ORIGINAL ARTICLE

Recurrent acute rhombencephalomyelitis in an adult or neuromyelitis optica? Presentation of a case

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Abstract

Introduction: The lack of accepted homogeneous criteria for the definition of some demyelinating diseases makes diagnostic characterization difficult and limits data interpretation and therapeutic recommendations. Recurrent encephalomyelitis (ADE-R) along with borderline cases of neuromyelitis optica (NMO) is especially controversial.

Objective: To describe the clinical and radiological evolution of an adult-onset ADE-R versus NMO case throughout 9 years of follow-up.

Patient and methods: Our patient presented with severe symptoms of rhombencephalomyelitis and the cranial and spinal magnetic resonance imaging (MRI) showed large lesions, with gadolinium enhancement in brainstem and spinal cord, correlating with the clinical picture. Infectious aetiology was excluded, IgG index was normal and NMO antibodies were negative. After treatment with intravenous corticosteroids and plasmapheresis, there was excellent recovery in the acute phase. During follow-up, seven relapses have occurred, mainly in the spinal cord, with good recovery and the same symptomatology, albeit with different severity. Immunosuppressive treatment was introduced since the beginning.

Conclusions: Our case shares common features of both ADE-R and NMO, illustrating that diagnostic characterization is not easy in spite of current criteria.

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reproducibility of the results and the recommendations therapeutic. Especially contro-
verted are the forms of encephalomyelitis recurrent (EAD-RR) and other forms infrequent
of neuromielitis optica (NMO).

**Objective:** Describing the evolution clinico-radiological of a case of EAD-RR of the adult versus
NMO, studied during 9 years.

**Patient and methods:** The patient debuted with severe symptoms of rhombencephalomyelitis and the
resonance magnetic (RM) cranial and spinal showed lesions extensive, with capitation of
Gadolinium in the tronco enCEFálico and of the médula, according to the symptoms clinical of the paciente.
Se excluyó etiología infecciosa, el índice IgG fue normal and fueron negativos los anticuerpos
for NMO. Tras tratamiento with corticoides per vía intravenosa and plasmapheresis the recuperación
of the episodio was excellent. During the follow-up has presented 7 recurrences, preferente-
mente medulares, with good recuperación, that produces with severity variable the same
symptoms. Since the inicio ha recibido tratamiento inmunosupresor.

**Conclusions:** Nuestro caso comparte características clinicas con EAD-RR and NMO e ilustra que,
pese a los criterios vigentes, la caracterización diagnóstica de estas entidades no es fácil.
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**Introduction**

Idiopathic acute disseminated encephalomyelitis (ADEM) is
an inflammatory demyelinating disease. It primarily affects
children and is usually preceded by viral infections or vac-
cines, with a latency between 2 and 30 days and a higher
incidence in winter. Its causes do not include infections or
eosplasms. The aetiological hypothesis explains it as an inadequate immune response against antigens of the
central nervous system (CNS), released after damage by neu-
rotropic agents or by molecular analogy. The neurological
manifestations of ADEM are often polysymptomatic, cerebral
and, less commonly, medullar. The most common signs of
ADEM in children are disturbances of level of consciousness
or behaviour, fever, meningism and epileptic crises.

In adults it is rare and the most prevalent symptoms are
motor, sensory, ataxia and alterations in speech or level of
consciousness. ADEM is usually monophasic, although 5.5%—25% of cases present recurrences.
These may occur in the same initial topography (ADEM-R) and, for some
authors, in other locations (multiphasic ADEM). Both
of them, especially the multiphasic form, are the subject
of much controversy since the differential diagnosis with
MS carries prognostic and therapeutic implications.

Radiologically, ADEM usually exhibits more extensive
lesions in the cerebral white matter than those caused by
MS. Gadolinium uptake is variable, but a simultaneous
uptake points more towards ADEM. Gray matter lesions,
maintained in the basal ganglia, may be bilateral and occur in
up to 60% of cases, while they are infrequent in the first
demyelinating event in MS. The presence of “Dawson’s
fingers” in T1-weighted sequences should direct towards
an alternative diagnosis to ADEM. Cerebrospinal fluid
(CSF) may be normal or present lymphocytic pleocytosis
and hyperproteinorrachia. Oligoclonal bands (OCB) are
often absent or disappear during follow-up, contrary
to what has been described in MS. Histopathologically,
ADEM can be distinguished from MS by the existence
in the former of perivenular demyelination “bands”
with prominent inflammatory infiltrates at the expense
of macrophages. Lesion margins are poorly defined.

Typically, patients are treated with intravenous methyl-
prednisolone (iMTP) at high doses during acute episodes.
Plasmapheresis and intravenous immunoglobulins are
therapeutic alternatives in severe cases that are unres-
ponsive to corticosteroids. The prognosis of monophasic
ADEM is variable; 37%—81% of patients present a complete
resolution of symptoms. Mortality (5%—25%) is associated
with respiratory failure due to bulbar involvement. There
is little experience regarding the treatment of ADEM-
R; some authors have proposed immunosuppressors,
cyclophosphamide and mitoxantrone.

For its part, neuromielitis optica (NMO) or Devic’s dis-
ease is characterised by recurrent episodes of optic neuritis
and myelitis, which are usually disabling, and Infrequently,
NMO may present bulbar symptoms, such as hyperemesis
and respiratory dysfunction, or even appear as a transverse myelitis. The MRI scan of NMO usually reveals extensive
medullar lesions of more than vertebral 3 segments and, in
most cases, the cerebral white matter is normal. Deter-
mination of the anti-aquaporin 4 antibody in 2004 enabled
differentiation between this entity and MS and the detection
of intermediate or “NMO spectrum” forms whose evolu-
tion is still to be determined. However, false negatives can reach 30%—45% of the total, especially in cases treated
with immunosuppressive drugs. Therapeutic options dur-
ing the acute phase include intravenous methylprednisolone
(iMTP and occasionally plasmapheresis or intravenous
immunoglobulins (ivIg). As in ADEM-R, there are currently
no randomised trials evaluating the treatment of recurrent
NMO to prevent recurrences.

**Objective**

The aim of this study is to describe the clinical and radi-
ological characteristics of a 21-year-old female patient with
recurrent rhombencephalomyelitis who was monitored for
9 years, as well as to discuss diagnostic options and therapeu-
tic considerations.

**Patient and methods**

The patient was a 21-year-old female with no prior his-
tory of systemic or autoimmune disease, diagnosed with
A) showed hyperintense lesions in T2 sequences in two-thirds of the dorsal bulb, with compression of the fourth ventricle and left cerebellar peduncle. A spinal MRI scan (Fig. 1B) revealed a hyperintense band from C4 to L1 in T2-weighted sequences. The CSF presented pleocytosis (50/μl) with monocyte predominance, sterility, proteins at 62 mg/dl and glucose at 84 mg/dl. The IgG index was normal and OCBs were not obtained. The microbiological study ruled out infectious aetiologies (Borrelia, Brucella, Mycoplasma, parvovirus, cytomegalovirus, herpes virus, varicella-zoster virus, Epstein-Barr virus, toxoplasmosis, enteroviruses, mycobacteria, acquired immunodeficiency virus, hepatitis C and HBV virus, Listeria, Gram, auramine). The serological study ruled out autoimmune or tumoural causes.

The initial diagnosis was autoimmune rhombencephalomyelitis. The patient was admitted to the intensive care unit with respiratory distress secondary to aspiration pneumonia. She was treated with broad-spectrum antibiotics and ivMTP for 5 days. Due to her poor response to corticosteroids, she was treated with 5 cycles of plasmapheresis followed by iv Ig at doses of 0.4 mg/kg/day for 5 days. At discharge, 1 month after admission, she presented paresis of the left sixth cranial nerve, multidirectional nystagmus and walked unaided, but was unsteady.

Subsequently, the patient presented 7 spontaneous relapses (Table 1). Of these 7 relapses, 4 consisted in mild-moderate myelitis with motor and/or sensory involvement, all at the dorsal level, from which she recovered after a few days. The first relapse coincided with removal of glucocorticoids. Treatment with azathioprine was started. The remaining relapses consisted of bilateral, paroxysmal pain in a half-band, associated with bilateral metameric hyperalgesia at the level of D5–D10. During the clinical course, visual evoked potentials were normal and serologies for HTLV-1 and anti-aquaporin 4, conducted during one of the relapses (May 2007), were negative. Regarding the MRI scan, the medullar lesion showed gadolinium uptake during various clinical relapses, whilst no other cranial or spinal injuries or signs of axonal damage were observed (Fig. 2).

The patient was chronically treated with azathioprine at doses of 50 mg/12 h and, given the persistence of relapses, azathioprine was replaced by mycophenolate mofetil at doses of 1–1.5 g/day. At present, the patient has not suffered relapses for 3 years, she can walk and jump normally and exploration has only revealed the persistence of upwards vertical and bilateral horizontal nystagmus, without functional interference.

**Discussion**

This case suggests a form of recurrent rhombencephalomyelitis compatible with ADEM-R by clinical and radiological criteria, with a good clinical course and therapeutic response to immunosuppressors. At present, the patient is clinically asymptomatic after 7 relapses, despite having presented moderate disability during 3 of them. Notably, all relapses were in the same location as the initial event, although with different severity, and only the first relapse could be attributed to the gradual withdrawal of glucocorticoids.
### Table 1  Clinical recurrences and treatment.

<table>
<thead>
<tr>
<th>Date</th>
<th>Symptoms</th>
<th>Neurological examination</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>April 2003 (2 months after the first episode)</td>
<td>Double vision when viewing close objects. Burning sensation from abdomen to lower limbs. Numbness and weakness in fine movements of right upper limb Gait instability and feeling of “swollen lower limbs”, difficulty urinating and defecating. Duration of symptoms, 2 weeks.</td>
<td>Multidirectional nystagmus in upwards gaze. Medial rectus paresis of left eye along with paresis to accommodate it Hypoalgesia in D6–D12 band and associated dysesthesia Proprioceptive ataxia, abolition of positional sensitivity in both lower limbs. Hypoesthesia in both lower limbs and bilateral Babinski sign</td>
<td>Azathioprine 50 mg/12 h, MTP 1 g/5 days</td>
</tr>
<tr>
<td>May 2003</td>
<td>Brief episodes of involuntary extension of both lower limbs alternately. Interpreted as phenomena of paroxysmal dystonia, with a frequency of 3–4 times/day. ”Tingling” ascending from both lower limbs up to navel. Sensation of “intermittent burning” in the right leg from knee to thigh. Duration of 1 week</td>
<td>Persistence of bilateral horizontal nystagmus and vertical upwards Mild impairment of positional sensitivity in the right leg. Left Babinski sign</td>
<td>Carbamazepine was added at 50 mg/8 h</td>
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<td>October 2003</td>
<td>Alteration in touch and temperature perception from the interscapular region, more accentuated in submammary and perianal bands, with unaffected sphincters. Clumsiness when walking. Duration of 1.5 months.</td>
<td>Eye movements similar to prior. Hypoalgesia from the umbilical region to the left thigh. No cerebellar signs. Normal strength. Indifferent CPR</td>
<td>Increase of carbamazepine 100 mg/8 h</td>
</tr>
<tr>
<td>May 2007</td>
<td>Very painful dysesthesia from inframammary level, half-abdomen and left leg. Lack of perception of temperature and ground texture. Difficulty to start urination and defecate.</td>
<td>Eye movements similar to prior. Bilateral sensitive level from D2 to D5. Mild impairment of positional sensitivity in lower limbs. Autonomous gait with proprioceptive ataxia. Closed-eye Romberg with oscillations. No weakness in limbs. Bilateral Babinski sign. Infra mammary hypoesthesia (touch and pain) in a band from D4 to inguinal region. Defective positional sensitivity in toes. Proprioceptive gait, positive tandem, oscillating Romberg. Rest of the examination (nystagmus and reflexes) similar to previous.</td>
<td>MTP 1 g/5 days Azathioprine without changes</td>
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Table 1 (Continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Symptoms</th>
<th>Neurological examination</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>October 2007</td>
<td>Painful dorsal dysesthesia in band. Numness of left side of body</td>
<td>Vertical nystagmus in all eye movements. Impaired convergence and left medial rectus paresis</td>
<td>MTP 1 g/5 days. Mycophenolate mofetil is introduced (1 g/day). Azathioprine is suspended</td>
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<td>Intermittent contractions of the muscles of the left abdomen 8–10 times/day</td>
<td>Slowness of alternating hand movements. Left extensor CPR, right indifferent</td>
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<td></td>
<td>Unsteady gait with a feeling of &quot;oppressive band&quot; at that level</td>
<td>Spontaneous abdominal contractions interpreted as segmental motor paroxysmal phenomena</td>
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<td></td>
<td>Does not feel ground</td>
<td>Hypoalgesia in D3–D10 band and knees, with proprioceptive disorder in all 4 limbs</td>
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<td></td>
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<td>Proprioceptive gait. Hesitation in finger–nose manoeuvre</td>
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<tr>
<td>March 2009</td>
<td>Altered sensitivity in subaxial mammary region band of 5 days duration</td>
<td>Eye movements similar to previous Torpid dorsiflexion</td>
<td>ivMTP 1 g/10 days. Increase of mycophenolate mofetil (1.5 g/day)</td>
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<td></td>
<td>Reduced thermal sensitivity and proprioception in lower limbs</td>
<td>Asymmetrical hypoalgesia at D2–D5 level and lower limbs: in the right leg up to the knee and in the left leg up to the groin.</td>
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<td></td>
<td>Difficulty urinating</td>
<td>Affected perineum</td>
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<td></td>
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<td>Proprioceptive impairment (abolished in left foot, 40% in right foot)</td>
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<td></td>
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<td>Ataxic gait</td>
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CPR: cutaneous-plantar reflex; MTP: methylprednisolone.

Images from the brain and medullar MRI scans were extensive, with medullar thickening similar to that described in exceptional cases of ADEM, and unusually for MS. The medullar images captured contrast on at least 2 occasions, coinciding with an exacerbation of symptoms. It is striking that after 7 recurrences, there were no observations of medullar necrosis or black holes in the brain MRI, suggesting the absence of axonal lesions, more typical in MS. The evolution of the case and the data presented excluded the diagnosis of MS.

The boundary with NMO is even more controversial. From the clinical standpoint, our patient did not present the visual symptoms typical of NMO at any time during her evolution, and her evoked potentials were normal. Full recovery of the episodes without disability is rare in NMO. Although in our patient the medullar images resembled those described for NMO, they did not show evidence of tissue necrosis, as is usual in NMO. Nevertheless, there have recently been reports of cases in which radiographic abnormalities improved or even disappeared between episodes. The determination of IgG versus AQP4 was negative, although this determination was conducted under immunosuppressive treatment, so we cannot definitively rule out the possibility that our patient suffered an uncommon form of recurrent NMO according to the current criteria.

The clinical evolution and negative result of microbiological and immunological tests conducted at the onset and during several of the episodes excluded other entities which could mimic these symptoms.

There is no clear consensus regarding treatment. During the initial outbreak, the patient was treated with ivMTP at high doses. Due to the severity of the outbreak and the incomplete response, she was subsequently treated with plasmapheresis and iv Ig, with marked clinical improvement. Treatment with azathioprine was established after the first relapse, following reports of good response to this drug. The outbreaks persisted, so it was switched to mycophenolate mofetil, useful in other autoimmune diseases including NMO and MS. This drug acts by inducing apoptosis of reactive T cells and decreasing humoral reactivity. The patient has remained asymptomatic for two and a half years.
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August 2007. (A) Medullar MRI image with intravenous gadolinium. There is a hypodense lesion in T1 sequences, from C2 to D10, with contrast uptake at the level of D8—D9. At the brain level, axial FLAIR (B) and sagittal T1 (C) sequences show no white matter lesions or signs of atrophy.

Conclusions

Our study illustrates the observation that in certain cases of demyelinating diseases, diagnostic characterisation is not easy, despite the current criteria. We believe that our case presents clinical and radiological data matching both adult onset ADEM-R and an unusual form of NMO. The excellent medium-term prognosis with immunosuppressive therapy is more suggestive of a rare form of ADEM-R. Treatment with mycophenolate mofetil may be an alternative therapy for these patients.

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Conflict of interest

The authors have no conflicts of interest to declare.

References


