEDs.[27] Similarly, our study found that AEDs withdrawal within six months did not affect the risk of development of epilepsy. Thus, it was understandable that there were other potential factors affecting seizure outcomes in AIE, such as IEDs and immunotherapy delay. Thus, long-term AEDs use may not be necessary for AIE patients. In fact, the same phenomenon was also observed in other neurologic diseases, such as MOG antibody-associated disease. It has been proved that long-term AEDs use did not significantly reduce the occurrence of epileptic seizures in cases of MOG antibody-associated disease.[28,29]

The study has some limitations. First, patients with seizure remission after the acute stage were diagnosed by clinical symptoms without long-term EEG information or follow-up MRI. Second, if patients achieved persistent seizure remission within six months after disease onset, they were not considered to have epilepsy in our study. However, those patients are still at the risk of epilepsy development if the follow-up period extends, as seizure episodes with quite a long period may have contributed to the epileptogenesis network. Finally, the current study was conducted at a local tertiary hospital, and the sample may not be representative for all the regions in China and other countries. In the future, a prospective multicenter study with a larger sample size should be required.

Conclusion

In summary, immunotherapy delay and IED were identified to be related to the development of epilepsy in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis, suggesting early recognition and immunotherapy of autoimmune encephalitis were of great value. Regarding the duration of AEDs utilization, early withdraw of AEDs could be considered after a comprehensive assessment.

Author Contributions

Chun-Hong Shen and Yin-Xi Zhang involved in drafting the manuscript. Chun-Hong Shen and Yin-Xi Zhang involved in study concept or design. Chun-Hong Shen, Gao-Li Fang, and Fan Yang contributed to analysis or interpretation of the data. Meng-Ting Cai, Yang Zheng, Wei Fang, Yi Guo, Yin-Xi Zhang, and Mei-Ping Ding involved in acquisition of data. Chun-Hong Shen and Gao-Li Fang performed statistical analysis. Yin-Xi Zhang and Mei-Ping Ding involved in study supervision or coordination. All authors contributed to revision of the manuscript and involved in contribution of vital reagents/tools/patients.

Conflict of Interest

The authors have no conflicts of interest to report.

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