Internal carotid artery occlusion associated with *Mycoplasma pneumoniae* infection in a child

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SUMMARY: Tanır G, Aydemir C, Yılmaz D, Tuygun N. Internal carotid artery occlusion associated with *Mycoplasma pneumoniae* infection in a child. Turk J Pediatr 2006; 48: 166-171.

We describe a seven-year-old girl with severe pneumonia probably associated with *Mycoplasma pneumoniae* who developed right-sided hemiparalysis and right central facial paralysis soon after the onset of the disease. Cerebral magnetic resonance imaging revealed left corpus striatum acute infarction and magnetic resonance angiography demonstrated left internal carotid artery occlusion. She also had positive antiphospholipid and anticardiolipin antibodies and increased fibrinogen and D-dimer levels.

Key words: Mycoplasma pneumoniae, severe pneumonia, stroke, child.

Mycoplasma pneumoniae (*M. pneumoniae*) infection is common during childhood, and pneumonia is the most prominent clinical manifestation[1]. Lower respiratory tract illness due to *M. pneumoniae* is typically mild and self-limited. There are, however, numerous reports of serious and life-threatening cases of *M. pneumoniae* in adults and children[2]. Neurologic complications of *M. pneumoniae* infection are rare (0.1%)[1]. The incidence of neurologic complications is higher in hospitalized patients with severe *M. pneumoniae* infection (7%). Meningoencephalitis is the most frequently reported central nervous system complication of *M. pneumoniae* infection[3]. The less common manifestations are cranial neuropathy, polyradiculopathy, focal encephalitis, transverse myelitis, Guillain-Barre syndrome, and cerebellar ataxia[1,4-7]. However, ischemic stroke as a complication of *M. pneumoniae* infection is rarely reported in children[1,8-13]. We report a case of stroke in a seven-year-old girl who was hospitalized for acute severe pneumonia caused by *M. pneumoniae*. Cerebral magnetic resonance angiography (MRA) of the patient revealed internal carotid artery occlusion and her anticardiolipin and antiphospholipid antibodies were positive.

Case Report

A previously healthy seven-year-old girl with cough, fever and dyspnea was admitted to the Department of Infectious Diseases of Dr. Sami Ulus Children's Hospital. Five days before admission she experienced an abrupt onset of high fever and cough that did not improve after intravenous ampicillin-sulbactam treatment. Two days before admission, treatment was changed to ceftriaxone but the symptoms persisted. She was then transferred to our hospital with the presumed diagnosis of staphylococcal pneumonia from the local hospital.

The patient's family history and past medical history were unremarkable. Her parents were cousins.

Physical examination on admission revealed an alert, oriented girl. Her weight was 18 kg (10-25p) and height was 117 cm (25-50p). Her body temperature was 36.9°C, pulse rate 136/min, respiratory rate 44/min and blood pressure 90/70 mmHg. She had tachypnea with intercostal retractions. The saturation of oxygen on admission was 73% and after supplemental oxygen was 95%. Chest examination revealed crackles on the left side. Neurological examination and the rest of the physical examination were normal.

Initial laboratory studies showed a white blood cell count of 6,500/mm^3 with 86% neutrophils, 14% lymphocytes; hemoglobin 10.3 g/dl; and platelets 348,000/mm^3. The erythrocyte sedimentation rate was 20 mm/h and C-reactive protein (CRP) 276 mg/L (normal <2.9 mg/L). Arterial blood gas investigation revealed pH 7.4, HCO_3 24.8 mEq/L, PaO_2 74 mmHg, and $PaCO_2$ 36 mmHg. Biochemical investigations were normal. Direct and indirect Coombs tests were negative. The chest radiograph demonstrated homogeneous consolidation and atelectasis on the left lung (Fig. 1). The patient was considered to have severe pneumonia probably due to methicillin-resistant *Staphylococcus aureus* (MRSA) or ceftriaxone-resistant *Streptococcus pneumoniae* and was given intravenous ceftriaxone and vancomycin.
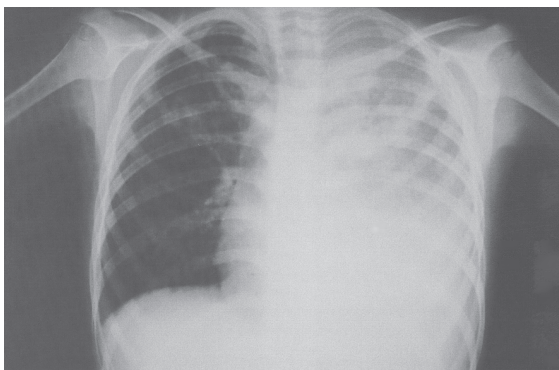

Fig. 1. Homogeneous consolidation and atelectasis on the left lung in the chest X-ray.

On the fifth day of hospitalization, right-sided hemiparalysis and right central facial palsy developed, high body temperature and dyspnea persisted, and increased infiltration on the chest radiograph was recognized. Clarithromycin treatment was commenced intravenously with the presumptive diagnosis of atypical pneumonia. Treatment with ceftriaxone and vancomycin was stopped when IgM positivity was detected on the 10th day of admission. Antibody titers to *M. pneumoniae* determined by the enzyme-linked immunosorbent assay (ELISA) were IgM 4.5 RU/ml (reference range: 0.0-1.1 RU/ml) and IgG 156.9 RU/ml (reference range: 0-20 RU/ml). Cerebrospinal fluid (CSF) investigation was normal. Bacteriological cultures of blood and CSF were sterile. Human immunodeficiency virus (HIV) and *Chlamydia pneumoniae* antibody were negative.

Magnetic resonance imaging (MRI) revealed an acute infarction of the left corpus striatum; MRA showed complete occlusion of the left internal carotid artery near the bifurcation and no blood flow in the middle cerebral artery. Vascular contrast was enhanced on left frontal lobe as a result of collateral vessels (Figs. 2, 3). Echocardiography was normal.
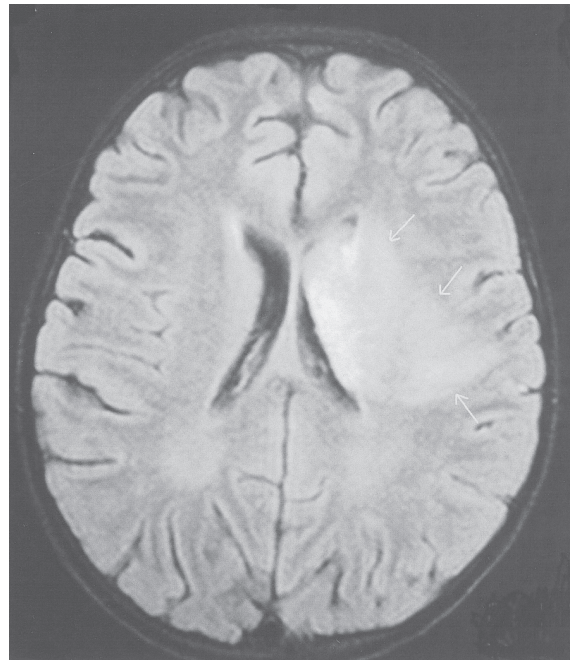

Fig. 2. Infarction of the left corpus striatum in the magnetic resonance imaging of brain.

Fig. 3. Complete occlusion of the left internal carotid artery near the bifurcation in the magnetic resonance angiography.

Prothrombin time and partial thromboplastin time, complement factors (C_3, C_4), protein C level, protein S level, antithrombin III level, resistance to activated protein C and homocysteine levels were normal. Fibrinogen and D-dimer levels were 480 mg/dl (normal: 180-350 mg/dl) and 1800 µg/L (normal: 50-228 µg/L), respectively. The factor V Leiden mutation and the prothrombin G 20210-A genotype studies were negative. Antinuclear antibodies and anti-DNA antibodies were negative. Anticardiolipin IgM antibody was 16.1 RU/ml (normal range: 0-12 RU/ml) and antiphospholipid IgM antibody was 18.2 RU/ml (normal range: 0-12 RU/ml). Anticardiolipin IgG and antiphospholipid IgG antibodies were absent. Three days after clarithromycin treatment, respiratory symptoms began to improve. Within seven days, the right-sided hemiparesis and the right central facial paralysis also started to resolve. Clarithromycin treatment was administered for 21 days. *M. pneumoniae* IgM and IgG titers four weeks after the onset were 3.8 RU/ml and 144.6 RU/ml, respectively. During the fourth week of hospitalization her neurological symptoms totally subsided and she was discharged. Control MRI six months after admission revealed partial occlusion of left internal carotid artery and chronic infarction of the left frontal region and basal ganglia.

Discussion

We report a pediatric case of acute, severe, community-acquired pneumonia with acute ischemic stroke. Because of acute onset of tachypnea, cough, presence of high fever, elevated serum CRP levels and current use of ceftriaxone treatment with no benefit, MRSA or ceftriaxone-resistant *S. pneumoniae* were considered responsible for pneumonia. Atypical pneumonia or coinfection with typical and atypical pathogens was suspected because the pulmonary symptoms and radiological findings did not respond to ceftriaxone and vancomycin treatment. In a comprehensive investigation including microbiological, serological, and molecular tests for maximum diagnostic yield, a pathogen was identified in 79% of 154 hospitalized children with acute community-acquired pneumonia. Bacteria accounted for 60% of infections, of which 73% were caused by *S. pneumoniae*. *M. pneumoniae*, *C. pneumoniae* and coinfections with typical and

atypical pathogens were detected in 14%, 9% and 9% of all cases, respectively[14] *M. pneumoniae* infection usually follows a benign course. Severe pneumonia may be seen in the presence of concomitant infection[15]. However, protracted course of fever, respiratory distress and elevated CRP levels were reported in cases of isolated *M. pneumoniae* infection[16]. Patients with clinically severe pneumonia, notably after treatment failures with β-lactam antibiotics, are most likely to profit from comprehensive Mycoplasma diagnosis and subsequent adequate antimicrobial treatment[17]. Our patient responded well to clarithromycin.

The IgM serology test was chosen because when compared with culture, complement fixation test and PCR, it proved to be the most reliable tool for diagnosing *M. pneumoniae* infections in children. It has been reported that elevated IgM antibodies are a reliable indicator of Mycoplasma infections in children in contrast to adults. The detection of specific IgM antibody, which appears 7 to 10 days after infection, has been shown previously to indicate a recent or current infection with *M. pneumoniae*.[18] In our case, the diagnosis of M. pneumoniae infection was supported by the detection of specific IgM and IgG antibodies by ELISA. *M. pneumoniae* cases have been reported as having positive specific IgM and IgG titers on admission and no increasing antibody titers 3-4 weeks later.[18] Acute ischemic stroke has been considered as a neurological complication of *M. pneumoniae* because of clinical and radiological improvement with clarithromycin treatment, no growth on bacterial cultures and presence of specific IgM positivity. To our knowledge, there is no case in the literature of *S. aureus*, *S. pneumoniae* or *Haemophilus influenzae* associated with cerebral artery thrombosis.

Sudden onset of right hemiparalysis was evident 10 days after the onset of respiratory illness, which is consistent with reports of other patients with central nervous system complications associated with *M. pneumoniae* infection.[1, 9, 10] Stroke is uncommon in childhood, with an incidence of only 3/100,000. Half of the reported events present as ischemic strokes[19]. Infectious diseases precede a significant proportion of strokes in childhood. At least one third of cases of childhood stroke occur in the context of infection[20]. *M. pneumoniae*, varicella - zoster virus, *Chlamydia pneumoniae*,

Parvovirus B[19], *Borrelia burgdorferi,* influenza A virus, HIV, and mumps virus have been identified as potential risk factors for arterial ischemic stroke during childhood[9-11, 21-27].

Multiple mechanisms are described in childhood stroke, including congenital or acquired heart disease, sickle cell disease, hypercoagulable states, trauma, dehydration (resulting in venous sinus thrombosis), meningitis/encephalitis, acquired immune deficiency syndrome, hemolytic uremic syndrome, moyamoya disease, mitochondrial disorders, and fibromuscular dysplasia. Nevertheless, a specific etiology can be determined in only 50%[19,20]. In our patient, the CSF examination after the onset of hemiparalysis was normal. No known risk factors for stroke except for a hypercoagulable state emerged after clinical and laboratory evaluations in our patient. Infections may cause hypercoagulability, perhaps by activating coagulation and inhibiting fibrinolysis[25]. In vitro experimental studies have suggested that lipoglycans from some Mycoplasma species, including *M. pneumoniae,* could induce procoagulant activity (tissue factor-like activity) by human mononuclear cells[28]. Increased titers of anticardiolipin and antiphospholipid IgM antibodies, and elevated fibrin D-dimer and fibrinogen levels, as found in our patient, have been described during *M. pneumoniae* infection[10,29]. These findings may represent the presence of a prothrombotic state associated with systemic infection. However, in contrast to primary phospholipid antibody syndrome, patients with anticardiolipin antibodies induced by infection were not thought to have increased risk for thrombosis[30].

Ischemic stroke as a complication of *M. pneumoniae* has been rarely documented. To our knowledge, there are seven cases in the literature of cerebral infarctions with *M. pneumoniae* in childhood[1,8-13]. All of the reported cerebral artery occlusion cases, including our patient, were girls. However, the case of acute stroke and cerebral vasculitis was a boy. This could be a chance event. All the documented cerebral infarctions associated with *M. pneumoniae* infection occurred in the anterior circulation of the brain, as was the case in our patient. The reason for this affinity remains unknown[10]. A case of a child with posterior cerebral artery occlusion and resultant hemiparesis associated with *M. pneumoniae* infection was recently reported[13].

Different mechanisms of cerebral infarction by *M. pneumoniae* have been suggested, including direct CSF invasion, an autoimmune mechanism with autoantibodies to brain or circulating immune complexes and the production of a neurotoxin[31-33]. In our patient, CSF findings were normal, but we could not investigate *M. pneumoniae* DNA in the CSF. Despite the absence of concurrent inflammatory CSF changes, *M. pneumoniae* DNA can be found in CSF as described by Padovan[30]. Because of the normal CSF findings in most patients with *M. pneumoniae*-associated stroke, the central nervous system invasion of *M. pneumoniae* remains to be considered as a possible cause[12]. An autoimmune mechanism has been proposed because of a two-week delay between the onset of respiratory symptoms and the occurrence of stroke[9]. Although a 10-day delay was present in this case, symptoms and radiological findings of severe pneumonia were also present at the time of stroke. Autoantibodies to host tissues such as brain and immune complexes have been demonstrated in *M. pneumoniae* infection[31]. We could only investigate antinuclear antibodies and anti-DNA antibodies, which were negative.

We treated our patient with clarithromycin, which is active against *M. pneumoniae.* However, it is not known whether the antibiotic treatment alters the neurologic course of infection because some evidence suggests an immunologic mechanism causing neurologic complications rather than direct invasion of *M. pneumoniae*[9,34]. Corticosteroids, plasma exchange, and intravenous immunoglobulin have been reported as beneficial therapies for different types of central nervous system complications of *M. pneumoniae* infection[1,35]. The respiratory symptoms of our patient improved three days after the onset of clarithromycin treatment. Systematic investigation to discriminate between the proposed mechanisms of para-infectious immune-mediated disease and parenchymal invasion of the central nervous system is essential to select appropiate antibiotic and immunomodulatory therapies[35].

The prognosis of *M. pneumoniae* neurologic disease is variable. The overall mortality has been reported as approximately 10%[1]. Recovery of neurologic deficits in children with cerebral infarction has been reported as early as two weeks, or up to one year[1,9]. Our patient recovered in four weeks.

In conclusion, the risk for complete cerebral infarction and resultant ischemic stroke as a complication during the clinical course of severe *M. pneumoniae* pneumonia should be kept in mind. Furthermore, a hypercoagulable state with increased titers of anticardiolipin and antiphospholipid IgM antibodies, fibrinogen, and D-dimer, as seen in our patient, might be determined.

REFERENCES

1. Papaevangelou V, Falaina V, Syripoulou V, et al. Bell's palsy associated with Mycoplasma pneumoniae infection. Ped Infect Dis J 1999; 18: 1024-1026.

2. Oerman C, Sockrider MM, Langston C. Severe necrotizing pneumonitis in a child with Mycoplasma pneumoniae infection. Pediatr Pulmonol 1997; 24: 61-65.

3. Ogata S, Kitamoto D. Clinical complications of Mycoplasma pneumoniae disease: central nervous system. Yale J Biol Med 1983; 56: 481-486.

4. Pfausler B, Engelhardt K, Kampfl A, et al. Post-infectious central and peripheral nervous system diseases complicating Mycoplasma pneumoniae infection. Eur J Neurol 2002; 9: 93-96.

5. Rothstein TL, Kenny GE. Cranial neuropathy, myeloradiculopathy and myositis: complications of Mycoplasma pneumoniae infection. Arch Neurol 1979; 36: 476-477.

6. Nadkarni N, Lisak RP. Guillain-Barre syndrome (GBS) with bilateral optic neuritis and white matter disease. Neurology 1993; 43: 842-843.

7. Coleman RJ, Brown JS, Butler P, Swash M. Cerebellar syndrome with hydrocephalus due to Mycoplasma pneumoniae infection. Postgrad Med J 1990; 66: 554-556.

8. Parker P, Puck J, Fernandez F. Cerebral infarction associated with Mycoplasma pneumoniae. Pediatrics 1981; 67: 373-375.

9. Visudhiphan P, Chiemchenya S, Sirinavin S. Internal carotid artery occlusion associated with Mycoplasma pneumoniae infection. Pediatr Neurol 1992; 8: 237-239.

10. Fu M, Wong KS, Lam WW, Wong GW. Middle cerebral artery occlusion after recent Mycoplasma pneumoniae infection. J Neurol Sci 1998; 157: 113-115.

11. Ovetchkine P, Brugieres P, Seradj A, et al. 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: 307-309.

12. Sotgiu S, Pugliatti M, Rosati G, Deiana GA, Sechi GP. Neurological disorders associated with Mycoplasma pneumoniae infection. Eur J Neurol 2003; 10: 165-168.

13. Antachopoulos C, Liakopoulou T, Palamidou F, Papathanassiou D, Youroukos S. Posterior cerebral artery occlusion associated with Mycoplasma pneumoniae infection. J Child Neurol 2002; 17: 54-57.

14. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004; 113: 701-707.

15. Ferwerda A, Moll HA, Groot R. Respiratory tract infections by Mycoplasma pneumoniae in children: a review of diagnostic and therapeutic measures. Eur J Pediatr 2001; 160: 483-491.

16. Wang RS, Wang SY, Hsieh KS, et al. Necrotizing pneumonitis caused by Mycoplasma pneumoniae in pediatric patients. Report of five cases and review of literature. Pediatr Infect Dis J 2004; 23: 564-567.

17. Daxboeck F, Krause R, Wenisch C. Laboratory diagnosis of Mycoplasma pneumoniae infection. Clin Microbiol Infect 2003; 9: 263-273.

18. Waris ME, Toıkka P, Saarinen T, et al. Diagnosis of Mycoplasma pneumoniae pneumonia in children. J Clin Microbiol 1998; 36: 3155-3159.

19. Kirkham FJ. Stroke in childhood. Arch Dis Child 1999; 81: 85-89.

20. Riikonen R, Santavuori P. Hereditary and acquired risk factors for childhood stroke. Neuropediatrics 1994; 25: 227-233.

21. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood. A study of frequency and causation. Stroke 2001; 32: 1257-1262.

22. Cook PJ, Honeybourne D, Lip GY, et al. Chlamydia pneumoniae antibody titers are significantly associated with acute stroke and transient cerebral ischemia. Stroke 1998; 29: 404-410.

23. Guidi B, Bergonzini P, Crisi G, Frigieri G, Portolani M. Case of stroke in a 7-year-old male after Parvovirus B19 infection. Pediatr Neurol 2003; 28: 69-71.

24. Heinrich A, Khaw AV, Ahrens N, Kirsch M, Dressel A. Cerebral vasculitis as the only manifestations of Borrelia burgdorferi infection in a 17-year-old patient with basal ganglia infarction. Eur Neurol 2003; 50: 109-112.

25. Bell ML, Buchhalter JR. Influenza A-associated stroke in a 4-year-old male. Pediatr Neurol 2004; 31: 56-58.

26. Narayan P, Samuels OB, Barrow DL. Stroke and pediatric human immunodeficiency virus infection. Case report and review of the literature. Pediatr Neurosurg 2002; 37: 158-163.

27. Grau AJ, Eckstein HH, Schafer B, et al. Stroke from internal carotid artery occlusion during mumps infection. J Neurol Sci 1998; 155: 215-217.

28. Joo CU, Kim S, Han YM. Mycoplasma pneumoniae induced popliteal artery thrombosis treated with urokinase. Postgrad Med J 2001; 77: 723-724.

29. Snowden N, Wilson PB, Longson M, Pumphrey RS. Antiphospholipid antibodies and Mycoplasma pneumoniae infection. Postgrad Med J 1990; 66: 356-362.

30. Padovan CS, Pfister HW, Bense S, Fingerie V, Abele-Horn M. Detection of Mycoplasma pneumoniae DNA in cerebrospinal fluid of a patient with M. pneumoniae infection "associated" stroke. Clin Infect Dis 2001; 33: 119-121.

31. Biberfeld G. Antibodies to brain and other tissues in cases of Mycoplasma pneumoniae infection. Clin Exp Immunol 1971; 8: 319-333.

32. Biberfeld G, Norberg R. Circulating immune complexes in Mycoplasma pneumoniae infection. J Immunol 1974; 112: 413-415.

33. Abramovitz P, Schvartzman P, Harel D, Kis I, Naot Y. Direct invasion of the central nervous system by Mycoplasma pneumoniae: a report of two cases. J Infect Dis 1987; 155: 482-487.

34. Candler PM, Dale RC. Three cases of central nervous system complications associated with Mycoplasma pneumoniae. Pediatr Neurol 2004; 31: 133-138.

35. Sakoulas G. Brainstem and striatal encephalitis complicating Mycoplasma pneumoniae pneumonia: possible benefit of intravenous immunoglobulin. Pediatr Infect Dis J 2001; 20: 543-545.