

# Long-term outcome of acute central nervous system infection in children

Tianming Chen | Gang Liu

Department of Infectious Diseases, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

## Correspondence

Gang Liu, Department of Infectious Diseases, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

Email: liugangbch@sina.com

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## ABSTRACT

**Importance:** Central nervous system infection is a severe illness in children. Little is known about the long-term outcome in children with central nervous system infection of various etiologies.

**Objective:** The aims of this study were to investigate the long-term outcomes of childhood acute central nervous system infection and to examine possible prognostic factors.

**Methods:** Of 172 children who were treated for acute central nervous system infection from January 2009 through December 2009, 139 were eligible for follow-up evaluations. A structured interview was conducted with the parents 3.8–4.7 years after hospital discharge. The global outcome was determined in all patients using the Pediatric Version of the Glasgow Outcome Scale–Extended. Clinical features of the acute episode were retrieved from medical records.

**Results:** The outcome was favorable in 109 of 139 patients (78%), 38 (27%) were mildly impaired, six (4%) were moderately impaired, 14 (10%) were severely impaired and two (1%) were in a vegetative state. There were eight deaths. The most frequent symptoms were difficulty concentrating (16%), epilepsy (12%), limb paralysis (12%), memory impairment (10%), speech disorders (9%), irritability (9%). Significant risk factors for epilepsy included the presence of recurrent seizures or status epilepticus, the existence of pure spikes in the electroencephalogram, brain parenchyma abnormalities on neuroimaging and herpes simplex virus encephalitis (HSVE). A multivariate analysis identified three factors that were independently associated with poor outcome: coma, brain parenchyma abnormalities on neuroimaging and HSVE.

**Interpretation:** Most children with acute central nervous system infection experienced a favorable outcome 3.8–4.7 years after discharge from the hospital. Minor to severe disability persists in a high proportion of cases. Coma, brain parenchymal abnormalities on neuroimaging and HSVE may predict poor long-term outcome.

## KEYWORDS

Central nervous system infection, Long-term, Outcome, Prognosis, Children

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## INTRODUCTION

Central nervous system (CNS) infection is a severe illness in children. It can involve the meninges and/or brain parenchyma. A wide range of pathogens, such as virus, bacteria, mycoplasma and fungi, can be causes of the disease. Most articles describe the persistent symptoms and sequelae after CNS infection at short-term follow-up evaluations, or focus on specific pathogens; for example, viruses causing encephalitis.<sup>1-4</sup> Some research focuses on the long-term outcome of CNS infection in adults and viral encephalitis in children,<sup>5-7</sup> but published studies on the long-term outcome and sequelae in children with encephalitis of various causative agents are rare. The aims of this study were to investigate the long-term outcomes and sequelae of childhood acute CNS infection in patients at Beijing Children's Hospital and to examine possible prognostic factors.

## METHODS

### Study population

The study population consisted of patients who had a clinical diagnosis of acute CNS infection. Patients hospitalized from January 2009 through December 2009 in Beijing Children's Hospital were retrospectively identified based on hospital records.

A patient with meningitis and/or encephalitis was defined as a patient with (1) an acute onset of illness; (2) at least one abnormality of the cerebrospinal fluid (CSF): WBC count  $> 15\text{cells}/\text{mm}^3$  or protein level  $> 400\text{g}/\text{L}$ ; (3) temperature  $> 38^\circ\text{C}$ ; and (4) decreased consciousness, seizures, altered mental status or focal neurologic signs.

Demographic features, causes of CNS infection, and clinical symptoms present at admission were collected based on the Hospital records.

Exclusion criteria were: (1) age  $\leq 28$  days or age  $\geq 16$  years; (2) tuberculous meningitis; (3) proven or probable noninfectious etiology of CNS disease.

### Viral meningitis and/or encephalitis

Viral meningitis and/or encephalitis was confirmed when viral antibody IgM and/or DNA/RNA was detected in CSF and no alternative cause for the infection was identified. Viral meningitis and/or encephalitis was probable when the WBC count was  $< 500\text{cells}/\text{mm}^3$  and protein was  $< 1000\text{g}/\text{L}$  without viral IgM antibody and/or DNA/RNA detected in CSF and no alternative cause was identified.

### Bacterial meningitis

Bacterial meningitis was confirmed when CSF bacterial culture was positive and no alternative cause was identified. Bacterial meningitis was probable when the WBC count was  $> 500\text{cells}/\text{mm}^3$  and protein was

$> 1000\text{g}/\text{L}$  in CSF and/or positive CSF gram staining and/or positive blood bacteria culture without positive CSF bacteria culture and no alternative cause was identified.

### *Cryptococcus neoformans* meningitis

*C. neoformans* meningitis was diagnosed by positive India ink staining of the CSF and/or a positive test for CSF cryptococcal antigen and/or a positive CSF or blood culture for *C. neoformans* and/or a positive test for blood cryptococcal antigen (titer  $> 1:10$ ).

### CNS candidiasis

CNS candidiasis was diagnosed by a positive CSF culture for *Candida* and no alternative cause was identified.

### Follow-up

For the assessment of long-term outcome, data were collected by telephone 46–56 months after the onset of acute CNS infection using standardized questionnaires about general and neurological symptoms. The Pediatric Version of the Glasgow outcome scale–extended (GOS-E Peds) was used as the main outcome measure.<sup>8</sup> A favorable outcome was defined as a GOS-E Peds score  $\leq 2$ . If a patient had died since discharge, information about the cause of death was collected.

### Statistical analysis

For quantitative variables, data were given as mean  $\pm$  SD; for qualitative variables, data were given as N (%). Univariate prognostic analyses associated with postencephalitic epilepsy (PEE) and long-term outcome were identified. Proportions were compared with the chi-squared test or Fisher's exact test as appropriate. Differences between means were assessed by Student's t-test. A *P*-value  $< 0.05$  (two-tailed) was considered statistically significant. Multiple factors associated with the long-term outcome were identified by logistic regression analysis. Variables associated with the long-term outcome with *P*  $< 0.05$  in univariate analysis were included in the logistic regression. Statistical analysis was performed using SPSS for Windows, Version 13.0.

## RESULTS

### Demography

We included 139 of 172 prospective patients in our study. Of the 33 excluded patients, 28 were unavailable for follow-up, and five declined to participate. The causative agents of acute central system infection and the demographic features of the patients are described in Table 1. The average age was 46 months and there was a slight predominance of male patients. Of the 139 patients, 68 came from rural areas, and the other 71 came from urban areas.

**TABLE 1** Demographic features of patients with CNS infection, by causative agent

Causative Agent	Patients N (%)	Months of age (Range)	Favorable outcome N (%)	CNS infection-related deaths N (%)
All patients	139 (100)	46 (1–180)	109 (78)	8 (6)
HSV	13 (9)	23 (4–93)	3 (23)	2 (15)
Enterovirus	12 (9)	58 (3–112)	11 (92)	1 (8)
JEV	5 (4)	56 (29–96)	1 (20)	2 (40)
Other virus	43 (31)	74 (7–170)	42 (98)	0
<i>S. pneumoniae</i>	6 (4)	35 (2–163)	5 (83)	0
Other bacteria	49 (35)	19 (1–165)	41 (84)	3 (6)
<i>M. pneumoniae</i>	4 (3)	144 (120–180)	2 (50)	0
<i>C. albicans</i>	4 (3)	5 (3–8)	3 (75)	0
<i>C. neoformans</i>	3 (2)	90 (56–151)	2 (67)	0

HSV, herpes simplex virus; JEV, Japanese Encephalitis Virus; *S. pneumoniae*, *Streptococcus pneumoniae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. albicans*, *Candida albicans*; *C. neoformans*, *Cryptococcus neoformans*. Other viruses included mumps virus (N = 1), Epstein-Barr virus (N = 4) and probable viral meningitis and/or encephalitis (N = 38). Other bacteria included *Klebsiella pneumoniae* (N = 2), *Escherichia coli* (N = 2), *Streptococcus agalactiae* (N = 2), *Streptococcus intermedius* (N = 2) and probable bacterial meningitis (N = 41).

**Clinical information in acute phase of infection**

The mean deduced delay between onset of symptoms and admission was 12.2 days. Of the 139 patients, 78 presented with seizures within the acute phase period. Of the 78 patients, 17 presented with single seizures, while 54 had two or more seizures and seven presented with status epilepticus. Of the 139 patients, 29 were comatose at presentation. Twenty-eight patients received corticosteroids therapy. Overall, 8 (6%) of 139 required respiratory support with mechanical ventilation. All 139 patients underwent 12-channel EEG examination. Normal EEGs were seen in 44 (32%) patients. The other 95 (68%) had abnormal EEG findings, 26 of which showed epileptiform activity. CT scan was performed for 23 patients, and MRI was done for 139 patients. Brain imaging revealed parenchymal involvement in 52 (37%) of 139 patients. The clinical information in the period of acute phase is described in Table 2. All 13 patients with herpes simplex virus encephalitis (HSVE) in our study were treated with acyclovir (10 mg/kg, q8h) for 19 ± 4.3 days. The delay between hospital admission and the initiation of acyclovir therapy was 6.3 ± 3.2 days.

**Long-term outcome**

Follow-up interviews were performed 3.8–4.7 years after hospital discharge. Among the 139 patients available for evaluation, eight (4%) died. All deaths were a direct result of CNS infection from herpes simplex virus (N = 2), Japanese encephalitis virus (N = 2), bacteria (N = 3), or enterovirus 71 (N = 1). The deaths occurred on days 3 to 29 after hospital discharge. Of the 139 patients, 71 (51%) completely recovered, 38 (27%) had mild disability, six (4%) had moderate disability, 14 (10%) had severe disability, and two (1%) were in a vegetative state. Thus, the long-term outcome was favorable for 109 (78%) and poor for 30 (22%) of the patients.

HSVE was diagnosed in 13 (9%) of the 139 patients. Only three (23%) patients with HSVE experienced a favorable outcome, compared with 106 (84%) patients with other CNS infection (*P* < 0.05). All four patients with encephalitis due to EBV experienced favorite outcomes. Of the 12 patients with encephalitis due to enterovirus (coxsackie virus = 10, echo virus = 1), 11 experienced favorable outcomes, and other one patient with enterovirus 71 encephalitis died. Of the four patients with Japanese encephalitis, three survived; one had fully recovered at follow up; and the other two experienced a poor outcome.

Among the 55 patients with bacterial infection, 46 (84%) had a favorable outcome, and nine (16%) had a poor outcome. six of 55 had had brain abscesses. Among these six patients, one received brain abscesses recession and other three underwent brain abscesses puncture. All six patients experienced favorable outcomes.

Among the 139 patients, two of four patients with mycoplasma encephalitis, two of three patients with cryptococcal meningitis and three of four patients with candidiasis experienced favorable outcome.

**Persisting symptoms**

Among the 129 survivors with GOS–E Peds score < 7, the most common residual symptoms were trouble concentrating (16%), PEE (12%), limb paralysis (12%), memory impairment (10%), speech disorders (9%), irritability (9%), and ataxia (9%) (Table 3).

Patients with HSVE more frequently experienced trouble concentrating (50%), PEE (40%), memory impairment (40%) and speech disorders (40%). The most common sequelae in patients with bacterial meningitis were hearing impairment (11%), speech disorders (9%), trouble concentrating (9%), and memory impairment (9%).

**TABLE 2** Univariate analysis of factors associated with long term outcome

Variables	All patients	Favorable outcome	Poor outcome	P
Numbers	139	109	30	
Age (month)	46.6 ± 48.6	51.6 ± 50.3	28.7 ± 37.3	0.06
Living in rural areas, N (%)	68 (49)	50 (46)	18 (60)	0.17
Days from onset of illness to hospital admission	12.2 ± 8.1	13.2 ± 9.2	10.2 ± 5.3	0.09
Length of hospital stay (day)	26.4 ± 20.4	23.1 ± 14.2	38.4 ± 32.3	0.16
Body temperature	38.8 ± 0.8	38.7 ± 0.8	38.9 ± 0.7	0.27
Initial seizures during acute phase, N (%)				
No	61 (44)	57 (52)	4 (13)	<0.01
Single	17 (12)	15 (14)	2 (7)	
Recurrent or status epilepticus	61 (44)	37 (34)	24 (80)	
Coma during acute phase, N (%)				
No	110 (79)	97 (89)	13 (43)	<0.01
Yes	29 (21)	12 (11)	17 (57)	
Steroid treatment, N (%)				
Yes	49 (35)	34 (31)	15 (50)	0.06
No	90 (65)	75 (69)	15 (50)	
CRP (mg/L)	41.8 ± 66.0	41.9 ± 69.1	41.7 ± 53.9	0.17
CSF parameters				
Leukocyte count ( $\times 10^6/L$ )	2428 ± 2086	2814 ± 2353	1026 ± 2471	0.75
Protein level (g/ml)	881.6 ± 869.3	795.4 ± 756.4	1194.8 ± 1155.7	0.05
Pure spikes in electroencephalogram during acute phase, N (%)				
Yes	26 (19)	13 (12)	13 (43)	<0.01
No	113 (81)	96 (88)	17 (57)	
Parenchymal involvement in brain imaging, N (%)				
Yes	52 (37)	29 (27)	23 (77)	<0.01
No	87 (63)	80 (73)	7 (23)	
Mechanical ventilation, N (%)				
Yes	8 (6)	2 (2)	6 (20)	<0.01
No	131 (94)	107 (98)	24 (80)	
HSVE, N (%)				
Yes	13 (9)	3 (3)	10 (33)	<0.01
No	126 (91)	106 (97)	20 (67)	

HSVE, herpes simplex virus encephalitis; CRP, C-reactive protein; CSF, cerebrospinal fluid.

Among the 139 patients in our study, four had mycoplasma encephalitis; two of them had fully recovered at follow up. The other two patients had fully recovered at hospital discharge, but they had experienced a poor outcome at follow-up (48 months and 51 months after hospital discharge, respectively). One child was 10-years-old at the time of follow-up. He was unable to write and had the symptom of claudication. The other 13-year-old boy had

irritability, memory impairment and motor deficits.

Two of three patients with cryptococcal meningitis experienced a favorable outcome. Among four patients with candidiasis, three without parenchymal involvement experienced a favorable outcome. One patient with *Candida albicans* infection suffered middle cerebral artery and had moderate disability with trouble concentrating, memory impairment and limb paralysis.

**TABLE 3** Sequelae in patients with a GOS-E Peds score < 7, by causative agent [N (%)]

Signs	All patients with GOS-E Peds < 7(N = 129)	HSVE (N = 10)	Enterovirus (N = 11)	Other virus (N = 45)	<i>S. pneumoniae</i> (N = 6)	Other bacteria (N = 46)	<i>M. pneumoniae</i> (N = 4)	<i>C. albicans</i> (N = 4)	<i>C. neoformans</i> (N = 3)
Headache, dizziness	3 (2)	0	0	2 (4)	0	0	1 (25)	0	0
Nausea, vomiting	1 (1)	0	0	0	0	0	1 (25)	0	0
Irritability	12 (9)	2 (20)	2 (18)	1 (2)	0	3 (7)	2 (50)	0	2 (67)
Anxiety	1 (1)	0	0	1 (2)	0	0	0	0	0
Depression	1 (1)	0	0	0	0	1 (2)	0	0	0
Trouble concentrating	21 (16)	5 (50)	2 (18)	7 (16)	0	5 (11)	1 (25)	1 (25)	0
Memory impairment	13 (10)	4 (40)	1 (9)	2 (4)	1 (17)	4 (9)	0	1 (25)	0
Disorientation	0	0	0	0	0	0	0	0	0
Limb paralysis	15 (12)	3 (30)	0	5 (11)	1 (17)	2 (4)	2 (50)	1 (25)	1 (33)
Ataxia	9 (7)	3 (30)	0	1 (2)	0	3 (7)	1 (25)	1 (25)	0
Facial palsy	1 (1)	0	0	0	1 (17)	0	0	0	0
Speech disorders	12 (9)	4 (40)	1 (9)	1 (2)	1 (17)	4 (9)	1 (25)	0	0
Visual impairment	3 (2)	0	0	0	0	1 (2)	0	0	2 (67)
Hearing impairment	6 (5)	0	0	0	1 (17)	5 (11)	0	0	0
Seizure	16 (12)	4 (40)	0	5 (11)	2 (10)	5 (11)	0	0	0

GOS-E Peds, Pediatric Version of the Glasgow Outcome Scale–Extended; HSVE, herpes simplex virus encephalitis; JEV, Japanese Encephalitis Virus; *S. pneumoniae*, *Streptococcus pneumoniae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. albicans*, *Candida albicans*; *C. neoformans*, *Cryptococcus neoformans*.

Other virus included mumps virus (N = 1), Epstein-Barr virus (N = 4), Japanese encephalitis (N = 3) and probable viral meningitis and/or encephalitis (N = 37).

Other bacteria included *Klebsiella pneumoniae* (N = 2), *Escherichia coli* (N = 2), *Streptococcus agalactiae* (N = 2), *Streptococcus intermedius* (N = 2) and probable bacterial meningitis (N = 38).

**Factors associated with PEE**

Of the 131 survivors, 16 suffered PEE. The significant risk factors for PEE included: (1) the presence of status epilepticus or recurrent seizures during hospitalization (OR = 1.35, 95%CI [1.18–1.65], *P* = 0.001); (2) herpes simplex virus encephalitis (OR = 5.14, 95%CI [1.31–20.15], *P* < 0.05); (3) pure spikes in electroencephalogram (EEG) during the acute phase of the infection (OR = 5.00, 95%CI [2.28–12.01], *P* < 0.001); (4) parenchymal involvement on brain imaging (OR = 11.74, 95%CI [3.13–44.01], *P* < 0.001). These factors are detailed in Table 4.

**Factors associated with long-term outcome**

Variables significantly associated with poor outcome in univariate analysis were included in the logistic regression (Table 2). They were consciousness level in the acute phase, ICU hospitalization, requirement for mechanical ventilation, pure spikes in EEG during the acute phase, parenchymal involvement on brain imaging, HSVE. In the final logistic regression model, factors independently associated with a poor outcome were coma in the acute phase (OR = 0.27, 95%CI [0.08–0.91], *P* < 0.05), parenchymal involvement on brain imaging (OR=0.23, 95%CI [0.08–0.68], *P* < 0.05) and HSVE (OR = 0.08, 95%CI [0.02–0.39], *P* < 0.001). These factors are detailed in Table 5.

**DISCUSSION**

We evaluated the outcome of patients with CNS infection of various causes 3.8–4.7 years after hospital discharge. As shown previously, patients with full recovery from CNS infection at the time of discharge may suffer from new sequelae at follow-up evaluations 6–12 months later.<sup>6</sup> Previous studies also showed that most patients with Japanese encephalitis who recovered completely achieved their full recovery within 6 months.<sup>9–10</sup> Thus, 3.8–4.7 years between onset and follow-up in our study may allow a good overview follow-up interval for sequelae.

We used the GOS-E Peds to measure the main outcome of CNS infection. The GOS-E Peds is sensitive to the severity of brain injury and is associated with changes in sequelae over time.<sup>8</sup> GOS-E Peds provides a valid outcome measure for traumatic brain injury and encephalitis in infants, toddlers, children, and adolescents.<sup>8</sup>

Of the included 139 patients, 78% had a favorable outcome and 22% had a poor outcome. Because of differences in our study population, the length of follow-up and the assessment method, it is difficult to compare with other studies. Recently, Khandaker et al<sup>11</sup> performed a systematic review and meta-analysis of long-term outcome in 1 018 pediatric survivors who suffered from



**TABLE 4** Univariate analysis of factors associated with post-encephalitic epilepsy

Variables	Non-PEE	PEE	PEE %	P	OR (95% CI) Non-PEE vs PEE
Numbers	115	16	12.2	-	-
Age (month)	51 (1–180)	28 (1–120)	-	-	-
Sex					
Male	82	10	10.9	0.67	0.67 (0.23–2.00)
Female	33	6	15.4		
length of hospital stay (d)	25.9 ± 19.0	37.9 ± 28.3	-	0.12	-
Initial seizures during acute phase					
Yes	54	16	22.9	<0.01	1.30 (1.14–1.47)
No	61	0	0.0		
Seizure frequency during acute phase					
Single	16	1	5.9	0.06	1.06 (0.94–1.20)
Recurrent or Status epilepticus	38	15	28.3	<0.01	1.35 (1.18–1.65)
Coma during acute phase					
No	97	12	11.0	0.56	1.80 (0.52–6.20)
Yes	18	4	18.1		
Steroid treatment					
Yes	41	5	11.9	0.73	1.22 (0.40–3.75)
No	74	11	11.6		
HSVE					
Yes	7	4	36.4	0.04	5.14 (1.31–20.15)
No	108	12	10.0		
Pure spikes in electroencephalogram during acute phase					
No	111	0	0.0	<0.01	5.00 (2.28–12.01)
Yes	4	16	80.0		
Parenchymal involvement in brain imaging					
No	84	3	3.4	<0.01	11.74 (3.13–44.01)
Yes	31	13	29.6		

PEE, post-encephalitic epilepsy; HSVE, herpes simplex virus encephalitis; OR, odds ratio; CI, confidence interval; -, not done.

infective encephalitis. In their review, complete recovery was reported in 57% of the children which is similar to our data (51% of the children with complete resolution). Mailles et al<sup>6</sup> evaluated the long-term outcome of 176 patients with acute encephalitis. They used the Glasgow Outcome Scale as the main outcome measure. The study included 24% patients with HSVE, 9% with varicella zoster virus encephalitis, 6% with tuberculosis, 13% with other causes and 48% with encephalitis of unknown etiology. The long-term outcome was favorable in 61% of the patients and poor in 39% of the patients. Compared with our study, their patients had a poorer outcome. There are potential reasons for these differing results. First, their patients were all adults and did not include patients with meningitis; second, there were more patients with

HSVE and varicella zoster virus encephalitis in their study. Asa Fowler et al<sup>7</sup> evaluated the outcome of 71 children with encephalitis 3–8 years after hospital discharge. At long-term follow-up evaluation, 60% reported sequelae. Common residual symptoms were personality changes, cognitive problems, headache, fatigue, and irritability. Their study had no aggregative indicator for the long-term outcome and did not show how much these sequelae impacted everyday life. GOS-E Peds was used as the main outcome measure in our study. Of the included patients, 51% had complete resolution and 27% were mildly impaired, but their everyday life was not significantly affected. Moderately impaired patients comprised 5%, six of whom could not function in school. Severely impaired patients (10%) needed frequent help from a caretaker to

accomplish tasks that a child of that age should be able to accomplish. A small number of patients (1%) patients were in a vegetative state and 6% died.

We found that factors independently associated with a poor outcome were coma in the acute phase, parenchymal involvement on brain imaging and HSVE. There are few studies about prognostic factors associated with long-term outcome. Mailles et al<sup>6</sup> found that HSVE and varicella zoster virus encephalitis were associated with long-term outcome, whereas no clinical features of the acute episode were associated with the long-term outcome. By contrast, in our study, coma and parenchymal involvement on brain imaging in the acute phase were associated with poor outcome. Mailles et al study also showed that younger age was associated with a favorable outcome; 13% of their patients were children. By contrast, our study population was all children and there was no significant correlation between age and long-term outcome, perhaps because our patient population was exclusively children.

Of 131 surviving patients in our study, 11% developed epilepsy. The incidence of PEE was similar to that in previous studies. Fowler et al<sup>7</sup> found that children who presented with seizures during the acute phase had an eight-fold increased risk of developing epilepsy. Their study also showed that girls had an almost five-fold increased risk of developing PEE, compared with boys. Rao et al<sup>12</sup> also showed that the presence of seizures on admission was associated with an ongoing seizure disorder at follow-up. In our study, the presence of status epilepticus or recurrent seizures in the acute phase (other than single seizure) was associated with PEE. There was no significant correlation between gender and PEE. As shown in a previous study, HSVE, pure spikes in EEG during the acute phase and parenchymal involvement on brain imaging were associated with PEE in our study.

The conclusions in several studies assert that the length of the delay between hospital admission and the initiation of acyclovir therapy affects the outcome of HSVE. All patients with HSVE in our study were treated acyclovir without delay. Furthermore, the number of patients with HSVE was small. Thus, it was difficult to analyze the correlation between the antiviral therapy and the long-term outcome. Patients with HSVE had the poorest outcomes in our study. Of the 13 patients with HSVE, only three (23%) experienced a favorable outcome, compared with 106 (84%) patients with other CNS infection ( $P < 0.05$ ). This result is the same as in the previous study.<sup>6</sup> HSVE most commonly involves temporal lobe, followed by the frontal lobe and the limbic system. The medial temporal lobe contains several structures that are critical for declarative, anterograde memory: the hippocampus, the amygdala, the entorhinal and perirhinal cortices, and the parahippocampal gyrus. Of the 10 patients with HSVE whose GOS-E Peds score  $< 7$ , the most common residual

symptoms was trouble concentrating (50%), and 40% had speech disorders. These common sequelae were related to etiopathogenesis of HSVE.

The most common sequelae in patients with bacterial meningitis were hearing loss (11%), followed by speech disorders (9%), trouble concentrating (9%) and memory impairment (9%). Compared with 33.9% hearing loss in a systematic review and meta-analysis on the risk of disabling sequelae from bacterial meningitis by Edmond et al,<sup>13</sup> the incidence of hearing loss in our study was lower. This might be explained by the fact that our data were collected by telephone interview and some patients with mild hearing impairment might be regarded as normal. We emphasize that all patients with bacterial meningitis need hearing monitoring in follow-up. All six patients with pyogenic brain abscess had a favorable outcomes. Our outcomes were much better than those of a 15-year survey of pyogenic brain abscess in adult patients by Helweg-Larsen et al.<sup>14</sup> The difference might be explained by the single abscess in all our patients and none of the brain abscesses was complicated by intraventricular rupture.

Of four patients with mycoplasma encephalitis, two patients experienced moderate disability and the other two had full recovery. All four patients suffered severe *Mycoplasma pneumoniae* pneumonia and the diagnosis was made by demonstrating seroconversion during the acute episode. Rautonen et al<sup>15</sup> followed 462 children with encephalitis, including 41 with a *pneumoniae* infection; the mortality rate was 7.3% and 14.6% of the patients suffered severe disability. The authors concluded that the prognosis of mycoplasma encephalitis in children is worse than that of encephalitis caused by other pathogens, with the exception of herpes simplex virus. Sauteur et al<sup>16</sup> observed seven patients (median age 8.7 years, range 4.7–10.1 years) with *M. pneumoniae* encephalitis in Switzerland and three of them had neurological sequelae at 4–19 months' follow-up. We enrolled few patients with mycoplasma encephalitis; therefore, these two patients might not be representative of all pediatric patients with *M. pneumoniae* encephalitis. It is worth noting that two patients, who experienced moderate disability in the long-term, had achieved major improvement in the short-term outcome. In 2 years' follow-up, one of them gradually experienced a decline in motor function, while the other patient suffered headache, memory impairment and irritability. These delayed persisting symptoms might be explained by the pathogenesis of *M. pneumoniae* encephalitis, which includes direct neuroinvasion and immune-mediated damage. Immune-mediated damage might persist after the acute episode. Therefore, all patients with *M. pneumoniae* encephalitis should be followed with long-term evaluations.

Our study included four patients with CNS candidiasis. Only one patient who had left middle cerebral artery

territory infarction suffered moderate disability. The other three patients with meningitis all achieved full recovery. There are few reports on the long-term outcome of CNS candidiasis. Our study demonstrated that patients with CNS candidiasis restricted to the meninges had favorable outcomes.

Arciniegas et al<sup>17</sup> suggested that all patients with encephalitis require long-term management. Psychiatrists, particularly those working in general medical or rehabilitation settings, should be called on to participate in the long-term follow-up, using standardized, validated, and reliable measures for evaluation. This strategy enables them to prescribe pharmacologic and nonpharmacologic interventions for rehabilitation and many of the adverse consequences could be minimized.<sup>18-19</sup> Our results showed that 78% of patients with acute CNS Infection had a favorable long term outcome and 22% suffered a poor outcome. The persisting sequelae impacted their everyday lives to varying degrees. Furthermore, some patients with full recovery at discharge may have new sequelae at long-term follow-up evaluations. We suggest that all children with encephalitis should be monitored. Psychiatrists should participate in the rehabilitation program and in long-term follow-up evaluations.

Our study has some limitations. First, because our patients came from different regions across China, we were unable to perform direct examinations; telephone interviews were conducted instead. It was difficult to make an accurate assessment of sequelae; however, previous studies have demonstrated that telephone interview evaluation can be valuable.<sup>5,6</sup> Furthermore, although GOS-E Peds is sensitive to the severity of brain injury for all ages in children, mild sequelae might not be easily detected in some situations, especially in infants and toddlers. Second, our follow-up period of 3.8–4.7 years after hospital discharge might still not be enough. As children grow up, their disability might be gradually revealed. Thus, infants and toddlers who suffered acute CNS infection need to be followed for a longer period. Third, because the total number of included patients in our study is small, we did not analyze the long-term outcome of CNS infection each pathogen separately and we did not do a systemic analysis of the correlation between clinical manifestation in the acute phase and in the final outcome. More patients should be included in future studies.

Most children with acute CNS infection experienced a favorable long-term outcome. However, Minor to severe disability persists in a high proportion of cases. Children with HSVE carry the heaviest burden of sequelae. Coma, brain parenchymal abnormalities in neuroimaging and HSVE may predict poor long-term outcome. The presence of recurrent seizures or status epilepticus, the existence of pure spikes in EEG, brain parenchyma abnormalities on neuroimaging and HSVE were significant associated

with epilepsy. We suggest that all patients with encephalitis require long-term follow-up evaluation and neuropsychological rehabilitation should be carried out for them.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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