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Determining the Clinical Characteristics, Treatment Strategies, and Prognostic Factors for *Mycoplasma pneumoniae* Encephalitis in Children: A Multicenter Study in China

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Background and Purpose Most of the knowledge of *Mycoplasma pneumonia* (*M. pneumoniae*) encephalitis (MPE) in children is based on case reports or small case series. This study aimed to describe the clinical features and prognostic factors of MPE, and the efficacy of azithromycin with or without immunomodulatory therapy.

Methods The medical data of 87 patients with MPE from 3 medical centers in southwestern China over a 7-year period were reviewed.

Results MPE was found in children of all ages except for neonates. The most common neurological manifestations included consciousness disturbance (90%) and headache (87.4%), the most common extraneurological manifestations included fever (96.5%) and respiratory system involvement (94.3%); multisystem involvement (98.2%) and elevated C-reactive protein (CRP) (90.8%) were also prominent. *M. pneumoniae* was detected in cerebrospinal fluid (CSF) less often than in blood and respiratory tract secretions. Azithromycin with intravenous immunoglobulin or/and corticosteroid treatment can shorten the hospitalization duration and the clinical improvement process. Most patients (82.8%) received a favorable prognosis; serum lactate dehydrogenase (LDH) and CSF protein levels were higher in the poor-outcome group than in the good-outcome group ($p<0.05$). Neurological sequelae are likely to continue when the onset of this condition occurs during teenage years.

Conclusions MPE generally presented with nonspecific clinical manifestations. In children with acute encephalitis accompanied by multi-system involvement and prominently elevated CRP, *M. pneumoniae* should be considered as a possible pathogen. Immunomodulating therapies should be recommended regardless of the duration of the prodromal period. High CSF protein level, blood LDH elevation, and higher age may be associated with an unfavorable outcome.

Keywords *Mycoplasma pneumoniae* encephalitis; clinical characterization; prognostic factors; azithromycin; immunomodulating therapies.

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INTRODUCTION

Mycoplasma pneumonia (*M. pneumoniae*) is a common cause of respiratory tract illness in children. One of its extrapulmonary manifestations is nervous system involvement in the form of conditions including encephalitis, meningoencephalitis, cerebellitis, cerebral infarction, and acute disseminated encephalomyelitis.[1-4] *M. pneumoniae* is considered one of the main causes of encephalitis in children, accounting for 5%−10% of those encephalitis cases. *M. pneumoniae* encephalitis (MPE) is caused by direct invasion in the brain, immune-mediated inflammatory response, neurotoxin-mediated damage, or a thromboembolic phenomenon.[2,5-8] According to the duration of prodromal symptoms (defined as any illness that precedes neurological symptoms), MPE is divided into early-onset (prodromal

symptoms for up to 7 days) and late-onset (more prolonged prodromal symptoms) forms. The early-onset form is mostly related to direct invasion into the central nervous system (CNS) by *M. pneumoniae*, while the late-onset form is often principally characterized by an autoimmune CNS disease.[1,9]

The multiplicity of possible mechanisms suggests that a range of therapeutic approaches should be considered. It is widely accepted that antibiotics play a key role in the management of all children with suspected MPE.[1] However, the roles of immunomodulating medications such as corticosteroids and intravenous immunoglobulin (IVIG) have not been studied extensively.[1,10,11] Furthermore, few studies have evaluated the prognostic factors associated with MPE.[12] The purpose of the present retrospective study was to identify patients with MPE at three medical centers in southwestern China, describe their clinical features, determine differences between the efficacies of azithromycin and immunomodulatory therapy, and identify prognostic factors for outcomes associated with MPE.

METHODS

Diagnosis and definition of MPE

MPE was diagnosed based on the consistent presence of a clinical neurological syndrome, positivity for IgM in cerebrospinal fluid (CSF) and/or positivity for *M. pneumoniae* on polymerase chain reaction (PCR), and the exclusion of other probable causes.[5] Patients with underlying neuropsychiatric disorders and alternative diagnoses were excluded.

Study population and data collection

This retrospective study included patients with a confirmed MPE diagnosis between January 1, 2014 and December 31, 2020, who were admitted to one of three medical centers in southwestern China, including the Chongqing Ninth People's Hospital, Children's Hospital of Chongqing Medical University, and Maternal and Child Health Hospital in Chongqing Fuling District. This study included 87 patients for who data were available over the 7-year study period. A detailed review of medical data was performed, including clinical characteristics, laboratory data of blood and CSF, cranial MRI, electroencephalography (EEG), and treatments using antiviral agents or immunomodulating medications such as corticosteroids and IVIG. The patients were followed up for at least 6 months after discharge. The Glasgow Outcome Scale (GOS) was used to evaluate the prognoses. Patients with GOS scores of 4 or 5 and 1−3 at the main clinical evaluation time point of 6 months after discharge were included in the good outcome (GO) and poor outcome (PO) groups, respectively. Patients with prodromal symptoms for up to 7 days were classified into the early-onset group, and those with symptoms for more than 7 days were included in the late-onset group.

Statistical analysis

The data for different parameters are expressed as median values (ranges) or numbers (percentages). For further analyses and comparisons, the patients were divided into two subgroups according to the outcome (GO and PO groups) and the duration of their prodromal period (early- and late-onset groups). Statistical differences between different groups were analyzed using Pearson's chi-square test, Fisher's exact test, or univariable logistic regression according to the nature of the variables. In multivariable analysis, binary backward stepwise logistic regression was used for the independent-factor analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY, USA), with significance considered to be present for a two-tailed p of <0.05.

RESULTS

Demographic and clinical characteristics of the patients

During the study period, 87 patients were finally included. The demographic and clinical characteristics of these patients are listed in Supplementary Table 1 (in the online-only Data Supplement). The disease can affect children of any age except for neonates; most patients (49.4%) were aged 6−10 years, with a median age of 5.3 years. Most patients were city residents (64.4%), and the male:female ratio was 1.29:1. No specific clinical features were observed in this cohort. All patients had an abnormal body temperature: most had fever (96.5%) and only 3.5% had hypothermia. The most frequently reported neurological manifestations were disturbance of consciousness (90.0%), positive pyramidal tract sign (89.7%), headache (87.4%), and seizures (75.9%). Various extraneurological abnormalities were found in 96.5% of patients, most frequently in the respiratory system (94.3%) followed by the gastrointestinal system (73%). Furthermore, some patients presented with myocardial damage (24.1%), skin rash (21.8%), and urinary damage (5.7%) (Fig. 1).

Laboratory and imaging findings

Abnormalities were found most frequently in EEG (pleocytosis in 90.8% of patients), followed by the CSF analysis (73.6%) and then MRI (44.8%). Diffuse/focal slow waves were the most common finding in EEG (62/79, 78.5%), and epileptiform discharge waves were also observed (25/79, 31.6%). CSF findings included mild lymphocytosis and elevated CSF protein. Cortical involvement was the most com-

mon finding on neuroimaging (28.7%). It was particularly interesting that five patients (5.7%) presented reversible lesions involving the splenium of the corpus callosum, which were categorized as reversible splenial lesion syndrome (RESLES) (Table 1). All of these laboratory findings were generally compatible with common viral encephalitis, partially treated bacterial meningitis, autoimmune encephalitis, and encephalitis with unknown pathogen. Another interesting finding was that, unlike the commonly expected hemogram results in patients affected by viral and autoimmune encephalitis with leukopenia and a normal C-reactive protein (CRP) level, 62.1% of the patients in this cohort were found to have leukocytosis and 90.8% had elevated CRP, which may provide diagnostic clues for this pathogen (Table 2).

Treatment

Azithromycin was administered to all 87 patients, with 80 (91.9%) receiving intravenous (i.v.) followed by oral azithromycin treatment. The azithromycin regimen consisted of 10 mg/kg i.v. daily for 5–7 days, followed by 10 mg/kg given orally once daily for 3 days, then none given for 4 days repeatedly for 1 week, while 7 patients only received oral azithromycin treatment (10 mg/kg of body weight once per day for 3 days, and none given for 4 days repeatedly for 1 week). Immunomodulating therapy was administered to 55 patients (63.2%), including 37 (42.5%) who received IVIG treatment (400 mg/kg/day for 5 days or 1 g/kg/day for 2 days), 12 (13.8%) who received corticosteroids (methylprednisolone at 2 mg/kg/day i.v. for 5–7 days or methylprednisolone at 20 mg/kg/day i.v. for 3 days followed by oral prednisone acetate at 1 mg/kg/day for 10–14 days, withdrawn gradually), and 6 (6.9%) who received both IVIG and corticosteroids. Supportive care was given, which included mannitol, anticonvulsant, and cooling methods.

The mean duration of improvement in clinical and laboratory signs and the duration of hospitalization were significantly shorter for those who received azithromycin plus immunomodulatory therapy compared with those who received azithromycin alone, especially in the IVIG group. It was particularly interesting that the group that received

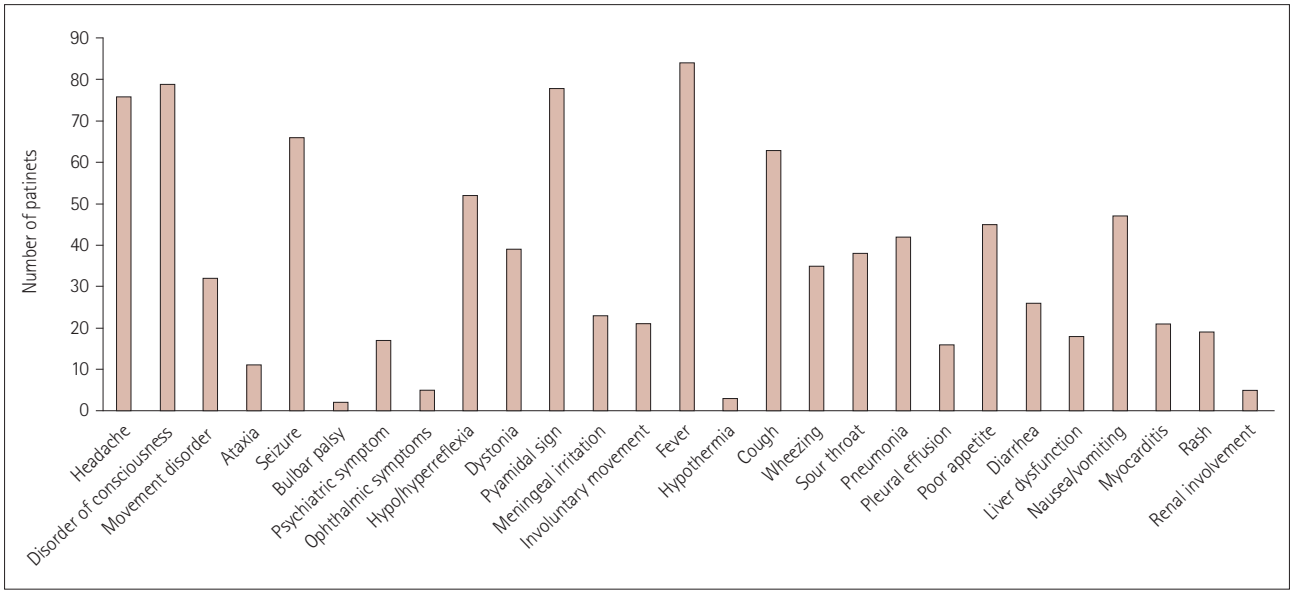

Fig. 1. Clinical presentation of patients in our series.

Table 1. Involved anatomical areas detected using MRI for the overall population with a comparison between different subgroups

Neuroimaging involvement area	*n* (%)	Prognosis		Onset type	
		Good outcome (*n*=72)	Poor outcome (*n*=15)	Early onset (*n*=49)	Late onset (*n*=38)
Gray matter	25 (28.7)	18 (25)	7 (46.7)	11 (22.4)	14 (36.8)
Corpus callosum	5 (5.7)	5 (6.9)	0 (0)	4 (8.2)	1 (2.6)
Basal ganglia	6 (6.8)	4 (5.6)	2 (13.3)*	4 (8.2)	2 (5.3)
Thalamus	4 (5.7)	3 (4.2)	1 (6.7)	2 (4.1)	2 (5.3)
Brainstem	2 (2.3)	2 (2.8)	0 (0)	0 (0)	2 (5.3)
Cerebellar	3 (3.4)	3 (4.2)	0 (0)	1 (2)	2 (5.3)

*$p<0.05$.

Table 2. Laboratory data of the study population with comparison between different subgroups

Variable	Value	Prognosis		Onset type	
		Good outcome (*n*=72)	Poor outcome (*n*=15)	Early onset (*n*=49)	Late onset (*n*=38)
Blood (*n*=87)					
WBC, $\times 10^9$/l	14.3	15.6	13.1	11.4	17.8
Leukocytosis	54 (62.1)	45 (62.5)	9 (60)	26 (53.1)	28 (73.7)
CRP elevation	79 (90.8)	68 (94.4)	11 (73.3)	46 (93.9)	33 (86.8)
LDH elevation	35 (40.2)	23 (31.9)	12 (80)*	18 (36.7)	17 (34.7)
Albumin decrease	17 (19.5)	7 (9.7)	10 (66.7)*	10 (20.4)	7 (18.4)
Hb decrease	18 (20.7)	14 (19.4)	4 (26.7)	8 (16.3)	10 (26.3)
M. pneumoniae IgM					
PN	73 (83.9)	67 (93)	6 (40)	40 (81.6)	33 (86.8)
Titer	1:283	1:280	1:352	1:260	1:380
CSF (*n*=87)					
WBC, $\times 10^6$/l	182	161	196	75	210
Leukocytosis	64 (73.6)	52 (72.2)	12 (80)	35 (71.4)	29 (76.3)
Lymphocytosis	53 (60.9)	47 (65.3)	6 (40)	31 (63.3)	22 (57.9)
Protein	0.806	0.735	0.956	1.223	0.594
Protein elevation	48 (55.17)	37 (51.4)	11 (73.3)*	27 (55.1)	21 (55.3)
Glucose decrease†	5 (5.7)	4 (5.6)	1 (6.7)	3 (6.1)	2 (5.3)
M. pneumoniae IgM, copy/mL					
PN	70 (80.5)	61 (84.7)	9 (60)	33 (67.3)	37 (97.4)
Median	1:277.3	1:276	1:280	1:180	1:320
M. pneumoniae PCR, copy/mL					
PN	25 (28.7)	19 (26.4)	6 (40)	22 (44.9)	3 (7.9)*
Median	99.3×10^3	113.3×10^3	74.9×10^3	168×10^3	45.7×10^3
Throat swabs (*n*=58)					
M. pneumoniae PCR, copy/mL					
PN	58 (66.7)	51 (70.8)	7 (46.7)	28 (57.1)	30 (78.9)
Median	920.3×10^4	969.8×10^4	831.2×10^4	742.5×10^4	1180.2×10^4

Data are *n* (%) or median values.
*$p<0.05$; †CSF/serum glucose ratio <0.4.
CRP, C-reactive protein; CSF, cerebrospinal fluid; Hb, hemoglobin; IgM, immunoglobulin M; LDH, lactate dehydrogenase; *M. pneumoniae*, *Mycoplasma pneumoniae*; PCR, polymerase chain reaction; PN, positive number; WBC, white blood cell.

azithromycin combined with IVIG and corticosteroids did not show this advantage. Moreover, there was no significant difference in efficacy between the early- and late-onset groups (Table 3).

Clinical course, outcomes, and prognostic factors

The median hospitalization duration was 11.2 days, and four patients (4.6%) were admitted to the intensive care unit due to status convulsion or respiratory failure. There were no deaths. At the main clinical prognosis assessment performed 6 months after discharge, 72 (82.8%) and 15 (17.2%) patients were classified into the GO and PO groups, respectively. According to the duration of prodromal symptoms, 49 patients (56.3%) presented with the early-onset form and 38 patients (43.7%) presented with the late-onset form (Fig. 2).

All clinical features and laboratory data were compared between the GO/PO and between the early/late-onset groups. The results indicated that the early-onset form was more likely to be observed in younger children, and *M. pneumoniae* copies were more easily detected in CSF of this type, and there were no significant differences in other clinical and laboratory findings between the early- and late-onset groups (Tables 1-3). In the univariable analysis, the factors significantly associated with the PO group were onset in adolescence (11–18 years) ($p<0.001$), originating in rural areas ($p=0.042$), hypothermia ($p=0.002$), convulsion status ($p=0.037$), involuntary movement ($p=0.028$), increased lactate dehydrogenase (LDH) level ($p<0.001$), elevated CSF protein ($p=0.004$), and basal ganglia involvement ($p=0.023$) (Tables 1-3 and Supplementary Table 1 in the online-only Data Supplement). In the multivariable analysis, the prognostic factors associated with PO were onset in adolescence ($p=$

Table 3. Clinical data with comparisons of different management regimes

	Defervescence time (days)	Time of disappearance of convulsion (days)	Time of consciousness normalization (days)	ICU stay duration (days)	Hospital stay duration (days)
Azithromycin monotherapy					
Total (*n*=32)	9.76±1.17	15.39±2.84	10.21±1.95	12.32±5.20	14.66±5.39
EO form (*n*=24)	7.39±1.92	18.25±3.75	8.75±3.28	14.65±1.98	17.89±2.43
LO form (*n*=8)	9.98±3.86	13.58±1.92	11.56±2.34	9.88±4.17	12.67±4.73
Azithromycin+IVIG use					
Total (*n*=37)	4.61±2.30*	8.82±4.26*	6.34±3.56*	10.83±1.97	9.32±1.48*
EO form (*n*=21)	2.89±2.94	5.79±3.82	7.21±4.79	8.48±3.25	12.74±2.35
LO form (*n*=16)	5.61±3.29	9.28±1.93	6.01±4.32	14.23±3.08	7.66±1.93
Azithromycin+steroid use					
Total (*n*=12)	4.28±1.45*	9.47±3.71*	7.69±2.48	3.57±3.91*	10.49±3.01
EO form (*n*=2)	2.57±1.09	7.89±2.63	5.99±2.71	2.82±1.03	8.35±2.47
LO form (*n*=10)	5.92±2.34	12.45±4.21	9.38±3.06	6.75±3.22	11.20±4.38
Azithromycin+IVIG+steroid use					
Total (*n*=6)	5.07±2.34	12.53±4.11	11.72±3.92	15.72±4.65	12.56±2.37
EO form (*n*=1)	7.92±3.26	10.65±2.73	8.89±2.04	18.32±4.21	15.98±5.36
LO form (*n*=5)	5.77±1.53	15.29±4.84	12.11±4.57	14.72±2.58	10.87±2.78

Data are mean±standard-deviation values.
*p<0.05.
EO, early onset; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LO, late onset.

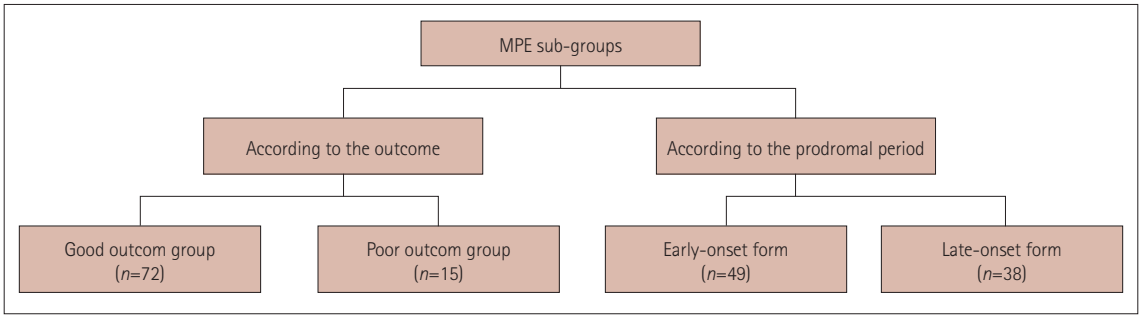

Fig. 2. Sub-groups of patients in our series. MPE, *Mycoplasma pneumonia* encephalitis.

0.001), increased LDH level (p=0.041), and elevated CSF protein (p=0.012) (Table 4).

DISCUSSION

This multicenter retrospective study investigated the clinical features of, differences in the efficacy of azithromycin and immunomodulatory therapy for, and prognosis of MPE in Chinese children. This was the largest multicenter cohort of children with MPE that we know of to have been assessed.

Most of the patients in this cohort presented with fever, disturbance of consciousness, headache, mild lymphocytosis, elevated CSF protein, diffuse slow waves in EEG, or cortical involvements on neuroimaging. The clinical manifestations and laboratory abnormalities were indistinguishable from those seen in viral encephalitis, partially treated bacterial meningitis, autoimmune encephalitis, and encephalitis with unknown pathogen. Moreover, compared with these conditions, varying multisystem involvement was found in 96.5% of the patients in our cohort, most frequently in respiratory tract lesions. The presence of respiratory symptoms also suggests that neurological disease is caused by immunological mechanisms rather than direct invasion.[2,5-7] Our study also found other clues, including a significantly increased CRP level and the presence of RESLES on neuroimaging; the possibility of *M. pneumoniae* infection should be considered, which would be consistent with the findings of previous studies.[13,14]

M. pneumoniae infections have been considered unusual among children aged up to 5 years.[1,5,15] In our study, the disease affected children of all ages except for neonates, with the most common onset age being 6–10 years, and our co-

Table 4. Prognostic factors associated with a poor outcome

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Onset in adolescence	18.934 (3.089–93.382)	<0.001*	20.743 (6.398–91.467)	0.001*
Originating in rural area	3.215 (0.843–12.561)	0.042*	4.290 (1.046–7.931)	0.158
Hypothermia	6.742 (2.598–23.237)	0.002*	5.397 (0.834–17.365)	0.083
Status seizure	1.276 (1.182–1.593)	0.037*	1.692 (0.217–5.341)	0.062
Pleural effusion	1.387 (0.115–14.131)	0.826	-	-
Involuntary movement	4.226 (0.917–13.264)	0.028*	-	-
Days from symptom onset to admission	9.889 (1.324–36.879)	0.071	-	-
IVIG+steroid use	1.093 (0.836–6.254)	0.092	-	-
LDH elevation	4.826 (3.451–29.756)	<0.001*	13.250 (5.729–46.512)	0.041*
Albumin decrease	0.595 (0.327–0.892)	0.058	-	-
CSF protein elevation	12.749 (6.932–37.698)	0.004*	10.572 (3.994–21.380)	0.012*
Basal ganglia involvement	3.278 (2.175–12.573)	0.023*	4.197 (1.348–8.216)	0.675

*$p<0.05$.
CI, confidence interval; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; OR, odds ratio.

hort also had a considerable proportion of patients younger than 5 years. Younger children likely presented with a shorter prodromal period, which could be explained by the blood–brain barrier (BBB) of young children not being well developed and prone to direct invasion from *M. pneumoniae*. A clear presentation of respiratory tract manifestations was also absent in 5% of the patients in our cohort. Therefore, while the value of the knowledge of respiratory tract manifestations is undeniable, the diagnosis of MPE cannot be ruled out in patients who do not present with these manifestations. However, our study did not identify any remarkable specific characteristics, including in the neurological manifestations, CSF, EEG, or neuroimaging findings of MPE, which contribute to distinguishing MPE from viral encephalitis. Therefore, *M. pneumoniae* should be considered a potential culprit of acute encephalitis in all children, irrespective of age, presence or absence of respiratory symptoms, and neurological manifestations. However, in those patients with acute encephalitis accompanied with multisystem involvement and considerably elevated CRP, *M. pneumoniae* should probably be considered as a possible pathogen.

Detection of *M. pneumoniae* in blood, CSF, and respiratory tracts by serological and PCR examinations is a critical step for confirming the diagnosis.[1,5,16] In the present cohort, all patients tested positive for *M. pneumoniae*-IgM in CSF and/or presented positive results in PCR testing of *M. pneumoniae*. There were more patients with *M. pneumoniae*-IgM positivity than *M. pneumoniae*-PCR positivity, and there were more patients with *M. pneumoniae*-PCR positivity in respiratory tract secretions than in CSF. Moreover, the number of *M. pneumoniae* copies in CSF was much lower than that in respiratory secretions. The difference in the copy number between the two samples due to respiratory tract rather than CSF are more suitable for the growth of *M. pneumoniae*.[5] These results also suggested that direct invasion was not the most common cause in our cohort. *M. pneumoniae* copies were also more easily detected in the CSF of patients with the early-onset form, which also supported the hypothesis that this form is mostly related to the direct invasion of *M. pneumoniae* in the CNS.

The lower detection limit of our detection technology was 400 copies/mL, so those below 400/mL may have been missed, which could account for the low *M. pneumoniae*-PCR positivity rate in CSF.

Daxboeck found that the mortality rate associated with MPE was 0.073–0.09, and that 0.146–0.34 of the surviving patients had neurological sequelae.[11] That study also found that a high cell count and elevated protein in the CSF as well as higher age were associated with unfavorable outcomes. There were no deaths in our cohort, although nearly 20% of the patients received a poor prognosis. Our univariable and further multivariable analyses indicated that onset in adolescence, increased CSF protein level, and elevated LDH were independent predictors of PO. The host immune response is often stronger in older children than in younger children, and cerebral plasticity after injury is also better in younger children than in older children, which may be reasonable explanations for those in the higher age group being more likely to have neurological sequelae.[17] Elevated CSF protein suggests abnormality in intrathecal protein synthesis or in the properties of the BBB, which are correlated with the clinical neurological symptoms of encephalitis and a PO.[18-21] LDH is a stable cytoplasmic enzyme that exists in all living cells, and is known to be a biomarker for which a high level means that

certain tissues have been damaged by disease or injury.[22,23] When the plasma membrane is damaged, LDH is rapidly released into the cell culture supernatant, which is key for cells to undergo apoptosis, necrosis, and other forms of cell destruction.[24] Some scholars[25,26] have recently applied LDH as a prognostic marker for *M. pneumoniae*-infection-related diseases, especially for refractory *M. pneumoniae* pneumonia. Several studies[27,28] also found that elevated serum LDH was a systemic biomarker for brain injury and encephalitis. However, there have been few investigations of the relationship between plasma LDH and MPE prognosis, especially in pediatric patients. Our study indicated that elevated LDH is a negative prognostic biomarker of MPE. After *M. pneumoniae* infection, brain cells become ischemic and hypoxic,[29] and LDH is released into the cellular space before diffusing into the CSF, finally entering the bloodstream via the damaged BBB, resulting in a rapid increase in serum LDH level. Elevated LDH therefore probably indicates a brain lesion,[27] which could help to identify patients with a high risk of a poor prognosis.

Antibiotic therapy has generally been considered for all children with suspected MPE and is associated with clinical improvement in most patients with MPE.[1,5,30] Because of its good CNS penetration, fewer adverse effects, and some anti-inflammatory effect, azithromycin is considered to be a first-line agent for most pediatric patients with MPE.[31,32] All patients in our cohort received azithromycin treatment, which can inhibit subsequent CNS invasion and immune system activation.[1] However, the role of immune-modulating therapies such as corticosteroids, IVIG, or plasmapheresis in MPE management remains undefined due to the lack of conclusive evidence from controlled studies in favor of such therapies, with most studies on MPE therapies being case reports. The common assumption is that immune-modulating therapies should be considered in those with immune-mediated syndromes such as acute disseminated encephalomyelitis or in those with prodromal symptoms.[5,9] Some research has suggested that corticosteroids should be used in patients diagnosed with *M. pneumoniae* who also present with severe extrapulmonary complications, and methylprednisolone should take precedence as the first recommendation.[33-35] A single-center cohort study by Daba et al.[9] found that early IVIG administration should be considered in patients with suspected MPE who do not respond to other therapies, particularly in those with prodromal symptoms of infection, for approximately a week or longer. In our cohort, the greater presence of prodromal respiratory symptoms and lesser detection of *M. pneumoniae* in CSF suggested that immunologically mediated infection rather than direct invasion was the most common cause, and so the immune modulatory therapy should be considered.

Our study also found that azithromycin combined with IVIG or corticosteroid therapy was correlated with shorter lengths of stay and symptom control compared with the azithromycin group alone, especially in the IVIG-combined group. However, in our study, the duration of prodromal symptoms did not affect the efficacy, which contrasts with the study by Daba et al.,[9] and could be explained by multiple mechanisms involved in MPE pathogenesis. It was particularly interesting that the group that received IVIG and corticosteroids with azithromycin did not have this advantage, which may be related to there being more critically ill cases in this group.

This study had some limitations. First, it had a retrospective design, and data loss was inevitable. Second, it was subject to referral bias due to it being conducted in a tertiary care referral center characterized by high proportions of patients in critical conditions and with advanced illness. Third, the sample was not nationally representative.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0328.

Availability of Data and Material

All data generated or analyzed during this study are included in this published article.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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