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# CASE REPORTS

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

### Plasmaferese na encefalomielite aguda disseminada associada a anticorpos anti-MOG – Dois casos clínicos

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**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 infeção 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

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## INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a presumably immune-mediated inflammatory demyelinating condition, particularly affecting the white matter of the brain and spinal cord.[1] ADEM is a rare disease with a global incidence of 0.2 to 0.4 cases per 100 000 people.[1] It affects both genders equally, with 80% of childhood cases occurring in the first decade of life.[1] A greater incidence is commonly observed in the winter and spring months.[1,2] ADEM typically presents as an acute monophasic disorder, but recurrence cases have been reported.[2-4] Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been identified in a variety of demyelinating syndromes, with predominance in pediatric age.[2-4]

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.

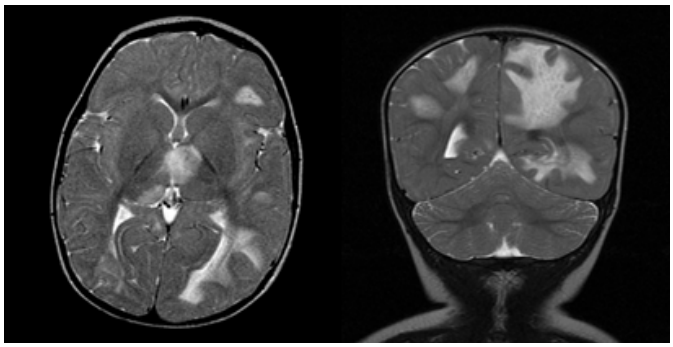

**Figure 1 -** Bilateral and asymmetric supratentorial T2-WI hyperintense lesions without contrast enhancement involving the periventricular and subcortical white matter and both thalami, with mass effect.

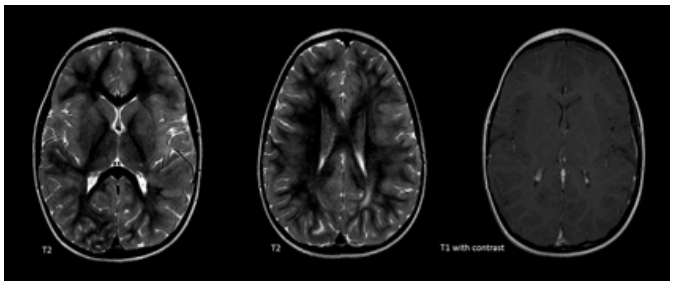


**Figure 2 -** Increased T2 hyperintensity of the cortex, which is thickened in some areas, particularly in the frontal and insular cortices. Areas of T2 hyperintensity of the supratentorial subcortical white matter and caudate and lenticular nucleus can be observed. No contrast enhancement.

**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.

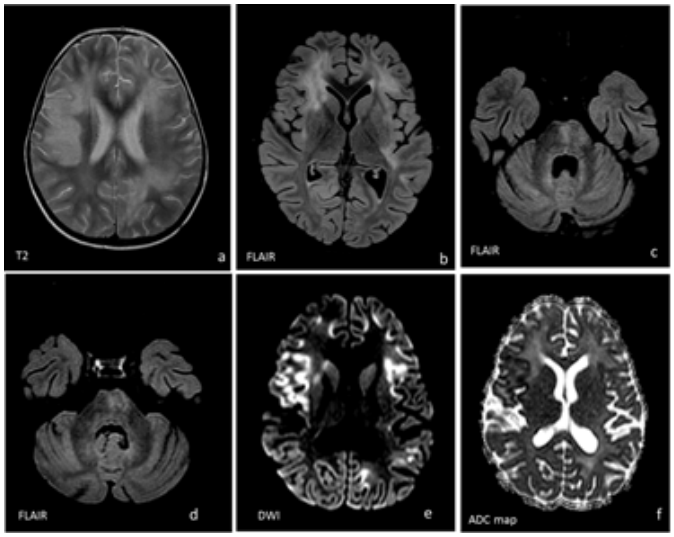


**Figure 3 -** (a) Areas of hyperintensity on T2-WI and FLAIR in the cerebral hemispheres, involving mostly the white matter but also the cortex, extending to the left anterior striatum and right lenticular nucleus (b). (c, d) In the posterior fossa, areas of T2 and FLAIR hyperintensity are seen in pons, middle cerebellar peduncles, dentate nucleus, and deep white matter of both cerebellar hemispheres. (e, f) Most of the affected cortex show restricted diffusion.

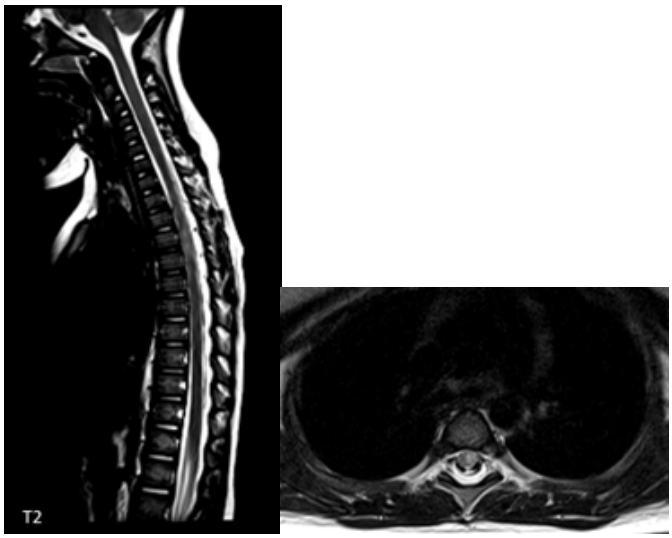


**Figure 4 -** T2 hyperintense lesion in the spinal cord, extending from Dorsal 1 to Dorsal 6, involving the grey and white matters.

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.[1,2,4,5] Disease onset is usually acute, preceded by prodromal symptoms such as fever, headache, myalgia, vomiting, or feeding refusal in approximately 75% of children.[2-4] 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.[1-5] Intensive care admission is usually required for patients with severe encephalopathy, seizures, or paralysis, most of whom require mechanical ventilation.[2] 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.[2] In the absence of specific biological markers or confirmatory tests, ADEM is a diagnosis of exclusion based on clinical and radiological findings.[1,2,4] CNS acute infection and other demyelinating or inflammatory syndromes should be excluded.[1,3] In most cases, CSF may show inflammatory features, such as elevated protein concentration and lymphocytic pleocytosis, although it can also be normal.[2,3] In pediatric populations, a minority of children with ADEM may have transiently positive anti-MOG antibodies.[2,3] 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; predominantly ADEM [53%], optic neuritis [40%], and transverse myelitis [18%]).[2,9] MOGAD is thus defined by the presence of demyelinating or encephalitic events associated with abnormal brain and/or spinal MRI and positive anti-MOG antibodies.[9] ADEM is more common in younger children, while opticospinal phenotype is more common in children older than nine years.[2]

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.[1,2] However, these tests are seldom positive, as in the present study.[1,2]

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.[10] 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.[1-5] Additional lesions may be found in deeper white matter, thalamus, basal ganglia, brainstem, cerebellum, and spinal cord.[5] In the spinal cord, large confluent intramedullary lesions extending over three or more vertebral segments are common.[1] The thoracic region is predominantly affected, and some lesions can extend over its entire length.[1,2] Spinal cord is more often affected in patients with anti-MOG antibodies (93%) compared to non-anti-MOG antibody counterparts (33%).[9] 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.[9] 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.[2,4] 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.[1,3,5,6] 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.[3,6] 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.[2,11,13] TPE has been reported in only a small number of refractory cases and requires trained personnel and specialized equipment.[2,6] There is no established TPE protocol, and treatment response is the best monitoring.[11] The literature reports clinical improvement after 2-3 TPE sessions, with most authors reporting 5-7 treatments.[11] Miyazawa *et al.* documented the case of an 11-year-old child with ADEM who was successfully treated with four TPE sessions.[12] 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.[12] Borras-Novel *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).[13] TPE is mostly well tolerated and has no significant adverse effects, representing an effective therapeutic tool in pediatric ADEM patients.[12,13]

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.[2] Empirical broad-spectrum antibiotics and acyclovir should also be administered until CNS infection is excluded.[2]

Most children show progressive clinical improvement with treatment.[1,7] 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.[1,7] Patients with anti-MOG antibodies have a higher risk of long-term cognitive impairment and epilepsy compared to those without anti-MOG antibodies.[9]

Follow-up should be maintained for a period of at least five years from the initial episode to exclude new inflammatory demyelinating lesions.[2]

Most children have a monophasic disease without new clinical relapse or demyelination over long-term follow-up.[2] The relapse frequency in pediatric patients with anti-MOG antibody-positive ADEM is variable between studies.[9] Long-term follow-up shows that patients have an increased risk of multiphasic disease, especially those who remain seropositive during follow-up.[2,9] Additionally,

the evolution to relapsing disease is more frequent in older children.[9] The same association between age and clinical phenotype has been observed in cases of relapse.[9] Most recurrences occur within the first two years, but new relapses can occur years later.[9] After recurrence, most children experience favorable recovery, but some may present mild-to-moderate impairment, including cognitive or motor deficits or seizures.[2,9] The risk of future impairment seems to increase after every new relapse.[9] 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 anti-MOG 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
Adapted from Krupp LB *et al*. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Multiple Sclerosis Journal 19(10). DOI: 10.1177/1352458513484547.

| Definition of monophasic ADEM |
|---|
| **Clinical features:**<br>• First polyfocal, clinical CNS event caused by a presumed inflammatory demyelinating disease.<br>• Encephalopathy unexplained by fever.<br><br>**Lesion characteristics on MRI:**<br>• 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.<br>• Without new clinical or imagiological findings three months or more after the beginning.<br>• 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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