

Encephalopathy and Axonal Neuropathy Associated With *Mycoplasma Pneumoniae* Infection: Response to Intravenous Immunoglobulin Therapy

Ali Saker, MD¹, Stephanie Athman, DO², Mohammed Aldosari, MD³, and Husn Frayha, MD⁴

Abstract

Mycoplasma pneumoniae infection frequently presents as a self-limited process, however, severe cases and even fatalities have been reported. The authors present a case of *Mycoplasma pneumoniae* infection associated with both encephalopathy and peripheral neuropathy that responded to intravenous immunoglobulin therapy. To our knowledge, this is the first documented case of *Mycoplasma pneumoniae* related to encephalitis and peripheral axonal neuropathy. To date, there is insufficient data on the effect of intravenous immunoglobulin on the course of mycoplasma-associated central nervous system/peripheral nervous system disease. While intravenous immunoglobulin has aided in a variety of autoimmune-mediated disorders, its efficacy in mycoplasma-mediated encephalitis treatment remains unclear. In this patient case, reversal of both central and peripheral nervous system symptoms after treatment with intravenous immunoglobulin suggested a possible therapeutic benefit.

Keywords

mycoplasma, encephalitis, axonal neuropathy, intravenous immunoglobulin

Received September 5, 2015. Received revised December 16, 2015. Accepted for publication December 29, 2015.

Mycoplasma pneumoniae is a common cause of respiratory illnesses in children. Of all cases, 0.1% of cases are estimated to have central nervous system involvement.^{1,2} It is also one of the major causes of encephalitis accounting for 5% to 10% of cases.³ In spite of the ambiguous mechanism, direct invasion into the nervous system, neurotoxin release, or an immune-mediated etiology have been suggested.^{2,4} Different mechanisms make it plausible to consider multiple therapies. The authors report a case of mycoplasma encephalitis and axonal neuropathy with recovery after gamma-globulin therapy.

Case Report

A previously healthy 4-year-old boy presented to the emergency department with fever and upper respiratory infection symptoms for 5 days. His primary care physician started oral antibiotics for otitis media. Over 3 days, the child developed lethargy, dysphagia, sialorrhea, and ataxia and presented to the hospital.

Upon admission, he was febrile and lethargic, without meningeal signs. Reflexes were +3/4 bilaterally. Respiratory, cardiovascular, and abdominal examinations were unremarkable. Laboratory evaluation is depicted in Table 1.

History revealed normal development, unremarkable prenatal, birth, medical, and surgical history. He was up-to-date on vaccinations and had 3 siblings in good health.

¹ Damascus University, Faculty Of Medicine, Damascus, Syria

² Nationwide Children's Hospital, Columbus, OH, USA

³ Department of Pediatric Neurology & Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH, USA

⁴ Section of Infectious Diseases, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Corresponding Author:

Ali Saker, MD, Cleveland Clinic Foundation (Research Volunteer), 2616 Mayfield Rd, Cleveland Heights, OH 44106, USA.
 Email: alisaker1990@gmail.com



Table 1. Laboratory Evaluation on Admission.

Variable	Result	Reference range
WBC, cell/mm ³	6,600	4500-11 000
Differential, %	71 N, 14.8 L, 8 M, 4 E, 0.4 B	
Na ⁺ , mmol/L	138	136-145
K ⁺ , mmol/L	4	3.5-5
Cl ⁻ , mmol/L	103	95-105
Ca ⁺⁺ , mmol/L	2.29	2.1-2.8
PO ₄ , mmol/L	1.46	1-1.5
Mg ⁺ , mmol/L	0.86	0.75-1
CO ₂ , mmol/L	23	20-29
Glucose, mmol/L	5.4	3.8-6.1
Hg, g/dL	10	13.5-17.5
Platelets, /mm ³	257 000	150 000-400 000
PT, seconds	11.7	11-15
PTT, seconds	25.8 seconds	25-40
Urea, mmol/L	4	1.2-3
Creatinine, μmol/L	22	53-106
Albumin, g/dL	3.4	3.5-5.5
Lactic acid, mmol/L	1.3	0.5-2.2
ALT, U/L	18	8-20
AST, U/L	38	8-20
UA (urinalysis)	Unremarkable	
CMV IgM	Negative	
EBV IgM	Negative	
Enterovirus RNA PCR	Negative	
HSV PCR	Negative	
Brucella IgM	Negative	
Cold agglutinin	1:2 (weakly positive)	
Mycoplasma IgG	Negative	
Mycoplasma IgM	Positive	

Abbreviations: L, lymphocytes; N, neutrophils; M, monocytes; E, eosinophils; B, basophils; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, Herpes simplex virus; WBC, white blood cell; Hg, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time; PCR, polymerase chain reaction; ALT, alanine transaminase; AST, aspartate aminotransferase; Ig, immunoglobulin.

On day 9 of the illness, he developed a semicomatose state (Glasgow Coma Scale = 6/15), quadriplegia, areflexia, and generalized tonic-clonic seizures. He was admitted to the pediatric intensive care unit, and his seizures were aborted by midazolam and phenobarbital. He required mechanical ventilation, and levetiracetam was added for maintenance. On day 11 of his illness, 1 g/kg/day intravenous immunoglobulin was administered for 2 days.

Two lumbar punctures showed lymphocytic pleocytosis and high cerebrospinal fluid protein (Table 2), 1 on admission and the other done 1 week afterward. Gram stain revealed no organisms, and bacterial and viral cultures yielded no growth. Polymerase chain reaction (PCR) failed to evidence Herpes simplex virus 1/2 or other viruses. Imaging studies were done during the first week of admission, computed tomography (CT) scan was normal. Magnetic resonance imaging, however, showed bilateral multifocal signal intensity of the cerebral cortex and basal ganglia with mild left diffuse meningeal enhancement (Figure 1). Electroencephalogram (EEG) showed focal discharges in the left temporoparietal region. A wide range of

Table 2. Cerebrospinal Fluid Values of the Lumbar Punctures Performed.

CSF Parameter	LPI	LP2
WBC, cell/mm ³	10	17
Differential, %	100 L	92 L, 8 M
RBC, cell/mm ³	90	8
Protein, mg/dL	300	290
Glucose, mmol/L	4.8	4
Lactic acid, mg/dL	24	20

Abbreviations: WBC, white blood cell; RBC, red blood cell; CSF, cerebrospinal fluid; L, lymphocytes; M, monocytes.

bacteriological and viral tests were performed. Apart from a positive *Mycoplasma pneumoniae* immunoglobulin M, all other tests were negative. Cold agglutinin yielded a weakly positive ratio (1:2). Mycoplasma testing revealed negative immunoglobulin G and positive immunoglobulin M serology indicating acute infection. No evidence of other causal pathogens could be found. The patient was started on acyclovir, ceftriaxone, clarithromycin, and vancomycin.

Upon further investigations, nerve conduction studies/electromyography confirmed severe motor-axonal neuropathy with predominant lower extremity involvement, particularly the peroneal nerve. A repeat EEG showed moderate to severe encephalopathy changes with a slow background and without epileptiform discharges. Spinal magnetic resonance imaging revealed no evidence of cord abnormality. Spectroscopy showed a normal pattern.

A few days after intravenous immunoglobulin was infused, he improved remarkably and was weaned from the mechanical ventilator. Although briefly manifesting aphasia, he was alert to surroundings and regained, and by day 14, spontaneous movements were seen in the lower limbs. Extubation ensued on day 17, and full consciousness returned the next day. The boy walked with support and regained swallowing function by day 20.

Discontinuation of all medications except levetiracetam 50 mg/kg/day followed, and the boy was discharged home. He was weaned off levetiracetam and returned to school. He exhibited mild lower limb weakness on his last follow-up at the age of 5 years.

Discussion

This was a rare case of *Mycoplasma pneumoniae* infection causing both central nervous system and peripheral nervous system disease.

The clinical spectrum of *Mycoplasma pneumoniae* neurologic disease is not well defined. This patient presented with fever, upper respiratory infection symptoms, and positive mycoplasma serology and then rapidly developed encephalopathy with positive cerebrospinal fluid, magnetic resonance imaging, EEG, and nerve conduction studies findings.

In Daxboeck's review, flu-like or respiratory illness preceded the onset of the neurologic disease in 76% of patients. Manifestations included meningeal signs, fever, nausea/vomiting, headache, fatigue, lethargy, and convulsions.⁵ This

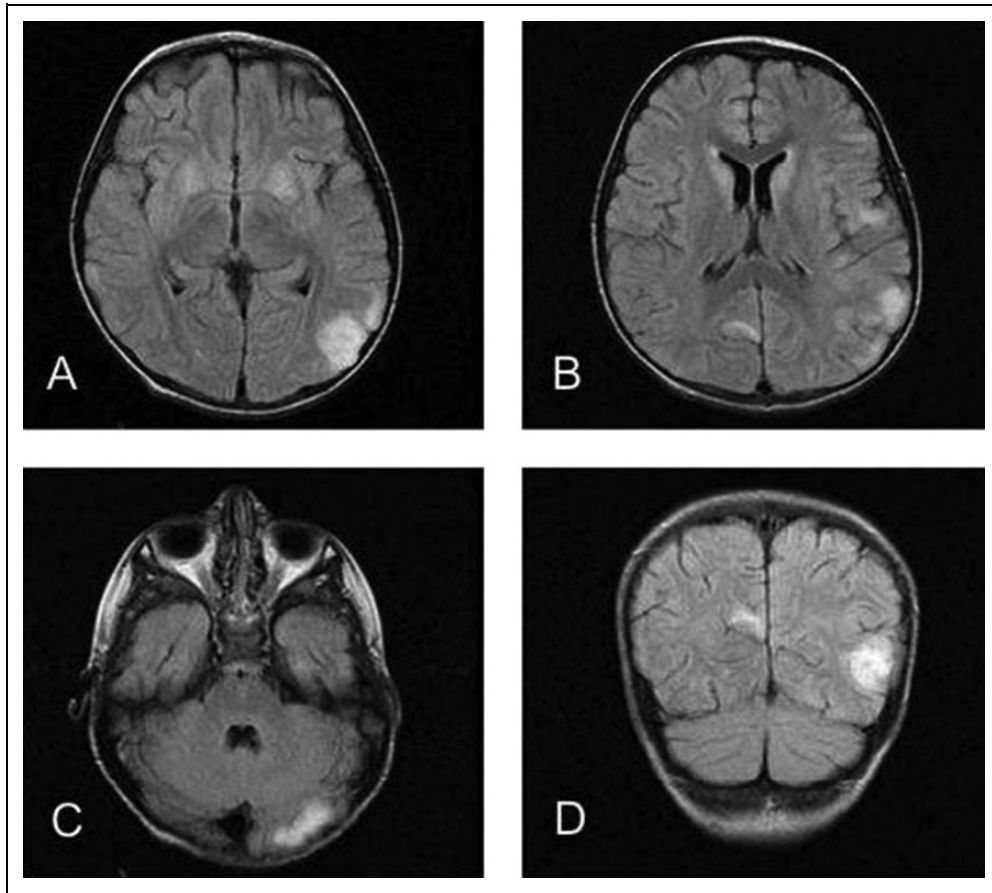


Figure 1. Unenhanced fluid-attenuated inversion recovery magnetic resonance imaging of the head (all panels) shows multifocal signal hyperintensities of the cerebral cortex (all panels) and basal ganglia (Panels A and B) with mild left diffuse meningeal enhancement (Panel D).

patient's clinical picture is consistent with findings reported in major studies focused on mycoplasma encephalitis.

For the diagnosis of *Mycoplasma pneumoniae*-associated encephalopathy, studies have suggested the sufficiency of immunoglobulin M in children.^{1,4} In comparison to adults, in childhood an immunoglobulin M study is efficient and shows consistency for titer changes during the acute phase.^{2,4,6} This diagnosis relies on consistent laboratory, clinical, and neuroimaging findings, accompanied by the absence of any features incriminating other etiologies.⁷

Cerebrospinal fluid PCR and intrathecal antibodies testing for *Mycoplasma pneumoniae* were not performed in this case due to the low yield of these studies.^{4,8-10}

According to the California Encephalitis project, magnetic resonance imaging abnormalities were up to 49%, EEG abnormalities were found in 79% of cases, while CT was often normal (82%).⁸ Cerebrospinal fluid in *Mycoplasma pneumoniae* meningitis or encephalitis usually contains a pleocytosis (mostly mononuclear) and elevated protein counts.¹⁰ In this patient, cerebrospinal fluid, EEG, and magnetic resonance imaging findings were consistent with those reported in literature.

Although evidence of antibiotics efficacy is still lacking, the authors started acyclovir, ceftriaxone, clarithromycin, and vancomycin as this patient's neurologic symptoms had emerged.

Antimicrobial agents have been reported to be effective in a few reports, however, they didn't achieve any therapeutic benefit in this case. This failure might be explained by insufficient penetration into the blood brain barrier, however, an immunologic etiology of the disease is another very important explanation as the exact etiology of the disease is still uncertain.

As his condition deteriorated, despite administering antimicrobial agents, a trial of intravenous immunoglobulin (1 gram/kg/day for 2 days) was tried. Interestingly, he recovered over a week without steroidal therapy.

The treatment decision was made based on a presumptive diagnosis of mycoplasma encephalopathy and was based on anecdotal reports. Trials determining adequate treatment do not exist.⁷ It is argued that immunoglobulins do not penetrate the blood-brain barrier, but lymphocytic encephalitis may have increased permeability. Although this patient has recovered after intravenous immunoglobulin, late effects of the antimicrobial agents might be considered. Another interesting issue is that some studies report spontaneous recovery^{4,9} which also cannot be excluded. Therefore, this case report does not give evidence for the proposed immune-mediated pathophysiology for *Mycoplasma pneumoniae* encephalitis but rather demonstrates a significant improvement of symptoms after administering intravenous immunoglobulin.

Although *Mycoplasma pneumoniae* neurologic disease is considered rare, and most cases run a benign course, significant morbidity and fatalities have occurred.³ Prospective studies are needed to establish evidence for efficacy and appropriate dosing in intravenous immunoglobulin treatment.

Acknowledgments

The authors gratefully acknowledge the contribution of (1) Mohammed Al-Muhaizea, MD, consultant, Section of Pediatric Neurology Department of Neurosciences King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; (2) Sohail Bajammal, MBChB, MSc, FRCS, PhD, chief executive officer at King Abdullah Medical City.

Author Contributions

All authors contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Koskiniemi M. CNS manifestations associated with *Mycoplasma pneumoniae* infections: summary of cases at the University of Helsinki and review. *Clin Infect Dis*. 1993;17(suppl 1):s52-57. doi:10.1093/clinids/17.Supplement_1.S52.
2. Yiş U, Kurul SH, Cakmakçi H, Dirik E. *Mycoplasma pneumoniae*: nervous system complication in childhood and review of the literature. *Eur J Pediatr*. 2008;167(9):973-978. doi:10.1007/s00431-008-0714 -1.
3. Lehtokoski-Lehtiniemi E, Koskiniemi M. *Mycoplasma pneumoniae* encephalitis: a severe entity in children. *Pediatr Infect Dis J*. 1989;8(9):651-653.
4. Christie LJ, Honarmand S, Talkington DF, et al. Pediatric encephalitis: what is the role of *Mycoplasma pneumoniae*?. *Pediatrics* 2007;120(2):305-313. doi:10.1542/peds.2007-0240.
5. Granstrom M, Holme T, Sjogren AM, Ortqvist A, Kalin M. The role of IgA determination by ELISA in the early serodiagnosis of *Mycoplasma pneumoniae* infection, in relation to IgG and capture IgM methods. *J Med Microbiol*. 1994;40(4):288-292. doi:10.1099/00222615-40-4-288.
6. Waris ME, Toikka P, Saarinen T, et al. Diagnosis of *Mycoplasma pneumoniae* in children. *J Clin Microbiol*. 1998;36(11):3155-3159.
7. Gorman MP, Rincon SP, Pierce VM. Case records of the Massachusetts General Hospital. Case 19-2014: a 19-year-old woman with headache, fever, stiff neck, and mental-status changes. *N Engl J Med*. 2014;370(25):2427-2438. doi:10.1056/NEJMcpc1400838.
8. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. *Clin Infect Dis*. 2006;43(12):1565-1577.
9. Bitnun A, Ford-Jones EL, et al. Acute childhood encephalitis and *Mycoplasma pneumoniae*. *Clin Infect Dis*. 2001;32(12):1674-1684. doi:10.1086/320748.
10. Daxboeck F, Blacky A, Seidl R, Krause R, Assadian O. Diagnosis, treatment and prognosis of *Mycoplasma pneumoniae* childhood encephalitis: systematic review of 58 cases. *J Child Neurol*. 2004;19(11):865-871. doi:10.1177/08830738040190110401.