Multiphasic ADEM reclassified in Multiple Sclerosis: a case with therapeutic implications

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Abstract

Introduction: Acute disseminated encephalomyelitis (ADEM) is classically defined as a multifocal encephalopathic and typically monophasic demyelinating inflammatory clinical event. A multiphasic form of ADEM has been recognized; differentiating multiphasic ADEM from Multiple Sclerosis (MS) may represent a diagnosis challenge.

Case Report: We present the case of a patient with five episodes of subacute encephalopathy together with various focal neurological deficits, suggestive of multiphasic ADEM. Lastly, a sixth event presented as a non-encephalopathic relapse. According to the new criteria for diagnosis of pediatric acquired demyelinating syndromes, the patient actually displays a chronic relapsing disease-like. However, 5 years after onset of illness, the patient is being treated with Azathioprine 150 mg/day and remains clinical and imagiologically stable.

Discussion: Progression to MS occurs in pediatric patients in which the initial presentation is ADEM; however, in this patient, the current stability raises questions about the need for changing the current therapeutic regimen.

Keywords: Acute disseminated encephalomyelitis, Multiphasic Acute disseminated encephalomyelitis, Multiple Sclerosis.

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Introduction

Acute Disseminated Encephalomyelitis (ADEM) is a demyelinating inflammatory disease, more common in pediatric age, which manifests as a polyfocal clinical CNS event, accompanied by encephalopathy. The vast majority (90%) of cases follows a monophasic course and are preceded in about 67% by an infection or vaccination [1]. According to the 2012 review of the criteria for diagnosis of pediatric acquired demyelinating syndromes, multiphasic ADEM comprehends only two clinical episodes consistent with ADEM. The occurrence of further events indicates a chronic relapsing disease, either Multiple Sclerosis (MS) or Neuromyelitis Optica. On the other hand, the diagnosis of pediatric MS may be established after an episode of ADEM followed (at least after three months) by a non-encephalopathic event with magnetic resonance imaging (MRI) findings consistent with MS, establishing dissemination in space. This “progression” to MS occurs in 5–18% of pediatric patients in which the initial presentation is ADEM [2].

Case Report

A 20-year-old woman, without relevant personal or familiar background until the age of 15, when she was hospitalized due to subacute encephalopathy, ataxia, ophthalmoparesis, extrapyramidal syndrome and dysautonomic symptoms, which improved after intravenous (IV) corticosteroids. CSF analysis showed an inflammatory pattern with positive oligoclonal bands (OCB) (negative in serum). Visual evoked potentials (VEP) revealed no changes. Infectious, metabolic, vascular and paraneoplastic causes were excluded, as well as other autoimmune diseases, including anti-NMDA and anti-glycine receptor encephalitis. Neuroaxis MRI showed T1 hypointense and T2 hyperintense bilateral lesions in the insular cortex, basal ganglia, thalamus, internal capsule, hippocampus, midbrain and periaqueductal gray matter, some with gadolinium enhancement; no spinal lesions (Figure 1). She recovered significantly, keeping as sequelae behavioral disinhibition and stereotyped movements. The MRI performed seven months later showed reduction of some previous lesions as well as new asymptomatic supratentorial lesions. The patient was admitted twice (14 and 16 months after the first event) for new subacute encephalopathic episodes, accompanied by focal neurological deficits, always with clinical improvement after corticosteroid therapy. MRI taken at this time showed T1 hypointensity in some of the previous lesions and re-emerging T2 hyperintensity in the pons, midbrain, basal ganglia and thalamus, as well as new frontal and parietal lesions in the periventricular and subcortical white matter (Figure 2). After multidisciplinary review, Multiphasic ADEM was settled as the main diagnostic hypothesis and azathioprine was introduced (together with quetiapine for behavioral changes control).

Approximately 18–19 months after the first event she was again hospitalized for subacute encephalopathic changes with new focal neurological deficits, and again slowly recovered after corticosteroid. The newly performed brain MRI showed new supratentorial white matter lesions and increased pons lesion with gadolinium enhancement. All neuroaxis imaging studies highlighted absence of corpus callosum or spinal cord lesions (Figure 3). Immunosuppression dosing was optimized adding chronic oral corticosteroids (1mg/Kg/day), which was subsequently withheld due to iatrogenicity (myopathy, skin ulcers, amenorrhea).

The patient remained clinically stable, despite evidence of a new parietal subcortical lesion with gadolinium enhancement on a MRI conducted 19 months after the last clinical

Figure 1. Brain MRI (Oct/10). (a) T2 TSE; (b) T1; (c) T1 GAD: axial images showing T1 hypointense and T2 hyperintense bilateral lesions in the insular cortex, basal ganglia, thalamus, internal capsule, hippocampus, midbrain and periaqueductal gray matter, some with gadolinium enhancement.
event. About 5 months later the patient had a non encephalo-pathic event with cerebellar dysfunction, which resolved after IV corticosteroid. The newer brain MRI showed stable lesion load without gadolinium enhancement (Figure 4).

Currently, 5 years after onset of illness, patient is being kept on azathioprine 150 mg/day, quetiapine 200 mg/day and remains on clinical and imagiological stability, despite cognitive/behavioral, ataxic and extrapyramidal sequelae.

Discussion

Some authors suggest the following features as an attempt to differentiate pediatric patients who will develop MS after a first episode of acute CNS demyelination: presence of T1 hypointense lesions and periventricular lesions on the initial brain MRI [3]; OCB presence on CSF, changes in the VEP and lack of involvement of thalamus or basal ganglia [4, 5]. However, actually, there are no definite clinical or imaging criteria to allow predicting the evolution of these patients.

The patient described had five episodes of subacute encephalopathy associated with various focal neurological deficits, with the progressive development of new inflammatory brain lesions, suggesting multiphasic ADEM. The last event was characterized by focal neurological signs without encephalopathy. According to current recommendations, the patient actually meets diagnostic criteria for relapse-remitting MS, both due to the number of clinical events—six—and to the development of a non encephalopathic event after one of typical ADEM. This diagnostic change carries therapeutic implications: MS has specific immunomodulatory drug treatment and there are reports that Beta-interferon may exacerbate ADEM [6]. The atypical presentation of this case, with few similar reports [7], as well as the current stability of the patient, raise questions about the need for changing the current therapeutic regimen.

Abbreviations

ADEM: Acute disseminated encephalomyelitis; IV: Intravenous; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; OCB: Oligoclonal bands; VEP: Visual evoked potentials

Competing interests

The authors declare no conflict of interest.

References


Figure 4. Brain MRI (07/2015). T2 FLAIR axial images showing stable lesion load (compare with Figure 2).