



# Psychiatric Manifestations Caused by *Mycoplasma pneumoniae* Encephalitis Mimicking Autoimmune Encephalitis

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## Abstract

A significant etiological factor for upper respiratory tract infections and community-acquired pneumonia is *Mycoplasma pneumoniae*. The incidence of extrapulmonary neurological problems in infected patients has been shown to range from 0.1 to 7%, often manifesting within a timeframe of 2 to 14 days following the onset of respiratory symptoms. Acute disseminated encephalomyelitis, Guillain–Barré syndrome, and transverse myelitis are among the immune-mediated illnesses encompassed under the syndrome. A 3-year-old male child exhibited symptoms of acute encephalopathy and behavioral disruption subsequent to an infection caused by *M. pneumoniae*. He presented with irritability, sleep disturbance, slurred speech, increased appetite, episodes of unresponsiveness, moving in circles, staring, and laughing episodes lasting for up to 15 to 30 minutes over a week. He lost his previous toilet training. Abnormal jerks were noted while awake and asleep. Symptoms were preceded by exposure to vague febrile illness 3 weeks prior to presentation. The patient’s brain magnetic resonance imaging was normal. Electroencephalography showed a slow background with no epileptiform discharges. Cerebrospinal fluid analysis and polymerase chain reaction for viruses were negative. The workup for autoimmune encephalitis was negative. Mycoplasma serology IgM was detected. Marked improvement was noted after methylprednisolone pulse therapy, intravenous immunoglobulin, valproic acid, and azithromycin. In conclusion, our report serves as a reminder that *M. pneumoniae* infection is a possible cause of encephalopathy and behavioral disturbance in children. Early recognition and promotion of immunomodulatory and antimicrobial treatment can prevent the affected child from experiencing different levels of long-lasting impairments in cognitive, physical, or visual abilities.

## Keywords

- ▶ *Mycoplasma pneumoniae*
- ▶ encephalopathy
- ▶ behavioral changes
- ▶ children

## Introduction

A significant etiological factor for upper respiratory tract infections and community-acquired pneumonia is *Mycoplasma pneumoniae*. The incidence of extrapulmonary neurological problems in infected patients has been shown to range from 0.1 to 7%, often manifesting within a timeframe of 2 to 14 days

following the onset of respiratory symptoms. The syndrome encompasses various conditions, including aseptic meningitis, encephalitis, meningoencephalitis, acute bilateral striatal necrosis, cerebellar ataxia, and immune-mediated disorders such as optic neuritis, acute disseminated encephalomyelitis, post-infectious hemorrhagic leukoencephalitis, transverse myelitis, and Guillain–Barré syndrome.<sup>1–5</sup>

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## Case Report

A previously healthy 3-year-old boy presented to a tertiary care center in the Riyadh region of Saudi Arabia with acute onset of irritability, sleep disturbance, slurred speech, increased appetite, episodes of unresponsiveness, moving in circles, and staring alternating with laughing episodes, each lasting for up to 15 to 30 minutes, over a week. He lost his previous toilet training during this period. Abnormal jerks were noted while awake and asleep. Symptoms were preceded by low-grade fever and flu-like illness 3 weeks before presentation. Multiple family members had a recent vague febrile illness and were treated as outpatients. There was no history of trauma or drug ingestion. There was no history of previous similar episodes, loss of consciousness, seizures, headache, visual problems, or hallucinations. He was a product of a nonconsanguineous marriage with unremarkable perinatal and birth history. He was fully vaccinated. There was no family history of early infantile deaths or neurological, metabolic, or psychiatric disorders.

## Clinical Findings

On examination, he had normal vital signs, including an oxygen saturation level of 95% on room air, and a normal level of consciousness. The patient's cranial nerves, as well as his motor, sensory, and cerebellar examinations, were normal without any signs of neurological deficits. The fundoscopic examination was normal. He had a mild cough with clear ears, a congested throat, and a normal chest examination.

## Diagnostic Assessment

Basic hemogram, biochemistry, renal, and liver profiles were normal. Brain magnetic resonance imaging (MRI) was unremarkable. Electroencephalography (EEG) showed a slow background with no epileptiform discharges. Cerebrospinal fluid (CSF) analysis revealed normal protein and glucose levels and an absence of white blood cells. CSF bacterial cultures and polymerase chain reaction (PCR) results for herpes simplex virus 1 (HSV-1) and other viruses were negative. Complete metabolic panels, including tandem mass spectrometry and urinary organic acid data, were unremarkable. The workup for autoimmune encephalitis, which included myelin oligodendrocyte glycoprotein antibody, anti-N-methyl-D-aspartate receptor, and voltage-gated potassium channel antibodies, was negative. Mycoplasma serology IgM was detected (► **Table 1** summaries all investigations).

## Therapeutic Intervention

Based on the clinical findings, EEG results, negative CSF viral panel, and bacterial cultures, the impression was *M. pneumoniae*-induced encephalopathy. Marked improvement was noted after methylprednisolone pulse therapy (30 mg/kg/d) for three consecutive days, followed by intravenous immunoglobulin (IVIG; 1 g/kg/d) for two consecutive days, valproic acid (VPA) twice per day, and azithromycin (10 mg/kg/d) once per day for 7 consecutive days.

## Follow-up and Outcomes

At the 6-week follow-up visit, the patient exhibited normal cognitive function and behavior, and he regained previous toilet training but had some irritability and sleep disturbance. The seizures were well controlled. He had a normal examination. VPA was discontinued at the 3-month follow-up visit after normalization of the EEG, as the child returned to his usual normal state of health. Interestingly, the Mycoplasma IgM antibody test was positive three times during the first 3 months of follow-up.

## Discussion

The pediatric age group has been extensively documented to experience extrapulmonary neurological complications caused by *M. pneumoniae*.<sup>1-3</sup> The most prevalent complication is encephalitis.<sup>6</sup> Approximately 20% of individuals exhibiting central nervous system (CNS) abnormalities do not have any prior or concurrent respiratory infection.<sup>2,3</sup> Acute encephalopathy/encephalitis is characterized by altered mental status, regression of developmental milestones, seizure or focal neurological signs (motor weakness or ataxia), and altered personality/behavior.<sup>7,8</sup> Enterovirus and HSV are the most common causes of infection among individuals in the pediatric age group.<sup>9</sup> Our patient presented with a vague clinical picture that included acute encephalopathy, behavioral disturbance, and seizure-like episodes where multiple differential diagnoses were entertained, including infectious/postinfectious autoimmune process, metabolic disorders, drug intoxication, focal (temporal lobe), hypothalamic hamartoma, paraneoplastic syndrome, pediatric acute onset neuropsychiatric syndrome (PANS), and childhood psychosis. Autism was ruled out by the psychiatrist in the emergency room due to the acute onset and characteristic clinical course of the disease. Further evaluation revealed evidence of acute *M. pneumoniae* infection. The constellation of clinical presentation, lack of CSF inflammatory findings, slow background on EEG, and the presence of normal brain MRI suggested that our patient had *M. pneumoniae* encephalopathy despite the absence of respiratory symptoms. His clinical status did not match the characteristic criteria for PANS caused by *M. pneumoniae*.<sup>4,10</sup>

The precise pathogenesis by which *M. pneumoniae* causes neurological complications has not been definitively established. However, it has been proposed that the underlying mechanism may involve either direct invasion into the CSF with positive PCR for mycoplasma or a systemic immune-mediated response triggered by molecular mimicry (antibodies or a cell-mediated response to the pathogen cross-react with the myelin autoantigens or specific epitopes of target in CNS) approximately 2 to 3 weeks after the respiratory disease subsides with positive mycoplasma antibodies.<sup>11,12</sup>

The diagnostic criteria for *M. pneumoniae* infection, which can lead to CNS complications, encompass the identification of *M. pneumoniae* using culture or PCR in respiratory or CSF samples, as well as the presence of positive serological test results.<sup>1</sup> Microbial culture is seldom used in routine medical practice. The most sensitive and specific

**Table 1** Laboratory and imaging profile of the patient in this report

Variables	Results
Total WBC per 10 g/L	8
Hemoglobin level g/dL	11.5
Platelet per 10 g/L	220
ESR mm/h	30
Electrolytes	Normal
Liver profile	Normal
Urea, creatinine	Normal
Hepatitis, Epstein–Barr virus, cytomegalovirus, herpes virus I, serology	Unremarkable
Mycoplasma serology	IgM positive, IgG negative
Nasopharyngeal swab/Mycoplasma culture	Not done
CSF analysis	Total WBC 0 per mm <sup>3</sup> , glucose 60 mg/dL (NR: 50–75), protein 0.25 mg/mL (NR: 0.15–0.6)
CSF oligoclonal bands	Negative
CSF culture	Negative
CSF viral multiplex	Negative
Electroencephalography	Slow background for age, with no epileptiform discharges
Metabolic workup <sup>a</sup>	Unremarkable
Autoimmune encephalitis workup <sup>a</sup>	Unremarkable

Abbreviations: CSF, cerebrospinal fluid; NR, normal range; WBC, white blood cell.

<sup>a</sup>Metabolic workup; serum ammonia, lactate, venous blood gas, tandem mass spectrometry, and urinary organic acid. Autoimmune encephalitis workup; myelin oligodendrocyte glycoprotein, anti-N-methyl-D-aspartate receptor, and neuronal voltage-gated potassium channel antibodies.

method for detecting *M. pneumoniae* infection is a PCR test, but its sensitivity is limited. PCR is less sensitive for diagnosis than serum specimens at acute and convalescent periods.<sup>13</sup> The diagnosis depends on the existence of a consistent clinical presentation that aligns with positive serological test results (IgM and IgG titers), as determined by techniques such as enzyme-linked immunosorbent assay and indirect immunofluorescence. *Mycoplasma pneumoniae*-specific IgM-positive results support acute infection.<sup>14</sup> Serological tests are limited by the reliance on convalescent sera for confirmation. IgM antibodies exhibit age-related variations and typically manifest as a positive result during acute infection. However, it is possible for these antibodies to remain negative during the duration of acute infection or to remain positive for several months.<sup>15</sup> Seroconversion is defined as a 4-fold increase in the titer between acute and convalescent serum<sup>16</sup> or a single high anti-*M. pneumoniae* complement fixation antibody titer >1:128 confirms the diagnosis. In the past, cold agglutinins were utilized due to their production occurring 1 to 2 weeks after infection in 50% of patients and their potential persistence for several weeks. However, their sensitivity and specificity are limited. Persistent positivity of the repeated serum *M. pneumoniae* IgM antibody test was observed in our patient. CSF analysis was unremarkable for our patient, which was the same as the findings of several case series reported in the literature on encephalitis secondary to *M. pneumoniae*.

The absence of controlled clinical trials and recommendations has resulted in the unavailability of standard therapy for the management of encephalitis or meningoencephalitis caused by *M. pneumoniae*. Spontaneous recovery has been reported in the literature.<sup>6</sup> According to several case series studies, the administration of immune-modulating therapy with intravenous pulse methylprednisolone at a dose of 20 mg/kg/d intravenously for 3 to 5 days, either as a stand-alone treatment or in combination with oral prednisone at a dose of 1 mg/kg/d for 10 to 14 days, with a gradual withdrawal for 4 to 6 weeks, has a beneficial effect.<sup>17,18</sup> The role of antimicrobial treatment remains controversial because it depends on the associated mechanism. Azithromycin (10 mg/kg of body weight once per day for 5 to 7 days orally or intravenously) is the first-line agent due to its good CNS penetration and anti-inflammatory effect, which prevents immune system activation with fewer side effects.<sup>18,19</sup> It is indicated in the direct invasion, while if an immune-mediated mechanism is suspected, the appropriateness of antimicrobial therapy, particularly after the resolution of the acute disease, remains uncertain,<sup>1,4</sup> but recent studies support its early use with reported significant clinical improvement. Despite the lack of established information regarding the optimal antibiotic, dosage, and length of therapy.<sup>12</sup> Practically, it is given alongside steroids when other potential causes have been ruled out and should be continued regardless of prodromal or neurological symptoms till more

evidence is obtained. The selection of other treatments, such as IVIG at a dose of 400 mg/kg/d for 5 days or 1 g/kg/d for 2 days, or plasmapheresis, depends on the complexity of the patient's symptoms and the response rate to steroid therapy.<sup>20</sup> A single-center cohort study suggested early IVIG therapy for patients with suspected *mycoplasma pneumoniae* encephalitis (MPE) who do not react to alternative therapy, especially those who experience prodromal signs of infection for a week or more.<sup>20</sup> A recent multicenter study included a total of 87 patients with MPE, where 55 individuals (63.2%) among these patients received immunomodulating medication.<sup>20</sup> Out of the 55 patients, 37 (42.5%) received IVIG, 13.8% received corticosteroids, and 6.9% of the participants received both IVIG and corticosteroids. The study found that giving azithromycin along with IVIG or corticosteroid therapy led to shorter stays in the hospital and faster management of symptoms compared with giving azithromycin alone.<sup>18</sup> Various clinical reports have reported that the rare use of immunomodulatory medication, based on potential immune-related mechanisms, effectively reduces illness severity and improves outcomes. However, further studies on the efficacy of immunomodulatory treatment are necessary in the pediatric age group. Our patient responded dramatically to intravenous steroid therapy and IVIG, and his behavioral disturbances subsided over 3 weeks.

## Conclusion

Our report serves as a reminder that *M. pneumoniae* infection is a possible cause of encephalopathy and behavioral disturbance in children. Early recognition and promotion of immunomodulatory and antimicrobial treatment can prevent the affected child from experiencing different levels of long-lasting impairments in cognitive, physical, or visual abilities.

### Ethics Approval and Consent to Participate

Written informed consent for publishing clinical details and images was obtained from the patient. Ethical approval to report this case was not required.

### Conflict of Interest

None declared.

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