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ORIGINAL ARTICLE

Prognostic values of a combination of intervals between respiratory illness and onset of neurological symptoms and elevated serum IgM titers in *Mycoplasma pneumoniae* encephalopathy

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Anti-*M. pneumoniae* immunoglobulin M (IgM);
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M. pneumoniae-associated encephalopathy;
Mycoplasma pneumonia;
Polymerase chain reaction (PCR)

Background/Purpose: To retrospectively analyze the clinical manifestations of *Mycoplasma pneumoniae* (*M. pneumoniae*)-associated encephalopathy in pediatric patients.
Methods: Pediatric patients with positive serum anti-*M. pneumoniae* immunoglobulin M (IgM) were enrolled in this study. Clinical signs and symptoms, laboratory data, neuroimaging findings, and electrophysiological data were reviewed.
Results: Of 1000 patients identified, 11 (1.1%; male:female ratio = 7:4) had encephalopathy and were admitted to the pediatric intensive care unit. Clinical presentation included fever, symptoms of respiratory illness, and gastrointestinal upset. Neurological symptoms included altered consciousness, seizures, coma, focal neurological signs, and personality change. Neuroimaging and electroencephalographic findings were non-specific. Specimens of cerebrospinal fluid (CSF) for *M. pneumoniae* polymerase chain reaction (PCR) were negative. Higher *M. pneumoniae* IgM titers and longer intervals between respiratory and CNS manifestations were associated with worse outcomes.

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Conclusion: Clinical manifestations of *M. pneumoniae*-associated encephalopathy were variable. Diagnosis of *M. pneumoniae* encephalopathy should not rely on CSF detection of *M. pneumoniae* by PCR. *M. pneumoniae* IgM titers and intervals between respiratory and CNS manifestations might be possibly related to the prognosis of patients with *M. pneumoniae*-associated encephalopathy.

Introduction

Encephalitis refers to an acute, usually diffuse, inflammatory process affecting the brain.[1] The incidence is approximately 1.5—13.8 cases per 100,000.[2,3] Encephalitis can be caused by a variety of afflictions, most often by a virus, but occasionally by bacteria or other pathogens. Encephalopathy is a brain disease, damage, or malfunction. The causes of encephalopathy are numerous and varied. The majority of cases arise from infection, liver damage, anoxia, or kidney failure. Whether known or unknown infections cause encephalitis, leading to infection-associated encephalopathy, remains unclear.[4]

A series of microbes can cause acute encephalopathy, but agents, in most cases, remain unknown. *Mycoplasma pneumoniae* is a common pathogen of the respiratory system in school-aged children and young adults.[5] The prevalence of *M. pneumoniae* was 10% in 2010, 17% in 2011, and 15% in 2012, supporting a trend of cyclic endemics every 3～5 years for *M. pneumoniae* infections in Taiwan.[6] This microorganism can affect blood, skin, joints, central nervous system (CNS), liver, pancreas, and the cardiovascular system, causing extrapulmonary manifestations.[7,8] *M. pneumoniae*-associated neurologic illness is not rare and is identified in 1% of encephalopathy cases.[9] Over the years, several case reports have described a wide variety of complications associated with *M. pneumoniae* infection, including cases with neurologic complications in the absence of systemic symptoms and cases that appear to be post-infectious, rather than being caused directly by the organism.[10,11] Despite several cases being reported for many years, the extent to which *M. pneumoniae* is involved in the causation of human neurologic disease is not yet known.

Several laboratory methods can detect *M. pneumoniae* infection, including isolation, complement fixation, serology, and molecular assays. However, each of these methods has limitations. Isolation of *M. pneumoniae* is inconvenient, time-consuming, and causes the generation of inconsistent results.[12] Although direct detection of *M. pneumoniae* from brain tissue and/or cerebrospinal fluid (CSF) supports the belief that *M. pneumoniae* is a major cause of encephalopathy, the positive rate of detection of *M. pneumoniae* from CSF specimens by polymerase chain reaction (PCR) is variable and low.[13] Commercially available serologic test kits for the detection of antibodies to *M. pneumoniae*, possess inherent limitations of specificity and sensitivity. The test relies on patient compliance with the timely acquisition of acute- and convalescent-phase serum samples for accurate interpretation. However, the serology testing for the diagnosis of *M. pneumoniae* is imprecise, because patients with neurologic involvement due to other agents may sometimes develop elevated antibody titers to *M. pneumoniae*.[5] Despite these drawbacks, serology is still a sensitive test for detecting acute *M. pneumoniae* infection in pediatric patients in contrast with adult patients.[8] Furthermore, several papers continue to suggest that the immunoglobulin M (IgM) test is a readily convenient method to assist in the diagnosis of *M. pneumoniae*-associated encephalopathy.[8,10—12]

Neurological sequelae in *M. pneumoniae*-associated CNS illness are very high. A mounting number of reports show neurological sequelae in 48—64% of cases of *M. pneumoniae*-associated encephalopathy.[14] Despite the fact that therapies including antibiotics, intravenous immunoglobulin (IVIG), and steroids have been proposed by several articles, the role of these treatments in *M. pneumoniae*-associated encephalopathy remains unclear, because the benefits of these treatments lack the comparison of control groups in clinical trials and spontaneous recovery in some cases without any treatment has been reported.[5,8,14] Therefore, because there is no strong evidence to support these treatments, it is worth exploring the related prognostic factors for *M. pneumoniae*-associated encephalopathy.

Narita et al[15] reported that "intervals between respiratory and CNS manifestations" may be pivotal in understanding the mechanism of *M. pneumoniae*-associated encephalopathy. They proposed that if the interval is $<$7 days, the mechanism for *M. pneumoniae* is direct invasion. Adversely, if the intervals are $>$7 days, the mechanism is immune-mediated. However, if the interval is a key point in approaching the mechanisms of *M. pneumoniae*-associated encephalopathy, a retrospective analysis of medical records may verify the connection between the mechanisms of this disease and the intervals. Moreover, whether these connections relate to the outcomes of patients with *M. pneumoniae*-associated encephalopathy, are worthy of further investigation. We therefore conducted a retrospective review of charts targeting *M. pneumoniae*-associated encephalopathy and analyzed their outcomes after discharge for $\geq$6 months.

Methods

Selection criteria

From January 1, 2003 to December 31, 2010 patients were selected for inclusion in this study if they fulfilled the following criteria: (1) $<$18 years of age; (2) positive for *M.*