Neurological Manifestations of *Mycoplasma pneumoniae* Infection in Hospitalized Children: A Single-Center Experience

Hastanede Yatan Çocuklarda *Mikoplazma pnömoni* Enfeksiyonunun Nörolojik Belirtileri: Tek Merkezli Bir Deneyim

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ABSTRACT

Objective: *Mycoplasma pneumoniae* is one of the major causes of upper and lower respiratory tract infection in childhood. Neurological diseases are among the most common extrapulmonary manifestations.This study aimed to share our center's experience regarding the treatment characteristics and clinical and radiological course of patients with *M. pneumoniae*-related neurological symptoms in light of the available evidence.

Material and Methods: The study included in hospitalized patients with positive primary *M. pneumoniae* serology *M. pneumoniae* serology was examined in serum from the acute period and, if possible, convalescent serum (1-4 weeks after disease onset) using *M. pneumoniae*-specific immunoglobulin M (IgM) and IgG enzyme-linked immunoassay. A 4-fold or greater increase in IgG titer between acute and convalescent serum samples was considered diagnostic for *M. pneumoniae* infection. The clinical, laboratory, and imaging results and demographic data of patients with CNS involvement were evaluated.

Results: Review of the patients' charts showed that 13 (25%) of the 52 patients with confirmed *M. pneumoniae* infection had neurological symptoms and findings. When evaluated together with clinical, laboratory, and imaging results, 6 patients were diagnosed with acute cerebellar ataxia, 4 patients with encephalitis, and 1 patient each with GBS, optic neuritis, and longitudinally extensive transverse myelitis.

Conclusion: Although *M. pneumoniae* is known as mainly a respiratory pathogen, it also causes various neurological disorders. Although all of our patients had symptoms of respiratory tract infection, it has been shown that that *M. pneumoniae* can also cause neurological disease without respiratory symptoms. Further studies are needed to evaluate the most appropriate methods for early diagnosis and treatment of neurological involvement, considering the long-term burden of the disease.

Key Words: Childhood, *Mycoplasma pneumonia*, Neurological signs and symptoms

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ÖZ

Amaç: *Mikoplazma pnömoni*, çocukluk çağında üst ve alt solunum yolu enfeksiyonlarının başlıca nedenlerinden biridir. Nörolojik hastalıklar en sık görülen ekstrapulmoner belirtiler arasındadır. Bu çalışma, *M. pnömoni* ile ilişkili nörolojik semptomları olan hastaların tedavi özellikleri, klinik ve radyolojik seyri ile ilgili merkezimizin deneyimlerini mevcut kanıtlar ışığında paylaşmayı amaçlamıştır.

Gereç ve Yöntemler: Hastanede yatan ve primer *M. Pnömoni* serolojisi pozitif çıkan pediatrik hastalar dahil edilmiştir. *M. Pnömoni* serolojisi akut dönemde serumda ve mümkünse konvalesan serumda *M. Pnömoni* spesifik IgM ve immünglobulin G (IgG) enzim immün assay yöntemi kullanılarak bakıldı. Akut dönemde ve hastalık başladıktan 7 gün-4 hafta sonra, konvalesan dönemde alınan serumlarda IgG titresinde dört kat ve üzeri artış *M. Pnömoni* enfeksiyonu için tanısal kabul edildi. SSS tutulumu olan hastalar demografik, klinik, labarotuvar ve görüntüleme sonuçları eşliğinde değerlendirildi.

Bulgular: Çeşitli nedenlerle Ocak 2019- Aralık 2020 tarihleri arasında hastanemizde yatan 52 hasta primer *M. Pnömoni* enfeksiyonu doğrulanmıştı. *Mikoplazma pnömoni* enfeksiyonu doğrulan 52 hastanın 13'ünde (%25) nörolojik semptom ve bulgular olduğu tespit edildi. Klinik, laboratuar ve görüntüleme sonuçları ile birlikte değerlendirildiğinde; 6 olgu (%46) Akut serebellar ataksi, 4 olgu (%30) ensefalit, bir olgu Guillain barre sendromu (GBS), bir olgu optik nörit bir olgu da Longitudinal ekstensif transvers miyelit (LETM) tanısı almıştı.

Sonuç: *Mikoplazma pnömoni* başlıca solunum yolu patojeni olarak bilinmesine rağmen çeşitli nörolojik rahatsızlıklara da neden olur. Nörolojik tutulumun erken tanı ve tedavisine yönelik en uygun yöntemlerin değerlendirilmesi için hastalığın uzun dönemli yükünü de göz önünde bulundurarak daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Çocukluk çağı, *Mikoplazma pnömonisi*, Nörolojik belirti ve semptomlar

INTRODUCTION

Mycoplasma pneumoniae is one of the major causes of upper and lower respiratory tract infection in childhood. Besides respiratory tract infection, *M. pneumoniae* also causes various extrapulmonary diseases such as hemolytic anemia, polyarthritis, erythema multiforme, and hepatic, cardiac, and neurological diseases in 25% of cases. Neurological diseases are among the most common extrapulmonary manifestations (1,2).

M. pneumoniae-related neurological disorders are the most difficult to diagnose and treat, and may represent a true medical emergency. Neurological symptoms have been demonstrated in approximately 7% to 10% of patients hospitalized with *M. pneumoniae* infection (3-5). Encephalitis and meningoencephalitis are the most common neurological diseases caused by *M. pneumoniae*, although there have also been reports of cerebellitis, polyneuropathy, acute disseminated encephalomyelitis (ADEM), stroke, transverse myelitis (TM), Guillain-Barré syndrome (GBS), myasthenia gravis (MG), peripheral neuropathy, and optic neuritis (6-9).

The time between the onset of respiratory symptoms and the onset of neurological symptoms ranges from 2 to 14 days (10). More than 80% of patients with central nervous system (CNS) symptoms also have a respiratory tract infection (11). The etiopathogenesis of these neurological manifestations is still unknown, although three different mechanisms have been proposed: direct CNS invasion by *M. pneumoniae*, indirect autoimmune mechanisms, and vasculitis or thrombotic vascular occlusions that occur by a direct and indirect mechanism (12).

This study aimed to share our center's experience regarding the treatment characteristics and clinical and radiological course of patients with *M. pneumoniae*-related neurological symptoms in light of the available evidence.

MATERIALS and METHODS

The study included pediatric patients hospitalized in the Dr. Sami Ulus Maternity and Pediatrics Training and Research Hospital between January 2019 and December 2020 and whose primary *M. pneumoniae* serology was positive. *M. pneumoniae* serology was examined in serum from the acute period and, if possible, convalescent serum (1-4 weeks after disease onset) using *M. pneumoniae*-specific immunoglobulin M (IgM) and IgG enzyme-linked immunoassay. A 4-fold or greater increase in IgG titer between acute and convalescent serum samples was considered diagnostic for *M. pneumoniae* infection. The study was approved by the Clinical Research Ethics Committee of Ankara Dr Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital (07.04.2021/ E-21-04-147)

The clinical, laboratory, and imaging results and demographic data of patients with CNS involvement were evaluated. The patients' neurological signs and symptoms were categorized as seizure, ataxia, muscle weakness, confusion or coma, altered mental status, visual disturbance, and speech disturbance. Detection of enterovirus, parechovirus, herpes simplex virus (HSV) 1 and 2, and varicella zoster virus (VZV) in cerebrospinal fluid (CSF) specimens was performed using multiplex real-time polymerase chain reaction (RT-PCR) kits in an RT-PCR device.

According to the consensus statement of the International Encephalitis Consortium (13), *M. pneumoniae*-related encephalitis was defined as encephalopathy (altered consciousness, lethargy, irritability, or personality change) lasting at least 24 hours and at least two of the following criteria: fever, seizures, focal neurological findings, CSF pleocytosis, and electroencephalography or imaging findings suggestive of encephalitis. According to the 2002 diagnostic criteria report of the Transverse Myelitis Consortium Working Group (14), GBS was diagnosed based on clinical and neurological examination findings, presence of albuminocytologic dissociation in CSF, and electromyography

(EMG) findings; cerebellitis was diagnosed based on clinical, examination, and radiological imaging findings; postinfectious cerebellar ataxia was diagnosed based on history, the nature of cerebellar ataxia, the patient's clinical findings, CSF findings, and convalescent characteristics.

RESULTS

Serum *M. pneumoniae*-specific IgM was detected in 158 patients hospitalized in our center for various reasons between January 2019 and December 2020. Of these, 52 patients exhibited an increase in IgG titer in the acute period and/or at an average of 2 weeks after disease onset that was consistent with the diagnostic criteria and confirmed primary *M. pneumoniae* infection. In the other 106 patients, primary *M. pneumoniae* infection could not be confirmed.

Review of the patients' charts showed that 13 (25%) of the 52 patients with confirmed *M. pneumoniae* infection and 21 (19.8%) of the 106 unconfirmed patients had neurological symptoms and findings (Figure 1). Of the 13 patients with confirmed infection and neurological symptoms, 12 (92%) were female and 1 (8%) was male, and the mean age was 10.1 years (range, 5-16).

In addition to neurological symptoms, 11 (84.4%) of the patients had upper respiratory tract infection symptoms and 2 (15.6%) had lower respiratory tract infection symptoms. Neurological symptoms included ataxia (n = 6), confusion (n = 4), visual impairment (n = 1), myasthenia/paralysis (n = 2), and seizure (n = 2). The patients' mean Glasgow Coma Score at admission was 14.

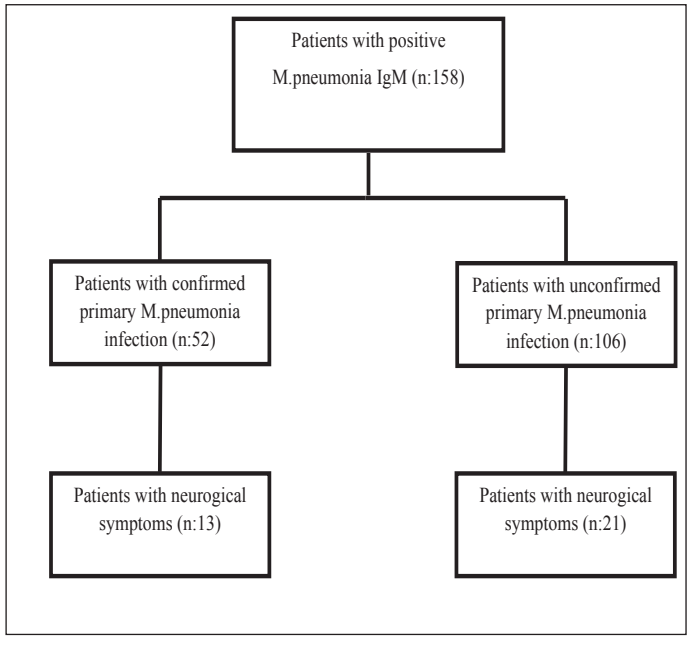

Figure 1: Algorithm of study.

The patients' reported neurological signs and symptoms as well as their CSF, electroencephalography, brain magnetic resonance imaging (MRI), and EMG findings were evaluated to establish a definitive diagnosis. CSF analysis revealed increased protein in 3 patients (21.4%) and cells on direct examination in 2 patients (14%). The detailed laboratory and imaging findings are presented in Table I.

RT-PCR tests for enterovirus, HSV 1 and 2, and VZV in CSF and tests for viral (EBV, cytomegalovirus [CMV], VZV) and bacterial (Borrelia burgdorferi, Brucella) pathogens in serum were performed for differential diagnosis and resulted negative in all patients. CSF culture was also negative in all cases. When evaluated together with clinical, laboratory, and imaging results, 6 patients (46%) were diagnosed with acute cerebellar ataxia, 4 patients (30%) with encephalitis, and 1 patient (8%) each with GBS, optic neuritis, and longitudinally extensive transverse myelitis (LETM).

The patients' mean length of hospital stay was 13 days, and 3 patients required admission to the intensive care unit due to isolated neurological symptoms. All patients were treated with clarithromycin starting a mean of 2 days after admission. In addition, 10 patients received intravenous immunoglobulin (IVIg) therapy (6 patients with cerebellitis, 2 with encephalitis, 1 with GBS, 1 with LETM), 4 patients received high-dose methylprednisolone (2 with encephalitis, 1 with LETM, 1 with optic neuritis), and the patient with LETM underwent plasma exchange. In 11 patients, empiric acyclovir therapy was initiated and discontinued when CSF HSV-PCR resulted negative.

The mean follow-up time after discharge was 13.4 months (range, 6-24). The patient with LETM exhibited moderate sequelae during follow-up, while the other patients had no sequelae.

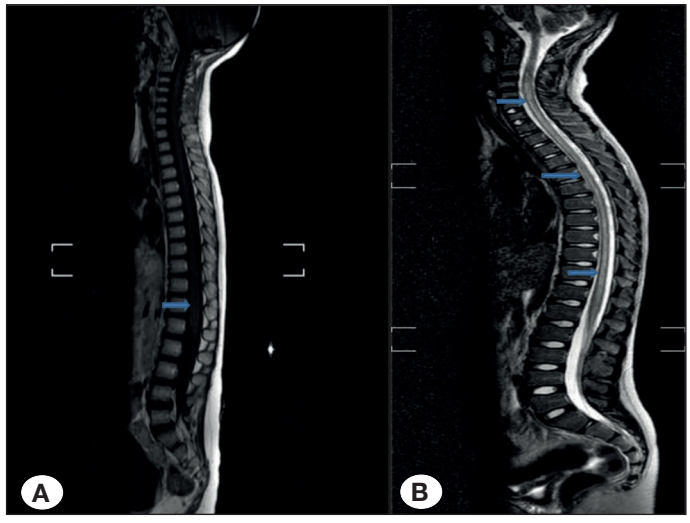

Figure 2: A) Pial enhancement in the distal thoracic plane. **B)** Sagittal longutidinal MR image showed increased signal in the gray matter starting from the C2 inferior end plate level to the subject in the whole spinal cord and expansion due to edema in the cervical.

Table I: The clinical findings in the pediatric patients presenting with *M. pneumoniae*-related neurological disorders.

Case	Age (y)/ Gender	Res. Findings	Neurological manifestation	GCS	CSF examination cell count (10^6/L)	CSF protein (g/L)	EEG	MRI findings	Diagnosis	Treatment	Hospital stay interval (days)	Prognosis
1	5/F	+	Ataxia, vomiting	15	-	22	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
2	14/F	+	Ataxia, vomiting, dizziness	15	-	34	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	14	CR
3	5/F	+	Ataxia, dizziness	15	-	32	N	N	Postinfectious Cerebellar Ataxia	IVIg, Antibiotic (macrolide) Acyclovir	8	CR
4	12/F	+	Ataxia, vomiting, dizziness	15	-	130	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
5	6/F	+	Ataxia, vomiting	15	-	120	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	14	CR
6	11/F	+	Ataxia, Dizziness	15	-	24	N	N	Postinfectious Cerebellar Ataxia	IVIg,Antibiotic (macrolide) Acyclovir	10	CR
7	6/F	+	Confusion, drowsiness, seizure	10	-	34	Generalized hypersynchronous discharges	Leptomeningeal enhancement Supratentorial white matter Basal ganglia	Encephalitis	High-dose methylprednisolone, IVIg, macrolide Acyclovir,	28	CR
8	12/F	+	Fever, confusion, drowsiness,	12	80	103	N	N	Encephalitis	IVIg, macrolide Acyclovir	20	CR
9	11/F	+	Confusion, drowsiness, seziure	12	-	55	N	N	Encephalitis	Antibiotic (macrolide) Acyclovir	14	CR
10	12/M	+	Confusion, drowsiness, seizure	12	120	50	Generalized slowing	N	Encephalitis	High-dose methylprednisolone, IVIg, macrolide Acyclovir,	28	CR
11	17/M	+	Blurred vision, painful eye movements	15	-	45	-	right optic nerve thickening	Optic neuritis	High-dose methylprednisolone, macrolide	7	CR
12	5/F	+	Pain in the legs, inability to walk	15	-	57	-	pial enhancement in the thoracic regionand filume terminale	Guillain-Barre syndrome	IVIg, macrolide	10	CR
13	16/F	+	Inability to walk, urinary incontinence	15	-	28	-	Spinal MRI T2 cervical, dorsal, lumbar patchy hyperintensities	Transvers myelitis	High-dose methylprednisolone, Macrolide, IVIg,PLX	26	Paraparesis

***F:** Female, **M:** Male, **GCS:** Glasgow coma scale, **CSF:** Cerebrespinal fluid, **IVIg:** Intravenous immunoglobulin, **PLX:** plasma exchange, **CR:** Complete remission, **N:** Normal*

DISCUSSION

Mycoplasma pneumoniae infection has been associated with various neurological diseases in children. Other than the many case reports and reviews, a few studies have systematically examined this relationship, but studies reporting the frequency and detailed analysis of neurological symptoms and predicting neurological involvement in children are rare (7,15,16). While neurological complications are observed in approximately 5% of patients hospitalized for *M. pneumoniae* infection, this pathogen has been detected in approximately 10% of patients presenting with acute, febrile CNS findings (3-5). In our study, 52

patients with primary *M. pneumoniae* infection were identified and neurological involvement was detected in 13 (25%) of them during hospitalization and treatment. Similarly, Kammer et al. (15) reported neurological involvement associated with *M. pneumoniae* in 22 (24.7%) of 89 patients in their study.

Approximately 80% of patients with neurological involvement have signs and symptoms of respiratory tract infection during or beforehand (2,10,17,18). All of our patients had respiratory signs and symptoms, but they were not severe enough to require hospitalization, and all were admitted because of neurological involvement.

Previous studies have shown encephalitis to be the most common extrapulmonary neurological disease caused by *M. pneumoniae* (7,8,15). In our study, the most common neurological involvement was acute cerebellar ataxia (6 patients), followed by encephalitis in 4 patients (30%), and GBS, optic neuritis, and LETM in 1 patient each (8%), which suggests that *M. pneumoniae* can be considered as a trigger in acute and otherwise unexplained neurological disorders.

Acute cerebellar ataxia often occurs after infections or appears suddenly during an infection, and usually causes only cerebellar signs and symptoms. Acute cerebellar ataxia is a diagnosis of exclusion; history, physical examination, laboratory, and imaging findings must be used to rule out conditions that should be considered in the differential diagnosis, including posterior fossa tumors, neuroblastoma (opsoclonus-myoclonus syndrome), acute bleeding, drug intoxications, acute labyrinthitis and metabolic diseases (Hartnup disease, maple syrup urine disease) (10,19). *M. pneumoniae*-related ataxia may occur in the early or late stages of infection. It is believed to occur due to direct invasion during the early period or the effect of immune complexes in the late period (20). Because acute cerebellar ataxia is generally associated with certain infections, especially VZV, all of our patients had serology and CSF PCR analysis for differential diagnosis from VZV, EBV, and CMV. Brain and spinal MRI were normal in all of our patients, and all were discharged without sequelae after a mean hospital stay of 8 days (range, 7-14).

Encephalitis is the most common extrapulmonary neurological disease caused by *M. pneumoniae* (21). In our study, it was the second most common neurological involvement (n = 4) after acute cerebellar ataxia. It has been suggested that *M. pneumoniae*-related encephalitis occurs as a result of both direct and autoimmune mechanisms. In previous studies, the low detection rates of *M. pneumoniae* DNA in the CSF of patients with *M. pneumoniae* encephalitis and the presence of a latent period after respiratory symptoms suggest indirect mechanisms in the pathogenesis of encephalitis (6,22). In our study, *M. pneumoniae* infection was demonstrated serologically in the serum of 4 patients with encephalitis. As all other causative factors were ruled out, we believe *M. pneumoniae* caused encephalitis as a result of indirect invasion.

Conjunctivitis is the most common ocular finding in *M. pneumoniae* infection, although others such as nystagmus, uveitis, and ocular motor nerve paralysis have been reported (23). *M. pneumoniae*-associated optic neuritis has rarely been described (24). In our study, optic neuritis was detected in 1 patient. This previously healthy patient presented with decreased vision and pain in the right eye after an upper respiratory infection. Their extraocular eye movements and other neurological examination were normal, but hyperemia and optic disc edema were observed on fundus examination and orbital MRI revealed thickening of the right optic nerve. In terms of all other causative factors, CSF analysis was normal, serology and PCR were negative for EBV, CMV, and VZV, serum anti-aquaporin 4 antibody (NMO IgG) and anti-MOG antibody were negative, and brain MRI was unremarkable. Based on these findings, optic neuritis associated with *M. pneumoniae* was suspected. Most cases of *M. pneumoniae*-related optic neuritis reported in the literature have been in children and young adults (24-27). *M. pneumoniae* should be considered in children diagnosed with isolated optic neuritis, even if they have no symptoms of respiratory tract infection.

GBS is an acute inflammatory polyneuropathy that is characterized by rapidly progressing symmetrical muscle weakness and loss of deep tendon reflexes, and can affect individuals of all ages. Symptoms of GBS usually occur after a viral or bacterial infection. *M. pneumoniae* is the second most commonly reported cause, after Campylobacter jejuni (28). The one GBS patient in our study developed weakness of the legs and gradual inability to walk starting 6 days after the onset of respiratory tract infection symptoms. On physical examination, the patient's vital signs were normal, there was loss of strength in the legs that was more pronounced distally, deep tendon reflexes were absent, while sensory and other system examinations were normal. CSF and spinal MRI findings (figure-2) were consistent with GBS and a pre-treatment serum sample was positive for *M. pneumoniae* IgM and IgG. The patient received IVIg therapy and serology performed 4 weeks after treatment was negative for *M. pneumoniae* IgM while IgG titer was increased. Serology and PCR are still the most accurate methods to determine the role of *M. pneumoniae* in GBS (29). Although PCR analysis could not be performed for our patient, the diagnosis of *M. pneumoniae*-associated GBS was based on the presence of respiratory tract infection findings, *M. pneumoniae* IgM and IgG positivity in serum before treatment, and the increase in *M. pneumoniae* IgG titer and lack of IgM at 4 weeks after treatment. *M. pneumoniae* should be considered as a common and treatable cause of GBS in childhood.

TM is one of the rare neurological diseases caused by *M. pneumoniae*. In a study evaluating 365 children with *M. pneumoniae* detected by PCR analysis of CSF or respiratory

swab sample, 42 patients were diagnosed as having *M. pneumoniae*-related neurological disease. TM was observed in 12% of those 42 patients, while in another study by Kammer et al. (15), LETM was observed in only 1 of 22 patients with *M. pneumoniae*-related neurological disease (7). In our study, a patient who presented with complaints of bilateral lower extremity weakness and urinary incontinence 7 days after respiratory tract infection was found to have spinal MRI findings consistent with LETM, but etiological studies of serum anti-aquaporin 4 antibody (NMO IgG) and anti-MOG antibody were negative (Figure 2). The results of CSF analysis, serology and PCR for EBV, CMV, VZV serology, and brain MRI also suggested no other causative factor, and *M. pneumoniae* IgM and IgG were detected in the patient's pre-treatment serum sample. When the desired response was not seen after high-dose methylprednisolone therapy, the patient was treated with IVIg and plasma exchange therapy. In serology performed 4 weeks after treatment, *M. pneumoniae* IgM was negative and IgG titer was increased. Based on the clinical and laboratory findings, the patient was diagnosed as having M. pneumonia-related LETM.

There is a lack of consensus regarding how to treat neurological diseases associated with *M. pneumoniae*. In most studies, it is suggested that administering systemic antibiotherapy is necessary independent of disease type and pathogenesis. Patients with suspected or confirmed cases of disease characterized by acute severe inflammation are treated with steroids and/or IVIg (22). All patients in our study received clarithromycin, 10 patients were treated with IVIg (4 with cerebellitis, 2 with encephalitis, 1 with GBS, and 1 with LETM), 4 patients received high-dose methylprednisolone (2 with encephalitis, 1 with LETM, 1 with optic neuritis), and 1 patient with LETM underwent plasma exchange therapy. The patients were followed for a mean of 13.4 months (range, 6-24) after discharge and only the patient with LETM had moderate sequelae, while no sequelae were observed in the other patients.

In conclusion, although *M. pneumoniae* is known as mainly a respiratory pathogen, it also causes various neurological disorders. Although all of our patients had symptoms of respiratory tract infection, it has been shown that that *M. pneumoniae* can also cause neurological disease without respiratory symptoms. Further studies are needed to evaluate the most appropriate methods for early diagnosis and treatment of neurological involvement, considering the long-term burden of the disease.

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