Clinical Article

Encephalitis and Acute Renal Failure Associated with *Mycoplasma pneumoniae*: A Case Presentation

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Abstract

We present a case of encephalitis and acute renal failure, requiring hemodialysis, in an otherwise healthy 10-year-old male. *Mycoplasma pneumoniae* (*M. pneumoniae*) infection was diagnosed based on the clinical findings and the presence of a serum IgM antibody titer and a negative IgG antibody titer. *M. pneumoniae* has been recognized as an important cause of respiratory infections, but occasionally extrapulmonary manifestations can occur, including the neurologic and renal systems. The pathophysiology involves not only direct invasion by the organism, but also an immune-mediated response with immune-complex formation. *Int Pediatr. 2003;18(4):209-212.*

Key words: encephalitis, Mycoplasma pneumoniae (M. pneumoniae)

Introduction

Mycoplasmas are the smallest free-living organisms. Five species have been isolated from the human respiratory system, but *Mycoplasma pneumoniae* (*M. pneumoniae*) is the only known human pathogen.

M. pneumoniae is one of the major causes of respiratory infections in the pediatric age group. It is uncommon before age 5 years, but accounts for 33% of pneumonias in children between 5-9 years and 70% in those between 9-15 years.[1,2] A variety of extrapulmonary manifestations have also been described, and although the frequency of these varies greatly, they include the renal and neurologic systems.

The pathophysiology of this condition remains unclear, and even though direct invasion by the organism has been postulated, an immune-mediated mechanism seems to play an important role as well.

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Case Report

A 10-year-old white male with no significant past medical history was admitted to a Medical Center due to altered mental status. Symptoms began two weeks prior to admission when the patient developed low-grade fever with upper respiratory symptoms. The fever disappeared for ten days, and then reappeared but this time associated to a severe headache primarily in the frontal area. Rest did not relieve the headache. There was nausea, but no vomiting or photophobia.

The next day the headache increased in intensity, and the patient presented fever up to 103° F. Twenty-four hours later the patient developed abnormalities in his speech, initially it was slurred, but over the course of the day was not understandable. He was disoriented, and combative. He was taken at this time to the ER at the local hospital.

The patient had not traveled outside the US. There was no history of recent head trauma, weight loss or other illnesses. There was no history of sick contacts or herpetic lesions.

Within hours the patient's combativeness decreased and he became lethargic with difficulty maintaining a stable airway. At that time he was intubated and placed on mechanical ventilatory support. Initial physical examination did reveal increased tone and mild hyperreflexia in the lower extremities, and an equivocal Babinsky. No rashes were noted.

A computed tomography scan without contrast did not show any significant abnormality of the brain. Complete blood count showed a white count of 9600 with a left shift. Sedimentation rate was 25 and C-reactive protein was 0.4. Electrolytes and renal function were normal with a blood urea nitrogen of 13mg/dl and a creatinine of 0.7mg/dl. Qualitative urine toxicology screen was negative; salicilate and acetaminophen levels were undetectable. A lumbar puncture was performed and the cerebrospinal fluid was remarkable for a white blood cell count of 176

with 91 lymphocytes, 7 monocytes and 2 polynucleotides; and a red blood cell count of 76, glucose of 58mg/dl and protein of 69mg/dl. The patient was started on ceftriaxone and acyclovir.

Hospital Course

A repeat CT scan was done upon admission and it showed generalized cerebral edema without any focal lesions. The initial electroencephalograph was abnormal due to bihemispheric slowing. His initial creatinine was 0.7mg/dl and blood urea nitrogen was 13mg/dl. Twelve hours after admission the patient's renal function began to deteriorate. At this time Herpes PCR was reported negative, so acyclovir was discontinued. Azithromycin was added. A repeat CT scan of the brain showed improvement of the cerebral edema.

After the first hospital day the patient's urine output was 1.5cc/kg/hr. He began to present hypertension with systolic readings up to 167 and diastolic readings of 109. Labetalol infusion was started and since the blood pressure did not improve enalapril was added. The urine output decreased on the second hospital day to 0.5cc/kg/hr. A fluid challenge and lasix were given with poor response.

Urine output continued to drop and on the third hospital day it reached 0.2cc/kg/hr. By this time the creatinine was 5.8mg/dl and BUN of 40mg/dl. Albumin was given and intravenous fluids increased. Due to the onset of acute renal failure, the patient was transferred to our hospital for hemodialysis. (Fig. 1)

Lasix and enalapril were discontinued and nifedipine was used for blood pressure control. The patient required hemodialysis on one occasion, and on the next day his urine output began to improve and his renal function slowly returned to normal.

Mycoplasma IgM by enzyme immunoassay (EIA) was positive on two occasions and Mycoplasma IgG was negative. Mycoplasma culture was not obtained. Lupus panel, antinuclear antibody and complement levels were normal. CSF bacterial culture and viral studies were negative. The patient's blood counts remained normal. He developed mild hypokalemia on the days following dialysis that resolved by increasing potassium intake.

The patient was extubated and at that time he was not oriented in time, place or person. He was able to recognize his parents but was unable to speak

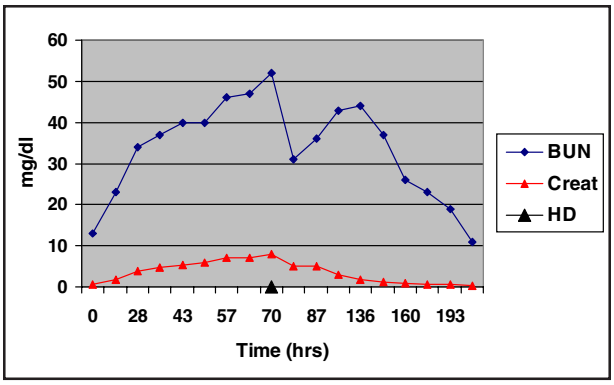

Fig. 1 - BUN, creatinine levels and time of hemodialysis throughout hospital stay.

adequately. He could not repeat phrases or name objects. His neurologic exam was remarkable for increased tone in lower extremities with hyperreflexia and bilateral Babinsky. These findings improved over the hospital stay.

The patient completed 14 days of azithromycin and was discharged home to continue physical, occupational and speech therapy.

Discussion

M. pneumoniae is a short rod, about 10 x 200 nm, which lacks a cell wall and is not visible on Gram staining or affected by beta-lactam antibiotics.

The first descriptions of *M. pneumoniae* were in 1944 by Eaton and colleagues.[3] The Eaton agent was believed to be a virus at that time. It was not until the 1960's when Clyde identified it as a mycoplasma.[4] Since that time, *M. pneumoniae* has been recognized as a major cause of respiratory infections, and although extrapulmonary manifestations have been described in almost every organ system, they are still uncommon.

Neurologic manifestations include both central and peripheral nervous systems. Peripheral neuropathy, Guillain-Barre syndrome, optic neuritis,[5] and encephalitis[6] have all been seen in patients with mycoplasma infection.

In the presence of acute childhood encephalitis, *M. pneumoniae* is an important etiologic agent. Diagnosis can be made in a patient with a recent or current respiratory infection, by having a positive immunoglobulin M antibody (in serum), a four-fold increase in complement-fixation antibody titers or by polymerase chain reaction. Cultures can be used for diagnostic purposes, but they require a special media;

and since *M. pneumoniae* has a doubling time of more than six hours, culturing can take anywhere from 7-21 days.[7-10] Cerebrospinal fluid analysis is not always abnormal. It was found to yield positive results in about one-third of patients.

Neurologic complications have been attributed to direct invasion of *M. pneumoniae* in the central nervous system.[11] Although *M. pneumoniae* DNA has been detected in cerebrospinal fluid by polymerase chain reaction, an immune mediated mechanism of action has also been postulated. Patients with post infectious encephalitis secondary to mycoplasma were found to have anti-Galactocerebroside antibodies.[12] These anti-Gc antibodies have been found in animal models to induce CNS demyelination, so they could play an important function increasing demyelination in patients with *M. pneumoniae* infection. Some data suggests that a galactocerebroside structure is found in *M. pneumoniae*, indicating molecular mimicry between a myelin glycolipid, galactocerebroside and *M. pneumoniae*.[13]

Serum antibodies to gangliosides GM1, GM2 and GT1b have also been detected, suggesting a mycoplasma-related immunologic mechanism.[14]

Renal involvement is an unusual manifestation of *M. pneumoniae* infection in children. Clinical presentation has been varied, ranging from proteinuria, glomerulonephritis to renal failure,[15-17] and although the pathophysiology is not understood completely, there is evidence to suggest that immune complex deposition plays an important role.[18,19]

The first report of acute glomerulonephritis associated to mycoplasma infection was in 1978. It occurred in an 11-year-old girl presenting initially with pneumonia followed by hematuria. Since that time few articles have been published associating *M. pneumoniae* to kidney disease, and only two other cases of acute renal failure requiring hemodialysis have been reported; one of them in a 17-year-old Japanese woman, and the other in a pediatric patient with a congenital solitary kidney.

The evidence tends to point to immune complex deposition as cause of renal disease. Mycoplasmas are capable of activating several components of the immune system, making them able to regulate immune response. They can activate B and T cells, induce immunoglubulin secretion and cytokine production.[20]

There is a report of IgA nephropathy associated to M. pneumonia, where the biopsied renal tissue demonstrated the presence for IgA, C3 deposits, as well as dense deposits in the mesangial region on electron microscopic examination.[18] Another report found deposits of IgG and C3 as well as mycoplasma antigens in a renal biopsy of a patient with acute glomerulonephritis.[21] Both findings suggest a mycoplasma induced immune-complex nephritis.

Patients that developed acute renal failure were diagnosed with mycoplasma infection by an elevated mycoplasma titer in serum and a positive polymerase chain reaction for mycoplasma. Although no tissue studies were obtained, the authors believed that the renal dysfunction was secondary to the mycoplasma infection.

Conclusion

M. pneumoniae infection is no longer a benign condition as it was thought to be, and extrapulmonary complications are well recognized, mostly as manifestations from the central nervous system and less frequently as renal disease. The advantages of rapid diagnostic tests with high sensitivity and specificity for *M. pneumoniae* like detection of specific immunoglobulins in serum, detection of specific antigens or mycoplasmal nucleotide sequences have facilitated the identification *M. pneumoniae* as the causal agent.

Not only is the direct invasion of the organism responsible for the pathophysiology of this condition, but also an immune-mediated response, with immune-complex formation and the possibility of molecular mimicry play an important and probably primary role as well.

In our patient, the diagnosis of encephalitis and acute renal failure was attributed to *M. pneumoniae* infection. The diagnosis was made by excluding other causes (primarily infectious and inflammatory) in the presence of a respiratory illness and a rise in the IgM titer to *M. pneumoniae* in serum with a negative IgG. As in most cases, the cerebrospinal fluid was abnormal, but failed to demonstrate mycoplasma-specific antibodies; renal biopsy was not indicated, due to rapidly improving renal function, so tissue studies were not available for evaluation.

Our patient was continued on azithromycin. This decision was made based on clinical, laboratory and radiologic information obtained throughout his hospitalization.

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