

Neurological manifestations of *Mycoplasma pneumoniae* infection

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ABSTRACT:

- **Background:** *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia. Little is known about the extrapulmonary manifestations of this organism that are dominated by central nervous system (CNS) involvement. We aimed to identify the epidemiological and clinical peculiarities of *M. pneumoniae* infection with neurological manifestations and to analyze its therapeutic and evolutionary modalities.
- **Patients and methods:** Patients with neurological manifestations due to *M. pneumoniae* infection admitted in our department were scanned in the light of demographic, clinical, radiological features and response to treatment.
- **Results:** Totally we conducted 15 patients with an average age 21.7 ± 8 years. There were 8 men and 7 women. The average consultation time was 4 ± 3 days. The most common symptoms were headache (73.3%), fever (60%), altered state of consciousness (20%) and focal signs (13.3%). Respiratory manifestations were associated in 7 cases (46.7%). The clinical entity was meningitis in 11 cases (73.3%), meningoencephalitis in 2 cases (13.3%), encephalitis and peripheral facial palsy in 1 case each (6.7%). All patients received probabilistic antibiotic therapy that was adapted after serology results. The molecules used were rovamycin in 5 cases (26.7%), doxycycline in 2 cases (13.3%) and chloramphenicol in 1 case (6.7%). The outcome was favorable without any sequelae in all cases.
- **Conclusions:** This study aims to prompt clinicians to consider extrapulmonary *M. pneumoniae* infection in the differential diagnosis for patients presenting with acute neurologic and respiratory symptoms.
- **Keywords:** *Mycoplasma pneumoniae*, Meningitis, Meningoencephalitis, Macrolide.

INTRODUCTION

Mycoplasma pneumoniae most commonly causes a mild, self-limiting respiratory illness, including pharyngitis and acute bronchitis. Typical presenting symptoms are headache, fever and malaise, followed by an intractable dry cough. Extrapulmonary, 'atypical' manifestations of *M. pneumoniae* infection can include central nervous system (CNS) involvement, cold agglutinin haemolysis, skin eruptions, cardiac involvement and arthritis¹. Numerous CNS manifestations have been described with *M. pneumoniae* and it is probably the most common site of involvement

in addition to the respiratory system². Our series analyzes characteristics of patients having *M. pneumoniae* infection with CNS manifestations in Southern Tunisia.

PATIENTS AND METHODS

This study retrospectively analyzes clinical record of patients hospitalized in our department for *M. pneumoniae* infection with CNS involvement during the last twenty years (2005-2019). The diagnosis was established by serology results.



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Table 1. Clinical signs and entity of patients having *Mycoplasma pneumoniae* infection with Neurological manifestations (n= 15).

	Number (N=15)	Male N (%)
Clinical signs		
Fever	9	6 (40)
Asthenia	7	4 (26.6)
Headache	11	5 (33.3)
Altered state of consciousness	3	1 (6.66)
Focal signs	2	1 (6.66)
Clinical entity		
Meningitis	11	6 (40)
Meningoencephalitis	2	1 (6.66)
Encephalitis	1	0 (0)
Peripheral facial palsy	1	1 (6.66)

RESULTS

Totally we conducted 15 patients with an average age 21.7±8 years. There were 8 men (53.3%) and 7 women (46.7%). The average consultation time was 4± 3 days. General signs were dominated by fever noted in 9 cases (60%) and asthenia in 7 cases (46.7%). The most common neurological symptoms were headache observed in 11 cases (73.3%), altered state of consciousness in 3 cases (20 %) and focal signs in 2 cases (13.3%). Respiratory manifestations were associated in 7 cases (46.7%). The clinical entity was meningitis in 11 cases (73.3%), meningoencephalitis in 2 cases (13.3%), encephalitis and peripheral facial palsy in 1 case each (6.7%) (Table 1). The lumbar puncture performed in 14 cases (93.3%) showed an increased rate of white cells in 13 cases (92.8%) predominantly lymphocytic. The average cerebrospinal fluid (CSF) leukocyte count was 488±900 white cells/mm³. Protein concentration in CSF was increased in all cases of meningitis, while glucose concentration was normal or slightly elevated. Serology performed 2 weeks apart showed seroconversion in 4 cases (26.7%) and 4-fold rise in antibody titer in 11 cases (73.3%). One patient underwent magnetic resonance imaging (MRI) performed on a patient showed extensive left temporo-fronto-parietal leucoencephalitis (Figure 1). All patients received probabilistic antibiotic therapy that was adapted after serology results. The molecules used were rovamycin in 5 cases (26.7%), doxycycline in 2 cases (13.3%) and chloramphenicol in 1 case (6.7%). The outcome was favorable without any sequelae in all cases.

DISCUSSION

M. pneumoniae belongs to the class Mollicutes, the smallest and most unusual group of self-replicating prokaryotes. These are distinguished phenotypically from other bacteria by the total lack of cell wall². This explain why the bacterium is invisible on gram stain and beta-lactam antibiotics are ineffective against it. The absence of a cell wall also confers some protection from innate immunity, due to the absence of cell wall-derived stimulators such as lipopolysaccharide and peptidoglycan¹. *M. pneumoniae* usually causes pulmonary infection

and CNS involvement is less common. The overall incidence of CNS complications associated with *M. pneumoniae* infection is about 0.1% or less³. Among patients with neurologic syndromes, *M. pneumoniae* association has been shown in 5% to 10% of cases⁴. CNS involvement appears to occur more commonly in children than in adults⁵. The pathophysiology behind the symptomology remains hypothetical. It is suggested that the complications may result either from direct invasion of *M. pneumoniae* into the brain, a neurotoxin produced by the organism, or immune-mediated damage. The immune-mediated injury could be caused by cross-reacting antibodies to antigen(s) shared by *Mycoplasma* and brain, organism-induced immunosuppression, immune complex vasculopathy, or vascular microthrombi². In the literature, encephalitis is the most frequent manifestation caused by *M. pneumoniae*. This was not the case in our study as we noted that meningitis was the most frequent entity. In fact, encephalitis could be underestimated. The

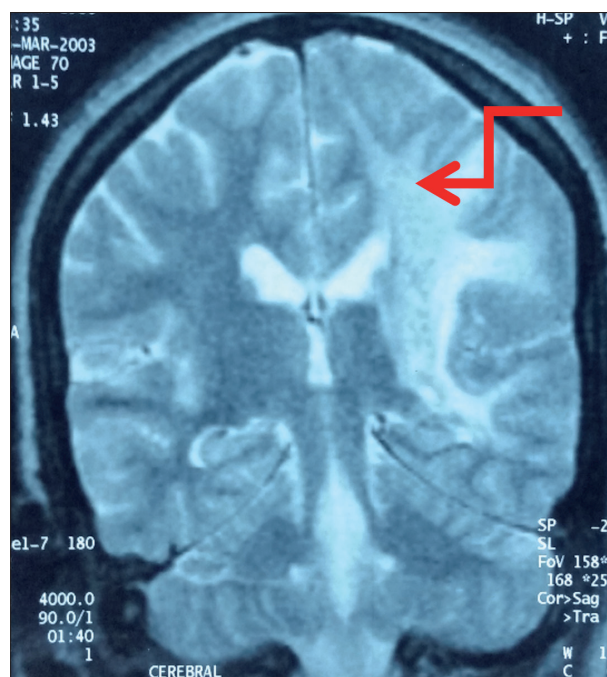


Figure 1. Axial cut of magnetic resonance imaging showing hypersignal of the left temporo-fronto-parietal white matter on T2 (arrow).

severity of this form often requires hospitalization in intensive care unit and not in a medical unit. The onset of neurological symptoms is usually acute with decreased consciousness, convulsions, paresis, and other neurologic signs. Those signs were also noted in our study. Encephalitis may be diffuse or focal, and often expansive. It may mimic encephalitis lethargica⁶. This manifestation may concentrate in the cerebellum or pons regions and may cause hydrocephalus. Sometimes encephalitis may be recurrent. In the literature, aseptic meningitis seems to be a benign syndrome. Also in our study, no deaths or permanent sequelae were found. Myelitis may appear in different forms: diffuse, transverse, or polio-like. In addition, there are some descriptive terms that characterize these terms include coma, stupor, ataxia, psychosis, and even stroke, after which real infarct may occur². In the literature, Leukocytosis and positive CRP are associated with severe *M. pneumoniae* infection and that was found in our series. Serologic tests have been most widely used and a 4-fold rise in antibody titer in acute and convalescent sera is considered the “gold standard”. However, the use of a single qualitative measurement of IgM has low sensitivity (32-77%), which increases (88.6%) when paired sera are analysed⁷. The interpretation of a positive serologic test is more problematic when it comes to extra-pulmonary form⁵. Because of the difficulties associated with serology, PCR is being utilized increasingly to establish a diagnosis of *M. pneumoniae* infection. Clearly, detection of *M. pneumoniae* in the CSF or brain tissue by PCR provides strong evidence of causality⁵. The fastidious nature and stringent growth requirements of *M. pneumoniae* and the need for prolonged incubation limit the utility of culture in the routine diagnosis of *M. pneumoniae* infections. However, isolation of the organism in culture from brain tissue or CSF of a patient with acute meningitis, meningoencephalitis, or encephalitis provides reliable evidence of causality³. Detection of *M. pneumoniae* in the throat but not the CSF provides reasonably good evidence of causality for those patients without convincing evidence of another infectious etiology, particularly when the clinical presentation is consistent with immune-mediated disease or a thromboembolic stroke. A chronic *M. pneumoniae* carrier state does not occur in immunocompetent individuals, but throat cultures may remain positive for as long as 10 to 16 weeks after the onset of illness⁵. Ultimately, the diagnosis of *M. pneumoniae* CNS disease requires a certain degree of clinical judgment and should be based on consideration of the clinical context and results of microbiologic investigations. The role of antibiotic therapy in the management of *M. pneumoniae* CNS complications remains undefined because of the lack of controlled trials assessing such therapy and uncertainties regarding the pathophysiology and natural history of CNS disease. Antibiotics with significant *in vitro* and *in vivo* activity against *M. pneumoniae* include the macrolides, tetracyclines, chloramphenicol, quinolones, ketolides, and streptogramins. Of these, the macrolides are considered the first-line agents. This was also the most used class of antibiotics in our study. The principal disadvantage of the macrolides, in the context of CNS disease,

is their inability to traverse the blood brain barrier and achieve therapeutic levels within the CNS. Azithromycin is a noted exception in as it has been shown to reach a high concentration in brain tissue although not in CSF or aqueous humor⁵. On the other hand, the beneficial effect of treatment with steroids suggests that this approach must be considered in patients in whom direct invasion of CNS with *M. pneumoniae* and other causative agents has been excluded⁸. Plasma exchange has also been reported and seemed to be beneficial⁹. *M. pneumoniae*-associated neurologic complications are usually reversible, but the mortality of patients is higher (10.3%)², and approximately one-third of the patients who have recovered are left with a permanent or persistent neurologic deficit¹⁰.

CONCLUSIONS

The lack of awareness and of sensitive and specific diagnostic techniques CNS infections caused by *M. pneumoniae* explain why this entity is considered only after other likely causative agents have been excluded or if there is no improvement with antimicrobial agents inactive against *Mycoplasma*. This entity must always be kept in mind in order to ensure early and adequate management.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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