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Two distinct molecular patterns of meningoencephalitis due to *Mycoplasma pneumoniae* infection in children: 2 cases and review of the literature

V. Ferrara[1], G. Vitaliti[1], V. Rapisarda[2], S. Cocuzza[3], L. Giunta[1], P. Pavone[1], R. Falsaperla[1]

[1]U.O. of Pediatrics and Pediatrics Emergency, Azienda Ospedaliera Universitaria "Policlinico-Vittorio Emanuele", Catania, Italy

[2]Occupational Medicine, Vittorio Emanuele-Policlinico Hospital, University of Catania, Catania, Italy

[3]Department of Medical Surgical Specialties, ENT Clinic, University of Catania, Catania, Italy

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 ontwo 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[1]. 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[2]. 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*[1]. 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[3]. 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 pathogenetic pathways of CNS involvement related to *Mycoplasma pneumonia* 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 (38.3ºC), 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-

CORRESPONDING AUTHOR: PIERO PAVONE, MD; E-MAIL: PPAVONE@UNICT.IT

ination. As for neurologic examination, he presented postural imbalance, negative Romberg test, nasal index and index-index tests showing tremor during movements, imbalance of the lower limbs when standing and preserved muscle strength. The cranial nerves examination was normal, as well as ocular funduscopy examination. Chest X-ray showed a left lower lobe pneumonia and diffuse bilateral interstitial involvement. Antibodies to *Mycoplasma pneumonia* were positive for both IgM and IgG. A diagnosis of pneumonia due to *Mycoplasma pneumonia* infection was made and antibiotic therapy with ceftriaxone IV and oral clarithromycin was started.

After 16 hours he became lethargic, the movement of the right arm was more evident. Complete blood count showed 24.100 white cells/mm^3 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, electrocardiogram and cardiac echocardiography, thatwere normal. Cold agglutinin values were positive. Rheumatoid factor, ASLO titer, immunoglobulins, IgA and IgG antigliadin antibodies (AGA), IgA antiendomysial antibodies (EMA), anti-cardiolipin antibodies, anti-phospholipid antibodies, antinuclear antibodies and anti-DNA were absent. Serum amino acid (including homocysteine), serum ammonia and blood lactic acid were also normal. Tests for hepatitis viruses and HIV-1 were negative. Rapid viral diagnostic tests for influenza, parainfluenza and respiratory syncytial viruses were negative. Serum titers for herpes simplex virus type 1 and 2, measles, cytomegalovirus, influenza virus, mumps, and *Borrelia burgdorferi* were all negative.

Brain imaging (MRI) showed marked unspecific signal changes and restriction of periventricular white matter, corpus callosum and at semioval centers. Electroencephalogram showed a diffuse slowing activity and lack of epileptiform waves. Cerebrospinal fluid examination was performed (CSF): protein 86 mg/dL, glucose 62 mg/dL, chloride 621 mEq/L. PCR of the CFS was negative for CMV, EBV, HSV1, HSV2, Varicella, Enterovirus and *Mycoplasma pneumonia*.

Based on neurologic signs and symptoms at physical examination and on laboratory tests we diagnosed meningoencephalitis of probable Mycoplasma etiology, treated with 2 g/kg/day of intravenous immunoglobulin (IVIG) for 2 days and azithromycin for 8 days (first dose 10 mg/kg/day, then 5 mg/kg/day). After two weeks, the child was discharged without complications. We follow up the child for two years and it was uneventful.

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 diagnostic procedures. On admission, the patient presented poor general condition, fever (37.5 ºC), sleepiness, saturation was 97% on room air, no signs of meningeal involvement, isochoric and photo-reagent pupils. She presented tremor during movements. The cranial nerves examination was normal, as well as ocular funduscopy examination. Complete blood count showed 14.100 white cells/mm^3 with 57% segmented neutrophils. Both C-reactive protein (CRP) (12.6 mg/L- n.v. 0-5 mg/L) and erythrocyte sedimentation rate (31 mm-n.v. 0-20) were slightly increased. Throat culture was negative. Rheumatoid factor, ASLO titer, immunoglobulins, IgA and IgG antigliadin antibodies (AGA), IgA antiendomysial antibodies (EMA), anti-cardiolipin antibodies, anti-phospholipid antibodies, antinuclear antibodies and anti-DNA were absent. She also underwent a sweat chloride test evaluation, electrocardiogram and cardiac echocardiography that were all normal. Serum amino acid (including homocysteine), serum ammonia and blood lactic acid were also normal. AMA was 1/120 and ANA 1/180, ASMA was normal.

Tests for hepatitis viruses and HIV-1 were negative. Rapid viral diagnostic tests for influenza, parainfluenza and respiratory syncytial viruses were negative. Antibodies for herpes simplex virus type 1 and 2, measles, cytomegalovirus, influenza virus, mumps, *Borrelia burgdorferi* were all negative. Serum IgG for *Mycoplasma 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 inconsistently, 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 84mg/dL, chloride 799 mEq/L. PCR of the CFS was negative for CMV, EBV, HSV1, HSV2, Varicella, Enterovirus and positive for *Mycoplasma pneumonia*.

She was treated with 2 g/kg/day of intravenous immunoglobulin (IVIG) for 2 days andazithromycin for 7 days (first dose 10 mg/kg/day, then 5 mg/kg/day). At follow 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 respiratory tract infections and is more common in school-age children and adolescents. The incubation period may vary between 1 and 3 weeks[4,5]. Up to 40% of community-acquired pneumonia in children admitted to the hospital are attributed to M. *pneumoniae* infection[6-9]. Although the

infection is rarely lethal, patients of every age can develop a severe and fulminant course[10]. This bacterium can cause extrapulmonary manifestations in up to 25% of clinically evident *Mycoplasma pneumonia* infections and may affect almost every organ, including the skin, blood, cardiovascular, musculoskeletal, as well as the central nervous system (CNS)[11]. Of importance, the mechanism can be either directly related to the pathogen or indirectlydue 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[12,13]. However, 20% of patients with CNS findings have no preceding or concomitant diagnosis of respiratory infection[2-4,6,8,13]. 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[3,12,14-19]. It is estimated that between 5% and 10% of acute childhood encephalitis in Europe and North America is attributable to *M. pneumoniae*[20], and up to 60% of them show neurologic sequelae[20,21]. Our cases highlight the extreme variability of the clinical symptoms associated with *Mycoplasma pneumonia* 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 pneumonia* is not fully elucidated[18]. 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[21-25], and/or by culture[25,26]; and an immune-mediated process, through the potential action of antibodies on the CNS, along with other immune factors[10,18].

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[3,19]. 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[27].

Venâncio et al[28] have reported the case of a boy with an encephalopathy associated with extrapyramidal and psychiatric symptoms and anti-N-methyl-D-aspartate receptor antibodies. He had positive serum antithyroid antibodies, IgM antibodies against *Mycoplasma pneumonia* 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[29], 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[12,30].

The diagnosis of neurological infection by *M. pneumoniae* is often very difficult, basedon the clinical history and signs along with the diagnostic tests. CSF analysis usually showsa 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[12,31]. For the diagnosis of *M. pneumoniae* infection in children with encephalitis serology and polymerase chain reaction (PCR) from throat samples (routine studies) are recommended[32]. In the presence of a positive test result and/or respiratory symptoms, PCR in cerebrospinal fluid is recommended[10]. Importantly, a negative result of *M. pneumonia* 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[33]. 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[34]. As for IgM, it is fast and convenient and the changes of serum titers are fairly consistent in childhood during the acute phase[35]. 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[2]. 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[2]. 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. pneumonia* encephalopathy[2].

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%)[36,37] makes it difficult to distinguish between colonization and infection in a clinically relevant time frame[36]; 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[10].

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 speculateabout the use of immunomodulatory treatment in *M. pneumoniae* encephalitis[10].

Finally, neuroimaging may reveal normal findings or focal diffuse edema in cases of encephalitis or meningoencephalitis. A focal infarction may be seenin *M. pneumoniae*-related stroke[3-13].

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[14,40,41-46]. 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 know that such class of antibiotic does not properly penetrate the blood brain barrier[42]. 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[18,43].

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[3]. *M. pneumoniae*-related encephalitis in children is correlated with a high rate of post-encephalitic epilepsy and refractory seizures[44]. Lin et al[44] 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[44].

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.

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