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Short communication

Neuro-ophthalmological manifestations as complication of an infection with *Mycoplasma pneumoniae* and subsequent development of disseminated acute encephalitis☆

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ABSTRACT

The purpose of this article is to describe two pediatric neuro-ophthalmological clinical cases caused by a systemic infection due to *Mycoplasma pneumoniae (M. pneumoniae)*. The cases are two girls aged 14 and 12 seen in the Emergency Department: The first one had internuclear ophthalmoplegia and second with loss of vision and headache. They had no other neurological foci. Magnetic resonance imaging showed hyperintense plaques in both, suggestive of a demyelinating disease. One month later, the neuro-ophthalmological symptoms resolved, with normal follow-up magnetic resonance imagings. The diagnosis was acute disseminated encephalitis secondary to *M. pneumoniae*. The diagnosis was made using PCR (gold standard) and/or IgM in serology. It is important to think about this possible etiology in cases of suggestive demyelinating disease. There is controversy about the role of antibiotics and on whether corticosteroids are contemplated. In conclusion, *M. pneumoniae* must be a differential diagnosis in acute neuro-ophthalmological disorders in children.

Manifestaciones neuroftalmológicas como complicación de una infección por *Mycoplasma pneumoniae* y desarrollo posterior de una encefalitis aguda diseminada

Palabras clave:
Mycoplasma pneumoniae
Encefalomielitis diseminada aguda

RESUMEN

El objetivo es describir dos cuadros clínicos neuroftalmológicos en niños por infección sistémica por *Mycoplasma pneumoniae (M. pneumoniae)*. Se presentan los casos de dos niñas de 14 y 12 años que acudieron a urgencias: la primera con oftalmoplejía internuclear y la

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la segunda con pérdida de visión y cefalea. No presentaban otra focalidad neurológica. En imagen de resonancia magnética se evidenciaron placas hiperintensas en ambas, sugerentes de cuadro desmielinizante. Al mes, los síntomas neuroftalmológicos se resolvieron y las resonancias magnéticas de control fueron normales. El diagnóstico fue encefalitis diseminada aguda secundaria a *M. pneumoniae*. El diagnóstico se hace por PCR (*gold standard*) y/o IgM en serología. Es importante pensar en esta posible etiología ante casos sugerentes de enfermedad desmielinizante. Existe controversia sobre el papel de los antibióticos y si se contemplan los corticoides. Como conclusión, *M. pneumoniae* debe ser diagnóstico diferencial en afectaciones neuroftalmológicas agudas en niños.

Introduction

Acute disseminated encephalomyelitis (ADEM) is one of the most frequent causes of white matter compromise in children in school age and in young adults. It is estimated that the incidence of ADEM is approximately 0.2–0.64 cases/100 000 inhabitants/year.[1,2]

ADEM is regarded as an immunomediated inflammatory-demyelinizing disease with neurological clinic expressing generally after an infection or vaccination, with acute or subacute onset.[3] Association with an infectious agent is assumed in the majority of cases although its etiology is confirmed in only 25% of cases. The most frequent microorganisms are varicella zoster, measles and rubella,[1] although it is recommended to conduct a large battery of serologies to discard other agents such as human immunodeficiency virus, hepatitis A, B and C virus, Epstein Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, parotitis, coronavirus, Coxsackie B, other nonviral agents such as *Mycoplasma pneumoniae* (*M. pneumoniae*), Campylobacter, Chlamydia and beta hemolytic streptococcus.[1,2]

The pathogeny includes selfimmune response to a common antigen present in myelin and in the infectious agent. Participation of lymphocyte B has been described through antiganglioside antibodies (GM1) and lymphocytes T against several myelin antigens such as proteolipid protein, oligodendrocyte myelin glycoprotein or basic myelin protein (BMP), among others.[3]

In what concerns clinic expressions, the literature describes first a prodromic phase similar to a fever-like condition with high temperature and general discomfort, developing with the triggering agent the predominantly neurological and neuro-ophthalmological clinic symptoms 3–6 weeks after the initial contact. In addition, aseptic meningitis has been described as well as polyradiculitis, hemiparesis, cranial neuropathy, ophthalmoparesis, optic neuritis, seizures, long pathways compromise with spasticity or hyper-reflexia and cerebellar ataxia, among others.[2,4]

In addition, complications secondary to this clinic condition have been described, including mucocutaneous lesions, arthritis, hemolytic anemia, hemorrhages, pericarditis and severe neurological alterations such as myelitis, meningoencephalitis or even coma.[5]

The imaging test of choice is nuclear magnetic resonance (MRI) which in T2 emphasizes reversible, well-defined and hyperintense lesions in the white matter, which generally affect the thalamus and basal ganglia. Said lesions could also be found in the gray matter. Even so, images isolated in MRI are not diagnostic for ADEM.[5]

M. pneumoniae is a free bacteria without cellular walls. It is a causative agent for community acquired pneumonia although it rarely causes central nervous system alterations (0.1%)[2,3] (Table 1).

The objectives of this paper are to describe 2 neuro-ophthalmological clinic conditions in children due to systemic *M. pneumoniae* infection and to raise awareness about this etiology and its prognostic importance.

Clinic case reports

Clinic cases of 2 girls aged 14 and 12 years old who visited the Emergency Dept. due to 2 different conditions involving ophthalmological and neurological symptoms. The first exhibited bilateral internuclear ophthalmoplegia with diplopia and left eye (LE) major adduction limitation. Major nystagmus was observed in right eye (RE) abduction in spring fashion with fast phase toward the left, constituting asymmetric internuclear ophthalmoplegia. Visual acuity (VA): 1 in both eyes. Normal convergence with rupture point less than 5 cm. neurological examination did not observe dysdiadochokinesia, ataxia or alterations in reflexes or muscular strength, with negative fatigue test. Relevant personal antecedents included idiopathic intracranial hypertension 7 years earlier that was resolved with acetazolamide and corticosteroids.

Multiple imaging tests were conducted (Fig. 1), with nuclear magnetic angioresonance being normal, the cervical and dorsolumbar spine did not exhibit demyelinizing lesions. However, T2 of the cerebral MRI (March 2018) showed multiple hyperintense lesions suggesting demyelinizing lesions that were resolved after 5 months.

Among other supplementary tests, spectral domain optical coherence tomography (SD-OCT) was taken, showing a defect in the retina nerve fiber layer in the temporal quadrant as well as an alteration in the ganglion cell layer that could have been a sequel of past intracranial hypertension. Humphrey 24.2 campimetry produce normal results in both eyes. Cerebrospinal fluid (CSF) was analyzed through lumbar

Table 1 – Comparative summary of clinic cases.

	Case 1	Case 2
Age (years)	14	12
Sex	Female	
Baseline symptomatology	Diplopia Internuclear ophthalmoplegia	Oppressive headache Diminished visual acuity
M. pneumoniae serology	Ig M positive	
Magnetic resonance (MRI)	Hyperintense lesions in capsulo-thalamic region	Hyperintense lesions in juxtacortical white matter
Diagnostic	Acute disseminated encephalomyelitis (ADEM) secondary to *M. pneumoniae* infection	
Prognosis	Resolution of lesions in MRI in 6 months No other sequels No recurrences	Resolution of lesions in MRI in 3 months No other sequels No recurrences

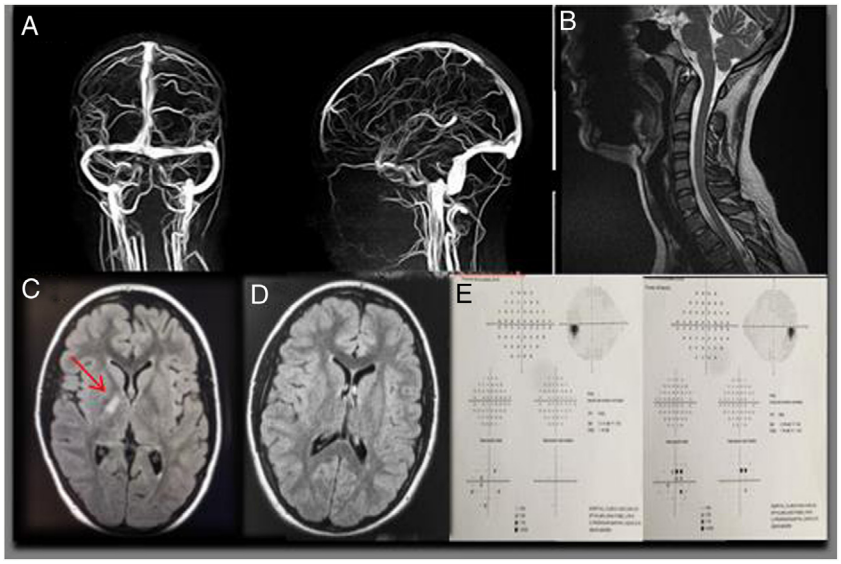

Fig. 1 – Supplementary tests of patient 1 (CPG) (A) angio-MRI images without alterations. (B) MRI with gadolinium of cervical spinal column without alterations. (C) axial MRI image in FLAIR sequence with gadolinium showing hyperintense lesions in the capsulo-thalamic region suggesting demyelinizing disease. (D) MRI taken 6 months after the first, showing absence of lesions. (E) Humphrey 24-2 campimetry within normal ranges in both eyes (minimum paracentral defect in LE).

puncture, producing negative results for oligoclonal bands. Complete analytics was conducted with normal metabolic profile, negative toxics, normal hemogram, high PCR negative serologies for human immunodeficiency virus, B and C hepatitis, Epstein–Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus and rubella. In addition, cultures of blood, urine and sputum were also negative. Serology for M. pneumoniae was positive, both for IgM and IgG, which enabled the identification of the etiological agent of the condition. The PCR results for *M. pneumoniae* was positive. In the authors hospital, serology is carried out in patients with suspected ADEM in order to discard this etiology due to a number of cases that occurred in 2018 and 2019. Among other supplementary tests, evoked potentials (EP) were carried out with normal speed and amplitude, and normal hearing EP. Electromyogram suggested minimum radiculitis probably in resolution phase, the Ishihara test was normal and the patient did not exhibit afferent pupil defect (AFPD).

The final diagnostic was Wall Eyed Bilateral InterNuclear Ophthalmoplegia [WEBINO]) due to disseminated acute encephalomyelitis caused by *M. pneumoniae*.

The treatment consisted in one cycle of IV methylprednisolone at high dosages of 10 mg/kg/day during 3 days and then oral regime of prednisone 1 mg/kg/day during 20 days, as well as cotrimoxazole for prophylaxis against *Pneumocystis jiroveci*. Evolution was positive and the patient did not exhibit new episodes and remains asymptomatic one year after the event.

The second patient visited the Emergency Dept. due to loss of vision with 2 h evolution (VA: RE perception of light and finger count in LE at less than 1 m) together with oppressive "helmet" holocranial headache with 2 h evolution. AFPD RE minor, AFPD LE. Relevant personal history included migraine with atypical visual aura, treated one month earlier with magnesium. MRI with contrast showed hyperintense lesions in T2 suggesting demyelinizing disease (Fig. 2).

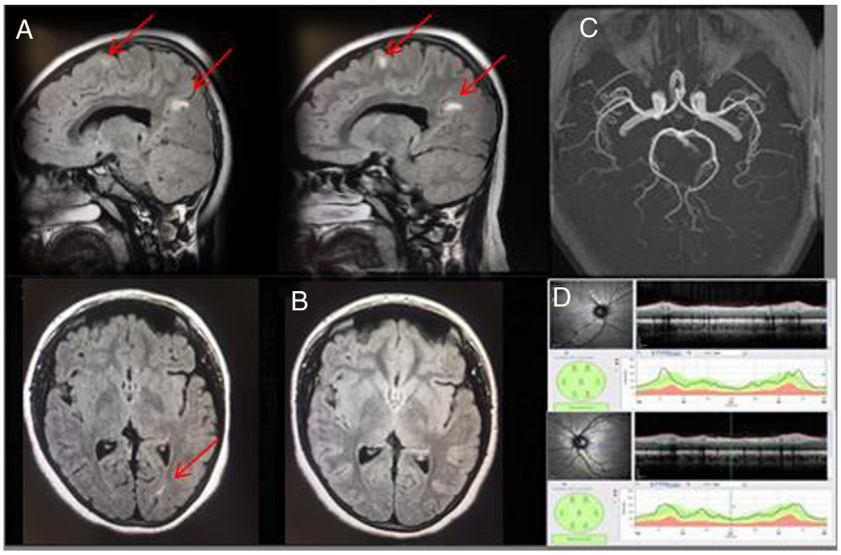

Fig. 2 – Supplementary tests of patient 2 (AOJ) (A) MRI sagittal and axial images with FLAIR sequence with gadolinium showing hyperintense lesions in juxtacortical white matter suggesting demyelinizing disease. (B) MRI gadolinium in T2 showing production and/or disappearance of some of the hyperintense lesions at month 3. (C) Angio-MRI images without alterations. (D) OCT-SD of the retina nerve fiber layer without alterations.

Two months after the episode, MRI with contrast showed smaller size and improvement of lesions. OCT of the retinal nerve fiber layer (RNFL) was normal as well as the Humphrey 24-2 campimetry. Metabolic profile and hemogram analyses were normal, toxics analysis negative and, as in the other case, PCR was also high. Serologies were negative for the human immunodeficiency virus, hepatitis B and C virus, Epstein–Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster and rubella virus, and positive (IgM and IgG) for *M. pneumoniae*. The rest of supplementary tests, including electroencephalogram, one normal (with normal awakened state background activity and without epileptiform activity, or asymmetries or other significant anomalies) and EP without significant alterations throughout the visual pathway. The final diagnostic was ADEM related to *M. pneumoniae* infection with retrobulbar neuritis.

The patient was treated with IV methylprednisolone during 3 days and oral prednisone at high doses of 1 mg/kg/day.

Despite suspecting *M. pneumoniae* infection with positive IgM, the patient was not treated with antibiotics because this treatment is controversial and immunosuppressant treatment has proven to be more effective.

None of the patients exhibited other neurological foci or macular lesion. After 3 and 6 months of evolution, respectively, the neuro-ophthalmological symptoms resolved in both cases and the control MRI provided surprisingly normal results.

Discussion

According to some sources, *M. pneumoniae* causes between 5 and 10% of central nervous system infections, even though it is known in that the main causes of ADEM are measles, rubella and varicella zoster.[1,2]

In some cases, exposure to *M. pneumoniae* produces a situation of asymptomatic carrier. In 75% of cases, ADEM caused by this infection is associated to a slight prodromic condition between 2 and 30 days after the appearance of neurological symptoms.[2,6]

The *gold standard* method for diagnosing *M. pneumoniae* is PCR in blood and CSF, although it is generally diagnosed with serology (IgM e IgG) despite poor sensitivity for IgM described in some studies (32–77%).[6]

The main differential diagnostic for ADEM are other infectious causes (human immunodeficiency virus, hepatitis B and C virus, Epstein–Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster and rubella virus, respiratory and gastrointestinal viral infections) as well as demyelinizing diseases.[2,4,7] It is important to discard the latter for the prognosis. According to the criteria of the 2013 *International Pediatric Multiple Sclerosis Study Group* (IPMSSG), the diagnostic of multiple sclerosis (MS) would be defined in MRI like (1) 9 or more lesions in the white matter or enhanced with gadolinium; (2) 3 or more periventricular lesions; (3) a juxtacortical lesion; and (4) an infratentorial lesion. CSF should exhibit oligoclonal bands or increased IgG index. The combination of altered CSF and to lesions in MRI (one of which must be located in the brain) could signify a dissemination criteria in the McDonald classification.[8]

In children, two different demyelinizing events, separated in time and space, constitute a criterion for MS, in contrast with an ADEM recurrence in which new lesions do not appear and existing lesions would increase.[8]

A study by Dale et al. compared the presentation of clinic conditions of ADEM and MS. They obtained as a demyelinizing infectious disease (74 vs. 38%, $p < 0.05$), polysymptomatic presentation (91 vs. 38%, $p < 0.002$), pyramid signs (71 vs. 23%, $p < 0.01$), encephalopathy (69 vs. 15%, $p < 0.002$) and bilateral

optic neuritis (23 vs. 8%, not statistically significant) and unilateral only in the MS cases.[7]

The importance of anti-MOG antibodies in childhood ADEM, above all in those caused by *Mycoplasma*, is described in a paper by Mol et al. in the Netherlands. It was observed that in patients with positive anti-MOG, the most frequent presentation phenotype was ADEM (56%) in children, and optic neuritis (44%) in adults. In addition, it was also associated with recurrence: 26% in children and 41% in adults, with a mean follow-up of 27.5 months. Said study also demonstrated that the majority of anti-MOG negative patients did not present relapses (89%).[9]

The role of antibiotics for treating ADEM is controversial. It has not been demonstrated that a specific antibiotic treatment is able to resolve the condition.

The antibiotics utilized for treating *M. pneumoniae* infections are azithromycin, erythromycin, tetracyclines (doxycycline) and latest generation fluoroquinolones, even though the latter are usually administered to adults.[6]

It is a fact that there are no clinic trials shedding light on the treatment of this condition and that management is based on experience and clinic judgment, as well as on clinic cases reported in the literature.

As ADEM is probably an immunomediated disease, immunomodulator drugs are utilized. The first proposed therapeutic step is administering intravenous corticosteroids such as methylprednisolone (20–30 mg/kg/day, not more than 1gm/day) during 3–5 days, followed by oral corticosteroids during 4–6 weeks (evidence 2 C). If corticoids fail or patient response is insufficient, treatment would begin with IV immunoglobulins (evidence 2 C) and, failing this, plasmapheresis would be performed (evidence 2 C).[10]

In what concerns prognosis, some studies have correlated ADEM with possible presentation prior to MS. A recent study by Papetti et al. comprising 91 patients has reported the evolution to MS of 21.2% of patients with ADEM, in a mean follow-up of 5.6 ± 2.3 years. After a multivariate analysis, said study indicates as predictive factors the presence of oligoclonal bands in CSF ($p < 0.001$), prior infection by the Epstein–Barr virus ($p < 0.001$), periventricular lesions ($p < 0.001$), hypointense lesions in T1 ($p < 0.001$) and lesions in the *corpus callosum* ($p < 0.001$). Even so, the IPMSSG has warned that an episode with the clinic characteristics of ADEM cannot be considered as the first MS events unless the course of the clinic disease fulfills the criteria described in the consensus.[7]

Conclusion

M. pneumoniae exists in the environment and, despite being infrequent, it should be part of the diagnostic approach in acute or subacute neuro-ophthalmological impairments in children. ADEM is within differential diagnostic of demyelinizing diseases and could even be a precursor thereof in some cases.

Conflict of interest

No conflict of interest was declared by the authors.

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