ABSTRACT:

We describe two pediatric clinical cases presenting with seizures, neurological signs and symptoms associated with meningoencephalitis due to *Mycoplasma pneumoniae* infection. The patients developed the disease after an infection of the upper airways, which led to critical CNS complications. In the first case, seizures appeared to coincide with the respiratory symptoms, while in the second case seizures appeared subsequently, almost 2 weeks after the respiratory symptoms. In the present study we report and speculate on two different pathogenic pathways of CNS involvement related to *Mycoplasma pneumoniae* infection, namely direct or indirect.

**Key words:** Children, *Mycoplasma pneumoniae*, Meningoencephalitis complications, Anti-*Mycoplasma pneumoniae*

INTRODUCTION

Meningoencephalitis is a severe inflammatory disorder involving the meninges and the cerebral parenchyma. The initial clinical presentation may include fever, symptoms of respiratory illness, and gastrointestinal upset; neurological symptoms include altered consciousness, confusion, somnolence, coma, seizures, irritability, headache, focal neurological signs and personality change. It can be caused by many etiologic agents: viruses, essentially enterovirus and herpes simplex virus 1 and 2; but also other agents should be considered, such as rickettsia, protozoa and atypical bacteria, more specifically *Mycoplasma pneumoniae*. It is important to report that following the meningoencephalitis, in 20%-60% of cases, sequelae, such as postencephalitic epilepsy, mental retardation, brain atrophy, hydrocephalus, visual changes, and global neurologic deficits with brainstem dysfunction and cerebellar ataxia can persist. Moreover, in the last years, uncommon neurologic manifestations due to *Mycoplasma pneumoniae* have been reported more frequently in the literature.

In the present study we report two different pathogenic pathways of CNS involvement related to *Mycoplasma pneumoniae* infection, with a review of the literature.

CASE REPORT

Case 1

An 8-year-old boy was referred to our hospital for fever lasting for four days, associated with cough and difficult breathing, daytime sleepiness for 2 days, weakness of the lower limbs, hypomobility of the right arm and slurred speech. On admission the patient had poor general condition, fever (38.3°C), heart rate of 103 bpm, sleepiness, blood pressure 112/55 mmHg, oxygen saturation 94% on room air, isochoric and photo-reagent pupils, no signs of meningeal involvement, Glasgow coma scale score 15/15. He presented bilateral basilar rales, the remaining physical evaluation was normal, including cardiac exam-
ination. As for neurologic examination, he presented pos-
tural imbalance, negative Romberg test, nasal index and
index-index tests showing tremor during movements, im-
balance of the lower limbs when standing and preserved
muscle strength. The cranial nerves examination was nor-
mal, as well as ocular funduscopy examination. Chest X-
ray showed a left lower lobe pneumonia and diffuse bi-
lateral interstitial involvement. Antibodies to My-
coplasma pneumonia were positive for both IgM and
IgG. A diagnosis of pneumonia due to Mycoplasma pneu-
monia infection was made and antibiotic therapy with
ceftriaxone IV and oral clarithromycin was started.

After 16 hours he became lethargic, the movement of
the arm was more evident. Complete blood count
showed 24.100 white cells/mm³ with 77% neutrophils.
Both C-reactive protein (CRP) (76.2 mg/L- n.v. 0-5
mg/L) and erythrocyte sedimentation rate (74 mm/h- n.v.
0-20) were increased. Throat culture was negative. He
also underwent a sweat-chloride test evaluation, electro-
cardiogram and cardiac echocardiography, that were nor-
mal. Cold agglutinin values were positive. Rheumatoid
factor, ASLO titer, immunoglobulins, IgA and IgG
antigliadin antibodies (AGA), IgA antiendomysial anti-
bodies (EMA), anti-cardiolipin antibodies, anti-phospho-
lipid antibodies, antinuclear antibodies and anti-DNA
were absent. Serum amino acid (including homocys-
teine), serum ammonia and blood lactic acid were also
normal. Tests for hepatitis viruses and HIV-1 were nega-
tive. Rapid viral diagnostic tests for influenza, para-
influenza and respiratory syncytial viruses were negative. Antibod-
ies for herpes simplex virus type 1 and 2, measles, cy-
tomegalovirus, influenza virus, mumps, Borrelia
burgdorferi were all negative. Serum IgG for My-
coplasma pneumonia was 1:1.112 and IgM was 1:2.357.

Brain MRI was normal. Electroencephalography showed
irregular background activity with slow waves in the
posterior regions. A mild asymmetry was present in-
consistently, slow components were prominent centrally
on the right side, and sharp waves were prominent on the
left side. Treatment with sodium valproate was initiated.

Cerebrospinal fluid examination was made (CSF):
protein 66 mg/dL, glucose 84 mg/dL, chloride 799
mEq/L. PCR of the CFS was negative for CMV, EBV,
HSV1, HSV2, Varicella, Enterovirus and positive for My-
coplasma pneumonia.

She was treated with 2 g/kg/day of intravenous im-
munoglobulin (IVIG) for 2 days and azithromycin for 7
days (first dose 10 mg/kg/day, then 5 mg/kg/day). At fol-
low up, electroencephalography (performed 1 month
later) revealed fewer epileptiform discharges, but the
background activity was slightly more irregular.

After six months, she developed a focal tonic clonic
seizure of the right arm and leg, followed by generalized
hypotonia lasting less than 10 minutes.

After 15 months, she developed a new seizure episode
lasting less than 1 minute affecting mainly the right focal
side. After two years of follow up no further clinical signs
were recorded.

DISCUSSION

Mycoplasma pneumonia is a common cause of respira-
tory tract infections and is more common in school-age
children and adolescents. The incubation period may vary
between 1 and 3 weeks. Up to 40% of community-ac-
quired pneumonia in children admitted to the hospital are
attributed to M. pneumoniae infection. Although the

Case 2.

A 12-year-old girl had a sore throat and cough treated with
azithromycin for 3 days. After 5 days, although apparently
improving, she spiked fevers for two days, treated with
paracetamol, followed by daily headache. She also had
episodes of panic attack. Hypotonia, sleepiness, and
tremor of her left and lower limbs were noticed. Two days
later, she was admitted to the hospital for further diagnos-

IN FECT D IS TRO P M ED
infection is rarely lethal, patients of every age can develop a severe and fulminant course. This bacterium can cause extrapulmonary manifestations in up to 25% of clinically evident Mycoplasma pneumoniae infections and may affect almost every organ, including the skin, blood, cardiovascular, musculoskeletal, as well as the central nervous system (CNS). Of importance, the mechanism can be either directly related to the pathogen or indirectly due to an autoimmune-mediated mechanism. Approximately 2.6 to 4.8% of patients affected by M. pneumoniae have clinical neurological manifestations such as encephalitis (30%), transverse myelitis (30%), meningitis (20%), cranial nerves involvement (20%), cerebellitis (14%), psychiatric changes (8%), stroke or other events; of note, 67% of patients present previous signs of airway infection. However, 20% of patients with CNS findings have no preceding or concomitant diagnosis of respiratory infection. Encephalitis is the most frequent extrapulmonary complication of M. pneumoniae, presenting with fever, seizures, meningeal signs, ataxia, focal neurologic deficits, and behavioral disturbance, ranging from minor changes to lethargy in the pediatric population. It is estimated that between 5% and 10% of acute childhood encephalitis in Europe and North America is attributable to M. pneumoniae, and up to 60% of them show neurologic sequelae. Our cases highlight the extreme variability of the clinical symptoms associated with Mycoplasma pneumoniae infection, due to either a direct or an indirect autoimmune mechanism. Further studies are needed to better clarify the pathogenesis of these clinical events and the treatment of these patients.

In fact, the pathogenesis of neurologic diseases associated with Mycoplasma pneumoniae is not fully elucidated. Two pathogenetic mechanisms have been proposed: direct damage at the level of the CNS by the microorganism, with the presence of M. pneumoniae DNA in the cerebrospinal fluid by PCR, and/or by culture, and an immune-mediated process, through the potential action of antibodies on the CNS, along with other immune factors. The neuropsychiatric symptoms, seizures, cerebral infarction, stroke or other focal neurologic deficits could be the expressions of CNS vasculitis. This phenomenon involving the cerebral blood vessels can be the result of direct pathogen invasion or an provoked by molecular mimicry, immune complex deposition, secretion of cytokines, and/or super antigen mediated responses. Intrathecal antibodies can be detected by widely accessible enzyme immunoassays (EIAs) or immunoblotting, while intrathecal antibody synthesis can be established by calculation of an antibody index.

Venâncio et al. have reported the case of a boy with an encephalopathy associated with extraparamidal and psychiatric symptoms and anti-N-methyl-D-aspartate receptor antibodies. He had positive serum antithyroid antibodies, IgM antibodies against Mycoplasma pneumoniae and human herpesvirus 7 polymerase chain reaction in the cerebrospinal fluid. He was successfully treated with rituximab, after steroids, intravenous immunoglobulin and plasma exchange. In another study, it was reported that intrathecal antibodies to M. pneumoniae were found to cross-react with galactocerebroside C (GalC) in 38% of M. pneumoniae encephalitis cases.

**DIAGNOSIS**

Serologic diagnosis of Mycoplasma is doubtful and sometimes of difficult interpretation. The utility of IgM antibodies to M. pneumoniae varies with age; it is usually positive in acute infection but may be negative in the course of acute infection. Moreover, positive antibodies may last for months.

The diagnosis of neurological infection by M. pneumoniae is often very difficult, based on the clinical history and signs along with the diagnostic tests. CSF analysis usually shows moderate number of lympho-monocytes, high protein and normal glucose levels. The etiologic agent can be found in these sites in about 2% of cases. For the diagnosis of M. pneumoniae infection in children with encephalitis serology and polymerase chain reaction (PCR) from throat samples (routine studies) are recommended. In the presence of a positive test result and/or respiratory symptoms, PCR in cerebrospinal fluid is recommended. Importantly, a negative result of M. pneumoniae DNA in the CSF does exclude its role in CNS involvement. M. pneumoniae culture is not recommended for the diagnosis of acute M. pneumoniae infection, because M. pneumoniae requires special media and it needs weeks to grow.

The diagnosis can also be made by serologic tests for IgM and IgG antibodies to M. pneumoniae in paired (acute- and convalescent-phase) serum samples. For the IgG study, it may take at least 3 weeks for a relevant rise of IgG titers in the acute infection. As for IgM, it is fast and convenient and the changes of serum titers are fairly consistent in childhood during the acute phase.

For these reasons, M. pneumoniae IgM test is commonly used in the screening of pediatric patients when M. pneumoniae infection is suspected. Higher M. pneumoniae IgM titers and longer intervals between respiratory and CNS manifestations are associated with worse outcomes. Patients with relatively low concentrations of IgM titers (<51.3 BU/mL) and shorter intervals (<9.5 days), could have a lower immunological dysregulation leading to an inferior level of tissue damage and sequelae. If the interval is long and the IgM titer is high, the consequences of induced/activated direct and/or indirect immune attack might result in a poor prognosis. These findings suggest that IgM titers and the interval between respiratory illness and the onset of neurological symptoms may be associated with a worse outcome in patients with M. pneumoniae encephalopathy.

PCR and serology may be of limited value in the diagnosis of M. pneumoniae encephalitis because the high prevalence of M. pneumoniae in the upper respiratory tract of healthy children (up to 56%) makes it difficult to distinguish between colonization and infection in a clinically relevant time frame; the detection of intrathecal antibodies to M. pneumoniae, including cross-reactive antibodies against GalC and gangliosides, may be regarded as a promising new diagnostic tool.
Therefore, the routine diagnostic workup of *M. pneumoniae* encephalitis should aim at detecting *M. pneumoniae* antibodies in both CSF and serum, in addition to *M. pneumoniae* PCR in CSF. Intrathecal antibodies can be detected by widely accessible enzyme immunoassays (EIAs) or immunoblotting, while their hypothesized role in the pathogenesis let us speculate about the use of immunomodulatory treatment in *M. pneumoniae* encephalitis.

Finally, neuroimaging may reveal normal findings or focal diffuse edema in cases of encephalitis or meningoencephalitis. A focal infarction may be seen in *M. pneumoniae*-related stroke.

**TREATMENT**

It is important to establish the cause of encephalitis at an early stage, in order to establish a tailored treatment. Treatment of neurologic complications of *M. pneumoniae* is controversial. Treatment approaches are based on antibiotics, corticosteroids and intravenous immunoglobulins. Plasma exchange has also been reported and seemed to be beneficial. The antibiotic of choice to treat the pulmonary infection in children is a macrolide, however, there is no consensus regarding the central nervous system treatment. It is well known that such class of antibiotic does not properly penetrate the blood brain barrier. However, because of its bacteriostatic and immunomodulatory effect, it is considered as a treatment option. In addition, the use of corticosteroids should always be considered since immunosuppression is needed to counteract the detrimental effect of immunity in the pathogenesis of CNS damage.

**PROGNOSIS**

Long-term neurological problems have been reported in 20-60% of cases, with severe disease resulting in mental retardation, brain atrophy, hydrocephalus, epilepsy, visual changes, and global neurologic deficits with brainstem dysfunction and cerebellar ataxia. *M. pneumoniae*-related encephalitis in children is correlated with a high rate of post-encephalitic epilepsy and refractory seizures. Lin et al. investigated clinical factors, electroencephalography, and neuroradiologic features of *M. pneumoniae*-related encephalitis in a series of children with post-encephalitic epilepsy to examine possible prognostic factors. According to their study, risk factors for post-encephalitic epilepsy are the presence of seizures during the acute phase, especially recurrent seizures or status epilepticus, and EEG abnormalities, including focal epileptiform discharges in initial EEG.

**CONCLUSIONS**

*M. pneumoniae* infection is common in the pediatric age, and therefore should be included in the differential diagnosis of neurologic problems in this population. The appropriated identification of this atypical agent enables more specific and early treatment. The mechanism of damage caused by *M. pneumoniae* remains unclear. The isolation of *M. pneumoniae* from the CSF undoubtedly confirms the invasion of the CNS or, at least, of the CSF.

**CONFLICT OF INTERESTS:**

The Authors declare that they have no conflict of interests.

**REFERENCES**


