ISSN 1669-9106 MEDICINA (Buenos Aires) 2026: 86: 539-544

Case report

MILD ENCEPHALITIS/ENCEPHALOPATHY WITH A REVERSIBLE SPLENIAL LESION: A RARE MANIFESTATION OF *MYCOPLASMA PNEUMONIAE* INFECTION IN ADULTS

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Received: 30-VIII-2025
Accepted: 3-XI-2025

Abstract

Mild encephalitis/encephalopathy with a reversible splenial lesion is a rare clinico-radiological syndrome in adults. It typically presents with altered consciousness, headache, or seizures, often preceded by a febrile prodrome. Brain magnetic resonance imaging (MRI) usually shows a transient lesion in the central portion of the splenium of the corpus callosum. We describe the case of a 23-year-old man who developed headache, confusion, and nausea after a brief febrile episode without respiratory symptoms. His neurological examination was unremarkable. Brain MRI demonstrated a small diffusion-restricted hyperintensity in the splenium of the corpus callosum. Serologic testing was positive for *Mycoplasma pneumoniae*. Chest CT was normal. He was treated with azithromycin and achieved complete clinical and radiological recovery. This case highlights the importance of recognizing this rare entity in adults, particularly as an uncommon neurological manifestation of *Mycoplasma pneumoniae*, even in the absence of pulmonary involvement.

Key words: encephalitis, encephalopathy, corpus callosum, Mycoplasma pneumoniae, Mycoplasma infections

Resumen

Encefalitis/encefalopatía leve con lesión reversible del esplenio: una manifestación rara de infección por Mycoplasma pneumoniae *en adultos*

La encefalitis/encefalopatía leve con lesión reversible del esplenio del cuerpo calloso es un síndrome clínico-radiológico infrecuente en adultos. Suele manifestarse con alteración de la conciencia, cefalea o crisis epilépticas, habitualmente precedidas por un pródromo febril. La resonancia magnética cerebral suele mostrar una lesión transitoria en la porción central del esplenio del cuerpo calloso. Describimos el caso de un hombre de 23 años que presentó cefalea, confusión y náuseas tras un breve episodio febril, sin síntomas respiratorios. El examen neurológico fue normal. La resonancia magnética cerebral evidenció una pequeña hiperintensidad con restricción a la difusión en el esplenio del cuerpo calloso. La serología resultó positiva para *Mycoplasma pneumoniae* y la tomografía computarizada de tórax fue normal. Recibió tratamiento con azitromicina y logró recuperación clínica y radiológica completa. Este caso subraya la importancia de reconocer esta rara entidad en adultos, en particular como una manifestación neurológica in-

frecuente de *Mycoplasma pneumoniae*, aun en ausencia de compromiso pulmonar.

Palabras clave: encefalitis, encefalopatía, cuerpo calloso, *Mycoplasma pneumoniae*, infecciones por Mycoplasma

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a rare clinicoradiological syndrome defined by transient neurological symptoms and a reversible lesion in the splenium of the corpus callosum (SCC)[1]. The typical presentation is characterized by altered consciousness, seizures, or delirium, usually preceded by a febrile illness[2]. Brain MRI typically demonstrates a transient ovoid lesion in the central SCC, with diffusion restriction and T2/FLAIR hyperintensity[1,3].

Although MERS is more frequently reported in children, adult cases are increasingly recognized[1]. A wide range of triggers have been identified, including infections, antiepileptic drug withdrawal, metabolic disorders, and autoimmune conditions[1].

Among infectious agents, *Mycoplasma pneumoniae* is a recognized but uncommon cause of MERS, and its true incidence remains unknown[3]. In most reported cases associated with this pathogen, respiratory symptoms or pulmonary radiologic abnormalities were present. We report a 23-year-old patient with *M. pneumoniae* –associated MERS who exhibited no respiratory involvement– an uncommon feature in previously described adult cases.

Clinical case

A 23-year-old man was brought to the emergency department after a transient episode of confusion. He reported moderate holocranial headache and confusion, accompanied by nausea, following a brief febrile episode two days earlier. He denied respiratory symptoms, vomiting, or photophobia. He had no history of medical illness, recent travel, or substance use.

On examination, his vital signs were normal. There was no neck stiffness or focal neurological deficit. He was alert and oriented, with no signs of meningeal irritation. Routine blood tests revealed mild hyponatremia (133 mmol/L), and serologic testing was positive for *Mycoplasma pneumoniae* (IgM and IgG). Brain magnetic resonance imaging (MRI) demonstrated a small focus of restricted diffusion in the central splenium of the corpus callosum, hyperintense on diffusion-weighted imaging (DWI) and without contrast enhancement (Fig. 1). Chest CT was normal.

The patient underwent lumbar puncture, which yielded clear and colorless cerebrospinal fluid (CSF) with an opening pressure of 22 cmH_2O, white blood cell count 5/µL, protein 0.34 g/L, and glucose 65 mg/dL. Flow cytometry and oligoclonal bands were negative, as were Gram stain and cultures. Electroencephalography was normal. Based on the clinical and radiologic findings, MERS was suspected.

He was started on azithromycin, with gradual improvement of symptoms over the next 72 hours. On day 7, repeat brain MRI showed complete resolution of the splenial lesion (Fig. 1). The patient remained asymptomatic, with no clinical recurrence at one-year follow-up.

Written informed consent was obtained from the patient for publication of this case.

Discussion

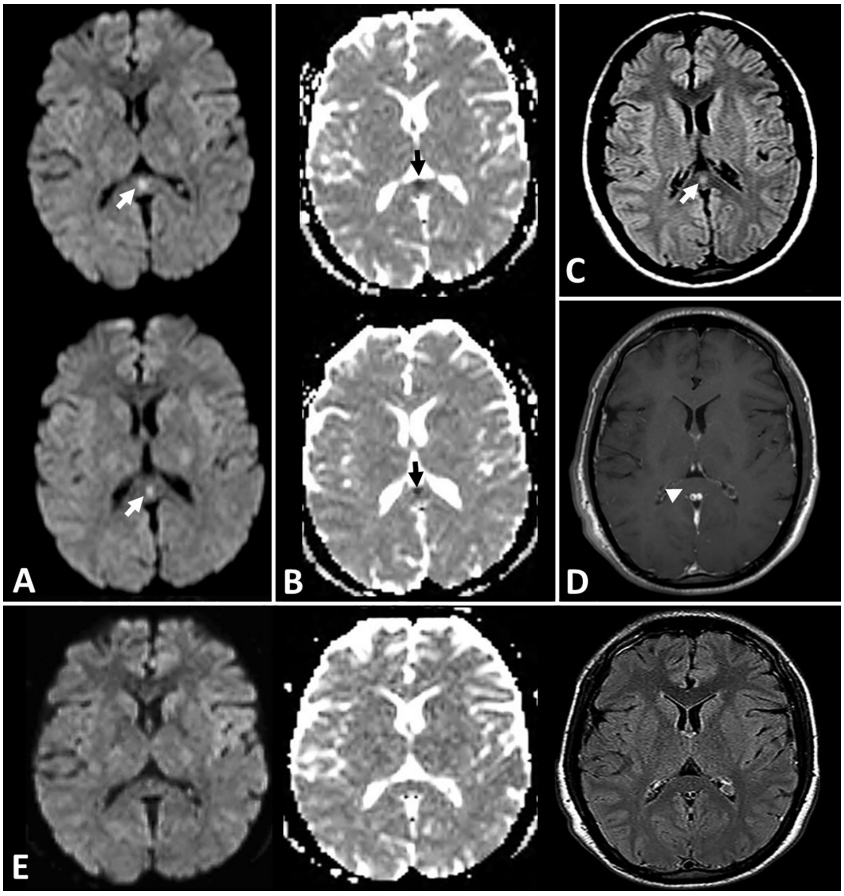
MERS is a transient clinicoradiological syndrome first described by Tada et al. in 2004 in a series of 15 pediatric patients with mild neurological symptoms, full recovery, and a well-demarcated, reversible lesion in the SCC evident on brain MRI[4]. Since its original description, MERS has been reported more frequently in the pediatric population, whereas adult cases are rare[5].

The pathophysiology of MERS is multifactorial. One of the most widely accepted mechanisms is glutamate-mediated cytotoxic edema, whereby activation of non-NMDA receptors promotes sodium and water influx into axons[6]. This preferentially affects regions with high axonal density and metabolic demand, such as the SCC[1,3]. Another proposed mechanism is osmotic dysfunction secondary to hyponatremia, occasionally linked to interleukin-6 (IL-6) release during systemic infection. IL-6 may induce SIADH and contribute to reversible intramyelinic edema[6,7].

Our patient exhibited mild hyponatremia (133 mmol/L), a finding present in three of the 13 previously reported adult MERS cases associated with *M. pneumoniae* (23%) and in 10 of 27 MERS cases of other causes reported by Rinaldi et al. (37%)[8–10]. This supports a possible pathogenic role.

An immune-mediated mechanism has also been proposed, involving no direct invasion of the central nervous system (CNS). In this model, antigenic fragments of *M. pneumoniae* activate

Figure 1 | Brain magnetic resonance imaging (MRI). A: Diffusion-weighted imaging (DWI) sequence showing a punctate high signal in the splenium of the corpus callosum (white arrows). B: Corresponding apparent diffusion coefficient (ADC) map demonstrates signal loss (black arrows), consistent with restricted diffusion. C: Fluid-attenuated inversion recovery (FLAIR) sequence shows hyperintensity of the lesion (white arrow), while D: post-gadolinium T1-weighted image shows no pathological enhancement. (arrowhead). E: Follow-up brain MRI on day 7: DWI, ADC, and FLAIR sequences demonstrate complete resolution



monocytes and trigger circulating immune complexes, leading to transient neuronal dysfunction[9]. This hypothesis is supported by the consistent negativity of PCR and CSF cultures, the absence of marked pleocytosis, and the generally benign clinical course[3,6].

Although PCR or LAMP (loop-mediated isothermal amplification) testing for *Mycoplasma pneumoniae* was not performed in our case, the diagnosis was supported by positive IgM and IgG serology, the clinical presentation, imaging findings, and rapid response to macrolide therapy. Given the mild severity of illness and rapid clinical improvement, additional molecular testing was not considered necessary.

The etiology of MERS includes viral infections (influenza A/B, rotavirus, adenovirus, human herpesvirus 6/7), bacterial infections (*M. pneumoniae, Escherichia coli, Streptococcus pneumoniae, Salmonella* spp.), and, less commonly, parasitic infections such as *Plasmodium* spp[1,6,10]. Non-infectious causes have also been reported, including initiation or withdrawal of antiepileptic drugs, autoimmune diseases, vaccination, hypoglycemia, and metabolic disturbances[1,6,7].

In most of the 51 adult cases analyzed by Rinaldi et al., the underlying cause remained unknown. Among those with a confirmed etiology, infections were predominant, with viral agents being most common, followed by bacterial pathogens. *M. pneumoniae* was the most frequently identified bacterium, accounting for 18% of cases[1].

The clinical presentation is nonspecific and may include altered consciousness, seizures, ataxia, or delirium, typically following a febrile or gastrointestinal prodrome[1-3]. In adults, impaired consciousness is the most frequent manifestation[1]. Among adult MERS cases due to *M. pneumoniae (*Table 1), the most common symptoms were fever, confusion, headache, and seizures, often in association with respiratory symptoms or pulmonary imaging abnormalities[3,10].

Our patient presented with holocranial headache, confusion, and nausea after a brief febrile episode, without respiratory symptoms or pulmonary abnormalities. This presentation is unusual[3,10].

CSF and EEG were normal. These findings are consistent with most published cases, in which CSF is normal or only mildly altered, and EEG findings are either normal or nonspecific[3,4].

Brain MRI is the key diagnostic tool in MERS, given the nonspecific clinical features and generally unremarkable ancillary studies[3,4]. The hallmark finding is a reversible, well-defined, ovoid lesion in the center of the SCC, with no contrast enhancement, hyperintense signal on T2-weighted and FLAIR sequences, restricted diffusion, and low signal on apparent diffusion coefficient (ADC) mapping[3,4,9].

Based on lesion extent, MERS is classified into type 1 (lesion confined to the SCC) and type 2 (extension to adjacent white matter or other corpus callosum regions) [4,9].

In 2012, Hoshino et al. proposed five diagnostic criteria: (1) neuropsychiatric symptoms within the first week after a febrile illness, (2) full clinical recovery within 10 days, (3) reversible SCC lesion on acute MRI, (4) potential extension beyond the SCC in type 2 cases, and (5) complete lesion resolution on follow-up imaging[8]. Our patient fulfilled all criteria and was classified as type 1 MERS.

Differential diagnoses include infarction of the SCC, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), neoplasms, posterior reversible encephalopathy syndrome (PRES), and hypoglycemic encephalopathy[3,6]. The absence of enhancement, lesion reversibility, and full clinical recovery are key to distinguishing MERS from these conditions[1,3].

There is no standard treatment for MERS, and most cases are managed supportively[2].

In infectious cases, targeted antibiotic therapy is usually administered. In the review by Sadohara et al., treatment included macrolides, fluoroquinolones, or tetracyclines, sometimes combined with corticosteroids or immunoglobulin depending on clinical severity or inflammatory findings in CSF[3].

Our patient received only azithromycin, with symptom resolution within 72 hours and radiologic resolution by day 7. This approach is consistent with other cases reporting favorable outcomes with antibiotics alone[3,9].

Some authors have suggested an immunomodulatory approach in severe cases, arguing that the underlying pathophysiology may be more immune-mediated than due to direct infection[6,7]. Treatment choice should be individualized based on clinical severity. Rising resistance of *M. pneumoniae* to macrolides presents a potential challenge, especially given the limited CNS penetration of antibiotics[6].

The prognosis of type 1 MERS in adults is excellent, with full recovery and no neurological sequelae in most cases[3,6,10]. All published adult cases with this etiology have shown no long-term neurological deficits[3,6,10]. Our case reinforces this pattern and highlights the importance of prompt recognition to avoid unnecessary investigations and overtreatment.

We report a case of MERS associated with *Mycoplasma pneumoniae* in an adult. This case is unusual not only because of the absence of respiratory involvement, but also because MERS is rarely described in adults and represents an uncommon neurological manifestation of *Mycoplasma pneumoniae*. Given the limited number of reported cases, it is essential to maintain a high index of suspicion and to apply appropriate diagnostic tools for timely identification, to ensure accurate diagnosis and avoid unnecessary interventions.

Conflicts of interest: None to declare.

Table 1 | Summary of reported adult cases of mild encephalitis/encephalopathy with a reversible splenial lesion associated with Mycoplasma pneumoniae

Authors, year	Age/sex	Neurological symptoms	Respiratory symptoms	Hyponatraemia	Diagnostic Test for *M. pneumoniae*	CSF	EEG	MRI scan of brain	CT scan of chest	Treatment
Sadohara et al.[3]	18/M	AC	NR	Yes (132 mmol/L)	PA; LAMP	Normal	NR	Type I	Air space consolidation	Levofloxacin; mPSL
Dong et al.[5]	17/F	Headache; meningeal sign	NR	No	MP IgM in CSF; IgM/IgG in serum	MP IgM detected	NR	Type I	NA	Azithromycin
Shibuya et al.[9]	30/M	AC	NR	NR	PA	NR	NR	Type I	Pulmonar infiltrates	Levofloxacin
Zhang et al.[7]	26/F	AC; headache; seizures	NR	NR	MP IgM in CSF	EP; MP IgM detected	Slow wave	Type I	NA	Macrolide (unspecified); moxifloxacin
JSIM RC DB, Japan.[3]	45/M	AC	NR	NR	PA	Normal	NR	Type I	Air space consolidation	Minocycline
JSIM RC DB, Japan.[3]	37/M	AC; seizures; vertigo	NR	NR	MP antigen test	NR	NR	Type I	Abnormalshadow	Levofloxacin; azithromycin
JSIM RC DB, Japan.[3]	21/F	Headache	NR	NR	PA	Normal	Sharp wave	Type I	Air space consolidation	Minocycline
JSIM RC DB, Japan.[3]	44/M	Headache	NR	NR	LAMP	Normal	NR	Type I	Air space consolidation	Moxifloxacin
Dong et al.[6]	31/F	Meningeal sign; AC; headache	NR	NR	Serum MP IgM; paired titers of serum MP IgG	EP; high WCC	NR	Type I	Infective lesion	Azithromycin
Dong et al.[6]	33/F	AC; meningeal sign; amaurosis; limb weakness	NR	NR	Serum MP IgM, Paired titers of serum	EP; high WCC	NR	Type I	Infective lesions	Azithromycin; mannitol; mPSL; IV immunoglobulin; ganciclovir
Dong et al.[6]	40/M	AC; meningeal sign blurred vision; limb weakness	NR	NR	MP IgG Serum MP IgG	EP; high WCC; high protein; low glucose	NR	Type I	Infective lesions	Mannitol; ganciclovir; ceftriaxone; azithromycin

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Authors, year	Age/sex	Neurological symptoms	Respiratory symptoms	Hyponatraemia	Diagnostic Test for *M. pneumoniae*	CSF	EEG	MRI scan of brain	CT scan of chest	Treatment
Sadohara et al.[3]	17/M	AC	Productive cough	Yes (132 mmol/L)	PA; LAMP	Normal	NR	Type I	Air space consolidation	Levofloxacin; mPSL
Arik et al.[10]	18/M	AC; right eye nystagmus	Cough	Yes (134 mmol/L)	PCR positive in oropharyngeal sample	High WCC; high protein	NR	Type I	NR (diagnosed pneumonia at prior hospital)	Ceftriaxone; doxycycline; acyclovir; moxifloxacin
Benetti et al. (current study)	23/M	AC; headache	No	Yes (133 mmol/L)	Serum MP IgM/IgG	Normal	Normal	Type I	Normal	Azithromycin

AC: altered consciousness; CT: computed tomography; CSF: cerebrospinal fluid; EEG: electroencephalogram; EP: elevated protein (in CSF); IgG: immunoglobulin G; IgM: immunoglobulin M; IV: intravenous; LAMP: loop-mediated isothermal amplification; MP: Mycoplasma pneumoniae; mPSL: methylprednisolone; MRI: magnetic resonance imaging; NA: not available (or not assessed); NR: not reported; PA: particle agglutination assay; PCR: polymerase chain reaction; WCC: white cell count

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