Korean Journal of Pediatrics Vol. 51, No. 5, 2008
DOI : 10.3345/kjp.2008.51.5.533
■ Case report ■

Two cases of central nervous system complications caused by *Mycoplasma pneumoniae* infection

Shin Mi Kim, M.D., Ji Seung Heo, M.D., Eun Jung Shim, M.D., Dae Hyoung Lee, M.D.
Do Jun Cho, M.D., Dug Ha Kim, M.D., Ki Sik Min, M.D., and Ki Yang Yoo, M.D.

Department of Pediatrics, College of Medicine, Hallym University, Korea

= Abstract =

Mycoplasma pneumoniae (*M. pneumoniae)* infection causes a wide variety of clinical manifestations in children and young adults, the main one being pneumonia. *M. pneumoniae* is transmitted from person to person by infected respiratory droplets. Symptoms caused by *M. pneumoniae* infection can be divided into those involving the respiratory tract, and those caused by extrapulmonary disease. *M. pneumoniae* infections may cause central nervous system (CNS) complications– with encephalitis being the most frequent– and stroke being a rare complication. The pathogenesis of the CNS disease is unclear; possibilities include direct infection and an immune-mediated reaction. We present two cases of CNS complications subsequent to infection with *M. pneumoniae;* both cases had convincing evidence of preceding *M. pneumoniae* respiratory disease with no evidence of viable *M. pneumoniae* in the cerebrospinal fluid. We report cases of encephalitis and stroke following a recent *M. pneumoniae* infection. **(Korean J Pediatr 2008;51:533-537)**

Key Words : Mycoplasma pneumoniae, Central nervous system, Encephalitis, Stroke

Introduction

Mycoplasma pneumoniae is a short (about 10×200 nm) rod without a cell wall that is bounded by a cell membrane and contains sterols, which are transmitted human-to-human. *M. pneumoniae* is endemic to most areas of the world. Epidemics occur at 4- to 7-year intervals, and infection rates may reach 35% in children during these outbreaks. *M. pneumoniae* infections occur in children of all ages, but lower respiratory tract disease is seen principally in school-aged children and young adults[1-3]. Respiratory disease may manifest as pharyngitis, bronchitis, bronchiolitis, croup, and pneumonia. Besides the lungs, this organism can also affect almost every organ system. The most frequently reported instances include neurologic complications, dermatologic involvement (exanthem, Stevens-Johnson syndrome), cardiac complications (carditis, conduction defects), musculoskeletal complications (polyarthralgia, arthritis), gastrointestinal complications (hepatitis, pancreatitis), hemolytic anemia, and Raynaud's phenomenon[4]. Neurologic manifestations are the most frequent extrapulmonary complications of *M. pneumoniae* infection[5]. CNS involvement occurs most frequently in children, and includes aseptic meningitis, encephalitis, meningoencephalitis, acute bilateral striatal necrosis, cerebellar ataxia, acute disseminated encephalomyelitis (ADEM), post-infectious hemorrhagic leukoencephalitis, transverse myelitis, Guillain-Barré syndrome and thromboembolic stroke[6]. The phathophysiology of *M. pneumoniae* associated CNS disease remains unclear. Among CNS complications associated with *M. pneumoniae* infection, encephalitis is the most frequent CNS manifestation, while strokes are a rare complication[7]. We report two cases of encephalitis and stroke after a recent *M. pneumoniae* infection.

Received : 5 January 2008, Accepted : 22 January 2008
Address for correspondence : Ki Sik Min, M.D.
Department of Pediatrics, College of Medicine, Hallym University
896, Pyeongchon-dong, Dongan-gu, Anyang-si, Gyeonggido 431-070, Korea
Tel : +82.31-380-3734, Fax : +82.31-380-3733
E-mail : ksmin@hallym.or.kr

Case report

Case 1

A 7-year-old girl, with 14 day history of fever, anorexia and cough, was referred to the Department of Pediatrics because of abdominal pain with vomiting that had de-

veloped abruptly. She had no underlying epileptic disorder. Family history for epileptic disorder was negative. Weight, height and head circumference were normal for her age.

Two weeks earlier, she had developed fever, cough, and rhinorrhea. At the time of admission she had a temperature of 36.7℃ and a respiratory rate of 26/min. Rhonchi and rales from the right lung field were present. A chest radiograph revealed an ill-defined consolidation in the right lung. Neurological examination upon admission revealed alert mental status, without signs of focal neurological defects or meningeal irritation. Pupillar reflexes were normal. On the second day, she complained of a headache. A computed tomographic scan (CT) of the brain was taken, and it appeared normal. Complete blood count was 15,400 cells/μL with 88.7 % segmented neutrophils. Platelet count was $247\times10^3/\mu$L. Normal values were recorded for hematocrit and glucose. Liver enzymes were raised (AST 5,037 IU/L, ALT 3,834 IU/L). Minimal hepatomegaly with a gall bladder wall edema was found by an abdominal ultrasonography. Serum antibodies to M. pneumoniae, tested by Serodia-Myco-Ⅱ gelantin particle agglutination test (SERODIA-MYCO Ⅱ, Fujirebio Inc. Japan), were 1:640 and cold agglutinins were positive. She was treated with oral clarithromycin and intravenous augmentin. On the seventh day of admission, a seizure attack with generalized tonic-clonic convulsions was observed. The convulsions lasted for few minutes. She was treated with diazepam intravenously. The next day, the seizure and consciousness disturbance was prolonged and intractable; additional behavior and personality change was accompanied by blurred vision. The patient was taken to the Intensive Care Unit. Magnetic resonance image (MRI) showed multifocal FLAIR, T2 high signal in both parietooccipital lobes, with relatively asymmetric distribution (Fig. 1). Irregular contrast enhancement was noted in the lesions. We diagnosed the patient as having encephalitis. Parenteral therapy was started with macrolide, phenytoin and methylprednisolone. Cerebrospinal fluid (CSF) contained leukocyte count (11 cells/L), glucose (93 mg/dL), protein (72 mg/dL). No infectious agents (bacteria and/or herpes simplex virus 1-2) were found in the CSF. CSF polymerase chain reaction for M. pneumoniae was negative. Serum samples, obtained repeatedly during the course of the illness, ruled out infection due to Herpes simplex viruses 1-2, Epstein-Barr virus, or A-B-C hepatitis viruses. During the subsequent 2 weeks the patient improved slowly, and was discharged without neurological symptoms and with a normalized chest-X ray and MRI (Fig. 2).

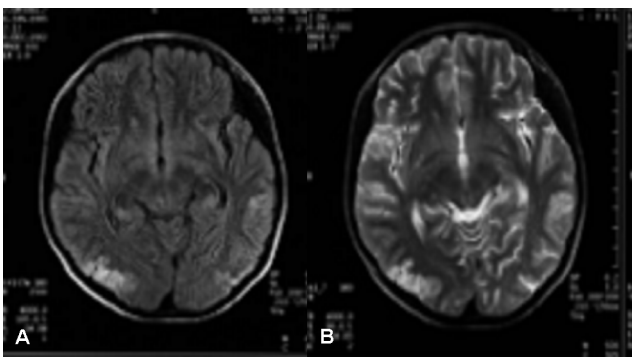

Fig. 1. A) Case 1. Brain MRI (FLAIR) showing high signal in parietooccipital lobes and irregular contrast enhancement. B) Case 1. Brain MRI (T2) showing high signal noted in parietooccipital lobes and irregular contrast enhancement.

Case 2

A 6-year-old girl was admitted to the Department of Pediatrics for evaluation and treatment of respiratory distress. She had no underlying cardiac abnormalities and no previous history of frequent infections. Family history was negative for vascular diseases or coagulation disorders. Weight, height and head circumference were normal for her age. Seven days earlier, she had developed fever, cough, and rhinorrhea. These symptoms progressed despite several days of oral antibiotic therapy. At the time of admission, she was febrile with a temperature of 39℃ and had a respiratory rate of 39/min. Rhonchi and rales from the right upper lung field were present. Chest radiograph revealed a lobar consolidation with air bronchograms, accompanied by a pleural effusion in the right lung. Further physical and neurological examinations were unremarkable. Cranial nerve function was preserved and there was no ptosis, ocular palsy, nystagmus or facial palsy. Complete blood count was 9,500 cells/μL with 86.2% segmented neutrophils. Platelet count was $107\times10^3/\mu$L. Normal values were recorded for hematocrit, glucose, creatinine, plasma urea and liver enzymes. Serum anti-mycoplasmal antibodies, tested by the Serodia-Myco-Ⅱ gelantin particle agglutination test (SERODIA-MYCO Ⅱ, Fujirebio Inc. Japan), were 1:160. Cold agglutinins were negative. She received cephalosporin intravenously and oral clarithromycin, but the fever persisted and respiratory symptoms remained. On the fifth day, a chest tube was inserted to drain pleural effusion. On the seventh day, because of somnolence and rapidly increasing lethargy and visual hallucinations, the patient was taken to the Intensive

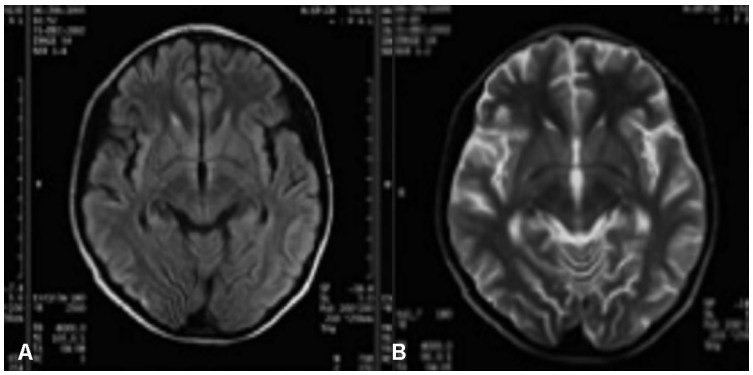

Fig. 2. A) Case 1. Brain MRI (FLAIR) showing improved high signal and irregular contrast enhancement, after one week. B) Case 1. Brain MRI (T2) showing improved high signal and irregular contrast enhancement, after one week.

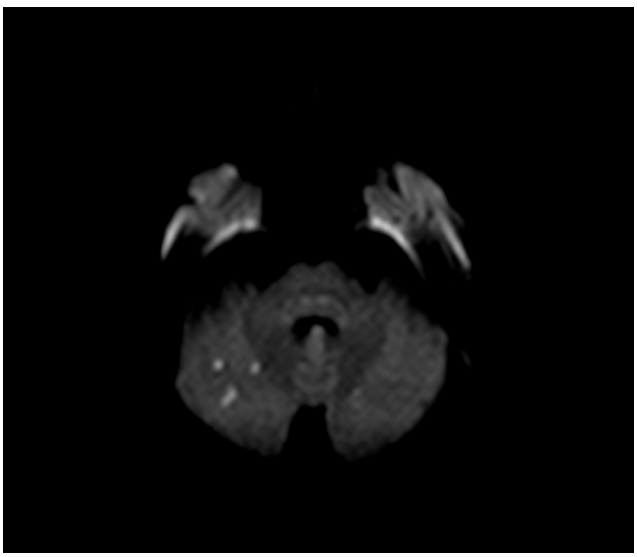

Fig. 3. Case 2. Brain MRI (diffusion) showing acute infarction in right cerebellum.

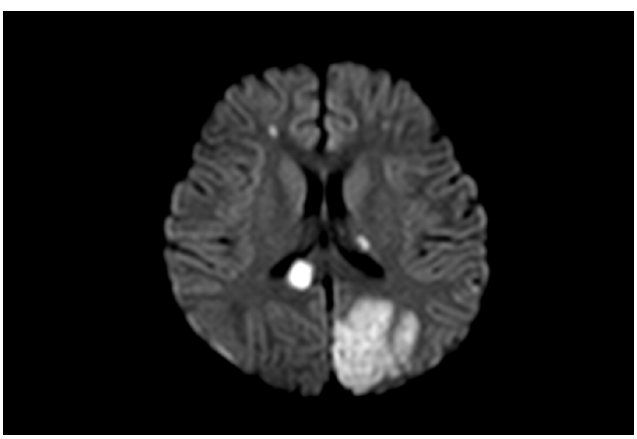

Fig. 4. Case 2. Brain MRI (diffusion) showing acute infarction in left parietooccipital lobe and right corpus callosum.

Care Unit. An electrocardiogram showed normal sinus rhythms and normal ventricular repolarization. Magnetic resonance angiography showed an acute infarct with altered deep signal in the right cerebellum (Fig. 3), left temporoccipitoparietal and left thalamus (Fig. 4). Another acute infarct on the right corpus callosum and frontoparietal was shown. Coagulation studies showed normal prothrombin time, and normal partial thromboplastin time. A lumbar puncture showed a normal CSF leukocyte count (2 cells/L), and normal amounts of glucose (78 mg/dL), and protein (23 mg/dL). No infectious agents (bacteria and/or herpes simplex virus 1-2) were found as a result of culturing CSF. CSF polymerase chain reaction for *M. pneumoniae* was negative. Parenteral therapy with macrolide, methylprednisolone was started. On the tenth day, visual hallucinations disappeared and mental status was alert. Serum antimycoplasmal antibodies were increased at 1:640 and cold agglutinins were positive. On the fifteenth day, cerebral angiography revealed multiple stenoses in both parietal and cerebellar branches, suggesting vasculitis (Fig. 5). The patient's symptoms had improved 3 weeks later.

Discussion

M. pneumoniae is a common cause of respiratory tract infections of varying severity. It accounts for 7-30% of cases of community-acquired pneumonia, with the highest attack rate among school-aged children.

The exact prevalence of *M. pneumoniae*-associated neurologic complications is variable. In patients hospitalized for *M. pneumoniae* infection, CNS symptoms were present in 1% to 7% of the cases[8].

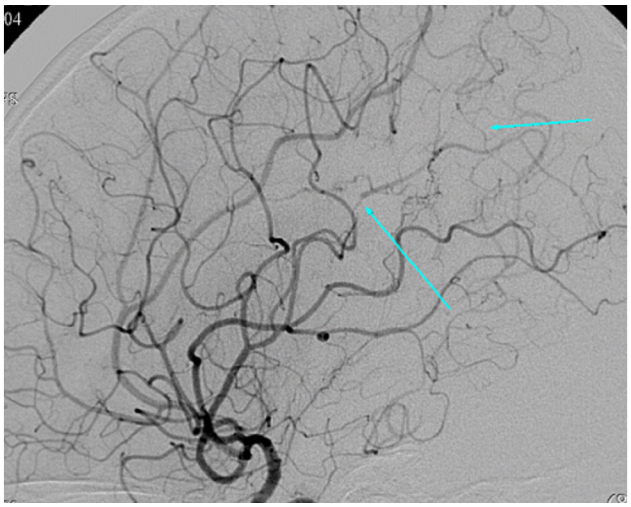

Fig. 5. Case 2. Four-vessel angiography showing luminal narrowing and dilatation in parietal branch and luminal irregularity in occipital and cerebellar branch.

M. pneumoniae is a potential cause of encephalitis in children. *M. pneumoniae* causes between 5 and 10% of acute childhood encephalitis in Europe and North America[6]. Children are more often affected than adults. The mean age of encephalitis cases in most series ranges between 5 and 10 years old[4].

Several mechanisms could theoretically explain the CNS manifestations seen in association with *M. pneumoniae* infections. These include direct invasion of the CNS, immune-mediated brain injury, vascular injury and hypercoagulable state and neurotoxin production.

Early and late onset encephalitis represent two distinct encephalitic patterns associated with *M. pneumoniae*[9]. Direct invasion of the brain parenchyma could be implicated in the former. But, the exact mechanism for invasion to extrapulmonary tissues, such as the CNS, remains unknown.

Late onset CNS disease may be better explained by immune complex mediated injury. Autoantibodies to brain tissue antigens may contribute to the neurological injury. However, their role is not clearly defined[10].

A hypercoagulable state has been noted in cases of *M. pneumoniae* infection; thus intravascular coagulation and thromboembolic phenomena of the cerebral vasculature may explain the observed neurologic injury[11]. Immune mediated vascular injury and the development of a vasculitis could further contribute to such effects.

Finally, in vitro release of a neurotoxin from some *Mycoplasma* species could contribute to neurologic injury. However, no such toxin has been demonstrated in humans infected with *M. pneumoniae* infection. In our cases, although there was strong supportive evidence of preceding *M. pneumoniae* infection, CSF polymerase chain reaction for *M. pneumoniae* was negative in two patients. We suggest that these cases resulted from a immune-mediated process rather than parenchymal invasion by the microorganism.

Several therapeutic measures have been used for the treatment of *M. pneumoniae* related CNS disease, such as antibiotics, corticosteroids, intravenous immunoglobulin and plasmapheresis. Antibiotic therapy has been associated with clinical improvement in several encephalitis cases. *M. pneumoniae* do not respond to β-lactam antibiotics because they lack a cell wall. Mycoplasmas are susceptible to antimicrobial agents that affect DNA, RNA, and protein synthesis. Antibiotics such as doxycycline (not in children), a macrolide or a fluoroquinolone can be used.

The possible immunological origin of *M. pneumoniae* encephalitis has led to the suggestion that treatment with corticosteroids may be beneficial. Use of IV immunoglobulin has not been associated with therapeutic benefit. Plasmapheresis may be effective in *M. pneumoniae* associated transverse myelitis or polyradiculitis cases[12].

Cerebral infarction is rare in children, and is usually detected by a CT or a MRI. Common causes are cardiac, hematologic and arterial occlusive diseases. These include moyamoya disease, tuberculous meningitis, and infectious vasculitis. Possible mechanism of ischemic stroke include 1) direct inflammation of the blood vessels in the CNS 2) hematological disturbances causing hypercoagulable states 3) cardiovascular disorders causing distant embolislms and systemic hypotension.

The role of infectious and inflammatory causes of stroke is much more significant in children than in adults. Although stroke after purulent bacterial meningitis is well accepted, other agents causing meningitis, potentially complicated by stroke, have recently been recognized. These include atypical bacterial agents such as Mycobacterium tuberculosis, Cryptococcus neoformans, Treponema pallidum (syphilis), Borrelia burgdorferi (Lyme disease), and *M. pneumoniae*[13].

Stroke is a rare complication of *Mycoplasma* infection. The CSF is usually normal, and an infectious agent is rarely found. In our cases, we did not find any evidence of cardiac or hematologic disease, and cerebral MRI confirmed the presence of cerebral ischcemic lesions. Furthermore, the

cerebral arteriography was suggestive of vasculitis.

Neurological complications of *M. pneumoniae* infection are rare. The majority of cases comprise encephalitis or meningoencephalitis and stroke is a rare complication especially in children. We report two cases of encephalitis and stroke after a recent *M. pneumoniae* infection.

한 글 요 약

Mycoplasma pnuemonia 감염에 의한 중추신경계 합병증 2례

한림대학교 의과대학 소아과학교실

김신미 · 허지승 · 심은정 · 이대형
조도준 · 김덕하 · 민기식 · 유기양

M. pnuemonia 감염은 사람에서 사람으로 전파되며 모든 연령의 소아에서 발생할 수 있으나 주로 학동기, 젊은 성인에서 하부 호흡기 계통의 질환을 유발하여 인두염, 기관지염, 모세기관지염, 크루프, 폐렴의 질환을 유발한다. *M. pneumoniae* 는 호흡기 감염 외에도 다양한 장기에 감염을 일으키며 합병증으로 다형홍반, Steven-Johnson syndrome, 수막뇌염, 무균성 수막염, 간염, 관절염, 심근염, 용혈성 빈혈 등이 발생할 수 있다. *M. pneumoniae* 의해 발생하는 신경계 합병증의 병태생리는 아직 명확하게 밝혀지지 않았으며 여러가지 가설이 제시되고 있다. 저자들은 *M. pneumoniae* 에 의한 중추 신경계 합병증으로 뇌염과 뇌경색의 각각 1례를 경험 하였기에 이를 보고하고자 한다.

References

1) Fernald GW, Collier AM, Clyde WA Jr. Respiratory infections due to Mycoplasma pneumoniae in infants and children. Pediatrics 1975;55:327-35.
2) Alexander ER, Foy HM, Kenny GE, Kronmal RA, McMahan R, Clarke ER, et al. Pneumonia due to Mycoplasma pneumoniae. Its incidence in the membership of a co-operative medical group. N Engl J Med 1966;275:131-6.
3) Foy HM. Infections caused by Mycoplasma pneumoniae and possible carrier state in different populations of patients. Clin Infect Dis 1993;17 Suppl 1:S37-46.
4) Lin WC, Lee PI, Lu CY, Hsieh YC, Lai HP, Lee CY, et al. Mycoplasma pneumoniae encephalitis in childhood. J Microbiol Immunol Infect 2002;35:173-8.
5) Cassell GH, Cole BC. Mycoplasmas as agents of human disease. N Engl J Med 1981;304:80-9.
6) Bitnun A, Ford-Jones E, Blaser S, Richardson S. Mycoplasma pneumoniae ecephalitis. Semin Pediatr Infect Dis 2003;14:96-107.
7) Ovetchkine P, Brugieres P, Seradj A, Reinert P, Cohen R. An 8-y-old boy with acute stroke and radiological signs of cerebral vasculitis after recent Mycoplasma pneumoniae infection. Scand J Infect Dis 2002;34:307-9.
8) Guleria R, Nisar N, Chawla TC, Biswas NR. Mycoplasma pneumoniae and central nervous system complications: a review. J Lab Clin Med 2005;146:55-63.
9) Bitnun A, Ford-Jones EL, Petric M, MacGregor D, Heurter H, Nelson S, et al. Acute childhood encephalitis and Mycoplasma pneumoniae. Clin Infect Dis 2001;32:1674-84.
10) Lind K. Manifestations and complications of Mycoplasma pneumoniae disease: a review. Yale J Biol Med 1983;56:461-8.
11) Mulder LJ, Spierings EL. Stroke in a young adult with Mycoplasma pneumoniae infection complicated by intravascular coagulation. Neurology 1987;37:1430-1.
12) 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:S52-7.
13) Takeoka M, Takahashi M. Infectious and inflammatory disorders of the circulatory system and stroke in childhood. Curr Opin Neurol 2002;15:159-64.