FULL-LENGTH ORIGINAL RESEARCH

Seizure outcomes in patients with anti-NMDAR encephalitis: A follow-up study

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Summary

Objective: **To evaluate the long-term seizure outcome and potential factors associated with seizure outcome in patients with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.**

Methods: **In the setting of a prospective, single-center, longitudinal cohort study, 109 patients were evaluated with ongoing follow-up. Patients underwent clinical evaluation every 3 months. Seizure outcomes and the potential risk factors were assessed with a median follow-up of 24 months (6–60 months).**

Results: **Of 109 patients (47 men; 62 women) with anti-NMDAR encephalitis, 88 patients (80.7%) had reported seizures at acute phase, including single seizure (17/88, 19.3%), repetitive seizures (27/88, 30.7%), nonrefractory status epilepticus (22/88, 25%), refractory status epilepticus (SE; 13/88, 14.8%), and super refractory status epilepticus (9/88, 10.2%). Seizure was more likely to recur in patients with tumor presence, status epilepticus (SE) development, coma, or intensive care unit (ICU) admission in the acute phase ($p < 0.05$). Seizure freedom was achieved within 2 years in all patients. More than 80% of the whole cohort with acute seizures had their last seizure within 6 months of disease onset.**

Significance: **Seizure is a common feature in the acute stage of anti-NMDAR encephalitis but not thereafter. The presence of tumor, SE, coma, and/or ICU admission in the acute phase predicts early seizure occurrence after the acute phase. Seizure freedom was typically achieved in our follow-up, and long-term use of antiepileptic drugs may not be necessary.**

KEY WORDS: **Antiepileptic drugs, Anti-NMDAR encephalitis, Epilepsy, Seizures.**

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, a form of autoimmune encephalitis associated with antibodies against heteromers of NR1 and NR2 subunits of cell-surface NMDA receptors, involves clinical features such as behavioral changes, memory deficits, and involuntary movements.[1–3] The disease can be severe and fatal, but it is potentially reversible with treatment.[4,5] Immunotherapy is an effective method for treating this disease.[3,6,7]

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Key Points

- Most of patients had reported seizures at acute phase, including single seizure (19.3%), repetitive seizures (30.7%), nonrefractory status epilepticus (25%), refractory status epilepticus (14.8%), and super-refractory status epilepticus (10.2%)
- Seizure freedom was achieved within 2 years in all patients
- Long-term use of antiepileptic drugs (AEDs) may not be necessary in anti-NMDAR patients with seizures

Seizures are a common feature of anti-NMDAR encephalitis, occurring in more than half of patients.[3,8] Seizures can occur as the initial presentation or in a later stage of the disease. Most patients develop generalized tonic–clonic seizures, whereas some exhibit a complex partial type.[1,9,10] Status epilepticus (SE) was also reported.[11–13] In addition, anti-NMDAR encephalitis is one of the most common forms of autoimmune encephalitis that is associated with SE.[14,15]

To date, some studies have described the prevalence of seizures and seizure types in patients at the acute phase of anti-NMDAR encephalitis,[1,3,6] although, as far as we know, studies that focused on seizures outcome in anti-NMDAR encephalitis patients are rare. With the purpose of obtaining estimates of the outcome associated with anti-NMDAR encephalitis in western China, a study named Outcome of anti-NMDAR Encephalitis Study in Western China (ONE-WC study) that continuously enrolled anti-NMDAR encephalitis patients and collected prospective observational data, was initiated in October 2011. The characteristics of cerebrospinal fluid (CSF) and the correlation of CSF results with prognosis in patients with anti-NMDAR encephalitis have been reported in our previous study.[7] In the cohort follow-up study, as one part of ONE-WC study, we systematically reveal seizure situations at the acute stage of the disease and the long-term outcome of seizures in patients diagnosed with anti-NMDAR encephalitis who received first-line immunotherapy. Furthermore, various impact factors that could potentially influence or predict the outcome of the seizure were also analyzed.

Participants and Methods

Participants

Patients in the ONE-WC study were recruited from the West China Hospital Department of Neurology between October 2011 and November 2016 and met the following inclusion criteria: (1) Rapid onset (less than 3 months) of one or more of the six following major groups of symptoms (abnormal (psychiatric) behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorder, decreased level of consciousness, autonomic dysfunction, or central hypoventilation[16]); (2) positive results of anti-NMDAR antibodies in CSF; (3) during the acute phase, patients with immunotherapy, including steroids and/or immunoglobulin.

Exclusion criteria were as follows: (1) HIV infection, meningitis, brain abscess, prion diseases, cerebral malaria, brain tumor, or a diagnosis of a noninfectious central nervous system disease, such as acute demyelinating encephalomyelitis (ADEM); (2) patients with laboratory evidence of infectious encephalitis, for example, viral, bacteria, mycobacterium tuberculosis (TB), parasitic, or fungal; (3) patients diagnosed with epilepsy, cerebral trauma, and/or other nervous system disease prior to the onset of encephalitis; (4) patients with coexisting other positive autoimmune or neurologic paraneoplastic antibodies such as a-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptors-1 and -2, contactin-associated protein-2 (CASPR2), leucine-rich glioma-inactivated protein-1 (LGI-1), and γ-aminobutyric acid receptor (GABAR) B1/B2, anti-neuronal nuclear antibody (ANNA)-1 (anti-Hu), ANNA-2 (anti-Ri), and Purkinje-cell cytoplasmic (PCA-1) (anti-Yo); (5) patients with anti-NMDAR encephalitis relapse during our follow-up (relapse of encephalitic signs of agitation, paranoid thoughts, irritability, or hallucinations).

Neurologists who have received the uniform training on the study interviewed all the target patients in the inpatient clinic of our center. If the inclusion criteria were met, a research assistant introduced the study to the supervisors. This study was approved by the West China Hospital of Sichuan University Research Ethics Committee. Written informed consent of each participant was obtained from their supervisors prior to enrollment in the study.

Determination of autoimmune antibodies

CSF examinations of patients were performed within one week after hospital admission. All specimens (CSF) were tested for immunoglobulin G (IgG) antibodies (Abs) with the following specificities: NMDAR, AMPA receptor, GABAR B1/B2; and anti-Hu, anti-Ri, and anti-Yo by indirect immunofluorescence assays (IFAs; Euroimmun, Luebeck, Germany). Radioimmunoprecipitation assays (RIAs) was used for Abs targeting neuronal voltage-gated potassium channel-complex (VGKCc). For all VGKCc IgG–positive specimens, cell-based assays (CBAs) for LGI-1 and contactin-associated protein 2 (CASPR2) IgG using transfected human embryonic kidney 293 cells were performed (Euroimmun).

Anti-NMDAR IgG antibody was evaluated using EU 90 cells transfected with the NMDAR1 subunit (NR1) of the

NMDAR complex and immobilized on BIOCHIPs (Euroimmun) as described previously.[7] Slides were incubated with undiluted CSF samples or serum samples at a starting dilution of 1:10, and analysis was performed according to the manufacturer's guidelines. Following incubation of samples with transfected or nontransfected cell lines, slides were washed and stained with fluorescein-labeled anti-human IgG antibodies (Fc-specific fragment) and visualized using a fluorescence microscope. Samples were classified as positive or negative based on the intensity of surface immunofluorescence of transfected cells compared to nontransfected cells, according to the manufacturer's suggested recommendations for reading and interpretation.

Definitions

The acute stage of anti-NMDAR encephalitis in our study was defined as the first 3 months after the onset of anti-NMDAR encephalitis symptoms. Acute seizures in our study were defined as seizures occurring in the acute stage of anti-NMDAR encephalitis. Seizure classification was based on clinical symptoms assessed by neurologists according to the International League Against Epilepsy (ILAE) 2017 classification proposal.[17] Repetitive seizures were defined as ≥2 seizures within the period of the acute phase, with the interval of 2 seizures >24 h apart.[18] Status epilepticus (SE) was defined as continuous seizure activity lasting longer than 5 min or recurrent seizures without regaining consciousness between seizures for >5 min.[19] Nonrefractory status epilepticus (NRSE) was defined as continuous seizure activity lasting longer than 5 min and responding to first- and second-line anticonvulsant drug treatment. Refractory status epilepticus (RSE) was defined as a life-threatening condition in which seizures did not respond to first- and second-line anticonvulsant drug treatment and needed therapy with general anesthesia.[20] Super-refractory status epilepticus (SRSE) was defined as status epilepticus that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anesthesia.[20] Coma was defined as a Glasgow Coma Scale (GCS) sum score of ≤8.[21]

Evaluation of seizure outcome

Seizure outcome was evaluated every 3 months after disease onset. Seizure severity was assessed using the National Hospital Seizure Severity Scale (NHS3) in which a higher score indicates greater seizure severity.[22] Neurologic status of anti-NMDAR encephalitis was assessed with the modified Rankin scale (mRS).[3] Patients were considered to have a good outcome if mRS score was ≤2.[8] Information regarding seizure situation and use of antiepileptic drugs (AEDs) in the acute stage was obtained from hospital medical records and face-to-face interviews. Seizure outcome was collected by telephone interview and/or follow-up clinic visits. Follow-up was discontinued when the patient was dead or lost to follow-up.

Statistical analysis

SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was applied for the statistical analyses. The Pearson chi-square or Fisher's exact test was used to evaluate the differences in the categorical variables. Student's *t*-test was used for comparisons of the continuous variables. Univariate binary logistic regression was performed to estimate the effects of different risk factors (i.e., sex, age, seizure types, seizure frequency, number of AEDs, coma, tumor, intensive care unit [ICU] admission, electroencephalography [EEG], brain magnetic resonance imaging [MRI], psychiatric symptoms, movement disorders, and autonomic dysfunction) in predicting seizure recurrence. Forward stepwise multivariate logistic regression was conducted for predictors with p-value <0.10 in the univariate analysis. Odds ratio (ORs) and 95% confidence intervals (CIs) were used to quantify the strength of associations.

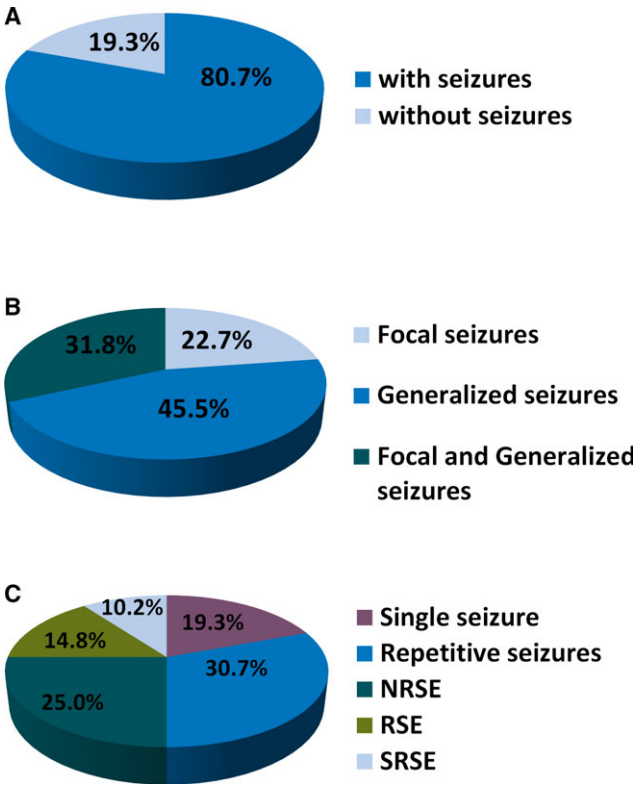


Figure 1.
Features of acute seizure in patients with anti-NMDAR encephalitis. (**A**) Percentage of patients with or without acute seizure (n = 109). (**B**) Percentage of patients with focal, generalized, and both focal and generalized seizures. (**C**) Percentage of patients with single seizure, repetitive seizures, nonrefractory status epilepticus (NRSE), refractory status epilepticus (RSE), or super-refractory status epilepticus (SRSE).
Epilepsia © ILAE

Table 1. Demographic and clinical features of patients with or without acute seizures

	Total (n = 109)	With seizures (n = 88)	Without seizures (n = 21)	p-Value
Age (years)				
9–17	13 (11.9)	8 (9.1)	5 (23.8)	0.03
18–44	88 (80.7)	75 (85.2)	13 (61.9)	
45–72	8 (7.4)	5 (5.7)	3 (14.3)	
Sex (female)	62 (56.9)	46 (52.2)	16 (76.2)	0.06
Initial symptoms				
Seizures	29 (26.6)	29 (33.0)	0 (0)	
Psychiatric symptoms	63 (57.8)	47 (53.4)	16 (76.2)	
Others	17 (15.6)	12 (13.6)	5 (23.8)	
Presenting symptom				
Cognitive impairment	76 (69.7)	61 (69.3)	15 (71.4)	0.85
Psychiatric symptoms	100 (91.7)	84 (95.4)	16 (76.1)	0.004
Movement disorder	59 (54.1)	56 (63.6)	3 (14.3)	<0.001
Autonomic dysfunction	41 (37.6)	38(43.2)	3 (14.3)	0.02
Tumor presence	18 (16.5)	15 (17.0)	3 (14.3)	0.76
Consciousness disorders	46 (42.2)	43 (48.8)	3 (14.3)	0.004
Coma	23 (21.1)	22 (25)	1(4.7)	0.04
EEG (abnormal)	81 (97.6)	73 (98.6)	8 (72.7)	<0.001
Brain MRI (abnormal)	37 (33.9)	32 (36.3)	5 (23.8)	0.27
ICU admission	23 (21.1)	22 (25)	1 (4.7)	0.04

EEG, electroencephalography (available information for 83 patients); ICU, intensive care unit.
$p < 0.05$, significant difference. Data presented as n (%).

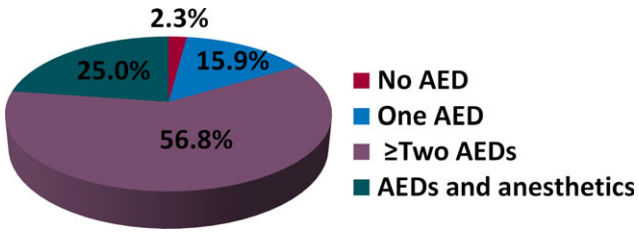


Figure 2.
Administration of antiepileptic drugs and/or anesthetic for acute seizures. Percentage of patients with different antiepileptic treatments (n = 88).
Epilepsia © ILAE

Results

Clinical characteristics of seizures in the acute stage

In total, 115 patients were recruited in our study, among which 6 patients with encephalitis relapse or without immunotherapy were excluded in our follow-up. There were no patients with coexisting other autoimmune or neurologic paraneoplastic antibodies. Finally, 109 patients of our cohort were evaluated and subject to continued follow-up. We extended a follow-up with a median 24 months (range from 6 to 60 months). Due to death, being lost to follow-up, the number of patients at each time point decreased, which was 79, 65, 58, 29, and 4 at 12, 24, 36, 48, and 60 months from disease onset, respectively.

Of the 109 patients (47 men; 62 women) with anti-NMDAR encephalitis, 88 patients (80.7%) were reported with acute seizures and 21 patients (19.3%) were reported without acute seizures (Fig. 1A). The demographic and clinical features of patients with or without acute seizures are presented in Table 1. Seizures in the acute phase occurred more often in patients younger than 45 years of age. No significant difference in the incidence of acute seizures was noted between male and female patients. Patients with acute seizures more frequently had abnormal movements, cardiac arrhythmia, and consciousness disorders ($p < 0.001$, $p = 0.02$, $p = 0.004$) compared with patients without acute seizures. Twenty-two (25%) of 88 patients with acute seizures required admission to the ICU, which was significantly different compared with patients without acute seizures ($p = 0.004$).

In our study, 29 (26.6%) of 109 patients were reported with seizures as the first manifestation of the disease, including 19 (40.4%) of 47 male patients and 10 (16.1%) of 62 female patients, respectively ($p = 0.004$). In addition, adult male patients (18 years of age or older) presented initially with a seizure (15/40, 37.5%). Conversely, adult female patients rarely presented with a seizure initially (8/56, 14.3%, $p = 0.01$). Of 13 children and adolescents (younger than 18 years of age), 61.5% (8/13) of patients were reported with seizure occurrence and 46.1% (6/13) patients started with seizures in the acute phase. As shown in Figure 1B, the seizure type of patients included focal (20/88, 22.7%), generalized (40/88, 45.5%), and both focal and generalized seizures (28/88, 31.8%). According to the frequency of seizures and drug response, the patients exhibited single seizure (17/88, 19.3%), repetitive seizures (27/88, 30.7%), NRSE (22/88, 25%), RSE (13/88, 14.8%), and SRSE (9/88, 10.2%) (Fig. 1C).

Application and efficiency of antiepileptic drugs for seizures in the acute phase

Information regarding administration of AEDs and/or anesthetic to control seizures in the acute stage is presented in Figure 2. Of 88 patients with acute seizures, 2 patients did not receive any AEDs. For 14 patients with single drug (levetiracetam, valproate, or topiramate), the median time to cessation of seizures was 2 weeks. Fifty patients (56.8%) were treated with more than one AED, and the median time of AED treatment to cessation of seizures was 5 weeks. Twenty-two patients with SE required AEDs and anesthetics (midazolam and/or propofol), among which 13 patients (59.1%) controlled SE and an additional 9 patients (40.9%) had SE that continued or recurred on the reduction or withdrawal of anesthetics and ultimately died in acute phase.

Application of antiepileptic drugs and seizure outcome after the acute stage

Thirty-three (38.3%) of these patients with AEDs discontinued the drugs within 3 months of follow-up, whereas 53 (61.7%) continued to receive AEDs drugs after 3 months.

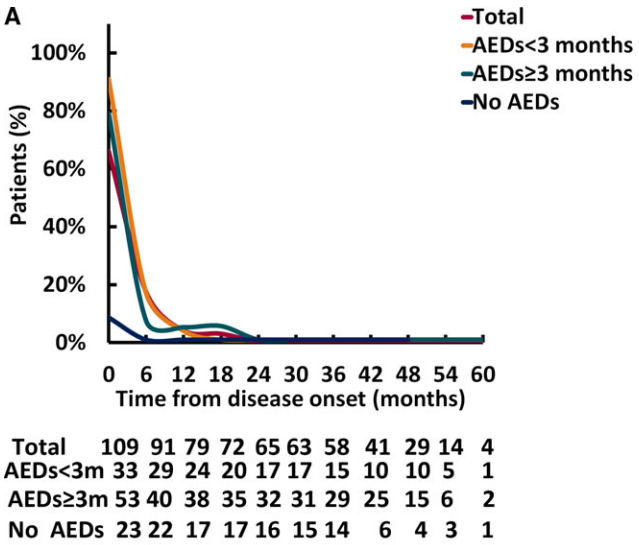
Information regarding seizure outcome in patients during extended follow-up is presented in Figure 3A. In our 5-year follow-up, the increasing proportion of patients who did not experience seizure occurrence was time dependent. Seizure freedom was achieved within 2 years in all patients. More than 80% of the whole cohort with acute seizures had their last seizure within 6 months from disease onset. In addition, seizures did not occur in all the patients (n = 21) without acute seizures in our follow-up assessments.

To further evaluate the relationship between the seizure outcome and the state of encephalitis, we use mRS to assess neurologic status (state of encephalitis) and NHS3 to assess the seizure severity. The relationships among seizure severity, neurologic status, and follow-up time are presented in Figure 3B. It was shown that both scores of mRS and NHS3 decreased over time synchronously, which suggests that the severity of seizures was relieved along with the recovery of encephalitis.

Potential predictive factors associated with seizure outcome

To determine whether seizure outcome was influenced or predicted by some features of the acute stage, the relationships between seizure occurrence after the acute phage and demographic or clinical characteristics (such as sex, age, seizure types, seizure frequency, number of AEDs, coma, tumor presence, ICU admission, EEG, brain MRI, psychiatric symptoms, movement disorders, and autonomic dysfunction) were assessed. Univariate analysis showed that the predictive factors related to early seizure occurrence after the acute phase included tumor presence, ICU stay, SE, and coma ($p < 0.05$) (Table 2). On multivariate analysis, ICU admission (OR 0.07, 95% CI 0.02–0.33; $p = 0.001$) was independently associated with early seizure occurrence after the acute phase.

In the cohort, no seizure occurrence was observed in all patients with >2 years of follow-up. Regarding the long-



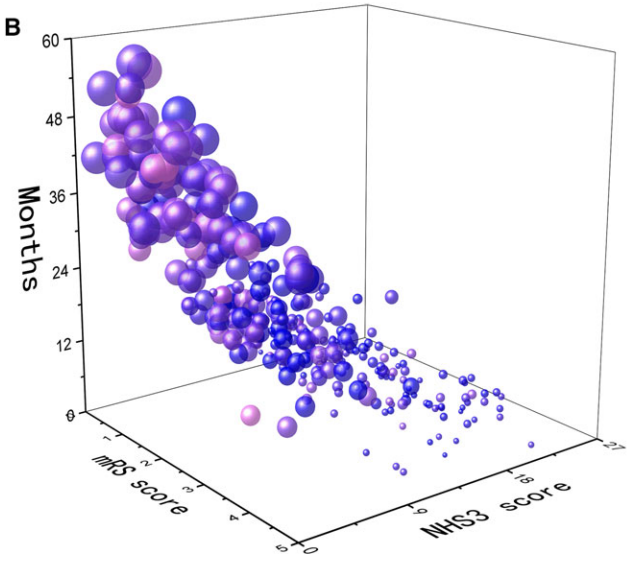


Figure 3.
Seizure outcomes of patients with acute seizures during extended follow-up. (**A**) Comparison of seizure outcomes in patients with different duration of AEDs. M, months. Patients (%), percentage of patients whose last seizure occurred at each time point. The data indicated that seizure freedom was achieved within 2 years in all patients. Due to death and being lost to follow-up, the number of patients at each time point decreased. (**B**) Scatter plot showing the relationship between seizure severity (NHS3 Score) and neurologic status (mRS score) of anti-NMDAR encephalitis during follow-up. Sphere in Figure 3B represents the data of each patient including seizure severity (NHS3 Score) and neurologic status (mRS score) at each follow-up point.

Table 2. Univariate analyses of predictors for early seizure occurrence after the acute phase of anti-NMDAR encephalitis

	Time from disease onset					
	6 months (n = 91)		12 months (n = 79)		18 months (n = 72)	
Potential predictors	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age	1.02 (0.28–3.72)	0.97	0.59 (0.09–4.02)	0.58	0.85 (0.06–9.22)	0.91
Sex (female)	0.21 (0.04–1.06)	0.059		0.99		0.99
Psychiatric symptoms	0.64 (0.11–3.81)	0.63		0.99		0.99
Movement disorder	2.19 (0.52–9.20)	0.28	0.40 (0.04–3.93)	0.43	0.75 (0.06–9.22)	0.82
Autonomic dysfunction	0.29 (0.08–1.08)	0.06	0.46 (0.69–3.09)	0.43	0.29 (0.02–3.57)	0.33
Tumor	4.64 (1.11–19.48)	0.04	1.14 (0.11–11.85)	0.91	4.50 (0.31–65.66)	0.27
ICU admission	13.87 (3.05–63.04)	<0.001	6.21 (0.87–44.58)	0.07	18.00 (1.23–262.65)	0.035
Coma	10.25 (2.22–47.24)	0.003	10.2 (1.35–76.93)	0.02	14.5 (0.64–328.46)	0.09
SE	4.94 (1.17–20.83)	0.03	4.67 (0.47–45.62)	0.19	2.62 (0.21–32.08)	0.45
Generalized seizures	2.05 (0.33–12.82)	0.44	4.21 (0.43–41.14)	0.22	0.44 (0.04–5.36)	0.52
Repetitive seizures	2.38 (0.27–21.15)	0.43		0.99		0.99
Numbers of AEDs (≥2)	8.04 (0.95–67.20)	0.055		0.99		0.99
EEG abnormality	0.92 (0.17–5.14)	0.93	1.03 (0.10–10.55)	0.98		0.99
Brain MRI abnormality	0.82 (0.22–3.16)	0.77	1.33 (0.19–8.99)	0.77	3.00 (0.24–36.88)	0.39

CI, confidence interval; SE, status epilepticus; EEG, electroencephalography; AEDs, antiepileptic drugs; ICU, intensive care unit.

term outcomes of seizures in patients with anti-NMDAR encephalitis, no difference in seizure-free was noted between short-term (i.e., <3 month) and long-term, (i.e., >3 month) AEDs treatments or other risk factors.

Discussion

In the literature, several important outcome studies address anti-NMDAR encephalitis overall,[3,6,8] but long-term follow-up studies focusing on seizures in these patients are lacking. During a median follow-up of 2 years, our study suggested that seizures in patients with anti-NMDAR encephalitis tended toward a good outcome of living seizure free. The factors at the acute stage that predicted seizure occurrence of short-term outcome included presence of tumor, SE, ICU admission, and/or coma. Thus our results definitively confirm that seizure is a symptom in the acute stage of anti-NMDAR encephalitis, and no seizure occurred along with recovery of the encephalitis. Consequently, long-term AEDs may not be necessary.

In our cohort of Chinese patients, 80.7% of patients was reported with seizures in the acute phase, which was consistent with the previously reported incidence of 76% in anti-NMDAR encephalitis patients in the United States.[1] However, this percentage is higher than the previously reported incidence of acute seizures in herpes simplex virus (HSV) encephalitis (33%, 46.7% ,or 50%, respectively[23–25]) and other viral encephalitis (24% of Nipah encephalitis and 7–67% of Japanese encephalitis[26,27]). The different incidence of acute seizures may indicate that acute seizures are a typical and more common clinical symptom in patients with anti-NMDAR encephalitis compared with viral encephalitis. In addition, in this study, seizures as first symptom of anti-NMDAR encephalitis are more common in male patients or adult male patients, which is consistent with the previous studies.[28,29] Regarding seizure situation in patients younger than 18 years of age, in our study, 61.5% was reported seizures in the acute phase and 46.1% patients started with seizures. Compared with the previous literature focusing on patients younger than 18 years of age, although this incidence of acute seizures is slightly lower than the previously reported incidence of 85%,[30] the incidence of seizures as first symptom is consistent with the previous study, which reported 42.8% patients starting with seizures.[30] Of all seizure types, generalized seizure was the most common seizure type, which was consistent with the reported seizure types of the disease.[1] Furthermore, data about the incidence of RSE and SRSE are lacking; however, some case studies reported the occurrence of RSE and SRSE in the acute phase of anti-NMDAR encephalitis.[12,13] In our cohort, 14.8% RSE and 10.2% SRSE occurred in the acute phase of this disease.

In this study, no new-onset seizure was noted in patients without seizures in the acute phase and no seizure occurred in patients with >2 years of follow-up. Studies reported that 30 to 45.5% of patients with acute seizures progressed to uncontrolled remote seizures in patients with herpes simplex encephalitis.[24,31] The different seizure outcomes in patients between herpes simplex encephalitis and anti-NMDAR encephalitis reflect the different potential mechanisms for the development of seizures. For the development of seizures in virus encephalitis, there is growing support for the role of the extensive parainfectious inflammatory response.[32,33] In addition, focal signal abnormalities of the temporal and frontal lobe often can be observed from brain imaging in patients with viral encephalitis.[23,34] However, limited data are available to clarify the potential mechanisms for the development of seizures in anti-NMDAR

encephalitis. One study demonstrated that the brain parenchyma of patients exhibits relatively few inflammatory cells and that neuronal loss was remarkably mild in patients with anti-NMDAR encephalitis.[35] Other studies reported that some patients with anti-NMDAR encephalitis have focal or multifocal areas of signal abnormalities in the acute phase, especially in white matter.[3] However, follow-up brain MRI studies did not detect permanent brain damage.[35,36] These reasons partly explained the good seizure outcome of anti-NMDAR encephalitis.

To the best of our knowledge, there is currently no evidence to support or refute the routine use of AEDs for prevention of seizure recurrence after the acute phase. Evidence about the duration of AEDs in anti-NMDAR encephalitis is also lacking. In our study, seizure freedom was achieved within 2 years in all patients; >80% of the whole cohort with acute seizures had their last seizure within 6 months of disease onset. Regarding the final seizure outcome, no difference is noted between short-term (≤3 months) and long-term (>3 months) AED treatments. Thus this result indicates that long-term AEDs may not be necessary. One important reason may be that immunotherapy contributed to the recovery of the encephalitis and played an important role in controlling seizures.

In this study, univariate predictors for early seizure occurrence after the acute phase included the presence of seizures, SE, coma, or ICU admission in the acute phase of anti-NMDAR encephalitis, which was consistent with risk factors of seizure outcome in virus encephalitic patients.[37,38] In addition, tumor was a unique predictor for early seizure occurrence after the acute phase. In multivariate analysis, only ICU admission was an independent predictor of early seizure occurrence. Although focal seizures or brain MRI with signal abnormalities as a risk factor for seizure recurrence was reported,[39] these factors may not be related to early seizure occurrence in our study.

Some limitations should be acknowledged in our study. First, the cohort is relatively small. However, the small size did not materially affect the precision of study estimates because the incidence rate of anti-NMDAR encephalitis was rather low (32 cases of 761 patients with encephalitis in the California Encephalitis Project between September 2007 and February 2011,[40] although the true rate of anti-NMDAR encephalitis in the general population is not yet fully clarified), indicating a relatively high precision of point estimates. In addition, the long follow-up time counterbalanced the relatively low sample size, as it plays a primary role in longitudinal studies such as ours. Second, epileptic seizures were diagnosed clinically, especially in the acute phase. The presence of both epileptic and nonepileptic paroxysmal manifestations in these patients could lead the physicians to overestimate the epileptic seizures. Third, this study was reported to be a mixed population with both pediatric and adult cases, with an obvious adult predominance but unexpectedly without children younger than 9 years of age. This could be a bias for a mixed population. Finally, longer follow-up may be necessary given that some relapse of anti-NMDAR encephalitis has been reported,[2,3] and the evolution of seizures in these patients and the relationship between them remain unknown.

Conclusion

In conclusion, patients with anti-NMDAR encephalitis may have a high rate of acute seizures. Clinical characteristics such as SE, coma, and ICU admission in the acute phase are potential risk factors for the occurrence of seizures after the acute stage. Regarding the final seizure outcome, all patients with acute seizures did not exhibit seizure occurrence. Regarding duration of use of AEDs, long-term use of AEDs may not be necessary. Our data are valuable for patient counseling, treatment decision, and seizure management in the clinic.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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