Plasmapheresis in acute disseminated encephalomyelitis associated with anti-MOG antibodies – Two clinical cases

ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous system. ADEM should be suspected when a patient develops multifocal neurologic abnormalities with encephalopathy, especially if occurring after a viral infection or immunization. In this study, the authors describe two cases of ADEM with positive anti-myelin oligodendrocyte glycoprotein (MOG) antibodies requiring hospitalization in a Pediatric Intensive Care Unit and plasmapheresis treatment.

Keywords: acute disseminated encephalomyelitis; demyelinating disease; anti-MOG antibody; neurologic signs

RESUMO

A encefalomielite aguda disseminada (ADEM) é uma doença desmielinizante aguda do sistema nervoso central. O diagnóstico de ADEM deve ser considerado quando o doente apresenta alterações neurológicas focais associadas a encefalopatia, sobretudo se as manifestações surgem após uma infecção vírica ou vacinação. Neste artigo, são descritos dois casos clínicos de ADEM com anticorpos anti-MOG positivos com necessidade de internamento em Unidade de Cuidados Intensivos Pediátricos e tratamento com plasmaferese.

Palavras-chave: anticorpo anti-MOG; doenças desmielinizantes; encefalomielite aguda disseminada; sinais neurológicos
INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a presumably immune-mediated inflammatory demyelinating condition, particularly affecting the white matter of the brain and spinal cord. ADEM is a rare disease with a global incidence of 0.2 to 0.4 cases per 100,000 people. It affects both genders equally, with 80% of childhood cases occurring in the first decade of life. A greater incidence is commonly observed in the winter and spring months. ADEM typically presents as an acute monophasic disorder, but recurrence cases have been reported. Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been identified in a variety of demyelinating syndromes, with predominance in pediatric age.

In this study, the authors report two cases of anti-MOG antibody-positive ADEM requiring hospitalization in a Pediatric Intensive Care Unit (PICU) and treatment with TPE.

CASE REPORTS

Case 1: The first case refers to a three-year-old girl with a history of anti-MOG-positive ADEM at the age of 12 months, characterized by encephalopathy and right hemiparesis manifesting after a viral infection. Cerebral magnetic resonance imaging (MRI) showed multiple areas of signal delay along the white matter of both cerebral hemispheres in long (PDF) transgressive-regressive (TR) sequences, without restrictions to water molecule diffusion or enhancement after gadolinium administration, associated with bilateral thalamic-capsular lesions compatible with ADEM (Figure 1). The immunological serum study performed showed positive anti-MOG antibodies, negative anti-aquaporin 4 (AQP4) antibodies, and no oligoclonal bands in cerebrospinal fluid (CSF). The patient was treated with corticosteroids (five days of methylprednisolone pulses, followed by maintenance with two months of oral prednisolone), with full recovery. Follow-up showed progressive lesion improvement in serial MRI and negative anti-MOG antibodies ten months later. At two years old, the patient showed normal neurological examination and normal motor and cognitive development.

Thirty-four months later, the girl was admitted to the Emergency Department (ED) due to irritability, dysarthria, loss of bladder control, and unbalanced gait since the previous day. She also presented nasopharyngitis without fever. Physical examination was normal. On neurological assessment, she showed mental status fluctuation, dysarthria, and right hemiparesis, without signs of meningeal irritation or other abnormalities.

Five cells/µl and normal glucose (0.5 g/L) and protein (0.29 g/L) levels were found in CSF. Brain MRI revealed T2 signal reinforcement of some cerebral cortex areas and symmetrical reinforcement of the supratentorial white matter and caudate and lenticular nuclei (Figure 2). Spinal MRI was normal.

The immunological serum study again showed positive anti-MOG antibodies, negative anti-AQP4 antibodies, and no oligoclonal bands in CSF. The patient was admitted to the Pediatric Department with suspicion of ADEM relapse. Treatment with intravenous (IV) methylprednisolone pulses (30 mg/kg/day) was started in combination with ceftriaxone and acyclovir until central nervous system infection was excluded.

On the third day of treatment, the girl was transferred to PICU due to progressive neurological deterioration, and TPE was initiated. She was submitted to six sessions of TPE on alternate days through central venous line using 1–1.5 liters of 5% albumin as replacement fluid. At the end of treatment, significant clinical recovery was observed, with normal consciousness and speech.

After hospitalization, the girl maintained treatment with oral prednisolone (tapering dosage) and initiated azathioprine to prevent new relapses. Without additional relapses and four months after hospitalization, anti-MOG antibodies were again negative. She currently presents normal neurological assessment, without motor or cognitive impairment.
Case 2: A four-year-old girl was admitted to the ED due to headache, sluggish speech, gait instability, and nocturnal enuresis with 24 hours of evolution. She had a seizure controlled with rectal diazepam administration. Afterward, she remained drowsy, with spontaneous eye opening but no response to verbal stimulation, and showed symmetrical osteotendinous reflexes, with no signs of meningeal irritation.

Brain computed tomography (CT) scan was normal, and CSF study revealed pleocytosis (63 cells/µl), with normal glucose and protein concentration. The patient was started on IV ceftriaxone and acyclovir. Electroencephalogram revealed very altered, wide-ranging, polymorphic, and very slow wakeful strokes and theta-delta frequencies (2-4 Hz), with predominance of slower activity in frontal areas and particularly in the left hemisphere.

Blood and CSF viral serologies were negative, and the immunological study revealed positive anti-MOG antibodies, negative oligoclonal bands, and negative anti-AQP4 antibodies. Brain and spine MRI showed multiple areas of high signal on T2 and fluid-attenuated inversion recovery (FLAIR) spread across both cerebral hemispheres (Figure 3), with bulge and spinal cord involvement, supporting the diagnosis of ADEM (Figure 4). Despite treatment with IV methylprednisolone pulses (30 mg/kg/day) and IV immunoglobulin (1 g/kg/day, two days), progressive neurological deterioration was observed, and the patient was transferred to PICU, requiring invasive mechanical ventilation. Due to clinical and imaging worsening, on the third day at PICU she was submitted to six sessions of TPE on alternate days using 1─1.5 liters of 5% albumin as replacement fluid.

Progressive clinical improvement was observed, and the patient was extubated on the fifth day without intercurrences. Antimicrobial therapy was discontinued after negative microbiological results. After discharge, the patient maintained treatment with prednisolone and multidisciplinary follow-up. Cerebral MRI performed nine months after the first episode showed new brain lesions, and despite the absence of new neurologic findings, she received three days of methylprednisolone pulses. Subsequently, she started prednisolone and azathioprine.

At present, the girl shows normal motor and cognitive development and normal neurological assessment. She experienced no further relapses but maintained positive anti-MOG antibodies.

DISCUSSION

The pathogenesis of ADEM is not completely understood but seems to be related to immune dysregulation triggered by an infection or immunization in a genetically susceptible host. Disease onset is usually acute, preceded by prodromal symptoms such as fever, headache, myalgia, vomiting, or feeding refusal in approximately 75% of children. It usually presents with encephalitis-like signs, focal neurological deficits, and symptoms that typically progress to more severe neurological ones, often occurring after hospital admission. Intensive care admission is usually required for patients with severe encephalopathy, seizures, or paralysis, most of whom require mechanical ventilation. In the present study, both cases investigated showed clinical deterioration after hospitalization and required PICU admission, although only one required invasive mechanical ventilation.

ADEM should be suspected in cases of multifocal neurologic
abnormalities with encephalopathy (Table 1), especially if occurring
after a viral infection or immunization. In the absence of specific
biological markers or confirmatory tests, ADEM is a diagnosis of
exclusion based on clinical and radiological findings. CNS acute
infection and other demyelinating or inflammatory syndromes should
be excluded. In most cases, CSF may show inflammatory features,
such as elevated protein concentration and lymphocytic pleocytosis,
although it can also be normal. In pediatric populations, a minority
of children with ADEM may have transiently positive anti-MOG
antibodies. Although anti-MOG antibodies were initially believed
to be potential biomarkers in multiple sclerosis (MS), several studies
have associated them with an expanding spectrum of demyelinating
syndromes in children, designated MOG-associated disease (MOGAD;
preponderantly ADEM [53%], optic neuritis [40%], and transverse
myelitis [18%]). MOG is thus defined by the presence of
demyelinating or encephalitic events associated with abnormal brain
and/or spinal MRI and positive anti-MOG antibodies. ADEM is more
common in younger children, while opticospinal phenotype is more
common in children older than nine years.

Laboratory tests are required to exclude or confirm the underlying
infectious cause and may include complete blood count, blood and
CSF culture, viral polymerase chain reaction (CSF, throat,
nasopharynx, stools), and serologic testing for a variety of agents.

However, these tests are seldom positive, as in the present study. In
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Brain and spine MRI with contrast is the first-line imaging
assessment for ADEM diagnosis, as it shows characteristic features
that may suggest the presence of anti-MOG antibodies even before
titration. In anti-MOG-positive ADEM, typical lesions are large (1-2
cm), diffuse, multifocal, bilateral and asymmetric, poorly marginated,
T2-hyperintense, and predominantly involving the cerebral white
matter but potentially also the grey matter. Additional lesions may
be found in deeper white matter, thalamus, basal ganglia, brainstem,
cerebellum, and spinal cord. In the spinal cord, large confluent
intramedullary lesions extending over three or more vertebral
segments are common. The thoracic region is predominantly
affected, and some lesions can extend over its entire length. Spinal
cord is more often affected in patients with anti-MOG antibodies
(93%) compared to non-anti-MOG antibody counterparts (33%).
Among patients with spinal cord involvement, only 62% of those with
positive anti-MOG antibodies develop spinal symptoms compared to
100% of patients with negative anti-MOG antibodies. In the present
study, multiple diffuse bilateral lesions were observed in both
patients, but only the second presented brainstem and spinal cord
involvement, explaining the more severe clinical course.

ADEM treatment focuses on immunosuppression and removal
of systemic antibodies in more severe, unresponsive cases. The
recommended first-line treatment is high-dose IV corticosteroids
(20-30 mg/Kg/day of methylprednisolone until a maximum dose
of 1 g/day) for three to five days, followed by oral taper for four to
six weeks. IV immunoglobulin (1-2 g/Kg/day for 1-5 days) is
recommended for patients with no response after two days of pulse
IV corticosteroids. TPE (5-7 exchanges on alternate days) is the
most effective way of reducing circulating antibody levels and should
be considered in more severe or unresponsive cases and in cases
refractory to steroids, alone or in conjunction with other therapeutic
modalities. TPE has been reported in only a small number of
refractory cases and requires trained personnel and specialized
equipment. There is no established TPE protocol, and treatment
response is the best monitoring. The literature reports clinical
improvement after 2-3 TPE sessions, with most authors reporting 5-7
treatments. Miyazawa et al. documented the case of an 11-year-old child with ADEM who was successfully treated with four TPE sessions.

Tripathi et al. reported the case of an eight-year-old patient with
ADEM who had a poor response to steroids and IV immunoglobulin,
being subsequently treated with five TPE sessions, with neurological
improvement. Borras-Novell et al. described a clinical series of five
ADEM cases with no clinical improvement after methylprednisolone
(30 mg/kg/day) and immunoglobulin (1 g/kg), who underwent four
to five sessions of TPE, with no adverse effects and progressive clinical
improvement (namely better neurosensory response to stimulation,
seizure cessation, and limb mobility recovery). TPE is mostly well
tolerated and has no significant adverse effects, representing an
effective therapeutic tool in pediatric ADEM patients.

Both patients in this study presented neurological deterioration
under IV corticosteroid therapy. In the first case, relapse of anti-MOG
antibody-positive ADEM was suspected, with TPE being chosen as
second-line treatment. In the second case, combination therapy with
IV immunoglobulin and pulse IV corticosteroids was started due to the
severe presentation, but TPE was nevertheless required. Both cases
underwent TPE using a Prismaflex continuous renal replacement
therapy (CRRT) machine, in a total of six sessions, without significant
complications and with progressive neurological improvement after
the first session.

Non-specific treatment includes support and neurological measures. Empirical broad-spectrum antibiotics and acyclovir should also be
administered until CNS infection is excluded. Most children show progressive clinical improvement with treatment. Complete symptom resolution can occur between weeks four to six, with 50–70% of patients experiencing full recovery
but a minority maintaining persistent motor or cognitive impairment.
Patients with anti-MOG antibodies have a higher risk of long-term
cognitive impairment and epilepsy compared to those without anti-
MOG antibodies.

Follow-up should be maintained for a period of at least five years
from the initial episode to exclude new inflammatory demyelinating
lesions.

Most children have a monophasic disease without new clinical
relapse or demyelination over long-term follow-up. The relapse
frequency in pediatric patients with anti-MOG antibody-positive
ADEM is variable between studies. Long-term follow-up shows that
patients have an increased risk of multiphasic disease, especially
those who remain seropositive during follow-up. Additionally,
the evolution to relapsing disease is more frequent in older children. The same association between age and clinical phenotype has been observed in cases of relapse. Most recurrences occur within the first two years, but new relapses can occur years later. After recurrence, most children experience favorable recovery, but some may present mild-to-moderate impairment, including cognitive or motor deficits or seizures. The risk of future impairment seems to increase after every new relapse. In the two cases reported in this study, azathioprine treatment was started during follow-up. In the first case, the child had multiphasic ADEM with positive antimoG antibodies and initiated azathioprine after hospitalization. In the second case, azathioprine was initiated after the identification of a new inflammatory demyelinating lesion in brain MRI, despite the absence of new neurologic findings.

Table 1 - Definition of monophasic ADEM

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**Clinical features:**
- First polyfocal, clinical CNS event caused by a presumed inflammatory demyelinating disease.
- Encephalopathy unexplained by fever.

**Lesion characteristics on MRI:**
- Diffuse, poorly demarcated, large lesions (> 1 to 2 cm in size), located predominantly in the cerebral white matter; T1 hypointense lesions in the white matter are rare; Deep grey matter, especially basal ganglia and thalamus, can be involved.
- Without new clinical or imagiological findings three months or more after the beginning.
- During the acute phase, brain MRI is abnormal.

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; MRI, magnetic resonance imaging

**CONCLUSION**

This study described two cases of ADEM with anti-MOG antibodies unresponsive to immunosuppression with methylprednisolone and immunoglobulin, which responded to TPE treatment. Neurologic improvement without adverse effects was observed in both cases, supporting the benefit of TPE in anti-MOG antibody-positive ADEM, as previously reported by other authors. Close follow-up is crucial, as relapse can occur, requiring long-term immunosuppression.

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