Status epilepticus associated with *Mycoplasma pneumoniae* encephalitis in children: good prognosis following early diagnosis and treatment

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To the Editor: Mycoplasma pneumoniae is a common pathogen that leads to respiratory tract infections in children, often causing immune-related injuries in multiple other organs and tissues. The involvement of central nervous system has been reported in 5% to 7% of patients with *M. pneumoniae* infection.[1] The clinical manifestations of *M. pneumoniae* encephalitis are highly heterogeneous, and more than half of patients experience seizures during the acute phase, with status epilepticus occurring in severe cases.[2]

Status epilepticus is a common yet critical illness of the nervous system in children. Although the frequency of *M. pneumoniae* encephalitis is well recognized, reports regarding this entity in children with status epilepticus are rare. Some scholars have proposed a three-level classification system in which *M. pneumoniae* encephalitis is diagnosed as follows[3]: (1) highly suspected – positive cerebrospinal fluid (CSF) or polymerase chain reaction (PCR) results, with or without positive serological test results, or positive pharyngeal swab culture/PCR results with positive serological test results; (2) suspected – serology positive with negative pharyngeal swab, CSF, and PCR results, or positive pharyngeal swab/PCR results with negative serological test results, and no other infections pathogens; and (3) not excluded – positive serological test results with negative pharyngeal swab, CSF, and PCR results, with at least one confirmed infectious pathogen.

This study directly tested *M. pneumoniae* in the CSF of children with *M. pneumoniae* encephalitis complicated by status epilepticus, to obtain direct evidence of this infectious agent in the central nervous system. In four cases, satisfactory results were observed following early identification and treatment of *M. pneumoniae*. All patients were diagnosed and treated early, thus, resulting in good prognosis.

This study recruited children who were admitted to the Department of Neurology, Children's Hospital Affiliated to Capital Institute of Pediatrics, from July 2017 to June 2018 and met the diagnostic criteria for acute encephalitis with status epilepticus. In all included patients, the RNA results for *M. pneumoniae* were positive, whereas the results for viruses, bacteria, and fungi were negative. We retrospectively analyzed clinical characteristics, examination results, treatment strategies, and prognosis of these four children with *M. pneumoniae* encephalitis complicated by status epilepticus.

Clinical manifestation: It included four children, three boys and one girl, aged 3, 4, 5, and 8 years, respectively. Acute onset was observed in all the four cases. The duration of hospitalization at our institution was 14, 4, 7, and 6 days for each patient, respectively. Initial symptoms included fever with a peak temperature of 39°C to 40°C (two to four times per day, irregular). Respiratory symptoms (eg, cough) were noted in two patients, whereas disturbance of consciousness (Glasgow Coma Scale scores of 11–12) was noted in three patients. The remaining patient was unconscious. The type of status epilepticus differed among the four cases. One patient presented with myoclonus secondary to tonic-clonic seizures, one with generalized tonic clonus, one with complex partial seizures, and one with generalized tonic clonus combined with subclinical electronic discharges. Neck rigidity was observed in one patient, whereas the remaining three exhibited no pathogenic neurological signs.

Examination results: Lumbar puncture was performed on the 4th, 6th, 7th, and 14th days after disease onset in each

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patient. The results of routine and biochemical CSF examinations were within the normal range, and no viral antibodies were detected in the CSF. Bacterial culture, acid fast staining, and ink staining results were negative. However, the CSF was positive for *M. pneumoniae* RNA. Video electroencephalography (EEG) revealed a slow-wave background rhythm of 1.5 to 3.0 Hz in each patient. Slow waves were observed in each hemisphere, and the left and right hemispheres were basically symmetrical. The interictal interval contained multifocal epileptiform discharges. Electrical status was observed in one patient. Three patients exhibited abnormal cranial magnetic resonance imaging (MRI) findings. Among these three patients, two exhibited long T1 and T2 signals in the hippocampus, whereas one exhibited demyelination of the paraventricular white matter. No definite abnormalities were observed in the remaining case.

Therapeutic response and prognosis: All four patients were treated with azithromycin for 2 weeks (5 days per week). In addition, three of the four patients were treated with dexamethasone, two with intravenous immunoglobulin (IVIG), and one with combined IVIG and glucocorticoids. Following treatment, body temperature returned to normal in all the four children. Three children experienced recovery of consciousness. Two children were free of epileptic seizures after treatment, whereas the remaining two took oral levetiracetam and topiramate to reduce seizure frequency. Although slow-wave background activity was observed on follow-up EEGs in all the four children, background activity had improved overall and epileptiform discharge had decreased significantly. In all the four cases, cranial MRI revealed varying degrees of brain atrophy. Treatment and recovery data are shown in Table 1.

M. pneumoniae encephalitis is accompanied by epileptic seizures in 41% to 48% of cases, with status epilepticus accounting for approximately 50% of all epileptic seizures.[4,5] In this study, three children exhibited status epilepticus, whereas electrical status was observed in the remaining patient. It has been reported that the rate of abnormal EEG findings is relatively high in patients with *M. pneumoniae* encephalitis,[6] mainly manifesting as diffuse slow waves and epileptic discharge. In this study, all the four children with status epilepticus exhibited abnormal EEG findings (ie, diffuse slow waves). Three of these children exhibited epileptiform discharges in multiple brain regions, whereas one exhibited sustained spikes and slow waves in the bilateral frontal regions.

EEG abnormalities were severe in all the four cases, indicating that brain damage may be more severe in the acute phase of *M. pneumoniae* encephalitis with status epilepticus. However, due to a disease in progression and timely treatment, EEG findings improved to varying degrees in our patients. Although the slow-wave background activity remained, epileptiform discharge decreased significantly and status epilepticus did not recur. The prognosis of *M. pneumoniae* encephalitis with status epilepticus is relatively good, and it is fairly easy to control status epilepticus.

The common pathological changes associated with *M. pneumoniae* encephalitis include demyelination of white matter, inflammatory infiltration, perivascular edema, and glial cell proliferation. Imaging findings in patients with *M. pneumoniae* encephalitis can be normal, but may also reveal focal changes, diffuse edema, or abnormal intensity in the gray/white matter.[7] Some studies have indicated that high signal intensity in the striatum and midbrain can be observed on magnetic resonance images obtained from patients with *M. pneumoniae* encephalitis, and that images obtained from patients with myelitis show abnormal signals in the spinal cord.[8] In our study, three patients with *M. pneumoniae* encephalitis complicated by status epilepticus exhibited abnormal cranial MRI findings. One patient exhibited demyelinating changes in the paraventricular white matter, one patient exhibited abnormal signals in the bilateral hippocampus, and one patient exhibited abnormal signals in the left hippocampus. These findings indicated that the rate of MRI abnormalities was high in children with *M. pneumoniae* encephalitis with status epilepticus, but that lesion location was nonspecific in such cases, which was similar to findings observed in patients with severe encephalitis.[9] Varying degrees of

Table 1: Treatment strategies and prognosis of four patients with status epilepticus associated with *Mycoplasma pneumoniae* encephalitis.

	Medication						
Patient no.	Azithromycin	IVIG	Dexamethasone	Symptoms	Follow-up MRI	Follow-up EEG	Outcome
1	1 week	Not used	5 days	Improved	Bilateral frontal lobe sulcus is obvious	Slow waves, no epileptiform discharges	Oral antiepileptic drugs, no seizures
2	2 weeks	Used	Not used	Recovery of consciousness	Bilateral extra cerebral space enlargement	Slow waves, no epileptiform discharges	Oral antiepileptic drugs, seizure reduction
3	2 weeks	Not used	5 days	Recovery of consciousness	Encephalatrophy	Slow waves, no epileptiform discharges	Oral antiepileptic drugs, seizure reduction
4	2 weeks	Used	6 days	Recovery of consciousness	Encephalatrophy	Slow waves, no epileptiform discharges	Oral antiepileptic drugs, no seizures

–: Not applicable. EEG: Electroencephalography; IVIG: Intravenous immunoglobulin; MRI: Magnetic resonance imaging.

brain atrophy on cranial magnetic resonance images during convalescence might indicate that *M. pneumoniae* severely damaged the brain parenchyma, thereby damaging nerve cells and affecting their function.

M. pneumoniae infection could lead to immune damage. Increases in *M. pneumoniae* antibody levels could be detected in the blood, and immunotherapy could improve the symptoms of *M. pneumoniae* infection.[10] In this study, IVIG was used in two cases, whereas dexamethasone was used in three cases, yielding good results in all cases. These findings suggested that although *M. pneumoniae* infection was the main mechanism in the early stage of the disease, immune responses might also play a role. Thus, early treatment strategies should utilize macrolides in conjunction with immunotherapy.

The prognosis of *M. pneumoniae* encephalitis is poor and that the mortality rate is high. It has been indicated that surviving children experienced neurological sequelae and were highly unlikely to recover to baseline levels.[11] A previous study collected follow-up data for 2011 children with epileptic seizures after *M. pneumoniae* encephalitis for 6 to 131 months.[11] Among the 99 enrolled patients with *M. pneumoniae*-related encephalitis, 47 (47.5%) developed post-encephalitic epilepsy. Nineteen of these children (40.4%) with post-encephalitic epilepsy experienced intractable seizures. In this study, our four patients were treated with azithromycin and immunotherapy immediately after the diagnosis of *M. pneumoniae* encephalitis. Symptoms were controlled after 1 to 2 weeks of treatment, and no status epilepticus or refractory status epilepticus occurred. Furthermore, the rate of epileptic seizures decreased significantly after treatment with oral antiepileptic drugs and no children exhibited cognitive impairment. Although our findings suggested that early diagnosis and treatment of *M. pneumoniae* encephalitis with status epilepticus resulted in relatively good prognosis, further studies that include more thorough neuropsychological testing at follow-up are required to verify this hypothesis.

In conclusion, *M. pneumoniae* encephalitis with status epilepticus occurs in relatively younger patients (ie, mainly in children with preschool age), who tend to exhibit abnormal MRI findings. Children with severe neurological diseases, such as status epilepticus, should be diagnosed and treated as early as possible to control symptoms and improve prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients' parents have given their consent for images and other clinical information to be reported in the journal. The patients' parents understand that the names and initials will not be published and due efforts will be made to conceal the patients' identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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