Case Report

Mycoplasma pneumoniae meningo-encephalitis: a case report

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Abstract

Central nervous system manifestations are a known complication in 0.1% of *Mycoplasma pneumoniae* infections. In this case report we present an 11 year old boy with meningo-encephalitis and pneumonia of the right lower lobe. There is clear seroconversion of *Mycoplasma pneumoniae*. After administration of adequate antibiotic therapy, there was complete clinical recovery. *Mycoplasma pneumoniae* should be taken into consideration when neurological symptoms complicate a respiratory tract infection.

Introduction

Mycoplasma pneumoniae is a known causative agent of meningo-encephalitis in children. It is transmitted by droplets and most frequently causes upper and lower respiratory symptoms (1–4). The central nervous system is only involved in 0.1% of the cases, with (meningo-)encephalitis, aseptic meningitis and myelitis as possible neurological presentations (5). Involvement of the central nervous system can be self-limiting, however early administration of adequate antibiotic therapy may be crucial.

Case report

An 11-year old boy is seen at the emergency department (ED) of a regional hospital with persistent fever for 7 days, aggravating headache and photophobia. He also complains of neck stiffness and nausea. For the last few weeks there have been multiple recurrent episodes of fever, accompanied with headache, conjunctivitis and a sore throat. He was seen by his own paediatrician 5 days prior to the ED visit. At that moment, he had a cough, bilateral conjunctivitis and a hyperaemic pharynx. Auscultation of the lungs is normal. Because of the recurrent febrile episodes, a blood test was done with negative inflammatory parameters (5400 WBC/µL; 4500-13000/µL) and CRP 17.5 mg/L (normal <5mg/L). Serologic analysis was negative for Cytomegalovirus (IgG and IgM) and *Mycoplasma pneumoniae* (IgM index <1.1 and IgG <45 U/mL). Epstein Barr virus serology shows a previous infection (IgM negative, IgG positive). A viral infection was suspected, supportive therapy was continued.

Initial clinical examination in the ED shows a drowsy but alert boy who responds to orders. Vital parameters are normal except for tachycardia (heart rate >120bpm, oxygen saturation 100%, blood pressure 101/74 mmHg). There is severe neck stiffness and photophobia. Further complete neurological examination is normal, Glasgow Coma Scale is 14 (E3M6V5). He has no more complaints of cough, although at lung auscultation diffuse crackles are heard in the right lung without respiratory distress. Ear, nose and throat evaluation is normal. There are no more signs of conjunctivitis.

Laboratory findings show leucocytosis (13000 WBC/µL), predominantly neutrophils (10960 neutrophils/µL; (1800-8000/µL)) , and a slightly elevated CRP of 11.7 mg/L. Radiology of the chest shows an infiltrate of the right lower lobe with bilateral hilar adenopathy. Prior to performing a lumbar puncture, a CT-scan of the brain was done, which showed no abnormalities and no evidence for raised intracranial pressure. Examination of the cerebrospinal fluid (CSF) reveals elevated WBC (930 WBC/µL; <5/µL) with 68% neutrophils and 10% lymphocytes, a low CSF glucose level (54 mg/dL; 60-80mg/dL) in relation to the blood glucose level (101 mg/dL) at the time of puncture and raised protein levels (141 mg/dL; 20-40mg/dL). Culture of the CSF remains sterile. Polymerase chain reaction (PCR) on CSF could not detect any causative agents.

However, serology (performed on day 0, but results on day 2) shows clear seroconversion for *Mycoplasma pneumoniae* with an elevation of both IgM (index 4.2) and IgG (>456U/mL) titres. In the ED as well as at his own paediatrician, the ELISA method was used for detection of antibodies. Nasal swab (PCR method) revealed *Mycoplasma pneumoniae* as well. Magnetic resonance imaging of the brain and electroencephalogram were not performed during initial work-up

The boy was diagnosed with meningo-encephalitis and pneumonia of the right lower lobe and hospitalized. An atypical causative agent was suspected and he was started on ceftriaxone, azithromycin and doxycycline.

Within 72 hours after admission, the boy was afebrile and his symptoms disappeared. Ceftriaxone and doxycycline were both administered for 5 days, azithromycin was given for a total of 10 days. He was discharged after 8 days of hospitalisation. There are no neurological sequels at 6 months follow up. Basic immunologic work-up did not reveal any abnormalities.

Discussion

Definition and pathogenesis

Mycoplasma pneumoniae is a common infectious agent in the paediatric population (5). The highest prevalence is noted among children between 5 and 15 years old (1,3,4,6–9). It is transmitted by droplets. Infections most frequently lead to upper and lower airway symptoms (1–4). However, several extrapulmonary manifestations have been described, with involvement of the central nervous system being the most common (1–3,5). Of all hospitalized patients with *Mycoplasma pneumoniae* infections, the reported incidence of neurological manifestations ranges from 1-10%(1,7–9).

Inflammation of the brain tissue and meninges in meningo-encephalitis causes headache, fever, meningeal signs, convulsions, focal neurological symptoms and an altered mental state (1,3,8–10). When these symptoms are preceded by an upper respiratory tract infection in the previous days to weeks, *Mycoplasma pneumoniae* must be taken into consideration(1,2,8). The interval between onset of respiratory and neurological symptoms ranges from 2 to 14 days (1,3,9). In our patient, onset of neurological symptoms was 1 week later than the respiratory symptoms. However, there is not always a precedent of an upper respiratory tract infection and some studies even state that there is no association with respiratory symptoms (1,3,8,10).

Several hypotheses for extrapulmonary manifestations have been suggested(1,7,9). Recently, the community-acquired respiratory distress syndrome (CARDS) toxin has been discovered (2,4). It is an adenosine 5'-diphosphate-ribosyl transferase and appears to have a significant role in the cellular damage and inflammation seen in

the respiratory epithelium of *Mycoplasma pneumoniae* infected patients (2,4). The extrapulmonary manifestations are now thought to be the result of an auto-immune response of the host (4). This could explain why failure to detect *Mycoplasma pneumoniae* in the CSF, by PCR or direct culture, is not uncommon (3,5,6,8–10). In our case, both PCR and culture on CSF were negative for Mycoplasma pneumoniae. In addition, central nervous system involvement is possible through direct invasion of the pathogen in the central nervous system(5,6). There is some evidence that infection with *Mycoplasma pneumoniae* makes the patient more susceptible to invasion by other pathogens, and vice versa (1,3,4,9,10). Other pathogens, known for their role in causing meningo-encephalitis, should thus be ruled out as co-infections are frequently seen.

Clinical and biochemical findings

On clinical examination, auscultation of the lungs often reveals expiratory wheeze and scattered rhonchi when lower respiratory tract involvement is present (4). Laboratory findings show a normal to elevated leukocyte count and possibly elevated sedimentation rate (2,4,6). On chest X-ray unilateral bronchopneumonia with hilar adenopathy might be observed, as was seen in our patient (2,4). Examination of the CSF in patients with *Mycoplasma pneumoniae* associated meningo-encephalitis often shows pleiocytosis and an elevated protein count with normal glucose levels (3,7–10). In some cases, this is only observed after repeated lumbar puncture (8). Isolation in the CSF of this pathogen is proof of direct invasion and thus establishes the diagnosis of *Mycoplasma pneumoniae* meningo-encephalitis (2,4,6,8,10). Imaging of the brain in suspected meningo-encephalitis patients ranges from normal to focal diffuse oedema, with abnormalities most frequently seen on MRI (3,8,9). Electroencephalogram is frequently abnormal, with focal or diffuse changes (3,9).

Serological methods can be used to detect *Mycoplasma pneumoniae* antibodies (4). Previously *Mycoplasma pneumoniae* infection was confirmed by complement fixation tests, but they lack sensitivity and specificity (6). Enzyme immunoassays (such as the ELISA technique) are more capable of detecting an acute infection than complement fixation tests (2). However, enzyme immunoassays lack sensitivity as cross-reaction with other Mycoplasma species makes them sensitive to false-positive results (2). IgM antibodies appear in the first weeks after onset of symptoms, with peak levels at about 3 weeks (2,4,6,9). Seroconversion with production of IgG occurs at 3 to 8 weeks after infection (2,5,6,9). In adults or immune-compromised patients, the rise of IgM might be less pronounced, since the current episode might be a re-infection, making the diagnosis on serology more difficult (3,9). The rise of IgM in paediatric patients is reliable to confirm ongoing *Mycoplasma pneumoniae* infection (6,8).

In children, the combined use of serology and PCR is recommended to establish the diagnosis of *Mycoplasma pneumoniae* infection (4). PCR is a sensitive detection method, to be used for direct detection on respiratory tract samples or CSF (6,8,9). In combination with serology, it is possible to differentiate colonization from active infection (6,9). Positive PCR does not necessarily indicate acute infection, as it can be detected beyond the death of the pathogen or in healthy asymptomatic carriers (2,3,6,10). However, PCR can be positive before antibody response (4,6).

This indicates that several diagnostic approaches must be used to establish the diagnosis (3).

Treatment

Mycoplasma pneumoniae is a small prokaryote, characterized by the absence of a rigid peptidoglycan cell wall (1,2,4). That is why they are insensitive to the administration of antibiotics that interfere with cell wall construction, such as β-lactam antibiotics (1,2,4,6). Antibiotic agents interacting with DNA-, RNA- or protein synthesis, such as quinolones, macrolides or tetracyclines are the first choice (1,3,5,6,8,9). However, their ability to cross the blood brain barrier is limited (3,7). Doxycycline might be an alternative, but its use is not recommended in children under 8 years old (6,9). In our patient, azithromycin and doxycycline were both associated.

Macrolides are the antibiotics of choice in the paediatric population (2,4,7). Macrolides also appear to have an immunomodulating effect, in addition to their bacteriostatic properties, which makes them even more suitable (2,5,7). Recent studies have shown that there is an emerging share of macrolide resistant mycoplasma strains (2,4). It remains uncertain if the administration of the appropriate antimicrobial therapy changes the course of the disease, since clinical improvement is not reported in all cases and full clinical improvement without administration of adequate therapy has been described (1,3,8,9). However, anti-mycoplasma therapy should always be considered when suspecting *Mycoplasma pneumoniae* (meningo-)encephalitis, because of the possible neurological sequels and even fatal outcomes (5,8,9).

There are no guidelines regarding the duration of the anti-mycoplasma therapy, specifically in patients with neurological manifestations (7). In patients with severe neurological manifestations or radiological abnormalities, the administration of corticosteroids or immunoglobulin should be considered given the possible immune-mediated pathogenesis (1,2,7–9).

Prognosis

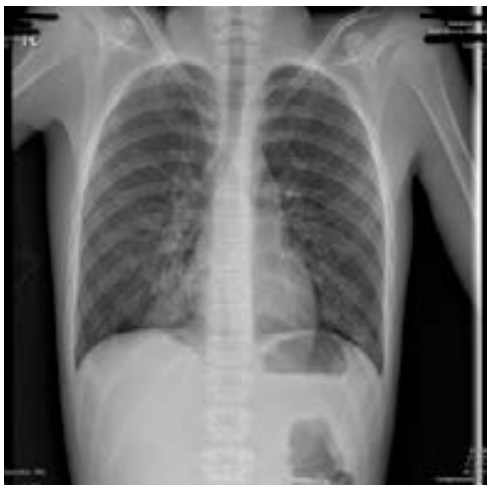
Neurological sequels have been described in 10 to 50% of patients with *Mycoplasma pneumoniae* associated meningo-encephalitis (1,8). These sequels range from mental retardation, epilepsy and cerebellar ataxia to mild cognitive impairments and might be permanent in 30% of patients (1,9).

Mycoplasma pneumoniae as the causative agent of meningo-encephalitis is associated with a worse prognosis in comparison to other pathogens and has a mortality rate of 5 to 10% (8,9).

Conclusion

We report the case of an 11 year old boy with meningo-encephalitis caused by Mycoplasma pneumoniae. Although this is rare, it is important to think of this pathogen in the differential diagnosis given that *Mycoplasma pneumoniae* needs specific antibiotic treatment and can have serious neurologic outcomes. Further research is indicated to establish guidelines for the treatment of *Mycoplasma pneumoniae* associated central nervous system manifestations.

Figure : *Bilateral hilar adenopathy and infiltrate of the right lower lobe*



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