Comparison of immunotherapy and prognosis of seizures caused by viral encephalitis and autoimmune encephalitis

Xianjun Zhang
The First Affiliated Hospital of Kunming Medical University
Yanbing Han (ynhyb@163.com)
The First Affiliated Hospital of Kunming Medical University
Xiaojuan Liu
First People's Hospital of Yunnan Province
Wenqiu Yang
The First Affiliated Hospital of Kunming Medical University
Ting Wang
The First Affiliated Hospital of Kunming Medical University
Liang Zhou
The First Affiliated Hospital of Kunming Medical University
Wufeng Yang
Dali Bai Autonomous Prefecture People's Hospital
Jinrong Ya
The Fifth Affiliated Hospital of Kunming Medical University
Shitao Wang
The First Affiliated Hospital of Kunming Medical University
Qian Wu
The First Affiliated Hospital of Kunming Medical University

Research Article

Keywords: viral encephalitis, autoimmune encephalitis, epileptic seizures, glucocorticoid, immunoglobulin

Posted Date: May 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-496349/v1

Abstract

Background: The immunotherapy that is more effective for seizures caused by viral encephalitis and autoimmune encephalitis and the long-term use of anti-epileptic drugs is not clear. We aimed to compare the immunotherapy and prognosis of seizures caused by viral encephalitis and autoimmune encephalitis.

Methods: Clinical data of 121 patients with seizures caused by viral encephalitis and autoimmune encephalitis diagnosed and treated in the two largest tertiary general hospitals in the Yunnan Province were retrospectively collected to compare the immunotherapy used. Dynamic follow-up was performed to observe seizures and the use of antiepileptic drugs.

Results: The seizure-free rates at 6 months and 12 months after the onset of viral encephalitis were 77.8% and 80.8%, respectively. In total, 79.1% of autoimmune encephalitis cases were seizure-free at 6 months after onset, and the seizure-free rate at 12 months was 91.9%. A total of 75.0% of viral encephalitis and 67.7% of autoimmune encephalitis patients discontinued antiepileptic drugs and were seizure-free at 12 months after onset. Patients with viral encephalitis treated with glucocorticoids alone had a lower risk of seizures after the acute phase than those treated with glucocorticoids combined with immunoglobulin ($P < 0.05$). The risk of seizures in patients with autoimmune encephalitis treated with glucocorticoids combined with immunoglobulin was lower than that in patients treated with glucocorticoids and immunoglobulin alone ($P < 0.05$).

Conclusions: Immunotherapy may improve the seizure prognosis of patients with acute encephalitis. The prognosis of seizures due to viral encephalitis may be determined as early as 6 months after onset, while the seizure outcome of autoimmune encephalitis is further improved 12 months after onset.

Introduction

Encephalitis has a high incidence and may lead to death and disability. Epileptic seizures are a common symptom of acute encephalitis and an important factor affecting its prognosis. The incidence of symptomatic seizures may be up to 70% or 50% in the acute phase of autoimmune encephalitis or viral encephalitis, and status epilepticus occurs in some patients [1-3]. Autoimmune encephalitis is gradually being recognized and valued. Immunotherapy is the main treatment for autoimmune encephalitis [4]. The application of immunotherapy and anti-epileptic drugs (AEDs) substantially improves the prognosis of autoimmune encephalitis, including symptomatic seizures [5-7]. In fact, immunotherapy, especially glucocorticoids, is sometimes used in acute viral encephalitis [8]. It was previously reported that viral encephalitis is mainly treated with antiviral therapy and can be supplemented with corticosteroid therapy [9,10,11]. However, whether immunotherapy has a positive effect on the prognosis of acute viral encephalitis and the conclusions of various studies are still inconsistent [12]. In addition, current research reports are mostly related to autoimmune encephalitis and childhood viral encephalitis. Our study observed and compared the clinical application of immunotherapy and the efficacy of epileptic seizure control in patients with new-onset epileptic seizures caused by viral encephalitis and autoimmune encephalitis. Prognostic research on symptomatic seizures can help identify good prognosis, avoid unnecessary use of anti-epileptic drugs for too long, guide early intervention measures, and improve prognosis.

Methods

Patient selection

Using "autoimmune encephalitis", "viral encephalitis", "Anti-N-methyl-D-aspartate Receptor (anti-NMDAR) encephalitis", "Anti-Leucine-rich Glioma-inactivated Protein1(anti-LGI1) encephalitis", and "limbic lobe encephalitis" as the search terms, we queried the two largest tertiary general hospitals in the Yunnan Province in Southwest China (The First Affiliated Hospital of Kunming Medical University and The First People's Hospital of Yunnan Province) from June 2010 to June 2019 in the hospital medical record systems. The included patients met the following criteria: (1) clinical manifestations, inflammatory cerebrospinal fluid(CSF), Magnetic resonance imaging(MRI) characteristics suggesting inflammation, or serum and/or CSF autoimmune encephalitis antibody test results meeting the diagnosis of autoimmune encephalitis or viral encephalitis [3,13]; (2) seizures; and (3) use of immunotherapy. The exclusion criteria included a history of epileptic seizures or the presence of brain trauma, tumours, vascular diseases and other diseases that may cause seizures. Demographic information (sex, age), main clinical manifestations in the acute phase (first symptom, fever, disturbance of consciousness, abnormal mental behaviour, type of seizures, status epilepticus), brain MRI results, intensive care unit (ICU) admission, AEDs and the immunotherapy programme of each patient were collected. The types of seizures were divided into tonic-clonic seizures and focal seizures [6]. In this study, the patients were divided into viral encephalitis and autoimmune encephalitis. Informed consent was obtained from the research subjects.

Immunotherapy

The immunotherapy drugs used were glucocorticoids (methylprednisolone, dexamethasone, prednisone) and intravenous immunoglobulin (5 days, 0.4 g/kg/day). There were no second-line immunotherapy drugs. Immunotherapy was divided into only glucocorticoids and only immunoglobulin and glucocorticoids combined with immunoglobulin. According to dexamethasone 0.75 mg = prednisone 5 mg = methylprednisolone 4 mg, all glucocorticoid doses were converted into equivalent methylprednisolone. The maximum dose of methylprednisolone $\geq$500 mg/day was defined as high-dose methylprednisolone, and <500 mg/day was defined as non-high-dose methylprednisolone.

Follow up

Epileptic seizures and AED administration at 6 and 12 months after onset were obtained by telephone or outpatient follow-up. During the follow-up period, if the patient and their relatives or specialists did not find any clinical symptoms (including aura) of seizures (focal or generalized seizures), it was defined as seizure-free [6].

Data analysis

SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software, San Diego, California USA) were applied for the statistical analyses. The continuous variables did not follow a normal distribution and were described as the medians (P25, P75). The Mann-Whitney U rank sum test was used for comparisons between two groups. The Pearson chi-square or Fisher’s exact test was used to evaluate differences in the categorical variables, described by n (%). Binary logistic regression was used to analyse the risk factors for seizures at 6 and 12 months after onset. The test level was 0.05, and $P < 0.05$ indicated a statistically significant difference.

Results

Demographics and baseline characteristics

The baseline characteristics of all included patients and diagnostic subgroups are shown in Table 1. Overall, 121 patients were enrolled, including 54 males and 67 females. The average age of onset was 32.3±15.1 years. There were 62 patients (51.2%) with fever, 59 patients (48.8%) with abnormal mental behaviour, and 35 patients (28.9%) with consciousness disorder. Forty-five patients (37.2%) had epileptic seizures as the first symptom. Ninety-five patients (78.5%) presented with tonic-clonic seizures, and 27 patients (22.3%) developed status epilepticus. Eighty-six patients (71.1%) had abnormal brain MRI reports, and 41 patients (33.9%) were admitted to the ICU. The vast majority (90.9%) of patients were treated with AEDs during hospitalization, and 57.9% of patients were treated with single AEDs, such as levetiracetam, valproate, and oxcarbazepine, to control their seizures.

According to the diagnosis, there were 54 patients (44.6%) in the viral encephalitis group and 67 patients (55.4%) in the autoimmune encephalitis group. There were no significant differences between the two groups in terms of demographic characteristics, most clinical manifestations in the acute phase, abnormal MRI rate or ICU admission rate.

Compared with the autoimmune encephalitis group, the viral encephalitis group had relatively fewer mental and behavioural abnormalities (P = 0.021), manifested as focal seizures (P = 0.001), and they developed status epilepticus (SE) (P = 0.008) at a lower rate. Nine patients in the viral encephalitis group were not treated with AEDs to control seizures, and fewer patients were treated with AEDs in combination than those in the autoimmune encephalitis group (20.4% vs 43.3%, P = 0.003).

Table 1 Baseline characteristics of acute encephalitis

Characteristics	Total (n=121)	Viral encephalitis (n=54)	Autoimmune encephalitis (n=67)	*F* value
Sex (Male)	54 (44.6)	28(51.9)	26(38.8)	0.151
Age (years)				0.064
0-17	26(21.5)	7(13.0)	19(28.4)	
18-40	58(47.9)	26(48.1)	32(47.8)	
40-70	37(30.6)	21(38.9)	16(23.9)	
Fever	62(51.2)	30(55.6)	32(47.8)	0.394
Consciousness disorder	35(28.9)	13(24.1)	22(32.8)	0.291
Abnormal mental behaviour	59(48.8)	20(37.0)	39(58.2)	0.021*
Seizures as the first symptom	45(37.2)	17(31.5)	28(41.8)	0.243
Types of seizures				0.001*
Tonic-clonic seizure	95(78.5)	50(92.6)	45(67.2)	
Focal seizure	26(21.5)	4(7.4)	22(32.8)	
SE	27(22.3)	6(11.1)	21(31.3)	0.008*
Brain MRI abnormal	86(71.1)	41(75.9)	45(67.2)	0.291
ICU	41(33.9)	18(33.3)	23(34.3)	0.908
AEDs				0.003*
One AED	70(57.9)	34(63.0)	36(53.7)	
≥Two AEDs	40(33.1)	11(20.4)	29(43.3)	
No AED	11(9.1)	9(16.7)	2(3.0)	
Immunotherapy				0.001*
Only glucocorticoids	50(41.3)	35(64.8)	15(22.4)	
Only immunoglobulin	8(6.6)	3(5.6)	5(7.5)	
Glucocorticoids and immunoglobulin	63(52.1)	16(29.6)	4 7(70.1)	

p values derived from Chi-square test, data presented as n (%). p values < 0.05 are given in *.

SE status epilepticus, *MRI* magnetic resonance imaging, *ICU* intensive care unit, *AED* antiepileptic drug

Immunotherapy

All patients received immunotherapy with first-line drugs. Glucocorticoids were administered to 113 patients (93.3%), of whom 50 (41.3%) were treated alone and 63 (52.1%) with combination immunoglobulin. Only 8 patients (6.6%) received immunoglobulin alone. Compared with autoimmune encephalitis, there were significantly more patients treated with glucocorticoids alone in the viral encephalitis group (64.8% vs 22.4%) and significantly fewer patients treated with glucocorticoids in combination with immunoglobulin (29.6% vs 70.1%). There were statistically significant differences between the two groups in terms of immunotherapy for encephalitis ($P < 0.001$) (Table 1). Patients in the viral encephalitis group received adjuvant corticosteroids, most of which were dexamethasone, prednisolone, or methylprednisolone <500 mg/day (42/51, 82.4%), and only nine patients received high-dose methylprednisolone. Patients in the autoimmune encephalitis group were mostly treated with intravenous pulses of high-dose methylprednisolone (44/62, 71.0%). The median dose of methylprednisolone was 106 mg/day in the viral encephalitis group and 500 mg/day in the autoimmune encephalitis group ($P < 0.001$) (Figure 1).

Follow-up results

At the follow-up 6 months after onset, 95 of the 121 patients (78.5%) with encephalitis were seizure-free, 53 (43.8%) continued to take AEDs, and 61 (50.4%) had no seizures after discharge and no seizures after discontinuation of AEDs. There were no statistically significant differences in the seizure-free rate (77.8% vs 79.1%) or AEDs rate (35.2% vs 50.7%) between the viral encephalitis group and the autoimmune encephalitis group ($P > 0.05$). A total of 61.1% of patients with viral encephalitis achieved discontinuation of AEDs without seizures, which was significantly higher than that of the autoimmune encephalitis group (41.8%) ($P = 0.009$) (Table 2).

A total of 26 (21.4%) of these patients with encephalitis still had seizures at 6 months after onset (Figure 2a); 19 were still taking AEDs, with a drug taking rate of 73.1%, which was significantly higher than the 35.8% taking rate of 95 patients without seizures ($P = 0.001$). The same trend was observed in the viral encephalitis and autoimmune encephalitis groups (Figure 2b).

A total of 56.2% of encephalitis patients (including 35 viral encephalitis and 33 autoimmune encephalitis) had withdrawn AEDs at 6 months after onset. The seizure-free rate among these patients was 89.7%, higher than the 64.2% rate among the 53 patients who took AEDs. Moreover, 33 (94.3%) patients with viral encephalitis and 28 (84.8%) patients with autoimmune encephalitis experienced remission of seizures after discharge, and there was no statistically significant difference between the two groups ($P > 0.05$) (Figure 2c).

Table 2 Seizure control and antiepileptic drug administration during follow-up of acute encephalitis

		Viral encephalitis	Autoimmune encephalitis	χ^2	*P* value
seizure-free	6 month	42(77.8)	53(79.1)	0.031	0.860
	12 month	42(80.8)	57(91.9)	3.086	0.079
	χ^2	34.479	-		
	P value	0.001*	[a]0.001*		
continue AED	6 month	19(35.2)	34(50.7)	2.941	0.086
	12 month	12(23.1)	20(32.3)	1.181	0.277
	χ^2	15.312	16.037		
	P value	0.001*	0.001*		
seizure-free and discontinue AED	6month	33(61.1)	28(41.8)	6.756	0.009*
	12 month	39(75.0)	42(67.7)	5.976	0.015
	χ^2	26.567	22.776		
	P value	0.001*	0.001*		

p values derived from Chi-square test. [a]*p* values derived from Fisher's test, *p* values < 0.05 are given in * . data presented as n (%). *AED* antiepileptic drug.

After 12 months, 4 patients were lost to follow-up, and 3 died of myocardial infarction or accident. In total, 114 patients, including 52 with viral encephalitis and 62 with autoimmune encephalitis, were followed up. Ninety-nine (86.8%) patients with encephalitis were seizure-free. The seizure-free rate of the autoimmune encephalitis group (57 patients, 91.9%) was higher than that of the viral encephalitis group (42 patients, 80.8%), but the difference between the two groups was not statistically significant (P > 0.05). The overall rate of taking AEDs was reduced to 28.1% (32 patients). The rate of taking in the viral encephalitis group (12 patients, 23.1%) was similar to that of the autoimmune encephalitis group (20 patients, 32.3%), and they all took only one AED. In this period, the rate of discontinuation of AEDs without seizures in the viral encephalitis group (75.0%) was higher than that in the autoimmune encephalitis group (67.7%), and the difference was statistically significant (P = 0.015) (Table 2).

By 12 months after onset, the epileptic seizure rate of encephalitis had dropped to 13.2%, 19.2% for viral encephalitis and 8.1% for autoimmune encephalitis (Figure 2a). Of the 15 patients who still had seizures (10 with viral encephalitis and 5 with autoimmune encephalitis), only one (6.7%) patient did not continue to take AEDs. Among those who were seizure-free, the rate of continued use of AEDs was reduced to 18.2% (18 patients), with only 3 (7.1%) patients with viral encephalitis and 15 (26.3%) patients with autoimmune encephalitis continuing to take AEDs (Figure 2b). The seizure-free rate of patients with autoimmune encephalitis and viral encephalitis who stopped taking AEDs was 100% and 97.5%, respectively, both of which were significantly higher than those in the continuing group (Figure 2c).

The seizure-free rates of viral encephalitis and autoimmune encephalitis at 12 months after onset were higher than those at 6 months after onset. The difference in seizures between the two follow-up periods was statistically significant (P < 0.001). Meanwhile, the rate of AED use at 12 months was lower than that at 6 months (P < 0.001). In addition, 6 new patients with viral encephalitis and 14 patients with autoimmune encephalitis achieved discontinuation of AEDs without seizures 12 months after the onset of disease, except for the 61 patients who had no seizures when the drug was stopped at the follow-up 6 months after the onset of the disease. Thus, 81 patients (71.1%) were seizure-free after the drug was stopped, and the drug was successfully withdrawn. There was a statistically significant difference in the seizure-free rate after AED withdrawal between the two follow-up

periods (P < 0.001) (Table 2). The prognosis of epileptic seizures at 12 months after onset was better than that at 6 months.

Demographic and acute phase characteristics and prognosis of epileptic seizures in viral encephalitis and autoimmune encephalitis

The relationships between the prognosis of seizures with viral encephalitis and autoimmune encephalitis and demographic information, clinical symptoms in the acute phase, and treatment were assessed (Table 3). Univariate analysis showed that fever in the acute phase (P = 0.026, OR 11.7 95% CI 1.4-101.1) affected the prognosis of epileptic seizures 6 months after the onset of viral encephalitis, while admission to the ICU and glucocorticoid therapy alone were correlated with the prognosis of epileptic seizures at 6 and 12 months (P < 0.05). Immunotherapy was related to the prognosis of epileptic seizures at 6 and 12 months after the onset of autoimmune encephalitis (P < 0.05) (Table 3).

The variables with P < 0.1 in the univariate analysis of the two groups of encephalitis as well as SE and ICU were included in the binary logistic regression analysis. The results showed that fever was the only risk factor for a poor prognosis of epileptic seizures after 6 months of viral encephalitis. Patients with fever were 9.5 times more likely to have seizures 6 months after onset than those without fever (P = 0.043, OR 9.5 95%CI 1.1-84.5). Patients with viral encephalitis treated with glucocorticoid alone had a lower risk of seizures after 12 months than those treated with glucocorticoids combined with immunoglobulin (P = 0.006, OR 0.95% CI 0.0-0.5) (Table 4).

Multivariate regression analysis showed that immunotherapy could affect the outcome of autoimmune encephalitis epileptic seizures. The risk of epileptic seizures in patients treated with glucocorticoids alone at 6 months and 12 months was 5.6 times and 13.5 times higher than that in patients treated with glucocorticoids combined with immunoglobulin, respectively (P = 0.015, OR 5.6 95%CI 1.4-22.4; P = 0.031, OR 13.5 95%CI 1.3-143.6). Patients treated with immunoglobulin alone were 12.6 times more likely to have seizures at 6 months than those treated with glucocorticoid combined with immunoglobulin (P = 0.014, OR 12.6 95%CI 1.7-94.5) (Table 4).

Table 3 Univariate analysis the factors associated with the prognosis of seizures

Variable	Viral encephalitis			Autoimmune encephalitis			
	6 month	12 month		6 month		12 month	
	OR(95%CI) P value	OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value
Sex (Male)	0.6(0.2-2.2) 0.426	1.7(0.4-6.7)	0.484	0.8(0.2-2.7)	0.727	0.9(0.1-5.7)	0.889
Age≥17 years[a]	0.8(0.3-2.3) 0.737	1.6(0.5-4.5)	0.418	0.7(0.3-1.5)	0.325	1.4(0.4-4.9)	0.629
Fever	13.3(1.6-112.7) 0.017*	4.4(0.8-23.2)	0.081	1.6(0.5-5.3)	0.432	4.8(0.5-45.4)	0.174
Consciousness disorder	0.6(0.1-3.0) 0.500	1.4(0.3-6.3)	0.685	1.2(0.3-4.0)	0.797	0.5(0.0-4.4)	0.503
Abnormal mental behaviour	0.8(0.2-3.1) 0.763	1.8(0.4-7.2)	0.408	2.1(0.6-7.4)	0.265	3.1(0.3-29.7)	0.322
Seizures as the first symptom	0.4(0.1-1.9) 0.223	0.2(0.0-1.7)	0.144	1.1(0.3-3.5)	0.928	2.1(0.3-13.3)	0.447
Tonic-clonic seizures	1.2(0.1-12.5) 0.890	1.4(0.1-15.6)	0.762	2.5(0.8-8.5)	0.131	0.5(0.1-5.2)	0.595
SE	0.7(0.1-6.4) 0.730	0.8(0.1-7.9)	0.866	0.8(0.2-3.1)	0.802	0.6(0.1-5.7)	0.646
Brain MRI abnormal	4.4(0.5-37.9) 0.178	3.6(0.4-31.6)	0.248	0.9(0.2-2.9)	0.797	2.0(0.2-19.2)	0.548
ICU	6.4(1.6-25.8) 0.009*	8.6(1.8-39.9)	0.006*	0.5(0.1-1.8)	0.261	0.5(0.0-4.4)	0.503
AEDs				0.6(0.2-1.7)	0.310	0.7(0.1-4.1)	0.728
≥Two AEDs[b]	2.2(0.5-9.7) 0.296	1.8(0.2-17.0)	0.618				
No AED[b]	0.5(0.1-4.5) 0.523	3.4(0.3-40.9)	0.330				
Only glucocorticoids[c]	0.2(0.1-0.8) 0.027*	0.1(0.0-0.5)	0.006*	5.6(1.4-22.4)	0.015*	13.5(1.3-143.6)	0.031*
Only immunoglobulin[c]	0.0(0.0-) 0.999	0.0(0.0-)	0.999	12.6(1.7-94.5)	0.014*	22.5(1.0-505.8)	0.050
High-dose methylprednisolone	0.3(0.1-1.4) 0.115	0.2(0.0-1.0)	0.060	1.5(0.4-6.0)	0.556	0.8(0.1-8.4)	0.862

p values < 0.05 are given in *. *SE* status epilepticus，MRI magnetic resonance imaging，*ICU* intensive care unit，*AED* antiepileptic drug .

The reference category of: a,17 years old; b, One *AED*; c, glucocorticoids combined immunoglobulin.

Table 4 Multivariate analysis the factors associated with the prognosis of seizures

Variable	Viral encephalitis			Autoimmune encephalitis			
	6 month	12 month		6 month		12 month	
	OR(95%CI) P value	OR(95%CI)	P value	OR(95%CI)	P value	OR(95%CI)	P value
fever	9.5(1.1-84.5) 0.043*	-	-	-	-	-	-
only glucocorticoids[c]	-	0.1(0.0-0.5)	0.006*	5.6(1.4-22.4)	0.015*	13.5(1.3-143.6)	0.031*
only immunoglobulin[c]	-	-	-	12.6(1.7-94.5)	0.014*	-	

p values < 0.05 are given in *.
The reference category of *c* was glucocorticoids combined immunoglobulin.

Acute immunotherapy programmes and prognosis of epileptic seizures in autoimmune encephalitis

Patients with autoimmune encephalitis received three immunotherapy programmes in the acute phase, and there were differences in the prognosis of epileptic seizures within 12 months of onset. The rate of achieving seizure-free AEDs in patients treated with glucocorticoids alone and immunoglobulin alone in the acute phase was 60.0% (9/15, 6 of the 9 (66.7%) discontinued AEDs) and 40.0% (2/5, 1 of the 2 (50%) discontinued AEDs), respectively, and the rate of seizure-free AEDs in patients who received glucocorticoids combined with immunoglobulin therapy reached 89.4% (42/47, 21 of the 42 (50.0%) discontinued AEDs) (Figure 3a). There were statistically significant differences in seizure-free status among the three different immunotherapies (P = 0.004), and there were no statistically significant differences in AED administration at follow-up among the three immunotherapies (P = 0.657 > 0.05).

At 12 months, the seizure-free rate of patients treated with glucocorticoids alone and immunoglobulin alone was 76.9% (10/13, 7 of the 10 (70.0%) discontinued AEDs) and 66.7% (2/3, 1 of the 2 (50%) discontinued AEDs), respectively, and the seizure-free rate of patients treated with the immunotherapy combination was as high as 97.8% (45/46, 34 of the 45 patients (75.6%) stopped taking antiepileptic drugs) (Figure 3a). There were statistically significant differences in seizure-free status among the three different immunotherapy programmes at 12 months (P = 0.014), and there were no significant differences in the AEDs taken during follow-up among the three immunotherapies (P = 0.143 > 0.05).

Prognosis of epileptic seizures in acute fever and AEDs and viral encephalitis during follow-up

Thirty patients (55.6%) in the viral encephalitis group had fever during the acute period. A total of 63.6% (19/30, 16 of 19 patients (84.2%) discontinued AEDs) of patients with viral encephalitis who had acute fever achieved seizure-free status at 6 months, which was significantly lower than the 95.8% of patients without fever (23/24, 17 of 23 patients (73.9%) did not take AEDs for a long time) (Figure 3b). There was a statistically significant difference in the prognosis of epileptic seizures at 6 months after the onset of disease (P = 0.004), and there was no significant difference in the use of AEDs during follow-up (P = 0.407 > 0.05). A total of 71.4% (20/28, 18 out of 20 (90.0%) of those without AEDs) of patients with fever achieved seizure-free status at 12 months after onset, which was still lower than the 91.7% (22/24, 21 of 22 patients (95.5%) who discontinued AEDs) of patients without fever (Figure 3b). At this time, there was no statistically significant difference in the prognosis of epileptic seizures between patients with fever and those without fever (P = 0.135 > 0.05).

Discussion

For the first time, we compared the prognosis of symptomatic seizures in acute viral encephalitis and autoimmune encephalitis under different immunotherapies. Patients with viral encephalitis are mostly treated with non-high-dose glucocorticoid monotherapy, while patients with autoimmune encephalitis are mainly treated with high-dose methylprednisolone combined with immunoglobulin. After discharge, the epileptic seizures of patients with both viral encephalitis and autoimmune encephalitis were gradually controlled over time, and the demand for AEDs was gradually reduced, with most patients, particularly those with autoimmune encephalitis, successfully withdrawing AEDs within 12 months. Immunotherapy can improve the prognosis of symptomatic seizures caused by acute autoimmune encephalitis, as well as acute viral encephalitis. Patients with autoimmune encephalitis treated with combined glucocorticoids and immunoglobulin and patients with viral encephalitis treated with glucocorticoids alone have a better prognosis for symptomatic seizures. This study will be helpful for optimizing the treatment strategy of symptomatic epileptic seizures caused by acute autoimmune and viral encephalitis and shortening the course of unnecessary AEDs.

In our study, 13.2% of patients with acute viral and autoimmune encephalitis still had seizures, and 28.1% insisted on taking AEDs. Moreover, these patients only needed to receive a single AED treatment 12 months after onset. Compared with some previous studies on similar causes of encephalitis, our study showed a better prognosis of seizures and a lower dependence rate of AEDs [14,15]. Singh defined post-encephalitis epilepsy patients as those who had taken AEDs for more than 12 months, with a median follow-up time of 43 months. Overall, 29.9% of patients with acute encephalitis developed post-encephalitis epilepsy, while 46.3% of patients with symptomatic seizures in the acute phase of encephalitis developed post-encephalitis epilepsy and required long-term medication [14]. In another study on the seizure prognosis of infective and autoimmune encephalitis in children, 21% of children with acute encephalitis developed post-encephalitis epilepsy, 10% had drug-resistant epilepsy, and 15% needed long-term antiepileptic drugs after a follow-up time ≥24 months [15]. All these studies were followed up for longer than 12 months, and the seizure rate during follow-up was higher than that in our study. In terms of the specific causes of encephalitis, 20.9% of patients with autoimmune encephalitis had seizures 6 months after onset, while only 8.1% of patients had seizures at 12 months after onset, which was similar to that in the study of seizures caused by autoimmune encephalitis [6]. In a study of post-encephalitis epilepsy in children in Taiwan, 35.3% of children with herpes simplex encephalitis and 60.0% of children with Japanese encephalitis virus developed post-encephalitis epilepsy during a follow-up period of 1.5 to 18.4 years [16]. In our study, only 19.2% of the patients with viral encephalitis still had seizures 12 months after onset. In our study, symptomatic seizures may have had a better prognosis because the subjects of our study were mainly adults. In contrast, the central nervous system of children has not yet been fully developed, and the outcome of epileptic seizures after encephalitis may be different from that of adults. In addition, in the Taiwan cohort, viral encephalitis with poor prognosis was the predominant aetiological encephalitis. Most importantly, our subjects were all treated with immunotherapy. Glucocorticoids contribute to the control of epileptic seizures [17,18], especially those associated with inflammation [19]. Children with herpes simplex viral encephalitis who are treated with glucocorticoids can be free of seizures after treatment [20]. After statistical analysis, our results showed that immunotherapy has a positive effect on the prognosis of epileptic seizures caused by viral and autoimmune encephalitis. Immunotherapy can therefore improve the prognosis of autoimmune-related seizures [21-23].

We compared the outcomes of symptomatic seizures with different immunotherapies. We found that patients with viral encephalitis treated with glucocorticoids alone had a better prognosis for seizures at 12 months after onset than those treated with glucocorticoids combined with immunoglobulin. Patients with symptomatic seizures caused by autoimmune encephalitis often use glucocorticoids combined with immunoglobulin in the acute phase, and glucocorticoids are used to suppress immune inflammation at high doses. The statistical results showed that the prognosis of symptomatic seizures treated with glucocorticoids combined with immunoglobulin was better than that treated with glucocorticoids or immunoglobulin alone.

In our study, patients with viral encephalitis had similar seizure rates at 6 months and 12 months after onset. However, patients with autoimmune encephalitis had significantly lower seizure rates at 12 months after onset than at 6 months. Therefore, we hypothesize that the duration of the acute phase of viral encephalitis is shorter than that of autoimmune encephalitis and that the rate of symptomatic seizures largely does not change after the acute phase. We speculate that most patients without risk factors for post-encephalitis epilepsy may not need long-term AED after 6 months of viral encephalitis onset.

Patients with acute epileptic seizures, epileptic status, abnormal electroencephalography (EEG) or admission to the ICU are at increased risk of epilepsy after the acute phase [15,16,24,25]. Our study found that acute fever is a risk factor for seizures in patients with viral encephalitis 6 months after onset. Fever can induce seizures in the acute phase of encephalitis [26,27], and the proinflammatory response of the brain caused by seizures can also cause fever. This process forms a vicious cycle, resulting in the recurrence or aggravation of seizures. Previous studies have shown that epilepsy in some patients after the acute phase of encephalitis is resistant to drugs, and patients are prone to developing drug-refractory epilepsy [28,29]. In this study, fever in the acute phase was a risk factor for poor prognosis of epileptic seizures in patients with viral encephalitis; thus, it is necessary to be cautious in the discontinuation of AEDs in such patients. Rismanchi proposed that children who require AEDs when discharged from the hospital were more likely to develop chronic epilepsy [30]. Statistically, we found that choosing whether to take AEDs for a long time was not the main factor affecting the prognosis of epileptic seizures. Long-term use of AEDs in patients with encephalitis led to a higher seizure rate than in those who stopped taking AEDs. This finding does not prove that long-term AEDs are a risk factor for seizures. Instead, the risk may be due to poor seizure control in patients with encephalitis and the need for long-term use of AEDs.

In this study, the identification rate of viral pathogens of viral encephalitis was relatively low, and the antibody types of some patients with autoimmune encephalitis were not completely determined. Clinical diagnosis and treatment were mainly based on clinical symptoms, blood, cerebrospinal fluid, and MRI. For patients with acute epileptic seizures who are clinically diagnosed with viral encephalitis or autoimmune encephalitis, the viral pathogens and antibody types are not yet clear. In addition to actively looking for the specific cause of encephalitis, we suggest that immunotherapy may be given in the acute phase as appropriate. Viral encephalitis can be treated with anti-inflammatory non-high-dose glucocorticoids, but the prognosis of seizures in patients with acute fever is poor. Patients should be followed up to observe the epileptic seizures, and targeted and personalized AED guidance should be given. Patients with autoimmune encephalitis are given high-dose glucocorticoids combined with immunoglobulin therapy in the acute period to improve the prognosis of symptomatic epileptic seizures. During immunotherapy, attention should be paid to the side effects of drugs.

However, this study also has some deficiencies. First, it was a retrospective observational cohort study, which may have partial recall bias. In addition, due to the limitation of sample size, this study did not analyse the

subtypes of autoimmune encephalitis antibody type or viral encephalitis virus type. A prospective study with a larger sample size will be conducted in the future to supplement and verify the results.

Conclusion

Immunotherapy can be used in acute autoimmune encephalitis, as well as acute viral encephalitis. Patients with autoimmune encephalitis are usually treated with combined glucocorticoids and immunoglobulin in the acute period. Viral encephalitis is mainly treated with non-high-dose glucocorticoid adjuvant therapy. After immunotherapy for acute encephalitis, the prognosis of epileptic seizures of viral encephalitis may be determined as early as 6 months after onset, while the seizure outcome of autoimmune encephalitis will be further improved 12 months after onset.

Abbreviations

AEDs:Anti-epileptic drugs; Anti-NMDAR: Anti-N-methyl-D-aspartate Receptor; anti-LGI1:Anti-Leucine-rich Glioma-inactivated Protein 1; CSF: Cerebrospinal Fluid; EEG:Electroencephalography; ICU:Intensive Care Unit; MRI:Magnetic Resonance Imaging; SE:Status Epilepticus;

Declarations

Ethics approval and consent to participate This study followed the ethical principles of the conference of Helsinki. This study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Kunming Medical University. Informed consent was obtained from the research subjects.

Consent for publication Not applicable.

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

Funding This study was supported by the National Natural Science Foundation of China (81260199, 81660228, and 81601134), Yunnan Province Talent Training Program (2017HB048, L-2019019 and H-2018056), and the Yunnan Science and Research Funding Program (2017FA041 and 2018HC008). the funders□Yanbing Han is responsible for conceptualization ,data analysis and investigation, manuscript review.Qian Wu is responsible for data analysis and investigation.

Authors' contributions Conceptualization: XZ and YH; Data collection: XZ□XL□WY□TW□LZ□WY and JY; Data analysis and investigation: XZ□YH□XL□SW and QW; Funding acquisition: YH and QW; Manuscript preparation: XZ; Manuscript review: XZ and YH. The authors read and approved the final manuscript.

Acknowledgements We gratefully thank Congguo Jin from the Kunming Medical University Third Affiliated Hospital for providing statistical guidance.

References

1. Huang Q, Wu Y, Qin R, Wei X, Ma M.Clinical characteristics and outcomes between children and adults with anti-N-Methyl-D-Aspartate receptor encephalitis. J Neurol. 2016;263(12):2446-2455. https://doi.org/10.1007/s00415-016-8282-1.
2. Wesselingh R, Butzkueven H, Buzzard K, Tarlinton D, O'Brien TJ, Monif M. Seizures in autoimmune encephalitis: Kindling the fire. Epilepsia. 2020;61(6):1033-1044. DOI:10.1111/epi.16515.
3. Misra UK, Tan CT, Kalita J. Viral encephalitis and epilepsy. Epilepsia. 2008;49(s6):13-18. https://doi.org/10.1111/j.1528-1167.2008.01751.x.
4. Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. Neuro Oncol. 2014;16(6): 771-778. https://doi.org/10.1093/neuonc/nou030.
5. Titulaer MJ, Mccracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al.Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurology. 2013;12:157-165.https://doi.org/10.1016/S1474-4422(12)70310-1.
6. de Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, Bastiaansen AEM, Schreurs MWJ, Rouhl RPW, et al.Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABAR encephalitis. Neurology. 2019; 92: e2185-e2196. https://doi.org/10.1212/WNL.0000000000007475.
7. Spatola M, Novy J, Du PR, Dalmau J, Rossetti AO. Status epilepticus of inflammatory etiology: a cohort study. Neurology. 2015;85(5): 464-470. https://doi.org/10.1212/WNL.0000000000001717.
8. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4): 391-404.https://doi.org/10.1016/S1474-4422(15)00401-9.
9. Habel AH, Brown JK. Dexamethasone in herpes-simplex encephalitis. Lancet. 1972;1:695. https://doi.org/10.1016/s0140-6736(72)90505-3.
10. Skoldenberg B, Aurelius E, Hjalmarsson A, Sabri F, Forsgren M, Andersson B, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol. 2006;253:163-170. https: // doi. Org / 10.1007 / s00415-005-0941-6.
11. Kamei S, Sekizawa T, Shiota H, Mizutani T, Ityama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry. 2005;76:1544-1549. https://doi.org/10.1136/jnnp.2004.049676.
12. Tyler KL. Acute viral encephalitis. N. Engl. J. Med. 2018;379□6□: 557-566. https: // doi.org / 10.1056/NEJMra1708714.
13. Zuiani L , Graus F , Giometto B, Bien C, Vincent A. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry. 2012; 83(6):638-645. https://doi.org/10.1136/jnnp-2011-301237.
14. Singh TD, Fugate JE, Hocker SE, Rabinstein AA. Postencephalitic epilepsy: clinical characteristics and predictors. Epilepsia. 2015;56(1):133-138. https://doi.org/10.1111/epi.12879
15. Pillai SC, Mohammad SS, Hacohen Y, Tantsis E, Prelog K, Barnes EH, et al. Postencephalitic epilepsy and drug-resistant epilepsy after infectious and antibody-associated encephalitis in childhood: Clinical and etiologic risk factors. Epilepsia. 2016;57(1):e7-e11. https://doi.org/10.1111/epi.13253.
16. Lee WT, Yu TW, Chang WC, Shau WY. Risk factors for postencephalitic epilepsy in children: a hospital-based study in Taiwan. Eur. J. Paediatr. Neurol. 2007;11(5): 302-309. https: // doi. org / 10. 1016 /

j.ejpn.2007.02.011.

17. Sevilla-Castillo RA, Palacios GC, Ramirez-Campos J, Mora-Puga M, Diaz-Bustos R. Methylprednisolone for the treatment of children with refractory epilepsy. Neuropediatrics. 2009;40(06):265-268. https: // doi.org / 10. 1055/s-0030-1249653
18. Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. PLoS One. 2011;6(3):e18200. https://doi.org/10.1371/journal.pone.0018200.
19. Pantazou V , Novy J , Rossetti AO. Intravenous corticosteroids as an adjunctive treatment for refractory and super-refractory status epilepticus: an observational cohort study. CNS Drugs. 2019;33: 187-192. https://doi.org/10.1007/s40263-018-0600-y.
20. Maraş GH, Uyur YE, Sayan M, Bayhan A, Öncel S, Arısoy ES, et al.Clinical outcomes in children with herpes simplex encephalitis receiving steroid therapy. J. Clin. Virol. 2016;80: 87-92.https://doi.org/10.1016/j.jcv.2016.05.002
21. Byun JI, Lee ST, Jung KH, Sunwoo JS, Moon J, Lim JA, et al. Effect of immunotherapy on seizure outcome in patients with autoimmune encephalitis: a prospective observational registry study. PLoS One. 2016;11: e0146455. https://doi.org/10.1371/journal.pone.0146455.
22. Toledano M, Britton JW, McKeon A, Shin C, Lennon VA, Quek AML, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmuneepilepsy. Neurology. 2014;82: 1578-1586. https: // doi.org / 10.1212 / WNL.0000000000000383.
23. Irani SR , Stagg CJ , Schott JM, Rosenthal CR, Schneider SA, Pettingill P, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain.2013;136(10):3151-3162.https://doi.org/10.1093/brain/awt212.
24. Fowler A, Stödberg T, Eriksson M, Wickström R. Long-term outcomes of acute encephalitis in childhood. Pediatrics. 2010;126(4):e828-835. https://doi.org/10.1542/peds.2009-3188.
25. Chen YJ , Fang PC , Chow JC. Clinical characteristics and prognostic factors of postencephalitic epilepsy in children. Journal of Child Neurology. 2006;21(12):1047-1051.https://doi.org/10.1177/7010.2006.00223.
26. Sellner J , Trinka E. Seizures and epilepsy in herpes simplex virus encephalitis: current concepts and future directions of pathogenesis and management. J. Neurol. 2012;259(10):2019-2030. https://doi.org/10.1007/s00415-012-6494-6.
27. Baulac S, Gourfinkel-An I, Nabbout R, Huberfeld G, Serratosa J, Leguern E, et al. Fever, genes, and epilepsy. The Lancet Neurology. 2004;3(7):421-430.https://doi.org/10.1016/S1474-4422(04)00808-7.
28. Liu YO, Zhou WJ, Hong B, Zhao T, Wang YF. Surgical outcomes in patients with epilepsy after viral encephalitis: contribution of SEEG study. BMC Neurol. 2019;19(1):165. https : // org / 10.1186 / s12883 -019-1396-1.
29. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NWS, Hart IJ, et al. National Encephalitis Guidelines Development and Stakeholder Groups. Management of suspected viral encephalitis in adults–Association of British Neurologists and British Infection Association National Guidelines. J. Infect. 2012;64(4):347-373. https: // doi.org/10.1016/j.jinf.2011.11.014.
30. Rismanchi N, Gold JJ, Sattar S, Glaser CA, Sheriff H, Proudfoot J, et al. Epilepsy after resolution of presumed childhood encephalitis. Pediatr. Neurol. 2015;53: 65-72.https://doi.org/10.1016/j.pediatrneurol.2015.03.016.

Figures

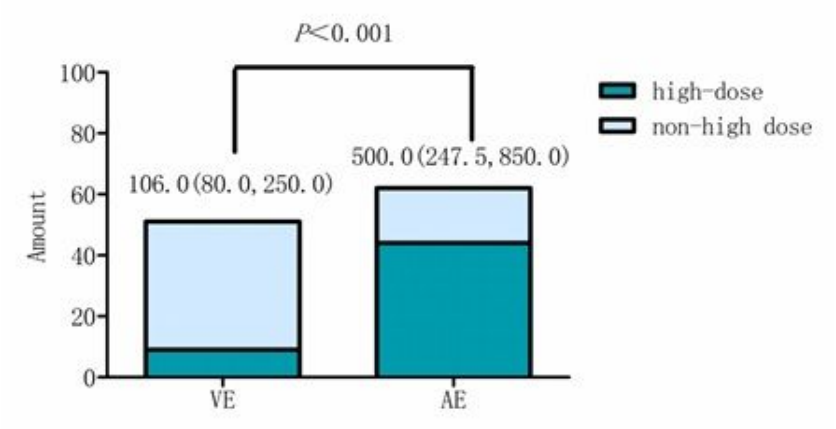

Figure 1

Glucocorticoids dose received at baseline in the viral encephalitis and autoimmune encephalitis VE viral encephalitis, AE autoimmune encephalitis. p values derived from Mann–Whitney U test. The glucocorticoids dose was expressed as the medians (P25, P75).

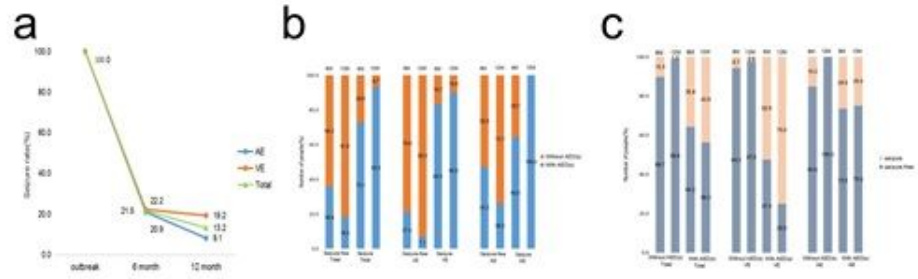

Figure 2

The seizure rate of acute encephalitis and subgroups in different periods (a); AEDs administration during the follow-up period based on the presence or absence of seizures (b); Seizure control during the follow-up period based on whether or not AEDs were taken (c) .M month;VE Viral Encephalitis, AE Autoimmune Encephalitis,AEDs antiepileptic drugs.

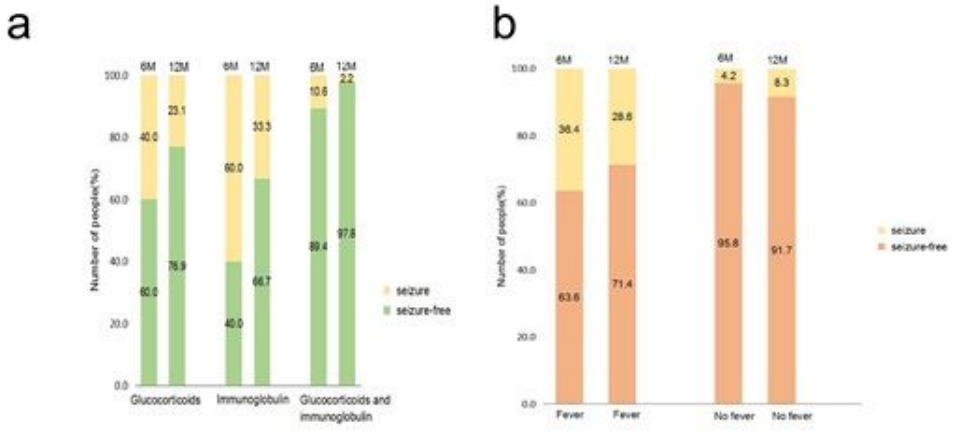

Figure 3

Acute immunotherapy and prognosis of seizures in patients with autoimmune encephalitis (a); prognosis of seizures in patients with acute fever and viral encephalitis (b) M month.