Hindawi
Acta Neurologica Scandinavica
Volume 2024, Article ID 6183939, 9 pages
https://doi.org/10.1155/2024/6183939

Research Article

Seizures as Initial Presentation and Enduring Predisposition to Seizures in Autoimmune Encephalitis

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Received 22 March 2023; Revised 25 February 2024; Accepted 8 March 2024; Published 21 March 2024

Academic Editor: Carlo Colosimo

Purpose. This retrospective study is aimed at investigating the clinical characteristics of autoimmune encephalitis (AE) and long-term prognosis of patients who initially present with seizures as well as risk factors for enduring predisposition to seizures in AE. *Methods*. From January 1, 2013, to October 31, 2021, a total of 343 AE patients from a single center diagnosed with autoimmune encephalitis (AE) were enrolled in this study, including 198 antibody-positive AE and 145 antibody-negative but probable AE. According to initial symptoms, AE patients were divided into two groups: onset with seizure group and onset with nonseizure group. The clinical characteristics were retrospectively reviewed. Patients were clinically evaluated at onset and at 6, 12, and 24 months of follow-up. Modified Rankin Scale (MRS) score, Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score, and seizure-related information were assessed. *Results*. In AE, patients with seizures as the first presentation were younger, with a median-onset age of 28 years old. Compared with other types of antibody-positive AE, anti-GABABR AE more frequently began with seizures, while anti-CASPR2, anti-AMPAR, and anti-DPPX encephalitis usually began with symptoms other than seizures. The most common type of initial seizures in AE was focal to bilateral seizure (67.6%), with a significant prevalence in antibody-positive AE ($P = 0.001$). In addition, compared with nonseizure group, patients with seizures as an initial presentation had higher MRS and CASE scores at 24 months of follow-up. Older age at onset and focal nonmotor seizure type were independent risk factors for an enduring predisposition to seizures in AE patients. *Conclusion*. The younger and anti-GABABR-positive AE patients are more prone to onset with seizures. AE patients who initially presented with seizures had worse long-term neurological recovery. Onset age and seizure type should be highly appreciated when formulating the strategy for therapy at post-AE status.

1. Introduction

Seizures are often a prominent manifestation of autoimmune encephalitis (AE), and 69.9% of antibody-positive AE patients experience seizures during the course of their illness [1]. Notably, 26.1%-49.2% of AE patients presented with seizures as the initial symptom [2, 3]. Initially presenting with seizures likely hints at the possibility of altered structures involving the cortex, mesial temporal lobe, and limbic system, as well as the level of molecular changes in the excitatory and inhibitory neurotransmitter network. Previous studies have mainly focused on treatment, but whether initial seizures play a role in prognosis of AE or the outcomes of seizures remains unclear. One study reported that the onset of AE with seizures may signal seizure recurrence after the withdrawal of antiseizure medications (ASMs) within three months of onset [2], while another study contradicted these findings, showing that onset with seizures did not influence the seizure recurrence [3]. The discrepancy in the long-term effect of seizures as the initial presentation of AE might affect disease management in the early stage of the disease. Therefore, following with interest the acute phase of the disease and post-AE status in terms of seizures and other characteristics is crucial.

Although 88% of seizure patients with neuronal surface-antibody-positive AE could achieve 12 months of seizure freedom [4], a proportion of AE patients still suffered from enduring seizures. Several studies have screened out potential risk factors associated with poor controlled seizures in AE, including delayed immunotherapy [5], intensive care unit (ICU) admission [6], antibody type [7], and interictal epileptiform discharges (IEDs) [8], but these studies were mainly based on the analysis in antibody-positive AE patients, which excluded antibody-negative AE patients. Besides, the inconsistency in the measurements of seizure outcomes in these studies was another issue. Recently, Matricardi et al. had reported that the prevalence of enduring seizures after the acute phase of antibody-negative AE was higher than antibody-positive AE (35.33% vs. 58.33%) [9]. A comprehensive study on potential risk factors for AE-associated chronic condition of persistent seizures remains lacking.

Therefore, we concentrated on seizures in both antibody-positive and antibody-negative AE patients. This study is aimed at investigating the clinical characteristics and the effect of seizures as initial presentation on the short- and long-term prognosis of AE as well as risk factors for an enduring predisposition to seizures in AE.

2. Materials and Methods

2.1. Subjects and Designs. We retrospectively reviewed the cases of patients with antibody-positive AE and antibody-negative but probable AE who had been treated at the department of neurology or the ICU of Tongji Hospital, Huazhong University of Science and Technology, from January 1, 2013, to October 31, 2021. According to the criteria published in 2016 [10], both definite and probable AE patients were enrolled in this study. Overall, a total of 343 AE patients were enrolled, including 198 antibody-positive AE and 145 antibody-negative AE patients. Then, these patients were divided into two groups according to the initial symptoms: the "onset with seizure group" and the "onset with nonseizure group." This retrospective observational study was approved by the Medical Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was not required.

2.2. Clinical Data Collection. The following baseline clinical data were collected: age at onset, sex, initial symptoms, the first-time antibody detection in cerebrospinal fluid (CSF) and serum during the course of illness, prodromal symptoms, accompanying symptoms, ICU admission, lung infection, confirmed tumors, the first-time CSF routine examination, brain magnetic resonance imaging (MRI) images and interictal electroencephalogram (EEG) findings after admission, and Modified Rankin Scale (MRS) scores at onset and discharge. Antibody-positive AE patients were positive for antineuronal antibodies using transfected cell-based assay and immunospot assay, and antibody-negative AE patients also underwent antibody detection but were negative. The targets of the detected antibodies included neuronal surface antigens, including N-methyl-D-aspartate receptor (NMDAR), contactin-associated protein 2 (CASPR2), leucine-rich glioma inactivated protein 1 (LGl1), γ-aminobutyric acid receptor-B (GABAB), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), dipeptidyl aminopeptidase-like protein 6 (DPPX), glycine receptor (GlyR), metabotropic glutamate receptor 5 (mGluR5), dopamine-2 receptors (D2R), and IgLON5, and intracellular antigens, including glutamic acid decarboxylase 65 (GAD65), Hu, Yo, Ri, SOX1, Ma2, and CV2. The initial dilution titres of the CSF and serum were 1 : 1 and 1 : 10, respectively. Serum antibody titres were marked "+" at 1 : 10, "++" at 1 : 32–1 : 100, and "+++" at 1 : 320. The titres of CSF antibodies were marked "+" at 1 : 1, "++" at 1 : 3.2–1 : 10, and "+++" at 1 : 32 or above. Neuropsychological deficit findings were based on electronic record of disease history. Immunotherapy consisted of steroids, intravenous immunoglobulin (IVIG), plasma exchange, and immunosuppressive agent.

2.3. Definitions. In this study, according to the International League Against Epilepsy (ILAE) 2017 operational classification of seizure type [11], seizure type at onset was recorded by generalized, focal motor, focal nonmotor, focal to bilateral, multiple seizure types and faciobrachial dystonic seizures (FBDS). FBDS were defined as frequent attacks (>8/d) with a dystonic posture of the arm, often combined with a facial contraction, lasting less than 30 seconds [12]. Drug resistant to ASMs was defined as failure to achieve seizure freedom during acute phase of the disease, despite prescribed with two tolerated, adequately dosed ASMs [9]. Prodromal symptoms included fever, headache, dizziness, fatigue, diarrhoea, and other nonspecific symptoms. Interictal EEG abnormal findings were recorded: focal/diffuse slow activity, diffuse IDEs, temporal IEDs, and extratemporal IEDs. Abnormal MRI findings referred that T2-Weighted Imaging-Fluid-Attenuated Inversion Recovery (T2 FLAIR) showed high signal intensity, including plus-temporal (unilateral and bilateral temporal lobes and medial temporal lobe), extratemporal (brain regions other than the former), and both. The normal range of CSF routine examination was as follows: white blood cell count ((0-8) $*10^6$), total protein level (150-450 mg/L), immunoglobulin G (7.51-15.6 g/L), immunoglobulin A (0.82-4.53 g/L), and immunoglobulin M (0.46-3.04 g/L). Early immunotherapy was defined as a period of less than 28 days elapsing between the onset of symptoms and the initiation of immunotherapy [13].

2.4. Follow-Up and Seizure Outcomes. Patients underwent clinical evaluation by inpatient, outpatient or phone inquiry at onset and at 6, 12, and 24 months of follow-up. Poor seizure outcomes were defined that there were persistent epileptic seizures 12 months after onset or died during follow-up, those patients were possibly regarded with enduring predisposition to seizures. MRS score was used to evaluate functional recovery prognosis. Clinical Assessment Scale in Autoimmune Encephalitis [14](CASE) is a new scale that rates the severity of AE.

2.5. Statistical Analysis. Statistical analysis was performed using SPSS 26.0 (IBM). Continuous variables were presented as the means ± standard deviations, and categorical variables

were described as counts and percentages. For group comparisons, we used the Mann–Whitney U test for continuous variables (all continuous variables were nonnormally distributed) and the chi-squared test for categorical data. The MRS and CASE scores of different groups were detailed as the median and interquartile range (IQR) and compared using the Wilcoxon test. Multivariate logistic regression analysis was used to explore the independent predictors of poor seizure outcomes, and the results were provided as odds ratios with 95% confidence intervals. Statistical analyses were performed using $P < 0.05$ as statistical significance. Variables with P values < 0.1 in univariate analyses were subjected to multivariate logistic regression analysis.

3. Results

3.1. Clinical Characteristics. As shown in Table 1 and Supplemental Figure 1, according to the initial presentations, a total of 343 patients with AE were divided into two groups: onset with seizure group and onset with nonseizure group. In our cohort, we found that patients who began with seizures were younger than nonseizures (median-onset age 28 vs. 46 years old, $P < 0.001$).

There was no significant difference in the prevalence of antibody-positive patients between the two groups, and anti-NMDAR encephalitis was the most common aetiology (Table 1, 60.8% and 55.4%, $P > 0.05$). Compared with other types of antibody-positive encephalitis, anti-GABABR encephalitis patients were more prone to present with seizures as the initial symptom (Table 1, $P < 0.001$) and among the 18.9% (3/16) began with status epilepticus. Anti-CASPR2, anti-AMPAR, and anti-DPPX encephalitis usually began with symptoms other than seizures (Table 1, $P = 0.014$, $P = 0.041$, and $P = 0.014$). But the antibody titre did not differ between the two groups.

Moreover, as for encephalitis-associated symptoms at acute phase of the disease, patients in the onset with seizure group were less susceptible to accompanying short-term memory deficits and behavior, cognitive, and speech disorders (Table 1, $P = 0.005$, $P < 0.001$, $P = 0.004$, and $P = 0.001$). The prevalence of tumors was higher in the onset with nonseizure than seizure group ($P = 0.015$).

CSF routine examination showed distinct inflammatory changes, elevated CSF protein, and pleocytosis. Besides, CSF immunoglobulin G and immunoglobulin A levels also markedly increased in the two groups. However, the increased level of CSF protein and immunoglobulin G and immunoglobulin A was more obvious in the onset with nonseizure group (Table 1, $P < 0.05$).

The most prominent abnormal interictal EEG findings were focal or diffuse slow activity in both groups (35.1% and 22.9%), which were more common in the onset with seizure group (Table 1, $P = 0.013$). The presence and localization of abnormal MRI findings did not differ between the two groups. There was no difference in MRS scores at onset between the two groups, while the onset with seizure group evaluated lower MRS scores at discharge (Table 1, $P = 0.017$).

As shown in Table 2, the most common type of initial seizures in AE was focal to bilateral seizure (67.6%), with a significant prevalence in antibody-positive patients ($P = 0.001$). No significant differences were detected in the frequency of seizures at onset between antibody-positive and antibody-negative patients. Forty-three (29.1%) patients who presented seizures as initial symptom showed drug resistance to ASMs during the acute phase of the disease. Valproate (29%), oxcarbazepine (24%), and levetiracetam (19%) were the first three common prescriptions of ASMs (Supplemental Figure 2). In addition, in onset with nonseizure group, 28.2% (55/195) experienced seizures during the subsequent course of their disease, the most common type of seizures was also focal to bilateral seizure (67.3%), and no difference was found between antibody-positive and antibody-negative AE (Supplemental Table 1). In these patients, thirteen (23.6%) showed drug resistance to ASMs during the acute phase of the disease, and oxcarbazepine (34%), valproate (31%), and levetiracetam (18%) were the first three common prescriptions of ASMs (Supplemental Table 1 and Supplemental Figure 3).

3.2. Short- and Long-Term Prognosis of AE Patients. Table 3 provided the follow-up data on MRS and CASE scores except for patients who lost to follow-up. The rate of lost to follow-up was 22.4% (77/343). The cumulative mortality rates in the "onset with seizure group" and the "onset with nonseizure group" during the 24 months of follow-up were 14.9% and 14.5%, respectively, which did not differ between groups ($P = 0.938$). There was no significant difference in MRS and CASE scores at 6 months of follow-up between the two groups, while AE patients who initially presented with seizures had higher MRS scores at 12 months and higher MRS and CASE scores at 24 months ($P < 0.05$).

3.3. The Potential Risk Factors for Poor Seizure Outcomes in AE Patients. In this study, we also analyzed the potential risk factors for poor seizure outcomes in AE patients who experienced acute symptomatic seizures and initiated immunotherapy less than 28 days after onset. A total of 78 AE patients (53 antibody-positive AE patients and 25 antibody-negative AE patients) were enrolled, and then, these patients were divided into two groups according whether there were persistent epileptic seizures 12 months after onset or died during follow-up (Table 3). The days between the initiation of immunotherapy and onset did not significantly differ between the groups ($P > 0.05$).

In our AE cohort, as shown in Table 4, the rate of developing to poor seizure outcomes was 25.6%, which was unrelated to the presence of neuronal antibody ($P = 0.377$). The univariate analysis revealed that the related factors associated with poor seizure outcomes included age at onset ($P = 0.069$), focal nonmotor seizure type ($P = 0.012$), drug resistance to ASMs ($P = 0.020$), and the number of prescribed ASMs during the acute phase of the disease ($P = 0.034$), accompanied with short-term memory deficits ($P = 0.021$) and the number of associated encephalitis symptoms at onset ($P = 0.037$) and MRS scores at discharge ($P = 0.067$). When performing the multivariable logistic

Table 1: The comparison of demographics and clinical characteristics between the onset with seizures group and the onset with nonseizures group in AE patients.

Variables	Onset with seizures (148, 44.1%)	Onset with nonseizures (195, 56.9%)	*P* value
Age at onset, Y, median [IQR]	28 [19-43.5]	46 [27-58]	<0.001
Sex: male, *n* (%)	70 (47.3%)	95 (48.7%)	0.794
Antineuronal antibodies findings			
Antibody positive, *n* (%)	90 (60.8%)	108 (55.4%)	0.314
NMDAR	59 (65.6%)	60 (55%)	0.108
LGI1	4 (4.4%)	10 (9.3%)	0.471
GABABR	16 (18%)	3 (3%)	<0.001
CASPR2	1 (1%)	10 (9%)	0.014
AMPA	0	5 (5%)	0.041
DPPX	2 (2.2%)	9 (8.3%)	0.014
Multiantibodies	5 (6%)	4 (4%)	0.513
Antibodies against cell surface antigens, *n* (%)	89 (98.9%)	105 (97.2%)	0.407
Antibody negative, *n* (%)	58 (39.2%)	87 (44.6%)	0.398
Antibody titres, *n* (%)			
+	19 (21.1%)	31 (28.7%)	0.221
++	37 (41.1%)	50 (46.3%)	0.464
+++	34 (37.8%)	27 (25.0%)	0.052
Seizure type at onset			
Generalized, *n* (%)	24 (16.2%)		
Focal motor, *n* (%)	50 (33.8%)		
Focal nonmotor, *n* (%)	14 (9.5%)		
Focal to bilateral, *n* (%)	100 (67.6%)		
Multiple seizure type, *n* (%)	40 (27.0%)		
FBDS, *n* (%)	3 (2.0%)		
Seizure frequency at onset			
Daily, *n* (%)	79 (53.4%)		
Weekly, *n* (%)	30 (20.3%)		
Monthly, *n* (%)	39 (26.6%)		
Drug resistance to ASMs during the acute phase, *n* (%)	43 (29.1%)		
Encephalitis-associated symptoms			
Prodromal symptoms, *n* (%)	79 (53.4%)	120 (61.5%)	0.129
Altered level of consciousness, *n* (%)	46 (31.1%)	68 (34.9%)	0.460
Behavior disorders, *n* (%)	61 (41.2%)	120 (62.5%)	<0.001
Short-term memory deficits, *n* (%)	26 (17.6%)	60 (30.8%)	0.005
Cognitive disorders, *n* (%)	45 (30.4%)	89 (45.6%)	0.004
Speech disorders, *n* (%)	12 (8.1%)	41 (21.0%)	0.001
Sleep disorders, *n* (%)	13 (8.8%)	22 (11.3%)	0.449
Autonomic dysfunction, *n* (%)	5 (3.4%)	12 (6.2%)	0.241
Central hypoventilation, *n* (%)	7 (4.7%)	3 (1.5%)	0.082
Admission in ICU, *n* (%)	53 (35.8%)	54 (27.7%)	0.108
Lung infection, *n* (%)	47 (31.8%)	50 (25.6%)	0.213
Confirmed tumors, *n* (%)	5 (3.4%)	20 (10.3%)	0.015
CSF routine examination			
CSF WBC count 10^6	60.06 ± 31.89	38.19 ± 8.11	0.856
CSF protein level (mg/L)	405.59 ± 28.38	498.80 ± 22.12	<0.001
CSF immunoglobulin G level (g/L)	44.41 ± 4.26	61.09 ± 3.77	<0.001
CSF immunoglobulin M level (g/L)	2.10 ± 0.37	2.67 ± 0.42	0.098
CSF immunoglobulin A level (g/L)	5.75 ± 1.03	7.92 ± 0.74	0.001

Table 1: Continued.

Variables	Onset with seizures (148, 44.1%)	Onset with nonseizures (195, 56.9%)	*P* value
Abnormal EEG findings, *n* (%)	83 (56.1%)	60 (31.3%)	<0.001
Diffuse/focal slow activity, *n* (%)	52 (35.1%)	44 (22.9%)	0.013
Diffuse IEDs, *n* (%)	21 (14.2%)	13 (6.8%)	0.024
Temporal IEDs, *n* (%)	6 (4.1%)	3 (1.6%)	0.156
Extratemporal IEDs, *n* (%)	4 (2.7%)	0	0.022
Abnormal MRI findings, *n* (%)	81(54.7%)	114 (58.5%)	0.489
T-plus, *n* (%)	62 (41.9%)	87 (44.6%)	0.614
Extra-T, *n* (%)	19 (12.8%)	27 (13.8%)	0.786
Both, *n* (%)	35 (23.6%)	61 (31.3%)	0.119
MRS scores at onset, median [IQR]	2 [1-3]	2 [1-3]	0.549
MRS scores at discharge, median [IQR]	1 [0-3]	1 [1-3]	0.017

In addition, there were also 1 anti-GAD65 encephalitis, 2 anti-mGLUR5 encephalitis, 4 anti-MOG encephalitis, 1 anti-Ri encephalitis, 1 anti-Yo encephalitis, and 1 anti-SOX1 encephalitis. Abbreviations: FBDS: faciobrachial dystonic seizures; ASMs: antiseizure medications (ASMs); MRS: modified Rankin Scale; IEDs: interictal epileptiform discharges; T: temporal.

Table 2: The characteristics of initial seizures in antibody-positive and antibody-negative AE patients.

Variables	Antibody-positive AE (90, 60.8%)	Antibody-negative AE (58, 38.9%)	*P* value
Seizure type at onset			
Generalized, *n* (%)	11 (12.2%)	15 (25.9%)	0.033
Focal motor, *n* (%)	28 (31.1%)	21 (36.2%)	0.520
Focal nonmotor, *n* (%)	6 (6.7%)	8 (13.8%)	0.148
Focal to bilateral, *n* (%)	70 (77.8%)	30 (51.7%)	0.001
Multiple seizure type, *n* (%)	25 (27.8%)	15 (25.9%)	0.798
FBDS, *n* (%)	3 (3.3%)	0	0.160
Seizure frequency at onset			
Daily, *n* (%)	45 (50.0%)	34 (58.6%)	0.305
Weekly, *n* (%)	20 (22.2%)	10 (17.2%)	0.462
Monthly, *n* (%)	25 (27.8%)	14 (24.1%)	0.624
Drug resistance to ASMs at onset, *n* (%)	28 (31.1%)	15 (25.9%)	0.492
The number of received ASMs, median [IQR]	2 [1-3]	2 [1-3]	0.411

Abbreviations: FBDS: faciobrachial dystonic seizures; ASMs: antiseizure medications.

regression analysis (Table 5), independent risk factors for the poor seizure outcomes were older age at onset ($P = 0.034$) and focal nonmotor seizure type ($P = 0.027$).

4. Discussion

In this retrospective study, we recruited both antibody-positive and antibody-negative AE patients, described the clinical characteristics, and evaluated the impact of seizures as the initial symptom on the short- and long-term prognosis of AE. In addition, we analyzed the potential risk factors for an enduring predisposition to seizures in AE. Our study may compensate for the potential incompleteness attributed to the lack of antibody-negative probable AEs in previous studies.

Seizures are well recognized and often prominent manifestations of AE syndromes, and 69.9% of antibody-positive AE patients experienced clinical seizures during the course of their illness [1]. The incidence of acute symptomatic seizures secondary to AE in our antibody-positive and antibody-negative subgroups was 57.6% and 57.9%, respectively, which suggesting that unknown antineuronal antibodies of probable AE are also related to seizure pathogenesis.

AE patients initially presented with seizures manifested a series of distinctive clinical characteristics. The rate of AE began with seizures in antibody-positive AE ranges from 26.1% to 49.2% [2, 3]. Our results suggested that 45.5% antibody-positive AE and 40% antibody-negative AE patients presented with seizures as the initial symptom. In our study, AE patients who began with seizures were younger, with a median-onset age of 28 years old, however, the possible molecule mechanism is unclear. Compared with other types of antibody-positive AE, anti-GABABR AE more frequently began with seizures. The association of anti-GABABR encephalitis with seizures has been reported frequently. The physiological function and structural localization of GABAR may well explain the higher occurrence of seizures in anti-GABABR AE. GABA is the major inhibitory neurotransmitter in the central nervous system, and its

Table 3: Short- and long-term prognosis analysis of AE patients between the two groups.

Follow-up duration	Onset with seizures	Onset with nonseizures	*P* value
6 months ($n = 115$, $n = 151$)			
MRS, median [IQR]	1 [0-3]	1 [1-2]	0.102
CASE, median [IQR]	2 [1-5]	2 [0-5]	0.104
12 months ($n = 105$, $n = 140$)			
MRS, median [IQR]	1 [0-2]	0 [0-2]	0.005
CASE, median [IQR]	1 [1-3]	1 [0-3]	0.137
24 months ($n = 87$, $n = 110$)			
MRS, median [IQR]	1 [1-2]	0 [0-1]	<0.001
CASE, median [IQR]	1 [1-4]	1 [0-3]	0.028

Abbreviations: MRS: modified Rankin Scale; CASE: Clinical Assessment Scale in Autoimmune Encephalitis.

receptors are widely distributed in the hippocampus and thalamus [15]. In animal models, the disruption of GABAB receptors results in epilepsy, hyperalgesia, and impaired memory [16]. A previous study argued that anti-LGI1 encephalitis patients were more prone to initially present with seizures [2]. However, these findings did not apply to our cohort. Notably, there were four patients with positivity to intracellular antigens in our antibody-positive AE cohort and only one anti-GAD65-positive patient. Intracellular antibodies appear unlikely to be pathogenic given the intracellular location of antigens and may instead be a surrogate marker of cytotoxic T-cell-mediated disease in patients with associated neurological syndromes [17]. Only high titres in serum (more than 20 nmol/L) reportedly confer high clinical specificity for GAD65-associatied neurological autoimmunity, while low titres lack clinical specificity for autoimmune neurological diseases [18, 19] Budhram et al.'s study on the clinical spectrum of anti-GAF65-related neurological syndromes had also revealed that the main core manifestations were stiff person spectrum disorders (33%), cerebellar ataxia (26%), epilepsy without encephalitis (17%), and limbic encephalitis with seizures (only 3%) [20]. Our study verified the previous opinion that few anti-GAD65-positive patients presented as acute encephalitis. We also found that the most common type of initial seizures in AE was focal to bilateral, with a significant prevalence in antibody-positive patients. In addition, AE patients who initially presented with seizures got lower MRS scores at discharge, suggesting that they were likely more sensitive to immunotherapy.

AE generally had a good prognosis, despite the numerous variables identified to be associated with the prognosis of AE [5]. The role of initial presentation in the prognosis of AE needs further investigations. The CASE score is a novel tool that was recently proposed in 2019 to specifically evaluate the clinical severity of a series of syndromes, including antibody-positive and antibody-negative AE. In this study, CASE scores were used to represent the rehabilitation status of patients during the follow-up period. Our results showed that AE patients who initially presented with seizures had higher MRS scores at 12 months of follow-up, as well as higher MRS and CASE scores at 24 months of follow-up. Seizures as initial presentation probably negatively impact the long-term prognosis of AE. Therefore, our findings likely widen the spectrum of potential predictive factors for outcomes in AE. A variety of initial presentations in AE may imply different changes in molecular mechanism and network oscillation at the initial phase of the disease. In particular, as an alarming nerve stimulation symptom, patients began with seizures usually gained timely effective immunotherapy and ASMs treatment, maybe that was why they got better MRS scores at discharge. However, immunotherapy and ASMs treatment likely just prevented the progression of immune inflammation reaction and epileptiform activity but not reversed the already substantial injury, which probably became persistent deficits or secondary structural abnormalities of brain in the long term.

Our results might present a comprehensive situation of prognosis for both definite AE and probable AE. About 60% of antibody-positive AE patients achieved good clinical outcomes (MRS ≤ 2) 12 months after discharge [21]. Besides, the frequency of achieving a good 2-year outcome (MRS ≤ 2) in seronegative autoimmune encephalitis was 56.5% [22]. In our cohort, 80.9% antibody-positive AE and 71% antibody-negative AE achieved satisfactory neurologic recovery (MRS ≤ 2) 12 months after onset. The higher favorable prognosis may be due to the timely diagnosis and treatment of AE.

Seizures are one of the most prominent manifestations of AE, and as the development of scientific discoveries is related to seizures in neural autoantibodies diseases, the awareness of autoimmune causes of epilepsy had increased. To ensure accurateness of terminology, in 2020, International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce proposed to replace the term "autoimmune epilepsy" with "acute symptomatic seizures secondary to AE" and "autoimmune-associated epilepsy," the former of which referred to seizures occurring in the setting of the active phase of immune-mediated encephalitis, caused by inflammation and was responsive to immunotherapy and the latter of which referred to enduring predisposition to seizures (Fitting the current conceptual definition of epilepsy) and determined to be secondary to autoimmune brain diseases [23]. However, in 2022, Budhram and Burneo modified the term "autoimmune encephalitis-associated epilepsy" to emphasize that encephalitis and the development of epilepsy are inextricably linked in this condition

Table 4: Univariate analysis of related factors for poor seizure outcomes in AE patients.

Variables	Yes (20, 25.6%)	No (58, 74.4%)	*P* values
Age at onset, Y, median [IQR]	30 [20-55]	25 [19-32]	0.069
Sex: male, *n* (%)	9 (47.4%)	29 (50.0%)	0.842
Antibody positive, *n* (%)	8 (40.0%)	17 (29.3%)	0.377
Onset with seizures, *n* (%)	14 (70.0%)	46 (79.3%)	0.394
Status epilepticus, *n* (%)	1 (5.0%)	4 (6.9%)	0.765
Seizure type at onset			
Generalized, *n* (%)	2 (10.0%)	9 (15.5%)	0.541
Focal motor, *n* (%)	8 (40.0%)	24 (41.4%)	0.914
Focal nonmotor, *n* (%)	5 (25.0%)	3 (5.3%)	0.012
Focal to bilateral, *n* (%)	14 (70.0%)	40 (69.0%)	0.931
Multiple seizure type, *n* (%)	8 (40.0%)	18 (31.0%)	0.463
FBDS, *n* (%)	0	1 (1.7%)	0.555
Seizure frequency at onset			
Daily, *n* (%)	11 (55.0%)	32 (55.2%)	0.989
Weekly, *n* (%)	7 (35.0%)	12 (20.7%)	0.199
Monthly, *n* (%)	2 (10.0%)	14 (24.1%)	0.177
Drug resistance to ASMs during the acute phase, *n* (%)	10 (50.0%)	13 (22.4%)	0.020
The number of prescribed ASMs during the acute phase, *n* (%)	2.5 (2-4)	2 (1-3)	0.034
Encephalitis-associated symptoms			
Prodromal symptoms, *n* (%)	12 (60.0%)	31 (53.4%)	0.611
Altered level of consciousness, *n* (%)	7 (35.0%)	16 (27.6%)	0.531
Behavior disorders, *n* (%)	12 (60.0%)	24 (41.4%)	0.150
Short-term memory deficits, *n* (%)	7 (35.0%)	7 (12.1%)	0.021
Cognitive disorders, *n* (%)	9 (45.0%)	18 (31.0%)	0.258
Speech disorders, *n* (%)	2 (10.0%)	5 (8.6%)	0.852
Sleep disorders, *n* (%)	2 (10.0%)	5 (8.6%)	0.852
Central hypoventilation, *n* (%)	0	3 (5.2%)	0.300
Autonomic dysfunction, *n* (%)	1 (5.0%)	3 (5.2%)	0.976
The number of associated symptoms at onset, *n* (%)	3 (2-3)	2 (1-3)	0.037
ICU admission, *n* (%)	9 (45.0%)	19 (32.5%)	0.325
Lung infection, *n* (%)	5 (25.0%)	20 (34.5%)	0.433
Tumors, *n* (%)	3 (15.0%)	3 (5.2%)	0.155
Abnormal EEG findings, *n* (%)	14 (87.5%)	31 (68.9%)	0.146
Slow activity, *n* (%)	10 (62.5%)	20 (44.4%)	0.215
IEDs, *n* (%)	4 (25.0%)	11 (24.4%)	0.965
Abnormal MRI findings, *n* (%)	14 (73.7%)	34 (58.6%)	0.240
T-plus, *n* (%)	10 (52.6%)	28 (48.3%)	0.742
Extra-T, *n* (%)	2 (10.5%)	7 (12.1%)	0.856
Both, *n* (%)	8 (42.1%)	17 (29.3%)	0.301
Days between initiation of immunotherapy and onset, days, median [IQR]	9 [7-13]	11 [5-16]	0.643
MRS scores at onset, median [IQR]	3 [1-4]	2.5 [1-4]	0.460
MRS scores at discharge, median [IQR]	2 [1-3]	1 [0-3]	0.067

Abbreviations: FBDS: faciobrachial dystonic seizures; ASMs: antiseizure medications; CSF: cerebrospinal fluid; EEG: electroencephalogram; MRI: magnetic resonance imaging; MRS: modified Rankin Scale; IEDs: interictal epileptiform discharges; T: temporal.

[24]. AE patients with acute symptomatic seizures probably achieve seizure free after immunotherapy, referring to acute symptomatic seizures secondary to AE, but also possibly finally develop to "autoimmune encephalitis-associated epilepsy." It is worthwhile to study the potential risk factor for persistent enduring predisposition to seizures, autoimmune encephalitis-associated epilepsy. Although many previous studies had reported several risk factors for poor seizure outcomes in antibody-positive AE patients, they excluded antibody-negative. Matricardi et al. found that

Table 5: Multivariable logistic regression analysis of related factors for poor seizure outcomes in AE patients.

Variables	OR (95% CI)	*P* values
Age at onset	1.043 (1.003-1.084)	0.034
Focal nonmotor seizure type	0.131 (0.021-0.797)	0.027
Drug resistance to ASMs during the acute phase	0.590 (0.078-4.445)	0.609
The number of ASMs during the acute phase	1.013 (0.554-1.854)	0.965
The number of associated symptoms at onset	1.355 (0.737-2.492)	0.328
Short-term memory deficits	0.272 (0.068 -1.083)	0.116
MRS scores at discharge	1.328 (0.856-2.061)	0.206

Abbreviations: ASMs: antiseizure medications; MRS: modified Rankin Scale.

the prevalence of enduring seizures after the acute phase of antibody-negative AE was higher than antibody-positive AE [9]. Therefore, we concentrated on seizures in both antibody-positive and antibody-negative AE patients.

In AE, seizures should mostly be considered acute symptomatic and transient, and 88% of AE patients with neuronal surface-antibody positive could reach seizure freedom [4]. Our results showed that 74.4% of AE patients with acute symptomatic seizures finally achieved seizure freedom and confirmed the high prevalence of favorable seizure outcomes in AE. Moreover, our results suggested that older onset age and focal nonmotor seizure type were independent risk factors for autoimmune encephalitis-associated epilepsy. Onset age was probably associated with seizure outcomes in AE, and previous research suggested that seizures in young patients with anti-NMDAR encephalitis present self-limited [25]. However, the relationship between seizure type and seizure outcomes was not definitely clear, we speculated that specific origin of epileptogenic foci might be involved in the development of persistent seizures in AE. The importance of early immunotherapy in patients with seizures secondary to AE had been repeatedly emphasized [3, 5, 13, 26, 27]. Therefore, our findings provide an informative perspective to clinicians, as well as potentially participating in making a strategic practical decision. Due to the possibility of developing into autoimmune-associated epilepsy, onset age and seizure type should be highly appreciated when formulating the strategy for therapy at post-AE status.

There is still a lack of systematic review on risk of chronic epilepsy in AE patients. Several studies have suggested that the risk factors contributing to chronic epilepsy may include delayed immunotherapy [5], anti-GABABR encephalitis [25], the presence of antibodies against intracellular antigens [28], IEDs [8], onset with seizure [3], statue epilepticus [3, 25], changes in consciousness, central hypoventilation and pneumonia [29], and cortical abnormalities [25]. However, these findings did not apply to our cohort.

This study has several limitations. First, all patients were retrospectively enrolled at a single center, regional selection bias and recall bias may consequently exist. Second, we did not measure the antibodies in antibody-positive AE patients during the follow-up period, and the relationship between antibody titre and seizure outcomes needs further investigations. Third, the sample sizes of several types of antibodies were small, such as anti-AMPAR/DPPXR/CASPR2 AE. Besides this, our spectrum of detection antibodies excluded those updated antibodies reported in the last several years, such as Kelch-like protein-11-related antibodies. Fourthly, we did not comprehensively consider the impact of immunotherapy pattern on seizure outcomes, given that a proportion of AE patients had been treated with immunosuppressive agent. Finally, we did not perform comprehensive cancer screening during follow-up, which might cause leaving out a part of cancer patients.

5. Conclusion

In conclusion, we fully described the detailed clinical characteristics of patients initially presented with seizures in AE. Moreover, in our AE cohort including antibody positive and negative, the results suggested that the younger and anti-GABABR-positive patients were more prone to onset with seizures. Compared with onset nonseizure group, AE patients who initially present with seizures had worse long-term neurological recovery. The role of the initial presentation played in prognosis of AE warrants further investigations. Significantly, older onset age and focal nonmotor seizure type were associated with enduring predisposition to seizures in AE patients; thus, it is urgent to explore an appropriate antiseizure therapeutic strategy.

Data Availability

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

Conflicts of Interest

The authors have no conflicts of interest or disclosures to declare.

Acknowledgments

This work was supported by two grants, one from the Hubei Technological Innovation Special Fund (CN) (Grant No. 2019ACA132) and the other from the Fundamental Research Funds for the Central Universities (Grant No. 2019kfyXKJC075).

Supplementary Materials

Supplemental Figure 1: the flow chart of this study. Supplemental Figure 2: the application of antiseizure medicines in AE patients onset with seizures. Supplemental Figure 3: the application of antiseizure medicines in AE patients onset with nonseizures. Supplemental Table 1: the clinical characteristics of seizures in AE patients onset with nonseizures. *(Supplementary Materials)*

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