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Mycoplasma pneumoniae encephalitis in childhood

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Mycoplasma pneumoniae is an important etiologic agent of acute childhood encephalitis. We retrospectively reviewed 17 cases of *M. pneumoniae* encephalitis at the Pediatric Department of the National Taiwan University Hospital from April 1997 through March 2000. These cases were diagnosed as having positive immunoglobulin M antibodies (94%), a minimum 4-fold change of complement-fixation antibody titers (47%), or nested polymerase chain reaction. The ages of these patients ranged from 1.5 to 10.9 years (mean, 5.3 years) with a male-to-female ratio of 8:9. The clinical manifestations included fever (94%), altered consciousness (65%), seizure (41%), personality or behavior changes (29%), meningeal sign (24%), visual hallucination (24%), ataxia (12%), Guillain-Barré syndrome (6%), blurred vision (6%), and aphasia (6%). Respiratory symptoms and signs were found in 76% of the patients. Abnormal electroencephalogram and neuroimage were observed in all cases, while abnormal cerebrospinal fluid examination was noted in about one-third of the patients. Five (29%) patients required intensive care because of intractable seizure or respiratory failure. Fourteen (82%) patients recovered completely, but 3 (18 %) had sequelae including epilepsy, hydrocephalus, and global neurologic deficits with brain stem dysfunction. In Taiwan, *M. pneumoniae* should be considered an etiologic pathogen of acute childhood encephalitis if fever and respiratory symptoms and signs are observed with or without abnormal cerebrospinal fluid findings. Supportive treatment is the basis of management.

Key words: Encephalitis, children, *Mycoplasma pneumoniae*

Mycoplasma pneumoniae is an important pathogen of atypical pneumonia syndrome. This microorganism is a short rod (about 10 x 200 nm) without cell wall, which divides by binary fission with a long doubling time (>6 h). Infection of *M. pneumoniae* is through human-to-human transmission in which the portal of entry is through the upper respiratory tract. The incubation periods vary from 1 to 3 weeks. *M. pneumoniae* infection may manifest as pharyngitis, bronchitis, bronchiolitis, croup, and pneumonia. This organism can also affect almost every organ system besides the lung. The frequently reported ones include neurologic complications (meningitis, meningoencephalitis, transverse myelitis, Guillain-Barré syndrome, peripheral neuropathy, brain stem dysfunction), dermatologic involvement (exanthem, enanthem, Stevens-Johnson syndrome), cardiac complications (carditis, conduction defects), musculoskeletal complications (polyarthralgia, arthritis), gastrointestinal complications (hepatitis, pancreatitis), hemolytic anemia, and Raynaud's phenomenon [1,2]. Neurologic manifestations are the most frequent extrapulmonary complications of *M. pneumoniae* infection [3]. Encephalitis seems to be seen most often in children [4]. However, the importance of *M. pneumoniae* as an etiologic agent of acute encephalitis in childhood is often underestimated. According to the studies by Kolski *et al* [5] on acute childhood encephalitis, etiologic agents were identified in 66% of the cases, and *M. pneumoniae* accounted for 70% of the known causes. Since *M. pneumoniae* encephalitis in Taiwan is rarely reported, this study therefore aims to investigate the role of *M. pneumoniae* in childhood encephalitis in Taiwan.

Materials and Methods

All case records from the Department of Pediatrics of the National Taiwan University Hospital, coded with diagnoses compatible with encephalitis (including meningoencephalitis, encephalomyelitis, and cerebellitis) from April 1, 1997 to March 31, 2000, were reviewed.

Patients over 18 years old or had a history of neurologic illness were excluded from the study. Patients with at least one symptom or sign of parenchymatous brain dysfunction (such as altered consciousness, personality or behavior change, pareses,

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seizure, sensory symptoms, mental dysfunction, ataxia, etc) were diagnosed as encephalitis. Patients also have to show at least 2 of the following criteria to be included: (1) fever (body temperature ≥38°C); (2) abnormal cerebrospinal fluid (CSF) examination (pleocytosis >5 white blood cells per μL and/or increased protein content >40 mg/dL); (3) abnormal electroencephalogram (EEG) finding compatible with encephalitis; (4) abnormal results of neuroimaging, including computed tomography and magnetic resonance image.

Viral cultures of CSF, stool, throat swab, rectal swab, and serologic studies for Epstein-Barr virus, some enteroviruses, influenza, varicella-zoster virus, Japanese encephalitis, and polymerase chain reaction (PCR) for herpes simplex virus were performed in the patients in search for the etiology of encephalitis.

The complement fixation test and immunoglobulin (Ig)M–capture enzyme-linked immunosorbent assay (ELISA; SeroMP Kit, Savyon Diagnostica, Israel) were used for the diagnosis of *M. pneumoniae* infection, and nested PCR was performed in selected cases. Nested PCR was performed using the method modified by de Barbeyrac [6]. Two oligonucleotides were chosen from a region of the P1 adhesin gene of *M. pneumoniae* as primers (MP-P11:TGCCATCAACCCGCGCTTAAC; MP-P12:CCTTTGCAACTGCTCATAGTA; a 466-bp fragment was amplified as a PCR product). Amplification of clinical samples (10 μL) was performed in a final volume of 50 uL. A second-round amplification was done using the same method with the exception of using 10 μL of the first-round amplification product as clinical samples.

The diagnoses of *M. pneumoniae* infection were classified as: confirmed, probable, and possible according to the likelihood of their roles in pathogenicity: (1) Confirmed: serologic evidence of an acute infection (a minimum 4-fold change of antibody titers by complement fixation test in paired serum samples) and *M. pneumoniae* detected in CSF (by nested PCR); (2) Probable: serologic evidence of an acute infection (as above); and (3) Possible: detection of *M. pneumoniae* (by nested PCR) from extracranial sources (without serologic evidence of an acute infection) or serology suggestive of an acute infection (positive IgM antibodies by ELISA only).

Results

Between April 1997 and March 2000, a total of 131 records were initially selected, and 111 cases were included as encephalitis according to the enrollment criteria. The etiologic agents were identified in 50 (45%) patients and evidences of *M. pneumoniae* infection were found in 17 (15%) patients, including one confirmed, 7 probable, and 9 possible cases (Tables 1 and 2). Almost all *M. pneumoniae*-infected patients (16/17, 94%) had positive IgM antibody to *M. pneumoniae* and 8 (47%) patients had a minimum 4-fold change of antibody titers by complement fixation test in paired serum samples. Either nested PCR for CSF, serum, or throat swab was performed in 3 patients. Positive PCR results were found in one of the 2 CSF specimens, 2 of the 4 serum specimens, and 2 of the 3 throat swab specimens (Table 2). The ratio of male to female was 8:9. Their age ranged from 1.5 to 10.9 years (mean, 5.3 ± 2.9 years). The duration of hospitalization ranged from 2 to 148 days (median, 6 days; mode, 5 days). Five (29%) patients required intensive care due to intractable seizure in 4 patients and respiratory failure caused by Guillain-Barré syndrome in one patient.

Fever was found in almost every patient (16/17, 94%), with durations ranging from 1 to 10 days (mean, 4.9 ± 2.9 days). The interval between fever onset and neurologic manifestations ranged from 1 h to 10 days (mean, 2.6 ± 2.6 days). At least one respiratory symptom and sign (cough, rhinorrhea, abnormal breath sound by auscultation, or abnormal chest X-ray) were found in 13 (76%) patients. The interval between the onset of respiratory symptoms and neurologic manifestations ranged from 2 to 14 days (mean, 6.7 ± 4 days). Chest X-rays were performed in 16 patients and abnormal results were found in 8 (50%), all of whom revealed increased interstitial infiltration. Pneumonia was diagnosed in 4 (24 %) patients.

The neurologic manifestations are shown in Table 3.

Table 1. Etiology of childhood encephalitis at the National Taiwan University Hospital, 1997-2000

Period	No. of cases (%)							
	Mycoplasma pneumoniae	Enterovirus	HSV	VZV	Adenovirus	Influenza	EBV	Unknown
Apr 97-Mar 98 (n = 23)	4 (17)	0	1 (4)	0	1 (4)	0	0	17 (74)
Apr 98-Mar 99 (n = 38)	3 (8)	15 (39)	1 (3)	1 (3)	0	0	0	18 (47)
Apr 99-Mar 00 (n = 50)	10 (20)	3 (6)	3 (6)	4 (8)	1 (2)	2 (4)	1 (2)	26 (52)
Total (n = 111)	17 (15)	18 (16)	5 (5)	5 (5)	2 (2)	2 (2)	1 (1)	61 (55)

Abbreviations: HSV = herpes simplex virus; VZV = varicella-zoster virus; EBV = Epstein-Barr virus

Table 2. Results of laboratory tests for *Mycoplasma pneumoniae* infection

Patient no.	Category	CF I[a]	CF II[b]	IgM	Nested PCR	CSF[c]	EEG[d]	Neuroimage (CT or MRI)
1	Confirmed	1:2	1:16	+	Serum (+); CSF (+); Throat (+)	4 (3/1); 40; 94	Moderate	CT: brain swelling; MRI: leptomeningeal enhancement
2	Probable	1:2	1:256	+	Serum (-); CSF (-); Throat (-)	0; 22; 94	Mild	CT: brain swelling; MRI: enhancement at the nerve roots of spinal cord
3	Probable	1:2	1:128	+	ND	0; 24; >50	Severe	CT: brain swelling
4	Probable	1:2	1:32	+	ND	225 (100/125); 400; 99	Mild	CT: brain swelling, meningeal enhancement; MRI: multiple abnormal signals in subcortical area
5	Probable	NS	1:32	+	ND	0; 17; 56	Mild	ND
6	Probable	NS	1:16	+	ND	102 (56/46); 75; 75	Moderate	CT: brain swelling
7	Probable	1:8	1:32	+	ND	0; ND; >50	Mild	ND
8	Probable	NS	1:8	-	ND	63 (58/5); 43; 50	Moderate	MRI: multiple abnormal signals
9	Possible	1:2	1:2	+	Serum (-); Throat (+)	0; 24; 51	Mild	ND
10	Possible	1:2	1:2	+	ND	0; 18; 65	Mild	ND
11	Possible	1:8	NS	+	ND	73 (63/10); ND; ND	Mild	MRI: focal abnormal signals
12	Possible	1:32	1:64	+	ND	1 (1/0); 22; 82	Mild	ND
13	Possible	1:32	1:32	+	ND	3 (2/1); 10; 13	Moderate; focal spike	ND
14	Possible	1:2	ND	+	ND	1 (1/0); 12; 62	Mild	ND
15	Possible	1:16	ND	+	ND	ND	Mild	ND
16	Possible	1:32	ND	+	ND	ND	Mild	ND
17	Possible	1:32	ND	+	ND	2 (2/0); 17; 56	Mild	CT: brain swelling

Abbreviations: CF = complement fixation test; IgM = immunoglobulin M by enzyme linked immunosorbent assay; PCR: nested polymerase chain reaction; CSF = cerebrospinal fluid; EEG: electroencephalogram; CT: computed tomography; MRI = magnetic resonance image; ND = not done; NS = not specific

[a]CF I: CF was done at acute stage.

[b]CF II: CF was done at convalescent stage.

[c]CSF analysis includes cell count (neutrophil/lymphocyte), protein (mg/dL), and glucose (mg/dL).

[d]EEG pattern: mild = mild diffuse slow wave; moderate = moderate diffuse slow wave; severe = severe diffuse slow wave.

About two-thirds of the cases suffered from altered consciousness (65%). Seizure and personality or behavior changes were found in 41% and 29% of the cases, respectively. Meningeal symptoms and signs (headache, vomiting, and neck stiffness) and visual hallucination were noted in about one-fourth (24%) of the cases. Ataxia, Guillain-Barré syndrome, blurred vision, and aphasia were observed in a few cases.

Table 3. Neurologic manifestations of *Mycoplasma pneumoniae* encephalitis (n = 17)

Symptom/sign	No. of cases (%)
Altered consciousness	11 (65)
Lethargy	8 (47)
Irritable	3 (18)
Seizure	7 (41)
Behavior/personality change	5 (29)
Meningeal signs[a]	4 (24)
Visual hallucination	4 (24)
Ataxia	2 (12)
Blurred vision	1 (6)
Guillain-Barré syndrome	1 (6)
Aphasia	1 (6)

[a]including headache, vomiting, and neck stiffness.

Abnormal white blood cell counts were found in 10 (61%) patients, in which 8 had neutrophile predominant leukocytosis and 2 had leukopenia. Abnormal C-reactive protein levels were seen in 13 patients (median, 0.58 mg/dL). Cerebrospinal fluid examinations were performed in 15 patients, in which 5 (33%) showed abnormal results (Table 2). All patients showed abnormal EEG results. Neuroimages (6 computed tomography, 5 magnetic resonance imaging) were performed in 8 patients, and abnormal results were noted in all patients (Table 2).

In addition to supportive treatment, 10 patients received a course of macrolide treatment (erythromycin

Table 4. Comparison of clinical manifestations and laboratory results between *Mycoplasma pneumoniae* encephalitis patients with confirmed/probable etiology and patients with possible etiology

Clinical features	Confirmed/probable	Possible	*p*
Age (mean, years)	4.1	6.4	NS
Sex (M:F)	4:4	4:5	NS
Fever	7/8	9 / 9	NS
Respiratory S/S	7/8	6 / 9	NS
Altered consciousness	8/8	3 / 9	<0.05
Behavior change	1/8	4 / 9	NS
Seizure	4/8	3 / 9	NS
Visual hallucination	1/8	3 / 9	NS
Ataxia	2/8	0 / 9	NS
Meningeal S/S[a]	3/8	1 / 9	NS
Abnormal CSF	4/8	1 / 7	NS
Abnormal EEG	8/8	9 / 9	NS
Abnormal neuroimage	6/6	2 / 2	NS
Sequelae	2/8	1 / 9	NS

Abbreviations: S/S = symptoms and sign; CSF = cerebrospinal fluid examination; EEG = electroencephalogram; NS = not significant
[a]Including headache, vomiting, and neck stiffness.

10-14 days or azithromycin 3-5 days). One patient received corticosteroid for severe brain edema and one received corticosteroid and intravenous Ig (IVIG) for Guillain-Barré syndrome with quadriplegia and respiratory failure. At the time of discharge, 9 (53%) patients recovered completely. During the outpatient clinic follow-up, 14 (82%) patients had total recovery without any sequelae. Sequelae were noted in 3 patients, including epilepsy, hydrocephalus with epilepsy, and global neurologic deficits with brain stem dysfunction and epilepsy each in one patient.

The age, sex, clinical manifestations, laboratory test results, and clinical examinations were compared between the confirmed/probable group and the possible group. No significant difference was found between these 2 groups except for the ratio of altered consciousness (Table 4).

Because of the increase in enterovirus encephalitis

Table 5. Comparison of clinical manifestations and laboratory results between patients of *Mycoplasma pneumoniae* encephalitis and enterovirus encephalitis

Clinical feature	*Mycoplasma pneumoniae* n = 17(%)	Enterovirus n = 18 (%)	*p*
Age (mean ± SD, years)	5.3 ± 2.9	4.1 ± 3.4	NS
Sex (M:F)	8:9	12:6	NS
Fever	16 (94)	14 (78)	NS
Respiratory S/S	13 (76)	6 (33)	0.026
Altered consciousness	11 (65)	13 (72)	NS
Behavior change	5 (29)	1 (6)	NS
Seizure	7 (41)	3 (17)	NS
Visual hallucination	4 (24)	1 (6)	NS
Ataxia	2 (12)	4 (22)	NS
Pareses	1 (6)	7 (39)	0.041
Meningeal S/S	4 (22)	10 (56)	NS
Abnormal CXR[a]	8 (50)	3 (17)	NS
Abnormal CSF[b]	5 (33)	17 (94)	0.001
Abnormal EEG[c]	17 (100)	14 (78)	NS
Abnormal neuroimage[d]	8 (100)	7 (88)	NS
Sequelae[e]	3 (18)	4 (24)	NS

Abbreviations: S/S = symptom/sign; CXR = chest X-ray; CSF = cerebrospinal fluid; EEG = electroencephalogram; NS = not significant
[a]Only 16 patients in the *M. pneumonias* group and 16 in the enterovirus group undergone this examination.
[b]Only 15 patients in *M. pneumoniae* group undergone this examination.
[c]Only 17 patients in the enterovirus group undergone this examination.
[d]Only 8 patients in the *M. pneumoniae* group and 8 in the enterovirus group undergone this examination.
[e]One patient in the enterovirus group lost long-term follow-up.

in Taiwan in recent years [7,8], the age, sex, clinical manifestations, laboratory test results, and clinical examinations between the patients of *M. pneumoniae* encephalitis (17 cases) and enterovirus encephalitis (18 patients) were also compared (Table 5). More respiratory symptoms and signs (76% vs 33%), less limb pareses (6% vs 39%), and less abnormal CSF routine examinations (33% vs 94%) were found in the group with *M. pneumoniae* infection ($p<0.05$). In addition, more behavior and personality change, seizure, visual hallucination, abnormal chest X-ray, and less meningeal signs were noted in *M. pneumoniae* infection, although these were not statistically significant ($p=0.088$, 0.146, 0.177, 0.137, and 0.112, respectively).

Discussion

Central nervous system (CNS) manifestations are the most common extrapulmonary complications of *M. pneumoniae* infection. The incidence of CNS involvement is about 0.1% among patients with *M. pneumoniae* infection, and about 7% among those who were hospitalized due to *M. pneumoniae* infection [9]. The incidence was 4.6% in a hospital-based survey in Taiwan [10]. Encephalitis is the major presentation in children [4,9]. However, the role of *M. pneumoniae* in childhood encephalitis seems to be underestimated. In this hospital-based study, *M. pneumoniae* infection accounted for 15% of all childhood encephalitis and 34% of the childhood encephalitis with known causes. *M. pneumoniae* was the leading cause of childhood encephalitis with known etiology except in 1998 when enterovirus 71 caused a huge outbreak. In recent pediatric studies in Helsinki [11] and Toronto [5], *M. pneumoniae* was also a predominated etiologic agent in childhood encephalitis.

The neurologic manifestations of *M. pneumoniae* encephalitis are variable. The most common features in this study were disturbed consciousness (65%) and seizure (41%). Behavior or personality changes were seen in 29% of the patients. About one-fourth of the patients presented visual hallucination. Preceding fever and respiratory symptoms and signs were commonly observed, and fever was universal. The rate of respiratory manifestation (76%) in this study was higher than those seen in 2 previous studies (38% and 23%) [9,11], but was close to a study by Lerer *et al* [10] (79%) and one study in Taiwan (67%) [13].

Because of the significance of enterovirus infection in Taiwan, we compared the clinical presentations of encephalitis caused by *M. pneumoniae* and enterovirus. The respiratory symptoms and signs with normal results of CSF routine examination favor a diagnosis of *M. pneumoniae* encephalitis rather than enterovirus encephalitis. Enterovirus infection was more likely to present limbs pareses.

In this study, 67% of the patients had initial normal findings in CSF examinations in which the results were similar to other recent studies [9,10,12]. Electroencephalogram and neuroimages such as computed tomography and magnetic resonance imaging were sensitive tools to detect any evidence of encephalitis in patients in this study. All patients presented abnormal EEG results, with diffuse slow wave as the most common finding. Neuroimaging revealed findings such as diffuse edematous brain parenchyma, leptomeningeal enhancement, focal or multiple abnormal signals, and enhancement at the nerve roots of the spinal cord.

Proposed mechanisms of *M. pneumoniae* encephalitis included direct invasion, neurotoxin, and immune-mediated mechanism [13-18]. In this study, the mean interval between fever onset and neurologic manifestations was 2.6 days. According to the study by Narita *et al* [14], early neurologic manifestations (interval ≤7 days), as in this study, suggest direct CNS invasion by *M. pneumoniae* in the pathogenesis of encephalitis. However, immune-mediated mechanism may also play an important role, as suggested in the clinical features of patient 2 in this study, who suffered from disturbed consciousness and Guillain-Barré syndrome with negative PCR results of serum, CSF, and throat swab, and the dramatic response to steroid and IVIG.

The treatment of *M. pneumoniae* encephalitis is still controversial. Supportive treatment, including seizure control, intracranial pressure control, cardiovascular and respiratory supports, and fluid and electrolyte balance, is most important. The role of antibiotic therapy in *M. pneumoniae* encephalitis is still unclear. Erythromycin and newer macrolides (clarithromycin, azithromycin) are widely used for the treatment of *M. pneumoniae* respiratory infection in children [19]. In theory, however, antibiotics such as chloramphenicol, doxycycline, and quinolone are better choices for the treatment of *M. pneumoniae* encephalitis because of their antimycoplasmal activity and ability to transverse the blood-brain barrier [20]. Because immune-mediated mechanism may be the working pathogenesis in some patients, immunosuppressants (corticosteroid or IVIG) were used for selected patients in some literature [10, 12,20,21] despite no conclusive evidence on the effect of these therapies.

The outcomes of *M. pneumoniae* encephalitis have been variable. In this study, 18% of the patients suffered from neurologic sequelae during the long-term follow-

up. Previous hospital-based studies in Taiwan [10] presented one mortality case and 6 completely recovered cases during a 21-month period. One study showed that the risks of neurologic sequelae and death due to herpes simplex virus and *M. pneumoniae* infections in children were 11.7-fold and 7-fold greater, respectively, than those due to other infections [22]. The study of Koskiniemi [9] showed 8% mortality and 23% of severe sequelae.

In conclusion, *M. pneumoniae* is an important etiology of encephalitis in children. The clinical presentations of *M. pneumoniae* encephalitis included fever, respiratory symptoms and signs, disturbed consciousness, seizure, behavior or personality change, meningeal sign, and visual hallucination. Complement fixation test, *M. pneumoniae*-specific IgM by ELISA, and PCR are useful diagnostic tools. Although supportive treatment is still the basis of management, steroids may be effective in selected patients.

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