CASO CLÍNICO/CASE REPORT

Neurological Complications of *Mycoplasma pneumoniae*: Three Paediatric Cases

Complicações Neurológicas por *Mycoplasma pneumoniae*: Três Casos Pediátricos

Vitória Cadete [1,*]; Beatriz Cordeiro Martins [1]; Rui Duarte Armindo [2]; Raquel Ferreira [1]; Clara Marecos [3]

1-Paediatric Department, Lisbon Luz Children and Adolescent Hospital, Lisboa, Portugal
2-Imaging Department, Lisbon Luz Hospital, Lisboa, Portugal
3-Paediatric Neurology, Lisbon Luz Children and Adolescent Hospital, Lisboa, Portugal

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Abstract

Mycoplasma pneumoniae is mainly responsible for respiratory diseases but neurological complications may occur through direct invasion or post-infectious immune response, as observed in three paediatric patients during the 2023/24 outbreak.

A 3-year-old boy presented with respiratory symptoms, ataxia, nystagmus, action tremor and somnolence. Cerebrospinal fluid (CSF) findings and positive serology suggested *M. pneumoniae*-associated encephalitis, treated with azithromycin.

The second case was a 13-year-old boy with MOG antibody-associated optic neuritis, six weeks after a respiratory infection, suggesting an immune-mediated process triggered by *M. pneumoniae* (positive serology). Antibiotics and corticosteroids led to recovery.

The third case involved a 14-year-old boy with reduced consciousness, headache, ataxia, and vomiting, one week after respiratory symptoms. Magnetic resonance imaging and CSF findings suggested acute disseminated encephalomyelitis, following M. pneumoniae infection (positive serology and PCR). Clinical improvement was observed after corticosteroids and intravenous immunoglobulin.

These cases highlight the importance of early recognition and prompt treatment of *M. pneumoniae*-related neurological complications.

Resumo

O *Mycoplasma pneumoniae* pode associar-se a complicações neurológicas por invasão direta do sistema nervoso central ou por mecanismos imunomediados. Reportam-se três casos pediátricos da época 2023/24.

Rapaz de 3 anos apresentou sintomas respiratórios, ataxia, nistagmo, tremor e sonolência, com diagnóstico de encefalite associada a *M. pneumoniae* (análise do líquido cefalorraquidiano (LCR) e serologias compatíveis), com melhora sob azitromicina.

Adolescente de 13 anos, sexo masculino, internado por nevrite ótica associada a anticorpos anti-MOG, seis semanas após infeção respiratória, sugerindo como desencadeante *M. pneumoniae* (serologia positiva). Cumpriu corticoterapia e azitromicina com melhoria.

Adolescente de 14 anos, sexo masculino, apresentou alteração do estado de consciência, ataxia, cefaleias e vómitos uma semana após sintomas respiratórios. Ressonância magnética e LCR sugestivos de encefalomielite disseminada aguda, após infeção por *M. pneumoniae* (serologia e PCR positivos). Observada melhoria progressiva após corticoterapia e imunoglobulina intravenosa.

Concluindo, é crucial o reconhecimento e tratamento precoces de complicações por *M. pneumoniae*.

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***Autor Correspondente / Corresponding Author:**
Vitória Cadete
Rua da Bombarda 76, 4ºB,
1100-096 Lisboa, Portugal
vitoria.cadete@gmail.com

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Introduction

Mycoplasma pneumoniae is a common cause of respiratory infections, with outbreaks occurring in Europe typically every 1 to 3 years.[1] After a three-year decline during the COVID-19 pandemic, infections resurged in 2023–2024, especially in Europe and Asia.[1]

Alongside the rise in *M. pneumoniae* infections, extrapulmonary manifestations have been reported, at a similar rate as in prepandemic years.[2] *M. pneumoniae* can lead to neurological complications due to direct invasion of the central nervous system (CNS), immune-mediated mechanisms or vascular occlusion, including encephalitis, transverse myelitis, acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome, cerebellitis, opsoclonus-myoclonus syndrome, and stroke, among others.[3-6]

We report a case of encephalitis, optic neuritis, and ADEM following *Mycoplasma pneumoniae* infections.

Case Report

Case 1

A 3-year-old boy presented to the emergency department somnolent and unable to stand or walk independently, preceded by three days of rhinorrhoea. His past medical history included chronic serous otitis, and he was on montelukast and inhaled fluticasone daily. His vaccination record was up to date. His family history was unremarkable. On physical examination he was somnolent, irritable when stimulated, with generalized hypotonia and hyporeflexia, ataxia, dysmetria, action tremor, occasional nystagmus and a slurred speech. The Kernig and Brudzinski signs were positive. There was no involvement of cranial nerves. Tonsillar hyperaemia was noted.

Cerebrospinal fluid (CSF) analysis revealed pleocytosis (22 leukocytes/μL) and hypoglycorrhachia (54% of serum glucose); electroencephalography showed mild diffuse slowing of baseline activity electrogenesis, and brain magnetic resonance imaging (MRI) was unremarkable. Etiological work-up revealed positive IgM and IgG for *M. pneumoniae* (IgM 2.9 UR/mL; IgG 128 UR/mL), suggesting *M. pneumoniae*-associated encephalitis.

He was treated initially with ceftriaxone and acyclovir, until DNA testing for *Borrelia burgdorferi* and neurotropic viruses in CSF returned negative. Once *M. pneumoniae* serology was known, azithromycin was added (5-day course). There was progressive clinical improvement during the hospitalization, achieving full recovery within one month, with normal deep tendon reflexes. Four weeks after the hospital discharge, IgM for *M. pneumoniae* was negative, while IgG was positive (IgG 46 UR/mL).

Case 2

A 13-year-old male was admitted with bilateral eye pain, reduced visual acuity, altered colour perception, photophobia, headache, and vomiting. Six weeks prior, he had an upper respiratory tract infection. His past and family medical history were unremarkable. The ophthalmological exam showed decreased visual acuity (right eye 0.05; left eye 0.4), painful eye movement, without diplopia or papilledema on fundoscopy. The physical and neurological exams were otherwise normal.

Brain and orbits MRI findings were suggestive of optic neuritis (ON) (**Fig. 1**), with bilateral thickening of the retinal nerve fiber layer on optical coherence tomography.

Etiological work-up revealed positive serum anti-myelin oligodendrocyte glycoprotein (MOG) antibodies (titer 1:20) and positive *M. pneumoniae* IgM and IgG antibodies (IgG 95 UR/mL), suggesting MOG antibody-associated ON, likely triggered by *M. pneumoniae*.

The patient was started on methylprednisolone 30 mg/kg/day for 5 days, followed by oral prednisolone for one month, plus azithromycin for five days. He was hospitalized for one week, with resolution of headaches and vomiting episodes. Visual acuity fully recovered within two months. Four weeks after hospital discharge, IgM for *M. pneumoniae* was negative, with positive IgG (IgG 89 UR/mL). Six months later, MOG antibodies remained positive.

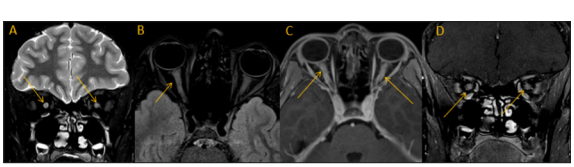

Figure 1. Coronal T2 STIR (A), axial T2 FLAIR (B), axial contrast-enhanced T1-weighted fat-suppressed (C) and coronal contrast-enhanced T1-weighted fat-suppressed (D) images showing increased T2 signal, mild enlargement and bilateral post-contrast enhancement of the retrobulbar segments of the optic nerves.

Case 3

A 14-year-old male presented with fever, headache, photophobia, phonophobia and vomiting. Examination showed erythematous rash on the neck and upper tho-

racic region, otherwise unremarkable. He had a nasopharyngitis and an acute otitis media a week before.

CSF analysis revealed hypoglycorrhachia (57% of serum glucose), hyperproteinosis (76 mg/dL) and pleocytosis (leukocytes 199/μL, predominance of mononuclear cells). Suspecting meningitis, ceftriaxone 4g daily was started.

On the second day of hospitalization, the patient developed confused speech, temporal disorientation, ataxia, and urinary retention. Acyclovir was added. On the following day, there was a progressive decrease in consciousness and bradycardia. After a 3% sodium chloride bolus, there was partial clinical improvement. Since there was a *Mycoplasma pneumoniae* outbreak in Europe at that time,[1] ciprofloxacin was initiated.

A brain and spinal cord MRI scan showed multiple lesions characteristic of ADEM (**Fig. 2**).

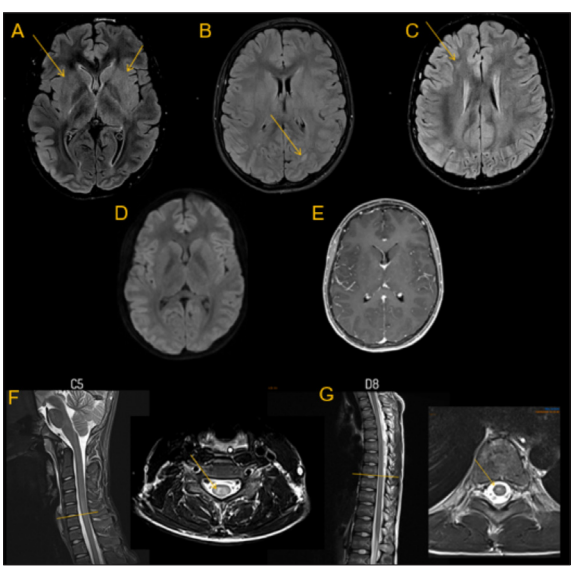

Figure 2. Axial T2 FLAIR (A-C); Axial DWI (D); axial T1 after gadolinium (E); Axial and sagittal T2 images (F-G). Involvement of the basal ganglia (arrows on A) and bilateral subcortical white matter is observed. Two focal lesions are slightly more evident in T2 and T2/FLAIR sequences: one in the left parieto-occipital juxtacortical region (arrow on B) and another in the right subcortical frontal white matter (arrow on C), without diffusion restriction or contrast enhancement. The spinal cord shows subtle, ill-defined T2 hyperintensities at the C5-C6 and D8-D12 levels, without mass effect or contrast enhancement. These findings suggest ADEM.

The electroencephalogram showed slow, poorly differentiated baseline electrophysiological activity, bifrontal slow activity, independent bilateral frontotemporal activity and bilateral rhythmic delta activity.

Further etiological workup revealed intrathecal IgG synthesis, positive serology (IgM and IgG) and nasopharyngeal polymerase chain reaction (PCR) for *M. pneumoniae*, suggesting ADEM following *M. pneumoniae* infection.

The patient underwent 5 days of methylprednisolone 30 mg/kg/day and 2 days of intravenous immunoglobulin (IVIG), due to poor response. He completed a month of prednisolone and a rehabilitation programme, with full recovery within 5 months.

Discussion

M. pneumoniae infections may lead to neurological complications and long-term sequelae, even in the absence of previous respiratory symptoms.[6] Encephalitis is the most frequent neurological complication of *M. pneumoniae* infection, although other neurological manifestations have also been described.[3-6] Some cases of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) secondary to *Mycoplasma pneumoniae* infections have been documented, presenting as MOG antibody-associated ADEM, MOG antibody-associated encephalitis and meningoencephalitis.[7-9] To the best of our knowledge, this is the first report of paediatric MOG antibody-associated ON secondary to *M. pneumoniae*.

Al-Zaidy *et al* proposed two mechanisms for *M. pneumoniae* neurologic disease: direct CNS infection, with a prodrome shorter than seven days and positive CSF PCR; and immune-mediated damage, with a longer prodrome, positive IgM, and negative CSF PCR.[4]

Linking neurologic symptoms to *M. pneumoniae* is challenging, as confirmation relies on PCR and/or serology.[3] IgM antibodies may indicate acute infection but can persist for months.[3] While seroconversion is more accurate, it might not be practical and only allows a retrospective diagnosis.[3] Nasopharyngeal PCR might help in the diagnosis, although it can represent a carrier state, especially during outbreaks.[3] A positive CSF PCR would be definitive, but often undetectable.[3,4]

Regarding treatment, antibiotics might play an important role. Theoretically, when there is direct CNS invasion, eradication of *M. pneumoniae* helps prevent its cytolytic activity and the production of cytokines and chemokines. In immune-mediated neurological complications, eliminating *M. pneumoniae* from the respiratory tract might interrupt autoimmunity and associated immune system alterations.[3]

Macrolides are the first-line treatment, due to their effectiveness, tolerability and immunomodulatory prop-

erties. However, apart from azithromycin, macrolides do not cross the blood-brain barrier and macrolide-resistant *M. pneumoniae* strains have successfully been emerging.[3,10,11] In such cases or if the patient cannot take oral azithromycin, fluoroquinolones might be considered, since they penetrate the CSF.[3,12]

Considering the immunologic pathogenesis in *M. pneumoniae*-related neurological disease, steroids, IVIG and plasma exchange (PLEX) have been used.[3]

In *M. pneumoniae*-associated encephalitis, treatment generally includes antibiotics, whereas adjunctive corticosteroids and IVIG may provide additional benefit. In a multicentre study from China, Fan *et al* demonstrated that azithromycin combined with IVIG or corticosteroids was associated with shorter hospital stays and better symptom control compared with azithromycin alone, with the greatest benefit observed in the IVIG group.[13] Daba *et al* further suggested that early IVIG administration should be considered in patients with a prodrome lasting more than one week.[14]

Regarding *M. pneumoniae*-associated ON, Choi *et al* reported successful treatment with antibiotics and methylprednisolone pulses followed by tapered prednisolone, though MOG antibodies were absent.[15] Despite the lack of evidence-based guidelines for paediatric MOG antibody–associated ON, first-line options include methylprednisolone pulses (30 mg/kg/day, 3–5 days), IVIG (2 g/kg divided over 2–5 days) and PLEX.[16] Methylprednisolone pulses with oral tapered steroids is the standard treatment, but relapse or steroid dependence may occur, requiring close follow-up and possible steroid-sparing therapy.[17] A European multinational cohort by Hacohen *et al* found monthly IVIG most effective in reducing relapses.[18]

On the other hand, in reported paediatric cases of other presentations of MOGAD secondary to *M. pneumoniae* infection, a combination of antibiotics and immunomodulatory therapies, such as glucocorticoids and intravenous immunoglobulin (IVIG), has been used, resulting in full recovery.[7-9] We speculate that antibiotic use may be beneficial in MOG antibody-associated ON secondary to *M. pneumoniae*, although evidence is lacking.

Finally, *M. pneumoniae* associated ADEM treatment includes methylprednisolone pulses, followed by oral corticosteroids for 4 to 6 weeks. In poorly responsive cases, IVIG and PLEX should be considered.[5]

The benefit of antibiotics in ADEM remains uncertain, as the condition is rare and its pathophysiology is not completely understood. A combination of direct microbial invasion and immune-mediated mechanisms may be involved, providing a rationale for antibiotic therapy, however, robust evidence supporting its use is limited.[19]

All patients received antibiotics: azithromycin in the first two cases and intravenous ciprofloxacin in the third, due to altered state of consciousness, which could compromise the oral intake of azithromycin. Regarding immunomodulatory therapy, the case of MOG-associated ON and the case of ADEM completed methylprednisolone pulses, followed by tapering oral steroids. Due to suboptimal response, the patient with ADEM received intravenous IVIG, with clinical improvement.

Conclusion

We present three rare cases that occurred during a recent rise in *M. pneumoniae* infections in 2024. The diagnosis of *M. pneumoniae*-related neurological complications is challenging. The latency between respiratory and neurological symptoms might help distinguish direct CNS infection from immune-mediated damage. Given the potential for significant morbidity, prompt recognition and management are crucial. Treatment includes a combination of antibiotics and immunomodulatory drugs. ■

Contributorship Statement / Declaração de Contribuição

All authors contributed to this work, approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

Todos os autores contribuíram para este trabalho, aprovaram a versão final do manuscrito para publicação e concordam em assumir a responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

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