

Original article

# Clinical analysis of psychiatric symptoms of Japanese encephalitis during the convalescent Period: A single center study in Chongqing, China

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## Abstract

**Background:** This study aimed to analyze clinical and imaging features of children with severe Japanese encephalitis (JE), and to analyze causes and solutions for psychiatric symptoms of JE during the convalescent period.

**Methods:** We analyzed clinical information for 78 children with severe JE at the Department of Neurology, Department of Infection, and Department of Rehabilitation in our hospital during 2014–2016. Seventy-eight cases of severe JE were divided into patients with psychiatric symptoms and no psychiatric symptoms groups. We focused on analysis of the patients with psychiatric symptoms group.

**Results:** The incidence of psychiatric symptoms during the convalescent period was 46.15% (36/78). Antipsychotic drugs can effectively control psychiatric symptoms and shorten duration of symptoms. Seventy-one patients underwent reexamination with a head MRI. Of these, 8 cases (8/36 = 22.22%) in patients with psychiatric symptoms group showed new lesions in the basal ganglia, insula, and hippocampus. During the 12-month follow-up, two cases showed reappearance of psychiatric symptoms that had been relieved previously.

**Conclusion:** This study found that severe JE cases revealed a considerable proportion with psychiatric symptoms during the convalescent period.

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**Keywords:** Japanese encephalitis; Psychiatric symptoms; Antipsychotic medications; MRI; Biphasic illness pattern; Autoimmune encephalitis

## 1. Introduction

Japanese encephalitis (JE) is a serious viral encephalitis affecting many people worldwide, especially residents

of Asia and the Pacific. The first confirmed case of JE was reported in Japan in 1924 [1,2]. Japanese encephalitis virus (JEV) is a zoonotic mosquito-borne flavivirus, the most important flavivirus diseases of the central nervous system include JE, West Nile encephalitis, Saint Louis encephalitis, and Murray Valley encephalitis [1,3]. It is estimated that there are about 67,900 cases of JE in children mainly aged <15 years old in 24 countries each year. The mortality incidence is between 20

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and 30%, and 30–50% of the survivors have extended periods of neurological or mental sequelae [2,4]. In addition to Xinjiang, Tibet and Qinghai, all provinces, in China have reported cases of JE. During the period from the 1960s to 1970s that lacked vaccination, more than one million cases of JE occurred in mainland China. Since initial administration of the JE vaccination, incidence of the disease has declined substantially for children under 10 years of age in the 1980s [5–7].

Symmetrical thalamic involvement is a characteristic manifestation of JE in MRI. In addition to basal ganglia and thalamic involvement, neuronal necrosis and atrophy in the temporal lobe, midbrain, cerebral cortex and striatum have been reported [8–11]. Manifestation in the extrapyramidal system is considered a characteristic manifestation of JE, and dystonia is more likely to occur in children than in adults [10,12]. The main manifestations of JE are hyperactivity disorder, gaze palsy, pupil changes, dystonia, paralysis, and seizures [1,5,13,14]. Aphasia, paralysis, and psychiatric disorders are the most common clinical manifestations of JE sequelae [5,13,15].

Mental impairments include slow responses, memory loss, apathy, aggressive behavior, irritability and hyperactivity excitement [15,16]. The main purpose of this study was to analyze clinical and imaging features of children with JE, and to analyze causes and solutions of psychiatric symptoms of JE in order to provide guidance for clinical diagnosis and treatment.

## 2. Methods

### 2.1. Patients

We analyzed clinical information of 78 children with severe JE from the Department of Neurology, Department of Infection, and Department of Rehabilitation during 2014–2016. The 78 cases of severe JE were divided into patients with psychiatric symptoms and no psychiatric symptoms groups, and we focused on analysis of the patients with psychiatric symptoms group. The children were diagnosed as laboratory confirmed diagnosis of JE according the following conditions [17,18]: 1) The clinical characteristics Conformed to the epidemiological characteristics of JE; 2) The clinical symptoms of the patients included the clinical manifestation of JE such as acute fever, convulsions, and disturbance of consciousness; 3) Testing for the JEV IgM antibody in cerebrospinal fluid or serum was positive [19]. Conforming to 1 and 2 was clinically diagnosed as JE. Patients with the temperature above 40 degrees centigrade, coma, restlessness, recurrent or continuous convulsions, light reflex even deep reflex disappearing, pupil narrowing, and light reaction existing were defined as children with severe JE. The psychiatric symptoms were mainly forced crying or laughing [20].

Informed consent was obtained from the legal guardian of each patient. This research was approved by the ethics committee of the Children's Hospital of Chongqing Medical University.

### 2.2. Statistical analysis

Statistical Product and Service Solutions 19 (SPSS19, 2010, IBM Corp, Armonk, NY, USA) was used to analyze the clinical data. The measurement data conformed to a normal distribution and were expressed as means with standard deviations. Categorical data were expressed as a rate or constituent ratio. Differences in proportions of the categorical data were assessed by the Pearson chi square test. The Pearson continuous correction chi square test and Fisher exact probability tests were used when assumptions for the chi square test were not met.  $P < 0.05$  was considered statistically significant.

## 3. Results

Patient clinical data are summarized in Table 1. The incidence of psychiatric symptoms during the convalescent period was 46.15% (36/78). All patients had disturbance of consciousness, and only 13 patients had no convulsions. The incidences for disturbance of consciousness  $< 7$  days and disturbance of consciousness  $> 7$  days were 57.7% and 42.3%. Except for nine patients, all tested positive for JEV IgM antibody. 40/78 of the patients had dysphasia. According to MRI, 52/78 of the patients had bilateral thalamic lesions and 26/78 had bilateral basal ganglia and cortical lesions.

In children with JE, 71 cases were rechecked with cranial MRI, and the average time of reexamination was  $50.73 \pm 6.67$  days. We found that 60/71 of the patients had softening cysts and atrophy of normal performance without new sites and neonatal lesions during the recovery period. In 11 cases, we found new signals in MRI of the basal ganglia, insula and hippocampus. 8/11 of these patients were in patients with psychiatric symptoms group. Disturbance in consciousness  $< 7$  days, disturbance in consciousness  $> 7$  days, positive for JEV IgM antibody, dysphasia, bilateral thalamic lesions, bilateral basal ganglia and cortical lesions, and new abnormal MRI signal of the patients showed no significant differences between the patients with psychiatric symptoms and no psychiatric symptoms groups ( $P > 0.05$ ). The incidence of change from normal MRI image during convalescence for the patients with no psychiatric symptoms group was much higher than for the patients with psychiatric symptoms group ( $P < 0.05$ ). The patients with psychiatric symptoms was treated with risperidone, sulpiride, tiapride, and nitrazepam for antipsychotic medication, and antipsychotic drugs can effectively control psychiatric symptoms and shorten duration of

Table 1  
Comparison of clinical characteristics between the patients with psychiatric symptoms and no psychiatric symptoms groups.

	Patients with psychiatric symptoms group (n = 36)		Patients with no psychiatric symptoms group (n = 42)		P value	Total (n = 78)	Ratio (%)
Gender (cases)	Male	20	27	47		47	60.3
	Female	16	15	31		31	39.7
Age* (years)		5.68 ± 3.52	5.62 ± 2.87	5.68 ± 3.52	0.796 <sup>†</sup>	5.68 ± 3.52	83.33
Convulsions				65		65	100
Disturbance of consciousness				78		78	100
Disturbance of consciousness <7 days		21 (58.3%)	24 (57.14%)	45	0.916 <sup>†</sup>	45	57.7
Disturbance of consciousness >7 days		15 (41.7%)	18 (42.86%)	33	0.916 <sup>†</sup>	33	42.3
Positive for JEV IgM antibody		31 (86.1%)	38 (90.47%)	69	0.547 <sup>†</sup>	69	88.46
Dysphasia		21 (58.3%)	19 (64.29%)	40	0.249 <sup>†</sup>	40	51.28
MRI: bilateral thalamic lesions		22 (61.1%)	30 (71.43%)	52	0.335 <sup>†</sup>	52	66.67
MRI: bilateral basal ganglia and cortical lesions		14 (38.9%)	12 (28.57%)	26	0.335 <sup>†</sup>	26	33.33
Change from normal MRI image during convalescence		21 (58.3%)	39 (92.86%)	60	P < 0.05 <sup>†</sup>	60	76.9
New abnormal signal in MRI		8 (22.22%)	3 (7.14%)	11	0.056 <sup>†</sup>	11	14.3

<sup>†</sup> Chi-square test.

symptoms. During the 12-month follow-up, two cases showed reappearance of psychiatric symptoms that had been relieved previously.

#### 4. Discussion

JE is a serious public health threat to people in subtropical regions, and its epidemic mortality rate has risen to 50% [15]. It has been reported that approximately 30–50% of survivors experience cognitive impairment, epilepsy, and various forms of dyskinesia caused by severe neurological sequelae [21]. In addition to symptoms of the nervous system, JE includes behavioral symptoms such as social inadaptation, invasiveness, aggression, indifference, and emotional instability due to frontal and temporal lobe dysfunction [15]. Psychiatric and non-psychiatric disorders show diffuse involvement in the frontal and temporal lobes, and their fibers are associated with the thalamus, hypothalamus, and marginal systems [22]. Saint Louis encephalitis and herpes simplex encephalitis with similar mental symptoms are usually treated with antipsychotics [15].

In our study, there was a considerable proportion of patients with psychiatric symptoms during the convalescent period. These symptoms were mainly forced crying or laughing. In addition, children with disturbance of consciousness <7 days and disturbance of consciousness >7 days constituted a large proportion of the patients in this study. It is suggested that JE causes significant impairment of brain function and mental dysfunction. Moreover, active rehabilitation therapy is required for patients with impairment of brain function, and it is a financial burden for the family. In this study, we found that patients with psychiatric symptoms who were treated with antipsychotic drugs showed significant improvement. We also found that most of the children who did not receive drug treatment recovered naturally within 1–8 weeks. However, use of psychotic drugs to treat children with psychiatric symptoms could quickly control symptoms. In this study, MRI imaging showed that symmetrical thalamus lesions and basal ganglia lesions accounted for a large proportion of lesions and is consistent with previous research [10]. According to MRI, compared with the patients with no psychiatric symptoms group, the patients with psychiatric symptoms group was more likely to show emergence of a new lesion. Thus, it is suggested that new lesions are more likely to occur in the patients with psychiatric symptoms group. We also found that new lesions were mainly new signals of the basal ganglia, the insula, and the hippocampus, which are predilection sites for emergence of psychiatric symptoms. The cause of psychiatric symptoms during the convalescent period may also be recurrence of the encephalitis virus infection, which we refer to as a biphasic illness pattern [23]. According to recent advances in autoimmune encephali-

tis, this disease process maybe associated with autoimmune encephalitis. Studies have shown that JE can trigger anti-NMDA encephalitis [16]. In this study, we found that new lesions in MRI of the patients with psychiatric symptoms group occurred in the basal ganglia, insula, and hippocampus. These findings are consistent with the predilection sites of anti-NMDA encephalitis reported in previous studies [24,25]. One of the two cases showing reappearance of psychiatric symptoms that had been relieved before was diagnosed with anti -NMDA encephalitis during the 12-month follow-up.

In summary, we conclude the following points: (a) There is a high incidence of psychiatric abnormalities during the recovery period of severe JE. (b) During the convalescent period of JE, antipsychotic drugs can effectively control psychiatric symptoms and shorten duration of symptoms. However, most psychiatric abnormalities resolve without antipsychotic therapy. For severe psychotic symptoms, antipsychotic drugs can be given. (c) The psychiatric symptoms of JE may be associated with new abnormal MRI signals that involve lesions of the basal ganglia, insula, and hippocampus. (d) The onset of mental symptoms during the recovery period may be due to recurrence of JE. This is known as a biphasic disease pattern, and it can trigger an autoimmune encephalitis.

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