Seizure: European Journal of Epilepsy 72 (2019) 49–53

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Chronic post-encephalitic epilepsy following Japanese encephalitis: Clinical features, neuroimaging data, and outcomes

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ARTICLE INFO

Keywords:
Seizure
Japanese encephalitis
Post-encephalitc epilepsy

ABSTRACT

Purpose: Japanese encephalitis (JE), the main cause of viral encephalitis in Asia, usually presents with acute symptomatic seizures; however, there have been very few systematic reports regarding late unprovoked seizures and epilepsy. We aimed to describe the clinical features and outcomes of post-encephalitic epilepsy following JE.
Methods: Patients with epilepsy with a previous confirmed diagnosis of JE visiting West China Hospital from 2013 to 2019 were enrolled in the observational case-controlled study. Patients with epilepsy with a history of other non-specific viral encephalitis were enrolled as controls. For all enrolled subjects, disease related information was recorded.
Results: Forty-eight patients with JE (20 males; median age, 21.0 years; average epilepsy duration, 8.55 years) were identified. The median duration from JE to the first unprovoked seizure was 7.73 years, which significantly differed from that of the controls (7.73 vs. 2.69 years, respectively; $p = 4.59 \times 10^{-6}$). Most patients had focal epilepsy, and 29 (78.38%) were drug resistant. Among 45 patients with available neuroimaging data, three in fourth had no obvious abnormality, and the temporal lobe and hippocampus (22.22%) were the most affected brain regions. Six patients had surgery, and three achieved class-one seizure-free status.
Conclusion: The latency to the first unprovoked seizure was longer in patients with JE than controls. Regarding chronic epilepsy, three in four had structural abnormalities, and the long-term outcomes of post-encephalitic epilepsy following JE were poor. Surgery remains an option for drug-resistant epilepsy.

1. Introduction

Central nervous system (CNS) infections are one of the leading causes of acquired epilepsy [1]. Patients with encephalitis have a risk of developing seizures at the acute stage, as well as later developing unprovoked seizures [2]. It is well recognized that the risk of developing unprovoked seizures in these patients is 7–16 times higher compared to the general population [3,4], especially in those with Herpes simplex virus and Japanese encephalitis (JE), and the odds ratio of subsequent epilepsy was reported to be 8.06 for JE [5]. JE, the most common endemic viral cause of encephalitis, infects nearly 7 million people annually, mostly in South East Asia, though the number of cases is decreasing rapidly owing to the beneficial effects of vaccination. However, a large proportion of the population, especially children, living in the area remains endemic to JE [6].

Most studies on the neurological sequelae of JE have focused on neurocognitive impairments and movement disorders, and the development of epilepsy from JE is only reported on a case by case basis or described vaguely in different studies, and no systematic research on the topic is available [7,8]. Thus, the features and outcomes of late-onset epilepsy following JE are largely unknown. This study systematically reviewed the data of patients with a history of JE who developed epilepsy with the aim of providing the general clinical features and outcomes of post-JE epilepsy.

2. Materials and methods

2.1. Study design

The study was approved by the institutional review board of West China Hospital Sichuan University. All patients with JE-induced post-encephalitic epilepsy visiting the epilepsy clinic of West China Hospital

Abbreviations: JE, Japanese encephalitis; HS, hippocampal sclerosis; CNS, central nervous system; IgM, immunoglobulin M; MRI, magnetic resonance imaging; EEG, electroencephalography; ILAE, international league against epilepsy; AEDs, anti-epileptic drugs; VEEG, video electroencephalography

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https://doi.org/10.1016/j.seizure.2019.09.010
Received 5 May 2019; Received in revised form 17 September 2019; Accepted 20 September 2019

Table 1
Demographic and clinical features of the post-JE group and control group.

Characteristic	Post-JE group n = 48	Control group n = 51	*p*
Age (years)	21.0(16.0,26.0)	19.0(13.50,23.00)	0.006**
Sex (M/F)	20/28	30/21	0.088
Age at encephalitis (years)	4.00(2.85,6.00)	7.00(3.5,11.0)	0.116
Patient had symptomatic seizure at encephalitis(no.)	28	35	0.287
Latency to epilepsy (years)	7.73 ± 6.43	2.69 ± 3.57	4.59×10^{-6}**
Epilepsy duration (years)	8.55 ± 7.11	6.75 ± 6.29	0.186
Seizure type (focal/generalized/unknown)	44/2/2	46/5/0	0.198
Patient had status epilepticus during late onset epilepsy (no.)	3	0	0.070
Neuroimaging (normal/abnormal/NA)	12/33/3	14/36/1	0.550
Drug-resistant	29/37	30/42[a]	0.620

Age and age at encephalitis are shown in median (interquartile range). Sex, patient had symptomatic seizure at encephalitis, seizure type, patient had status epilepticus during late onset epilepsy, neuroimaging, drug-resistant are shown in number. Latency to epilepsy and epilepsy duration are shown in means (standard deviations).

JE: Japanese encephalitis; NA: not available. *P < 0.05; **P < 0.01.

[a] represents the ratio of patients with uncontrolled seizure under at least 2 standardized regimens.

from January 2013 to February 2019 were asked to participate in the observational case-controlled study, and written informed consent was obtained after the enrollment. Epilepsy was diagnosed per the International League Against Epilepsy (ILAE) criteria [9]. Previous JE encephalitis was confirmed by its definitive diagnosis in previous medical records by a positive immunoglobulin M (IgM) antibody to the JE virus in serum or cerebrospinal fluid, as well as the patient being from a known JE endemic area during the mosquito biting season or visiting a JE epidemic area within 25 days before symptom onset. Exclusion criteria for this study were as previously described [10,11]: (1) epilepsy prior to encephalitis; (2) infection following surgical procedures; (3) brain abscesses; (4) chronic encephalitis; (5) other concomitant risk factors for epilepsy, including febrile seizures without evidence of central nervous system (CNS) infection, tumor, stroke, arteriovenous malformation, or head injury; and (6) post-vaccination and post-infectious encephalitis.

The control group consisted of 50 consecutively enrolled patients with epilepsy with prior history of non-specific viral encephalitis other than JE who visited the epilepsy clinic in the same hospital between January 2013 to September 2018. Controls were selected if they had epilepsy and a past clinical history of a viral encephalitis of caused by a non-JE virus or if the etiology was unknown with either negative serology for JE or onset beyond the JE virus transmission season.

2.2. Demographic and clinical information

The following information was collected for all subjects: sex, age at initial encephalitis, the city or town of residence during the development of encephalitis, presence of seizure at initial presentation of encephalitis, age at first unprovoked seizure, seizure characteristics determined by medical records or interview, the presence of status epilepticus (SE) after the acute phase of encephalitis, seizure type diagnosis performed according to the ILAE criteria [12], magnetic resonance imaging (MRI) scans after the acute phase of encephalitis, interictal and ictal scalp electroencephalography (EEG) with or without video, anti-epileptic drugs (AEDs), seizure frequency, and drug responsiveness.

2.3. Surgery evaluation and outcomes

Surgery was discussed with the patients and families for those with drug-resistant epilepsy. Drug-resistant epilepsy was defined based on the ILAE recommendation, i.e. patients had seizures within 12 months or 3 times the longest pre-treatment interseizure interval, whichever was longer, while receiving adequate trials of two tolerated, appropriately chosen and used AED schedules [13]. Presurgical evaluation, including ictal video EEG (VEEG) and MRI, was performed in all except one patient who had surgery 11 years prior in another hospital. In the patients who underwent surgery for epilepsy, the type of surgery, pathologic results, and outcomes were recorded. Patients were followed regularly after surgery, and their surgical results were assessed using ILAE classification [14].

2.4. Statistical analysis

Age and age at onset of encephalitis are shown as median (interquartile range), while all other data are shown as mean (± standard deviation, SD) and frequencies. T tests were used for group comparisons of continuous variables for the statistical evaluation of age, age of onset, disease course, and types and doses of AEDs. Chi-square tests with Bonferroni correction were used to compare seizure type, neuroimaging data, and drug resistance. Survival analyses were conducted, and a Kaplan-Meier curve was generated to investigate the latency to first seizure in post-encephalitis patients. Differences with $p < 0.05$ were deemed statistically significant in all tests (2-tailed). Data analysis was performed USING Microsoft Excel 2016 and SPSS 19.0 for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

Of the initial 60 eligible patients with JE, 12 were excluded from the analysis because of the absence of JE antibody testing, epilepsy prior to encephalitis, history of febrile seizure, or a history of head injury. A total of 48 patients with a laboratory-confirmed history of JE were eligible for inclusion in the analysis (Table 1). Among the 48 confirmed cases of JE, 41 patients lived in the Sichuan Province when they were diagnosed with JE, three lived in Yunnan, three lived in Guizhou, and one lived in the Gansu Province. There were 20 men included in the final cohort. The median age of the patients at the time of visit was 21.0 years, with an average epilepsy duration of 8.55 years. The average duration from JE to first unprovoked seizure was 7.73 years. The prevalence of acute symptomatic seizure during encephalitis was comparable between the two groups. When compared to those with epilepsy due to other types of viral encephalitis, the interval time between encephalitis to the first unprovoked seizure was notably shorter, i.e. 2.69 years ($p = 4.59 \times 10^{-6}$). More than half of patients (n = 26, 54.17%) with JE developed late-onset epilepsy after a 5-year interval, compared to 11 patients (21.57%) in the control group (Fig. 1). No other difference was observed between the two groups. There was no correlation between the age at onset of encephalitis and the latency to first unprovoked seizure in either group (data not shown).

Almost all patients with JE had clear seizure classification; however, two had no witness to their seizure and negative results on the EEG and neuroimaging investigations. Forty-four (91.67%) patients had focal

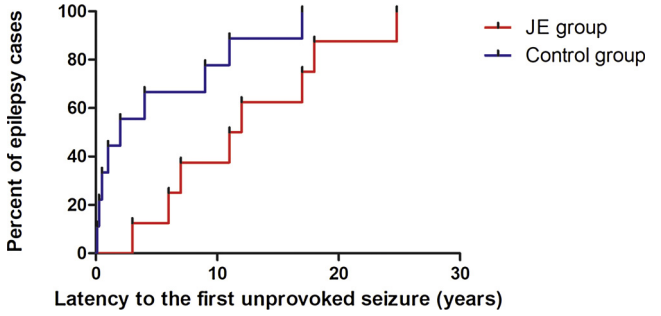

Fig. 1. Latency to the first unprovoked seizure in the JE and control groups.

Table 2
Neuroimaging features of patients in the JE and control groups.

Affected structure	Post-JE group n = 45	Control group n = 50[a]
Frontal lobe	4, 8.89%	7, 14%
Temporal lobe	10, 22.22%	17, 38%
HS	10, 22.22%	7, 14%
Bilateral HS	6,13.33%	0
Insular lobe	1, 2.22%	6, 12%
Parietal lobe	5,11.11%	9, 18%
Occipital lobe	5,11.11%	2, 4%
Thalamus	5,11.11%	2, 4%
Cerebellum	1, 2.22%	1, 2%
Brainstem	1, 2.22%	0
Negative	12, 26.67%	14, 28%

Data are shown in n, %.
JE: Japanese encephalitis; HS: hippocampal sclerosis.
Data of three patients in the JE group and one patient in the control group were not available.

epilepsy and three (6.25%) patients had SE during the chronic epilepsy course. Among those for whom neuroimaging data were available (n = 45), 12 (26.67%) had no obvious abnormality. The temporal lobe (10 patients, 22.22%) was the most affected brain region, followed by the parietal lobe (5 patients, 11.11%), thalamus (5 patients, 11.11%), and occipital lobe (5 patients, 11.11%). The changes included regional or diffuse atrophy, gliosis, cystic changes, or T2 signal changes. There was a notably higher presence of bilateral hippocampal sclerosis (HS) in the JE group than the control group (13.33% (6/45) vs. 0% (0/50)) (n = 6 vs. n = 0) (Table 2).

Thirty-seven patients were on regular medication of more than one appropriate regimen and 29 (78.38%) had medically uncontrolled seizures. Of the 33 patients with neuroimaging data available, the drug-resistant rate seemed higher in those with identifiable brain abnormality (81.48% (22/27) vs. 66.67% (4/6)). After presurgical evaluation of 16 patients, surgery was suggested for eight, and finally, six patients underwent surgery (Table 3), of whom one patient had the surgery performed in another hospital. Three patients were seizure free at the last visit. The median follow-up length after surgery was 3.41 years (SD, 4.61 years; range, 4 months to 12 years).

4. Discussion

In this study, we compared the clinical features of post-JE epilepsy to those in non-specific postencephalitic epilepsy, and the most significant difference was the longer latency period.

The highest risk of unprovoked seizure after viral encephalitis is during the first 5 years according to several previous studies [4,5,15]. In a Taiwanese study, the diagnosis of post-encephalitic epilepsy was made within 6 months of encephalitis in 80% of patients and 3 years in 94.4% of patients [5]. However, the latency in JE seems longer. In our study, seven (14.58%) patients had an unprovoked seizure in the first 6 months post-JE, and 13 (27.08%) patients had an unprovoked seizure within 3 years. More than half of the patients had a seizure 5 years after acute encephalitis. Seizures are common in patients with JE in the acute stage, but little is known about their recurrence and late chronic epilepsy, probably due to the short follow-up time of such patients. The reason for the late unprovoked and delayed seizure following JE is unclear, though neuronal injury results from direct viral cytopathy and a secondary inflammatory response and contributes to the onset of epilepsy [16]. To our knowledge, the longest follow-up period was 14 years, but no late-onset seizure was mentioned in this study [8]. Based on our findings, a longer follow-up of patients with acute JE should be performed in the future to evaluate the prevalence of secondary epilepsy.

Most patients had focal epilepsy in our study, although after thorough interview and investigation, most were found to be drug resistant, which was similar to the reports of post-encephalitis epilepsy due to other viruses [10,11,15]. Compared to the control group in our study, the seizure type in post-JE epilepsy was also indistinguishable from that of epilepsy following other viruses.

Three in four patients had abnormal neuroimaging results after the acute JE infection, and the high rate of abnormal MRI findings was consistent with previous studies [10,11]. The temporal lobe and hippocampus appear to be primarily involved in MRI positive post-JE epilepsy. Hippocampal atrophy, hippocampal signal changes, and a dilated temporal horn were the most frequently diagnosed abnormalities on MRI scans. It has been reported that mesial temporal sclerosis is associated with CNS infection because the hippocampus is sensitive to a lack of oxygen and ischemia [10]. Moreover, a study showed a rate of 17.7% patients had temporal lobe and hippocampus involvement with abnormal MRI in the acute phase of JE encephalitis, with or without thalami or substantia nigra involvement [17], since there is often sharing of blood supply by parts of the thalamus and hippocampus [18,19] and the JE virus might spread from the thalami to the hippocampus in a continuous and subclinical way from the onset of infection of the thalami during acute encephalitis [17,20]. Furthermore, bilateral HS was notably increased compared to the control group, and the underlying mechanism is unclear, but a possible hypothesis is that insult of the bilateral hippocampus occurs after insult of the bilateral thalami, which is a typical clinical feature in JE encephalitis. A previous history of SE at the acute stage of JE might also contribute to the bilateral HS; however, due to the lack of detailed previous history of patients we were unable to evaluate SE during acute encephalitis. Neuroimaging data for the latent period were scarcely available and so we were unable to assess how the lesion or damage was caused in our cases. During the acute stage of JE encephalitis, damage of the thalamus was a remarkable feature with diagnostic importance. In our study, only five patients had thalamic lesions during the chronic epilepsy phase, and it is not clear whether this was related to the seizure. Thus, the physiopathological mechanisms by which JE causes subsequent epilepsy requires further study.

It is well known that patients with post-encephalitic epilepsy are often resistant to medical treatment [16], and temporal lobe epilepsy might be predictive of a poor seizure outcome [15]. Our study showed that the drug-resistant rate of post-JE epilepsy and the proportion of temporal insults were high and comparable to epilepsy following other types of viral encephalitis. Furthermore, the presence of a detectable brain lesion appeared to have no impact on AED responsiveness, which was consistent with the control group and the findings of a previous study [21].

Previous studies have shown that a favorable surgical outcome could be achieved in patients with epilepsy compared to those without encephalitis history if the infection occurs at a younger age or HS was identified on MRI [10,22–24], which suggests that a surgical outcome might be influenced by the type of epileptic syndrome or the time of initial insult rather than the etiology of epilepsy. In our study, three patients had HS in their presurgical neuroimaging scans, and two acquired a seizure free status. Of the remaining three patients, one

Table 3
Clinical characteristics, MRI, EEG, and surgical outcomes of six patients with a history of Japanese encephalitis.

Patient	Age, years/ sex	Age at infection (years)	Age at first seizure (years)	Preoperative imaging	Scalp EEG ictal	Scalp EEG interictal	Surgical method	Pathology	Post-operative follow-up time	Outcomes[a]
N2	17/F	3	7	Softening lesion of right temporal-occipital lobe with right hippocampal sclerosis	Persistent right temporal spike waves	Right central-parietal area low-amplitude rhythmic theta	Right temporal occipital lobe and hippocampal amygdala resection	Right hippocampal sclerosis + FCD3b	4 months	Class 1
N7	21/M	4	14	Softening lesion of right temporal-parietal-occipital lobe	Bilateral spike and slow wave complex	Simultaneously bilateral spike and slow-wave complex, more evident in frontal lobe	Resection of the posterior quarter of the cerebrum	Gliosis	18 months	Class 5
N8	13/M	6	9	Bilateral hippocampal sclerosis	Right frontal and temporal interictal spike waves	Right frontal and anterior-middle temporal rhythmic theta	Selective amygdalohippocampectomy		16 months	Class 1
N9	31/M	11	18	Left hippocampal sclerosis	Epileptic discharge in left side	NA	Hippocampectomy	NA	147 months	Class 6
N13	13/F	9	4	Multiple lesions were found in bilateral dorsal thalamus, left brain stem, and left temporal lobe	Right frontal, left mid-temporal spike—slow wave or spike and slow wave complex	High-amplitude rhythmic theta in left posterior frontal	Partial excision of the left frontal cortex + left anterior temporal lobectomy + partial cortical excision of the left parietal occipital region + anterior division of the corpus callosum		61months	Class 5
N14	21/M	3	13	Softening lesion with local brain atrophy of left occipital lobe	Paroxysmal asymmetric slow waves in left or right frontal and temporal regions, and the left side is more evident	Rhythmic theta activity in all electrodes	Lesionectomy	Gliosis	8 months	Class 1

MRI: magnetic resonance imaging; EEG: electroencephalography; FCD: focal cortical dysplasia; NA: not available.
*Outcome was divided per the ILAE criteria.

acquired a seizure free status; however, it is difficult to explain the surgical outcome given the small sample. It seems that prior infection with JE was not a contraindication for surgery, even in those with a more diffused lesion. However, the decision regarding surgery in patients with post-JE epilepsy should be made with great caution since the infection occurs diffusely in the brain and limited improvement might be expected in a certain number of patients [21]. Unfortunately, no patients with MRI negative epilepsy had surgery performed and no patients had had vagal nerve stimulation in our cohort. A longer follow-up is needed to explore the outcomes of surgery and other forms of non-medication therapy in mostly drug-resistant patients with post-JE epilepsy.

Though JE vaccination was included in the national Expanded Program of Immunization of China and became free and mandatory from 2008, JE remains the primary cause of viral encephalitis, with thousands of cases reported annually [25]. The patients in our cohort all came from an underdeveloped area in southwest China, where the incidence of JE is much higher than the national average, even after the start of JE immunization owing to unbalanced economic development [25]. With such a high incidence of JE, it is important for clinicians and the government to draw attention to the possible subsequent life-long burden of JE, which may cause long-term damage to patients and their families. Thus, further work regarding earlier prophylactic strategies and potential neuroprotection and anti-epileptogenic management in the acute encephalitis stage is required.

There are several limitations to our study. Firstly, we enrolled patients with epilepsy with a history of non-specific viral encephalitis instead of one particular type of viral encephalitis, since virus testing was not widely available in the past decades. This means that the control group comprised a variety of patients. Thus, in future studies, a more select group of controls should be used to analyze the clinical difference between groups. Secondly, there was a lack of detailed data from the acute JE stage, including the existence of SE, which is a common and important predictor of outcome [26], and so the study is underpowered to examine the risk of developing post-JE epilepsy and the association of acute symptoms with long-term outcomes. A further prospective study is required to answer these questions. Thirdly, some clinical features of the patients with JE, such as the high prevalence of drug resistance, in our study may be due to a referral bias since the study was carried out in a tertiary hospital. Lastly, no intracranial EEG or stereoelectroencephalography data were available; hence, this study did not have an extensive presurgical evaluation. Further investigations to elucidate the exact risk of developing seizures and explore possible prevention strategies are needed and of great clinical importance.

5. Conclusion

JE is the main cause of viral encephalitis in Asia, and, to the best of our knowledge, we provide the first descriptive data on the clinical features and outcomes of chronic post-encephalitic epilepsy following JE in West China. The latency from the initial encephalitis insult to the first unprovoked seizure was longer in patients with JE compared to those with previous reports of other types of viral encephalitis, most patients had focal epilepsy, and three in fourth had identifiable brain abnormality, with a tendency of lesions in the temporal lobe. Long-term outcomes of post-encephalitic epilepsy following JE are rather poor, and surgery still remains an option for treating drug-resistant epilepsy.

Declaration of Competing Interest

None.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (Grant No. 81801294), National Key R&D Program of China (Grant No. 2018YFC1311405), China Postdoctoral Science Foundation (Grant No. 2017M620427), Postdoctoral Research Foundation of Sichuan University (Grant No. 2018SCU12038), Post-Doctor Research Project, West China Hospital Sichuan University China (Grant No. 2018HXBH023) to WX, and grants from the National Natural Science Foundation of China (Grant No. 81420108014), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (Grant No. ZY2017305) to DZ.

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