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Predisposing factors and prognosis of status epilepticus in patients with autoimmune encephalitis

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Abstract

The aim of this study was to study the predisposing factors and prognosis of status epilepticus (SE) in patients with autoimmune encephalitis (AE).

A total of 227 cases of AE were collected from the inpatient department of West China Hospital of Sichuan University from January 2010 to May 2018. All patients met the 2015 criteria for the diagnosis of AE. The binary logistic regression model was used to multivariate and retrospective chart analysis the predisposition factors for SE and its prognostic factors.

Of the 227 patients with AE, 50 (22.03%) had SE during hospitalization, and 19 patients with SE had a poor prognosis (modified Rankin score MRS = 3–6), and 7 patients with no SE had a poor prognosis. In the logistic regression model, electroencephalograms (EEGs) abnormalities ($P = .000$) and head magnetic resonance imaging (MRI) abnormalities ($P = .003$) were associated with a predisposition to SE, while Glasgow scores <8 ($P = .027$), abnormal EEG ($P = .046$), delayed immunotherapy ($P = .012$), and SE duration at admission lasting >30 minutes ($P = .023$) were risk factors for a poor prognosis of SE.

SE is a common complication in patients with AE. EEG and MRI abnormalities may be predisposing factors for SE. Glasgow scores <8 points, abnormal EEG, delayed immunotherapy, and SE duration lasting >30 minutes at admission are risk factors for a poor prognosis in patients with SE.

Abbreviations: AE = autoimmune encephalitis, CI = confidence intervals, CSE = convulsive status epilepticus, EEG = electroencephalograms, ILAE = International Association for the Prevention of Epilepsy, MRS = modified Rankin score, NCSE = nonconvulsive status epilepticus, OR = odds ratios, SE = status epilepticus.

Keywords: autoimmune encephalitis, prognosis, status epilepticus

1. Introduction

Autoimmune encephalitis (AE) refers to a class of encephalitis mediated by autoimmune mechanisms.[1] It is a relatively common disease in neurology with a high morbidity and mortality.[1] At present, the proportion of AE accounts for 10% to 20% of encephalitis cases, and anti-NMDAR encephalitis is the most common, accounting for 80% of patients with AE, followed by LGI1 antibody-related encephalitis and GABABR antibodies.[1,2–4,5–8] The pathogenesis of AE is mainly the relatively reversible neuronal dysfunction caused by humoral immune mechanism, with good immunotherapy effect.[1,5–8] The common clinical symptoms of AE include psychobehavioral abnormalities, cognitive disorders, speech disorders, involuntary movements, epilepsy, motor disorders, consciousness disorders, autonomic nervous dysfunction, and so on.[9–15] The status epilepticus (SE) is one of the more serious symptoms, and is a common factor for adverse results in the treatment of critical neurological diseases.[1,7,9–15] In the context of AE, the development of seizures and SE usually represents a symptomatic manifestation during acute encephalitis.[5,6,9–15] In 2015, the International Association for the Prevention of Epilepsy (ILAE) Alliance proposed a new view on the definition of SE, of which the most important is to propose 2 time points (T1 time and T2 time). T1 time (5–30 minutes) indicates that treatment needs to be started immediately, and T2 time (30–60 minutes) indicates that the patient may have a long-term poor prognosis. Refractory SE is defined as a clinical or electroencephalographic seizure after a sufficient dose of a benzodiazepine drug and an acceptable antiepileptic drug is given to the patient with SE.[16] At present, the definition of super refractory SE is that there is still seizure or relapse (including relapse during anesthetic reduction or withdrawal) 24 hours after intravenous anesthetic treatment for refractory SE. At present, there are many studies on the clinical features and prognosis of AE. Some studies have shown that 80% of patients with AE recover well (modified Rankin score MRS = 0–2), and patients with early immunotherapy have a

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better prognosis. The mortality rate of severe NMDAR encephalitis is approximately 2.9% to 9.5%.[1,6–8] However, susceptibility factors and prognosis-related risk factors for SE in patients with AE have not been previously reported. Therefore, the purpose of this study is to investigate the incidence, predisposing factors, and prognostic risk factors of SE in patients with AE.

2. Methods

This study included the clinical data and electroencephalograms (EEGs) and imaging data of 227 patients of AE patients from the Department of Neurological Intensive Care Unit and Neurology Department from January 2010 to May 2018 in Sichuan University West China Hospital. All patients were diagnosed in accordance with the 2015 diagnostic criteria for AE,[1] and all patients with SE were diagnosed in accordance with the latest ILAE diagnostic criteria for SE.[16] In accordance with the standards of the Helsinki Declaration, this study strictly abides by the principle of voluntary and informed patients. If patients did not have autonomy, they obtained voluntary and informed consent from their immediate family members. And the protocol was approved by the West China hospital ethics Committee.

2.1. Inclusion criteria

Inclusion criteria included (1) Age ≥18 years; (2) Patients who fulfilled the criteria for the diagnosis of AE in 2015; (3) All patients with SE were diagnosed in accordance with the latest ILAE SE diagnostic criteria; (4) all patients had available EEG data, and patients with SE had seizure EEG data; (5) voluntarily provided informed consent.

2.2. Exclusion criteria

Exclusion criteria included (1) Patients with epilepsy without available EEG data or nonepileptic EEG; (2) Patients with recurrent AE; (3) Patients without informed consent; (4) Possible AE.

2.3. Research methods

According to the inclusion criteria and exclusion criteria, retrospective collection of clinical data (including demographic information, type of AE, length of hospital stay, cost of labor, laboratory results), EEG, imaging data, etc. And all patients were evaluated for admission consciousness before the use of benzodiazepines were collected. Head MRI abnormalities are defined as abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke). EEG abnormalities are defined as focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms. Delayed immunotherapy is defined as the diagnosis of AE patients who have not received immunotherapy within 4 weeks, including hormones, gamma globulin, immunosuppressive agents, and so on. The outcome of AE in which SE persist indicates a poor prognosis (MRS score 3–6).

2.4. Data statistics and analysis

Statistical analysis was performed with SPSS Version 22.0 software for Windows. Categorical demographic and clinical variables were analyzed by Chi-square tests or Fisher exact tests, and continuous variables were analyzed by Mann-Whitney *U* tests, as the data did not show a normal distribution. Multivariable analyses were performed with a binary logistic regression model in which each variable with a *P* value of $<.05$ (based on the univariate analysis) was entered into the model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. The significance level was set at $P<.05$ (2-tailed).

3. Results

Fifty (22.03%) of the 227 AE patients enrolled in the study developed SE. There were no significant differences between the demographics of 50 patients with SE (34 females, average age 18–63 years) and 177 patients with AE without SE (94 females, average age 18–67 years). Patients with SE had poor Glasgow scores on admission, mechanical ventilation with tracheal intubation, a higher rate of admission to the ICU, higher rates of abnormal EEG and abnormal MRI, and longer hospital stays than patients without epileptic seizures. The cost of treatment was higher. All patients were given immunotherapy, including hormones, gamma globulin, immunosuppressive agents, of which 20 patients were delayed immunotherapy (Table 1).

The 227 autoimmune patients included in the study included 183 anti-NMDAR patients (81%), 21 anti-GABA patients (9.23%), 21 anti-LGI1 patients (9.3%), and 2 Casper2 patients (0.9%). The types of AE with SE were anti-NMDAR and anti-GABA, including 46 anti-NMDAR, 4 anti-GABA, and positive in both blood and cerebrospinal fluid (including weak positive, positive, and strong positive) in 38 cases. There were 137 anti-NMDAR patients, 17 anti-GABA patients, 21 anti-LGI1 patients, and 2 anti-Casper2 patients with AE who had no epilepticus. Both blood and cerebrospinal fluid were positive (including weak positive, positive, and strong positive) in 78 cases. Autoimmune patients with SE spend more on hospitalization, about 129.97 ± 155.31 (23–910) thousand dollars. Among the patients with AE with SE, 5 patients had teratomas (all anti-NMDAR), 40 patients had pulmonary infection during treatment, 31 patients had a good prognosis (MRS score 0–2), 19 patients had a poor prognosis (MRS score 3–6), including 4 deaths (8%) and 15 with disabilities at discharge. Among the patients with AE without SE, 9 patients with teratomas (7 with anti-NMDAR, 2 with anti-LGI1), and 15 patients with pneumonia during treatment. Epilepsy occurred in 113 of 177 AE patients without SE and 170 patients had a good prognosis at discharge (MRS score 0–2), 7 patients had a poor prognosis (MRS score 3–6), 2 patients died (1.1%), and 5 patients had disabilities (Table 1).

There were 42 cases (18.50%) of convulsive status epilepticus (CSE) in patients with AE, 28 patients with T1 time SE, 11 patients with T2 time SE, 2 people with refractory SE, 1 person with super refractory SE, and 8 patients with nonconvulsion status epilepticus (NCSE). Two people stabilize phase seizure free, 7 patients improved after the first phase of drug treatment, 9 patients improved after the second phase of drug treatment, and 32 patients improved after the third phase of drug treatment (Table 2).

After the binary logistic regression multivariate analysis of the collected data, EEG abnormalities (OR = 32.879, 95% CI: 7.608–142.083, $P=.000$) and MRI abnormalities (OR = 16.231, 95% CI: 3.713–70.799, $P=.003$) were statistically significant as risk factors for SE. Gender, age, mechanical ventilation, blood, and cerebrospinal fluid antibodies were

Table 1

Demographic and clinical data of patients included.

	SE	No SE	P
People	50 (22.0%)	177 (78.0%)	
Female	34 (15.0%)	94 (41.4%)	
Age, y	28.28 ± 13.56 (18–63)	33.66 ± 15.28 (18–67)	.070
Hospital stays, d	35.30 ± 29.27 (5–145)	25.81 ± 21.10 (5–113)	.039
Cost, thousand dollars	129.97 ± 155.31 (23–910)	24.24 ± 44.51 (5–600)	.000
AE types			
NMDA	46 (20.1%)	137 (60.4%)	
Degree of blood			
Negative	20 (8.8%)	67 (29.5%)	
Weakly positive	1 (0.4%)	14 (6.2%)	
Positive	24 (10.6%)	49 (21.6%)	
Strongly positive	1 (0.4%)	7 (3.1%)	
Cerebrospinal fluidity			
Negative	1 (0.4%)	4 (1.8%)	
Weakly positive	5 (2.2%)	13 (5.7%)	
Positive	23 (10.1%)	85 (37.4%)	
Strongly positive	17 (7.5%)	35 (15.4%)	
Gaba	4 (1.8%)	17 (7.5%)	
Degree of blood			
Negative	2 (0.8%)	6 (2.6%)	
Weakly positive	1 (0.4%)	1 (0.4%)	
Positive	1 (0.4%)	9 (4.0%)	
Strongly positive	0	1 (0.4%)	
Cerebrospinal fluidity			
Negative	0	0	
Weakly positive	1 (0.4%)	3 (1.3%)	
Positive	2 (0.8%)	9 (4.0%)	
Strongly positive	1 (0.4%)	5 (2.2%)	
LGI1	0	21 (9.3%)	
Casper2	0	2 (0.8%)	
CSF and blood antibodies are positive	38 (16.8%)	78 (34.4%)	
MRI abnormal	13 (5.7%)	24 (10.6%)	
Seizure	50 (22.0%)	113 (49.8%)	
EEG abnormal	46 (20.3%)	28 (12.3%)	
Mechanical ventilation	30 (13.2%)	12 (5.3%)	
Teratoma	5 (2.2%)	9 (4.0%)	
Pneumonia	40 (17.6%)	15 (6.7%)	
Delayed immunotherapy	15(6.6%)	5(2.2%)	
Glasgow score at admission			
>14	11 (4.8%)	130 (57.3%)	
13–14	9 (4.0%)	38 (16.7%)	
9–12	11 (4.8%)	4 (1.3%)	
3–8	19 (8.4%)	5 (2.2%)	
Glasgow score at discharge			
>14	26 (11.5%)	152 (67.0%)	
13–14	3 (1.3%)	15 (6.7%)	
9–12	10 (4.4%)	3 (1.3%)	
3–8	5 (2.2%)	5 (2.2%)	
Death	4 (1.8%)	2 (0.8%)	
MRS at discharge			
0–2	31 (13.7%)	170 (74.9%)	
3–6	19 (8.4%)	7 (3.1%)	

EEG abnormalities are defined as focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms.

Delayed immunotherapy is defined as the diagnosis of autoimmune encephalitis patients who have not received immunotherapy within 4 wks, including hormones, gamma globulin, immunosuppressive agents, and so on.

AE = autoimmune encephalitis, CSF = cerebrospinal fluidity, EEG = electroencephalograms, MRI abnormalities = abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke), MRI = magnetic resonance imaging, MRS = Modified Rankin score, SE = status epilepticus patient.

positive, teratoma, comorbid pneumonia, and consciousness disorder at admission were $P > .05$, which was not statistically significant (Table 3).

Binary logistic regression analysis was performed on data from patients with AE who had SE. Glasgow scores <8 (OR = 25.561, 95% CI: 1.511–987.826, $P = .027$), EEG abnormalities (OR = 1.972, 95% CI: 0.811–6.347, $P = .046$), delayed immunotherapy (OR = 2.876, 95% CI: 0.893–9.782, $P = 0.012$), and SE duration lasting >30 minutes (OR = 14.669, 95% CI: 1.630–696.792, $P = .023$) were risk factors for poor prognosis of the SE (modified Rankin score 3–6). Gender, age, mechanical ventilation, blood and cerebrospinal fluid antibodies were positive, comorbid encephalitis, and abnormal MRI of the head were all $P > .05$, which was not statistically significant (Table 4).

Table 2

Clinical data of patients with status epilepticus.

	SE
Total	50 (22%)
SE dynamics	
CSE	42 (18.5%)
T1time SE	28 (12.3%)
T2time SE	11 (4.8%)
Refractory SE	2 (0.8%)
Super refractory SE	1 (0.4%)
NCSE	8 (3.5%)
Treatment remission	
Stabilization phase seizure free	2 (0.8%)
Initial therapy phase	7 (3.1%)
Second therapy phase	9 (4.0%)
Third therapy phase	32 (14.1%)

CSE = convulsive status epilepticus, NCSE = nonconvulsive status epilepticus, SE = status epilepticus.

4. Discussion

AE is a common type of encephalitis. According to previous studies, the current proportion of AEs accounts for 10% to 20% of encephalitis cases, and anti-NMDAR encephalitis is the most common, accounting for approximately 80% of AE patients.[17–21] This study showed that 81.10% of the enrolled AE patients were anti-NMDAR, 9.3% anti-GABA, 9.3% anti-LGI1, and 0.9% anti-Casper2, consistent with previous studies. SE is a common first symptom of AE. SE usually leads to permanent neurological damage, with high mortality and high disability. This study showed that the proportion of SE in AE was 22.0%

Table 3

Analysis of risk factors associated with status epilepticus in patients with autoimmune encephalitis.

	Total (227)	P	OR	95% CI
Male	128 (56.4%)	.564	1.480	0.391–5.599
Age	32.74 ± 15.05	.428	0.971	0.927–1.017
Mechanical Ventilation	42 (18.5%)	.428	2.077	0.340–12.668
EEG abnormal	74 (32.6%)	.000	32.879	7.608–142.083
MRI abnormal	37 (16.3%)	.003	16.213	3.713–70.799
CSF and blood antibodies are positive	116 (51.1%)	.059	4.165	1.155–15.018
Teratoma	14 (6.2%)	.874	1.218	0.106–13.991
Pneumonia	55 (24.2%)	.068	3.258	0.880–38.228
Disorder of consciousness at admission	24 (10.1%)	.180	2.448	0.662–9.054

CI = confidence interval, CSF = cerebrospinal fluidity, EEG abnormal = focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms, EEG = electroencephalograms, MRI abnormal = abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke), MRI = magnetic resonance imaging, OR = odds ratios.

Table 4

Analysis of risk factors associated with poor prognosis in patients with autoimmune encephalitis who have status epilepticus.

	PP	*P*	OR	95% CI
Male	34 (15.0%)	.789	1.086	0.062–8.296
Age	28.28 ± 13.5602 (18–63)	.150	1.290	0.762–1.042
Mechanical Ventilation	30 (13.2%)	.088	7.571	0.684–242.355
CSF and blood antibodies are positive	38 (16.8%)	.106	10.326	0.567–365.873
MRI abnormal	30 (13.2%)	.111	3.781	0.620–104.319
EEG abnormal	46 (20.3%)	.046	1.972	0.811–6.347
Pneumonia	40 (17.6%)	.959	3.560	0.029–41.368
Glasgow score <8 points on admission	9 (4.0%)	.027	25.561	1.511–987.826
Duration >30 min	22 (9.7%)	.023	14.669	1.630–696.792
Delayed immunotherapy	15(6.6%)	.012	2.876	0.893–9.782

Delayed immunotherapy is defined as the diagnosis of autoimmune encephalitis patients who have not received immunotherapy within 4 wks, including hormones, gamma globulin, immunosuppressive agents, and so on.

CI = confidence interval, CSF = cerebrospinal fluidity, EEG abnormal = focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms, EEG = electroencephalograms, MRI abnormal = abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke), MRI = magnetic resonance imaging, OR = odds ratios, PP = poor prognosis patient.

and the main types were anti-NMDAR encephalitis and anti-GABA encephalitis. According to foreign literature reports, the mortality rate of SE is 3.45% to 39%, and the mortality rate in western China is approximately 15.9%.[17–21] However, this study showed that the mortality rate of patients with AE with epileptic seizure status was 8.00%, which was lower than in previous studies. This may be related to the high mortality rate of stroke, brain injury, and other patients with a previous status of epilepsy, and the patients with AE have a better prognosis and lower mortality.

This study showed that patients with AE who had SE had longer hospital stays and higher costs than patients with no SE. The reason for this is that patients with SE are critically ill when they are admitted to hospital. They often need ventilator support and stay in the ICU. The termination of SE requires large doses of sedative drugs, associated with additional complications. Patients with AE with SE have higher EEG abnormalities and abnormal MRI. Their Glasgow score is higher at admission. Most patients with SE present with them as their first symptoms of AE.

The risk factors for epilepticus in patients with AE are abnormalities in EEG and abnormal MRI of the head, which are consistent with previous studies. In this study, the CSF and blood antibody titers were statistically analyzed. It was found that both cerebrospinal fluid and blood antibodies were positive $P = .338 > .05$, which was not statistically significant, but the P value decreased when compared with either cerebrospinal fluid or blood positivity. We can assume that cerebrospinal fluid and blood antibody titers being positive or strong positive may be a risk factor for epilepticus, but because the study included fewer patients in that category, patients with strong blood and cerebrospinal fluid positivity were not included in the analysis; this idea requires more research to confirm.

At the time of admission, a Glasgow score <8, abnormal EEG, delayed immunotherapy, and an epileptic seizure lasting >30 minutes were risk factors for a poor prognosis in the status of SE (modified Rankin score 3–6). Patients who had severe consciousness disorder when they are admitted to the hospital are more likely to have complications such as lung infections and malnutrition, which may be the cause of poor prognosis. The longer the duration of seizure, the normal metabolism of the brain needs to be met, which can cause hypoxia, hypoglycemia, cerebral edema, aggravation of coma, autonomic dysfunction, blood pressure fluctuations, cardiopulmonary dysfunction, and irreversible damage to the brain. Previous studies have shown that patients >65 years of age and those with previous epilepsy are also risk factors for the prognosis of SE, but the mean age of the patients included in this study is low, which is often associated with AE in children, youths, and women. The comorbid encephalitis P value = .959, which was not statistically significant, but previous studies have shown that comorbidity was a factor affecting the prognosis of SE. Because this study only included lung infection data, no information was included on hypertension, diabetes, or immune diseases.

There are still some limitations to this study. First, these data are from West China Hospital of Sichuan University. Although they can reflect the predisposition factors and prognostic factors of epilepticus in patients with AE in western China to a certain extent, they are lacking in not being from a large-scale, multicenter study. This study only included patients over the age of 18 years, and younger patients may have some differences with the results of this study.

5. Conclusion

The incidence of SE in patients with AE in western China was 22.03%. EEG and head MRI abnormalities may be susceptibility factors for SE in patients with AE. Glasgow scores <8 when admitted to hospital, abnormal EEG, and seizure duration >30 minutes were risk factors for a poor prognosis in the status of epilepsy (modified Rankin score 3–6).

Author contributions

Data curation: Yu Zhang, Chen Deng.
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