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Case report

A unique case of multiphasic ADEM or what else?

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is a monophasic post-infectious demyelinating disease, clinically defined by the acute onset of polyfocal neurological deficits including encephalopathy. A subset of ADEM patients will subsequently be diagnosed with relapsing disorders, including recurrent DEM (RDEM), multiphasic DEM (MDEM), neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS). Here we describe the case of an adult patient, who presented two ADEM-like episodes after a very long (8 years) symptoms-free period.

Clinical case: A 48 years old man presented a first case of sub-acute onset of encephalopathy and dysarthria with MRI findings suggestive for ADEM for which he underwent an intravenous and oral steroid treatment followed by a complete clinical remission. After 8 years he presented a new sub-acute onset of encephalopathy and balance disorders with the onset of new lesions at the MRI. The search for oligoclonal band (OCB) showed a single CSF-restricted IgG band. Suspecting a new ADEM episode he was treated with intravenous steroids without benefit and 3 apheresis sessions with clinical improvement followed by an oral steroid treatment. After 2 months he experienced a paroxysmal episode of dysarthria, upper and lower left limbs impairment and urge incontinence with a stable new brain and spinal cord MRI. The search for anti-aquaporin-4 and anti-MOG (cell-based assay) antibodies was repeated twice within a 6 months span and resulted in both cases negative. The patient was treated with Rituximab (1g followed by 1g after 15 days, followed by 1g after 6 months) with stability of the neurological and radiological examinations at the last follow-up.

Conclusions: To the best of our knowledge, this is the first case of MDEM in which the two episodes of ADEM occurred 8 years apart. Although this case fulfills the diagnostic criteria for MDEM, the time elapsed between the two episodes is very long. Therefore, we cannot exclude that this disease might be a new nosological entity that could be included in the expanding range of demyelinating diseases.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic post-infectious demyelinating disease, clinically defined by the onset of acute polyfocal neurological deficits, including encephalopathy, mainly affecting children (Pohl et al., 2016) and rarely adult patients (Brinar and Poser, 2008). A subset of ADEM patients will subsequently be diagnosed with relapsing disorders, including recurrent DEM (RDEM), multiphasic DEM (MDEM), neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS). Until now there is no satisfactory consensus on the distinction between ADEM, RDEM and MDEM in adult population (Brinar and Poser, 2008; Brinar, 2004). In the International Pediatric Multiple Sclerosis Study Group consensus for definition of pediatric acquired demyelinating disorders (Krupp et al., 2013), the category of RDEM was deleted, and replaced by the term MDEM, describing 2 episodes consistent with ADEM separated by at least 3 months. A third ADEM-like event is no longer consistent with MDEM (Brinar and Poser, 2008). Here we describe the case of an adult patient, who presented two ADEM-like episodes after a very long (8 years) symptoms-free period.

2. Clinical case

A 48 years old man, affected by diabetes and hypertension, on March 2009, presented the sub-acute onset of ataxia, encephalopathy and dysarthria ten days after an upper respiratory tract infection for which he was admitted to another hospital. He underwent a brain and spinal cord magnetic resonance imaging (MRI) that showed the presence of multiple hyperintense areas in the T2 and FLAIR-weighted scans in the subcortical white matter, corpus callosum, semioval center

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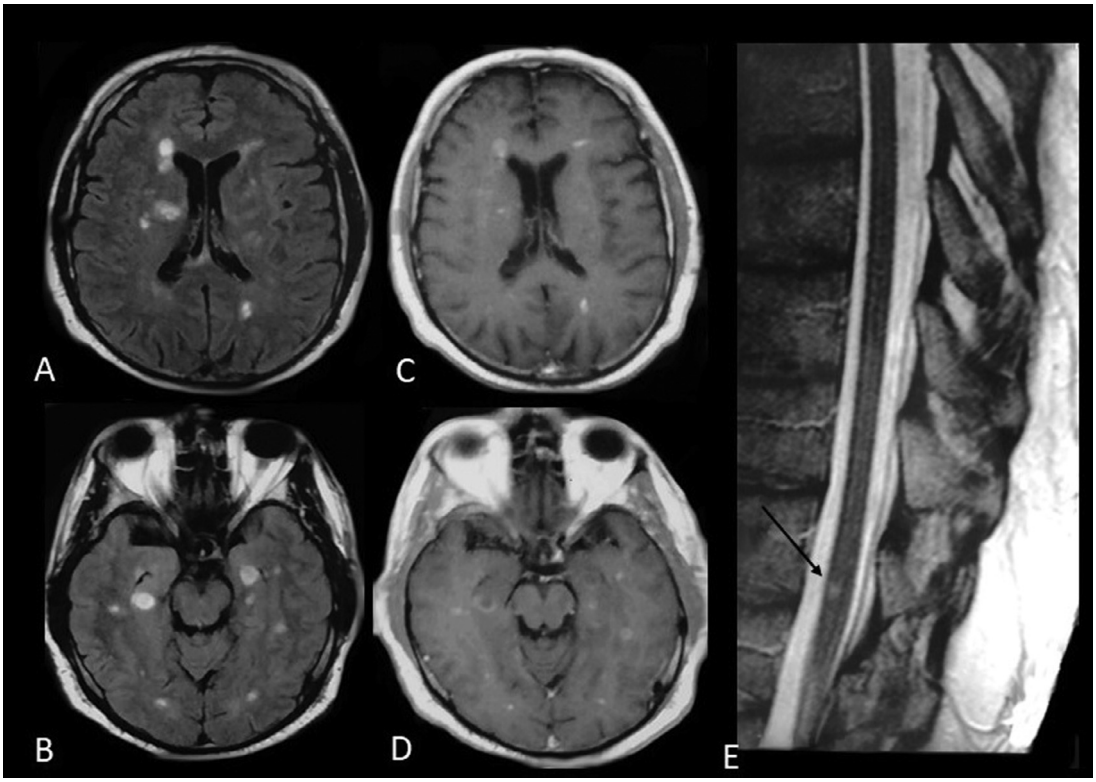

Fig. 1. MRI Findings in 2009: MRI scans at the initial presentation in 2009. The FLAIR-weighted sequences of the brain (A, B) show multiple hyperintense lesions in the subcortical white matter, corpus callosum, and semioval center. The T1-weighted sequences with Gadolinium (C, D) show multiple GE lesions. The T2-weighted sequences of the spinal cord (E) show a hyperintense lesion at D11-D12 level.

and spinal cord (D11-D12), some of them showing Gadolinium Enhancement (GE) (Fig. 1). The clinical onset and the MRI findings were suggestive for ADEM, so he was treated with intravenous methylprednisolone (1 g for 5 days) with clinical benefit followed by a tapering regimen of oral steroids for one year with full recovery. During the following years he underwent periodical brain and spinal cord MRI controls that showed a partial remission of the T2-weighted lesions and that remained stable during the follow-up.

On November 2017, at the age of 56 years, he developed a new subacute onset of encephalopathy and balance disorder preceded about 10 days earlier by fever for which he was admitted to our neurology department. At the admission, the neurological examination showed confusion, dysarthria, bilateral nystagmus, multidirectional oscillations at the Romberg's test and lowering of the right leg at the Mingazzini test. During the hospitalization he underwent a brain and spinal cord MRI that showed new multiple hyperintense areas in the T2 and FLAIR-weighted scans of the subcortical white matter, corpus callosum, bilateral semioval center, right thalamus, midbrain and pons of which thirteen with GE (Fig. 2). The Visual Evoked Potentials showed slow conduction of the left eye. The patient also underwent a lumbar puncture: the chemical analysis showed normal protein concentration (37 mg/dl), mild pleocytosis (10 cells/mm^3) and normal glycorrhachia, the search for oligoclonal band (OCB) showed a single CSF-restricted IgG band. The patient was also tested for anti-aquaporin-4 and anti-MOG (cell-based assay) antibodies twice within a 6 months span, that resulted in both cases negative. Suspecting a new ADEM episode he was treated with intravenous steroids (methylprednisolone 1 g for 5 days) without benefit and 3 apheresis sessions with clinical improvement. He was discharged with an oral steroid treatment. On January 2018 he experienced a paroxysmal episode of dysarthria, upper and lower left limbs impairment and urge incontinence with a stable new brain and spinal cord MRI. The patient was treated with rituximab (1 g followed by 1 g after 15 days, followed by 1 g after 6 months) with stability of the neurological and radiological examinations at the last follow-up.

3. Discussion

In this case the patient presented a first onset of symptoms that has been diagnosed as an adult case of ADEM. Eight years later he presented a new clinical and neuroradiological worsening that has been diagnosed as a new ADEM episode followed by a new clinical worsening within the first three months. A diagnosis of MDEM was made considering that MDEM is defined by the occurrence of two clinical-radiographic episodes of disseminated encephalomyelitis separated by at least three months. The clinical findings are defined as being new or a re-emergence of prior symptoms. Also a diagnosis of MS was supported by the new diagnostic criteria (Thompson et al., 2018) but the clinical onset of both episodes, characterized by encephalopathy, and the absence of oligoclonal bands (OCB) makes this diagnosis less likely. The diagnosis of anti-MOG antibodies associated encephalomyelitis and neuromyelitis optica (NMO) was ruled out by the two negative search for both the specific antibodies. NMO Spectrum disorder (NMOSD) seronegative criteria were not satisfied (Wingerchuk et al., 2015).

Our case seems to be similar to the one previously described by Shah et al. (2018), diagnosed as RDEM, because they both presented a first ADEM-like episode followed by a long hiatus period (8 years in our case and 10 years in the other case) but they differ for the second episode. In our case, the patient presented with a new onset of encephalopathy and showed a single CSF-restricted IgG band at the cerebrospinal fluid analisis while, in the case by Shah, the patient presented “minimal cognitive or personality change” (but not encephalopathy) and showed the presence of OCB at the cerebrospinal fluid analysis supporting also a diagnosis of MS. No other cases with similar features, to the best of our knowledge, are reported in literature.

In conclusion, this is the first case of MDEM in which the two episodes of ADEM occurred 8 years apart. Although this case fulfills the

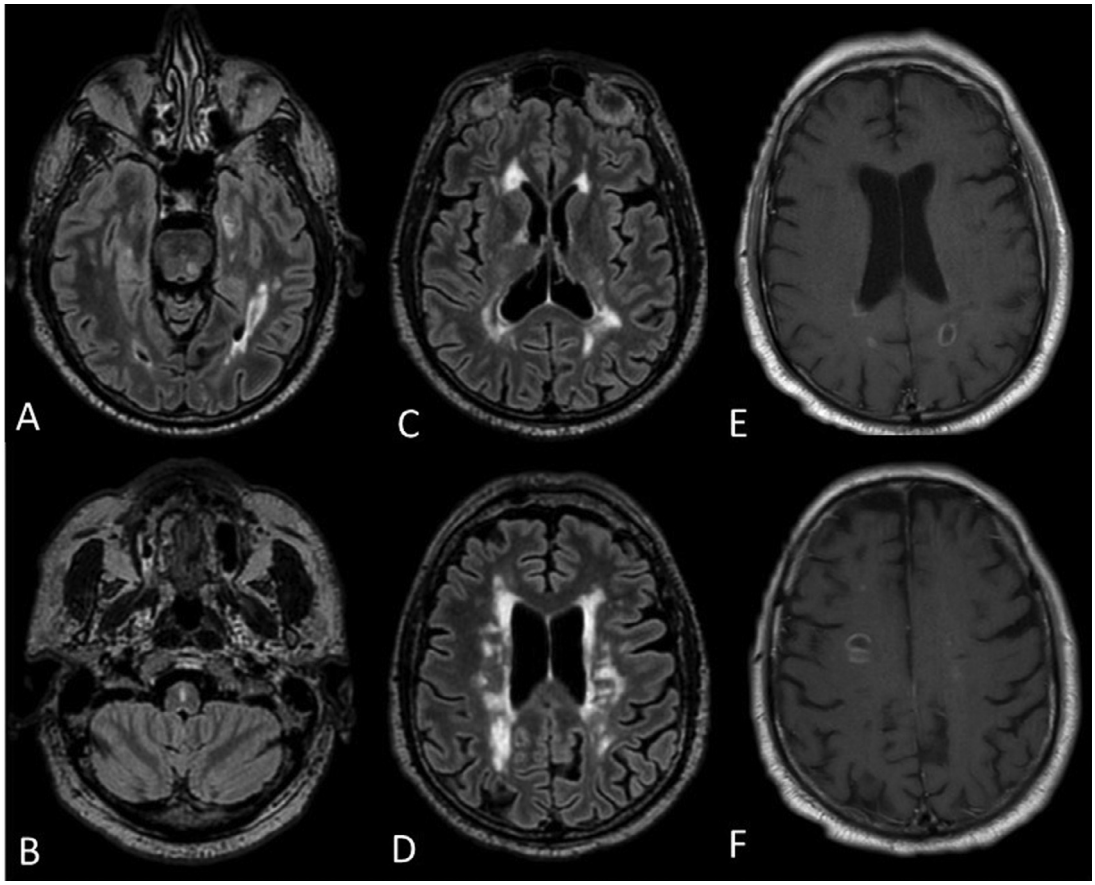

Fig. 2. MRI Findings in 2017: MRI scans in 2017. The FLAIR-weighted sequences of the brain (A, B, C, D) show new hyperintense lesions of the subcortical white matter, corpus callosum, bilateral semioval center, right thalamus, midbrain and pons. The T1-weighted sequences with Gadolinium (E, F) show multiple GE lesions.

diagnostic criteria for MDEM, the time elapsed between the two episodes is very long. Therefore, we cannot exclude that this disease might be a new nosological entity that could be included in the expanding range of demyelinating diseases.

Declaration of interest

The authors report no financial conflicts of interest.

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