



Short communication

## Meningeal inflammation and demyelination in a patient clinically diagnosed with acute disseminated encephalomyelitis



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### ABSTRACT

Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) are both CNS inflammatory demyelinating diseases with overlapping clinical features. A case is reported of a 51-year-old female who presented with headache, progressive aphasia and hemiparesis without preceding infection or vaccination. Brain MRI revealed multiple, often confluent, subcortical white matter lesions without enhancement, affecting predominantly the left cerebral hemisphere. CSF examination failed to reveal oligoclonal bands. Brain biopsy revealed both pathological features of ADEM and findings are consistent with the early stage of MS, including meningeal B and T lymphocytic infiltration, perivenular demyelination, subpial demyelination and discrete confluent plaque-like foci of demyelination. Steroid treatment resulted in remarkable clinical and radiological improvement and there has been no recurrence in six years of follow-up. This case highlights the difficulties in differentiating between ADEM and the first attack of MS and further suggests that ADEM and the early stage of MS, and its tumefactive variant, may have a common underlying pathologic mechanism, which may have a therapeutic implication in treating these diseases.

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### 1. Introduction

Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) have been considered clinically and immunopathologically distinct phenotypes of inflammatory demyelinating disorders of CNS [1,2]. Typically, ADEM presents with a monophasic course, while MS typically exhibits a relapsing and remitting course with accumulating neurological deficits with each exacerbation. However, despite several clinical and/or radiological criteria proposed to differentiate ADEM from MS, none has been proven to unequivocally separate them. Pathologically, the presence of perivenular demyelination has been considered as a pathological hallmark of ADEM, while MS is characterized by confluent demyelination, although cases with pathological overlap have been reported [3].

Here we report a patient with inflammatory CNS demyelination clinically and radiologically most consistent with ADEM including no recurrence after six years of follow-up. The brain biopsy findings revealed meningeal lymphocytic infiltration, subpial demyelination and confluent foci of plaque-like demyelination identical to those recently described for acute stage MS, in addition to perivenular inflammatory demyelination characteristic of ADEM.

### 2. Case report

A 51 year old right handed Japanese female started complaining of headache which became gradually unresponsive to over the counter medications over the course of 2 weeks. A week later, she was noted to have trouble understanding and expressing her thoughts and decrease in speech output. While having meals, she noted to have leaks of food from the right corner of her mouth. She had no difficulties in performing daily chores as a housewife. Three weeks after the headache onset, she was referred to our department for further evaluation.

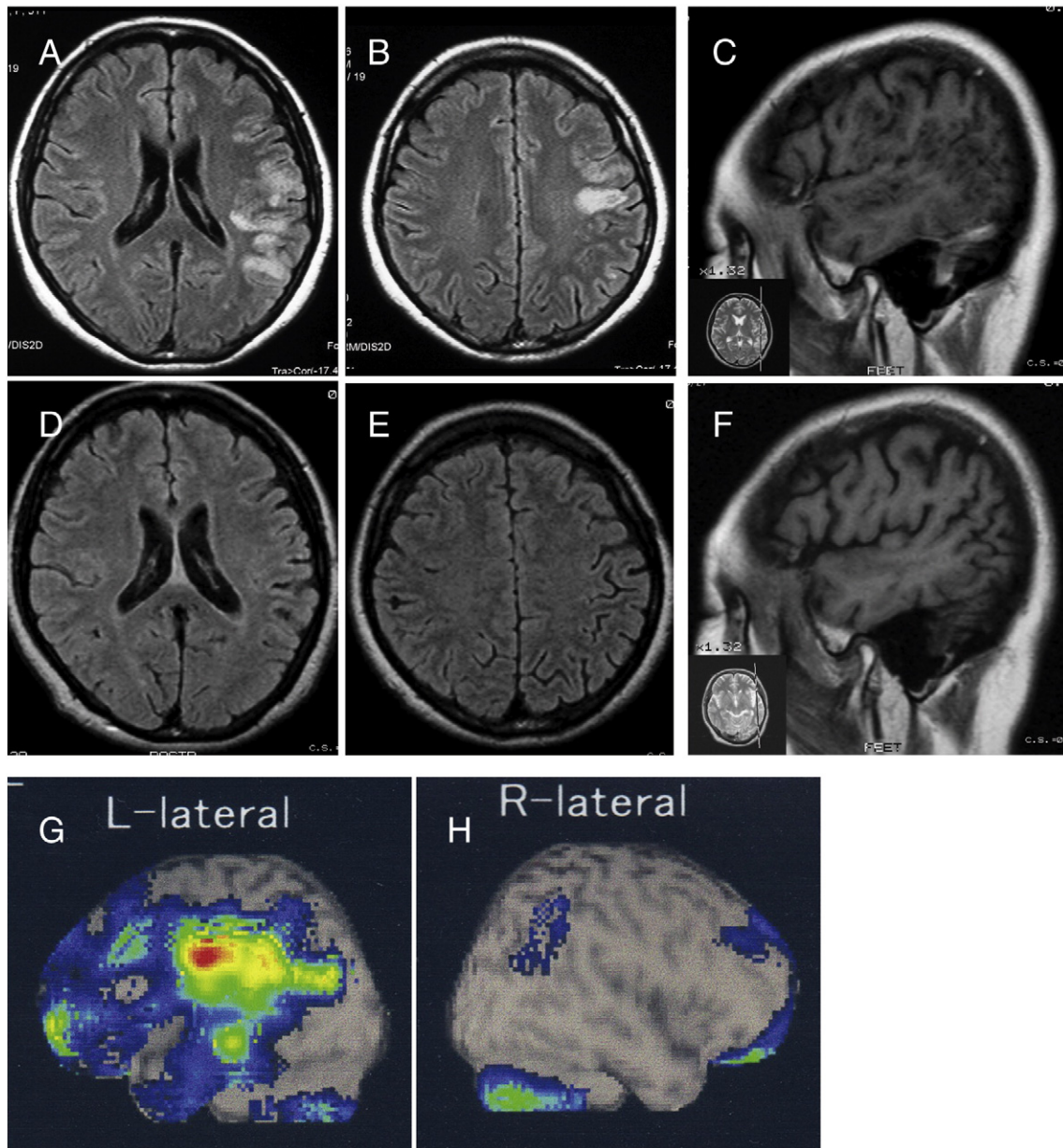
Her past medical and familial history was unremarkable. There were no preceding inciting infectious illnesses or vaccination.

General physical examination was unremarkable. She was awake and alert. There was no neck stiffness. Her speech was hesitant with word finding pauses, and she could follow only simple verbal commands. Repetition was difficult. She did not have apraxia or agnosia. There was mild weakness of the right side of her face and hand. Deep tendon reflexes were normal and no pathological reflexes were present. Visual field and sensory examination were difficult because of her poor comprehension. Coordination, posture and gait were normal. She was not incontinent of urine or stool.

Complete blood counts and routine blood chemistry were within normal range. Autoantibody screen including P-ANCA, C-ANCA, anti-nuclear antibody, anti-thymoglobulin antibody, and anti-thyroid peroxidase were all negative. The EBV anti VCA-IgG was  $\times 160$  (normal less than  $< \times 10$ ).

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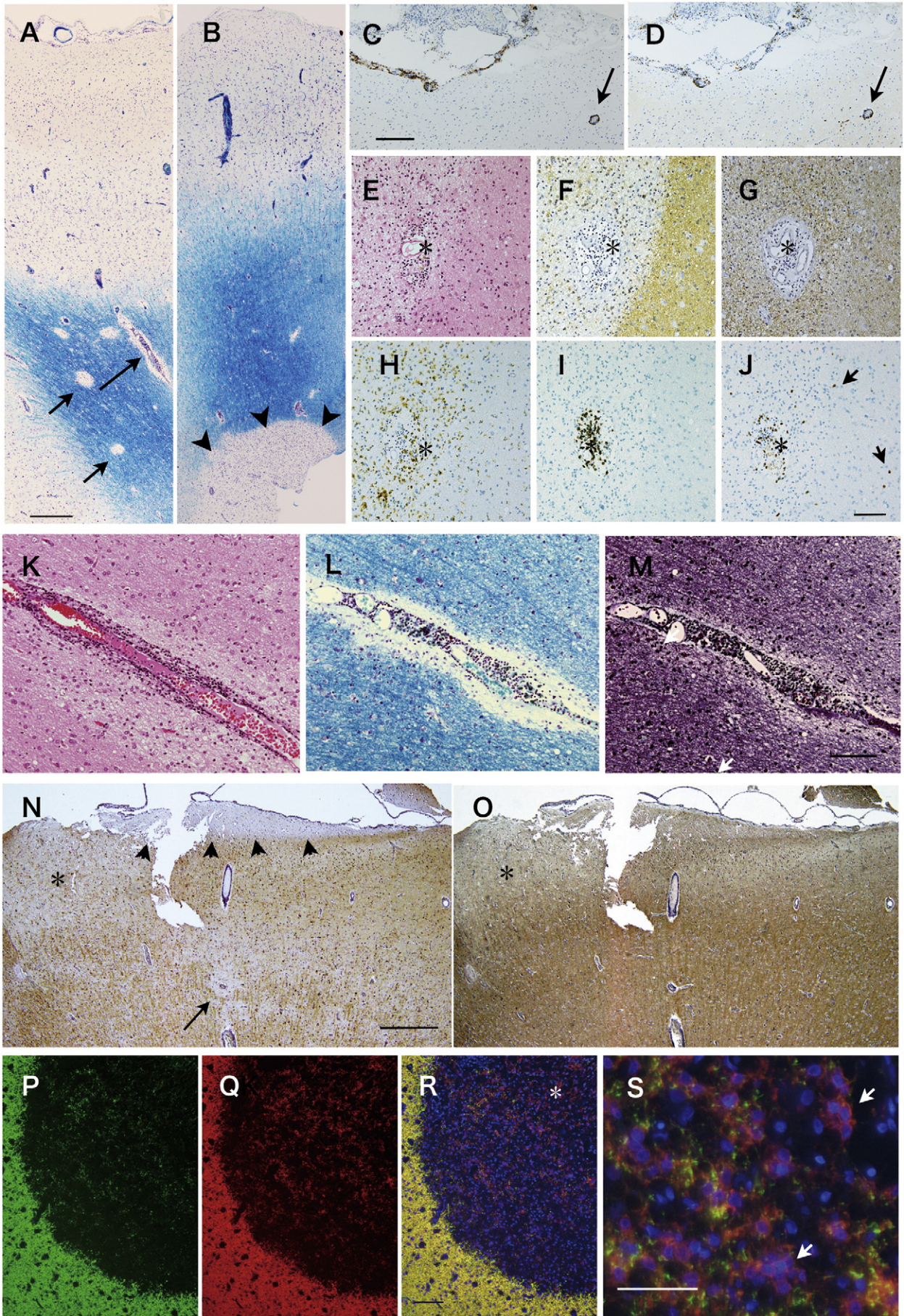
**Fig. 1.** (A–C) MRI images of the patient taken one month after the onset of the symptoms. (A, B) MRI FLAIR images show multifocal high signal intensities predominantly involving temporal and parietal subcortical white matter and overlying cortices. (C) Parasagittal section through the left temporoparietal lobe shows multiple lacuna-like low densities without enhancement. T1-weighted MRI with Gadolinium enhancement. (D–F) corresponding MRI images taken one year later. Atrophic changes were evident in the temporal and parietal cortices and underlying white matter on the left side. The lacuna-like densities on T1-weighted parasagittal MRI seen in (C) were nearly completely resolved (F). (G, H) SPECT images taken one month after the onset show hypoperfusion predominantly of the left temporoparietal lobes.

and anti VCA-IgM was  $< \times 10$ .  $\beta$ -D-Glucan and *Cryptococcus* antigen tests were negative. The serum AQP4 antibody was negative. Cerebrospinal fluid (CSF) examination revealed slight monocytic pleocytosis ( $28/\text{mm}^3$ ), slightly increased protein (46 mg/dl) and increased myelin basic protein (MBP) (1260 pg/ml; normal  $< 120$ ). There was no oligoclonal bands. CSF cytology revealed atypical lymphocytic cells.

Electroencephalogram revealed focal slow wave activities over the right frontotemporal convexities. Brain MRI revealed multifocal lesions involving subcortical white matter of the left temporal and parietal lobes (Fig. 1 A, B, C). By MRI there were confluent lesions in the periphery of the brainstem. The periventricular white matter, basal ganglia and thalamus were intact. There was no Gadolinium enhancement. Single

**Fig. 2.** Brain biopsy findings. (A, B) Kluver–Barrera myelin stain showing perivascular demyelination (arrows in A) and a confluent demyelination (arrowheads in B). (C, D) Serial sections of the leptomeninges show inflammatory cell infiltration positive for CD20 immunostain (C) and CD3 immunostain (D). Note that perivascular cuffing of a cortical vessel (arrow) is also intensely positive for both CD20 and CD3. (E–J) Hematoxylin and eosin stain and immunohistochemistry of a demyelinating plaque shown on the left side of each photograph, where the loss of CNPase activity (F) and preserved neurofilaments (G) and infiltration of macrophages/microglia (H) was evident. A vessel (asterisk) is associated with perivascular lymphocytic infiltration positive for CD20 (I), and CD3 (J). Of note, unlike CD20, CD3 positive cells are not restricted to the perivascular cuffing but they infiltrated into the parenchyma (arrowheads in (J)). (K–M) Perivascular demyelination in the subcortical white matter. Adjacent sections of the area are indicated with a long arrow in the figure. A, stained with hematoxylin–eosin (K), Kluver–Barrera (L) and Bodian stains for nerve fibers (M). (N, O) CNPase and neurofilament immunohistochemistry showing subpial demyelination. 7  $\mu\text{m}$  thick serial sections. (N) CNPase immunostain shows a well demarcated area of subpial demyelination (arrowheads), where neurofilaments are relatively well preserved (O). Arrow indicates perivascular demyelination. Note that the area indicated with \* reveals relatively decreased immunoreactivities both for CNPase and neurofilaments. (P–S) Immunofluorescence of the demyelinating plaque with MBP antibody (P), anti-CNPase antibody (Q) and merged picture (R). (S) The enlarged photograph of the area indicated with (\*). Cluster of oligodendrocytes with CNPase positive and MBP negative cytoplasm (arrows). Bar = 500  $\mu\text{m}$  for (N) and (O), 400  $\mu\text{m}$  for (A) and (B), 200  $\mu\text{m}$  for (C) and (D), 100  $\mu\text{m}$  for (E) to (M) and (P) to (R) and 50  $\mu\text{m}$  for (S).







photon emission tomography (SPECT) revealed hypoperfusion in the left temporo-parietal areas (Fig. 1G, H).

After admission, aphasia further worsened over the 2 weeks to the point of global aphasia. Right hemiparesis became evident and she began having focal motor seizures involving the face. A left temporal lobe brain biopsy was performed. She was then given intravenous methyl prednisolone (1 g for 3 days) followed by oral prednisolone taper. The patient responded remarkably both clinically and radiologically (Fig. 1D, E, F). At the time of discharge two months later, she felt herself back to her baseline except for a slight word finding difficulty. MMSE scored 30. There have been no signs of clinical and radiological recurrence during the 6 years of follow-up at the outpatient clinic.

### 3. Neuropathology

The biopsied materials consisted of two pieces 10 mm and 5 mm in length containing cortex and the underlying white matter. They were fixed in 10% formalin, dehydrated in graded alcohols and embedded in paraffin. H&E stains, stains for myelin (Kluver–Barrera) and axons (Bodian), as well as an immunohistochemistry with the following antibodies were performed. Mouse monoclonal antibodies against anti-human neurofilament (DAKO 1:200), myelin basic protein (MBP 1:150, Novocastra), the T-cell marker CD3 (1:50, DAKO), the B cell marker CD20 (1:200, DAKO), the macrophage/microglial marker CD68 (1:100, DAKO), rabbit polyclonal antibodies against CNPase (1:5000, Abcam), human immunoglobulin kappa chain and lambda chain (1:50,000, 1:100,000 respectively, DAKO), and used DAB as a chromogen. For double immunofluorescence, appropriately FITC or Cy3 labeled secondary antibodies were used (Jackson Labs) and mounted with the medium containing DAPI (Vector, Vectorshield H-1200).

The biopsied brain tissue revealed multiple demyelinating lesions in the junctional and subcortical white matter (Fig. 2). Many of them were in the form of a restricted rim of demyelination around veins with perivascular cuffing (Fig. 2A, K–M) and a few of them forming discrete and confluent demyelinating plaques (Fig. 2B, E–J). The leptomeninges revealed an inflammatory cell infiltrates, composed of CD20+ (a B cell marker) or CD3+ (T cell marker) (Fig. 2C, D). There were no ectopic B cell follicle-like structures. In the confluent demyelinating lesions, increases in the number of CD68 immunoreactive macrophages/microglia and lymphocytes were typically distributed in a perivascular pattern (Fig. 2E–J). Unlike B cells, whose appearance was restricted to perivascular cuffs, T cells were also found infiltrating in the brain parenchyma (Fig. 2J). Axonal swellings (“spheroid formation”), a feature of acute axonal injury, could be found only in the confluent foci of demyelination. On the other hand, areas of subpial and intracortical demyelination could be identified using thicker sections and sensitive immunohistochemistry (Fig. 2N, O). Unlike the confluent foci of demyelination in the white matter, subpial demyelination generally lacked an inflammatory infiltrate except for perivascular extension of leptomeningeal inflammation through Virchow–Robin spaces (Fig. 2C, D). There was no immunoreactive deposition of IgG lambda and kappa antibodies. Double immunofluorescence localization of MBP and CNPase showed clusters of oligodendrocytes immunoreactive only for CNPase, a myelin protein that has an essential role for mediating process outgrowth in oligodendrocytes [4], which were abundant in the confluent demyelinating lesions, suggestive of ongoing remyelination activities (Fig. 2P–S).

### 4. Discussion

The clinical differentiation of ADEM from the first attack of MS is an important issue, particularly given the recent development of an immunomodulatory therapy to prevent MS relapse. In our patient, the lack of altered consciousness or signs of encephalopathy may favor the

diagnosis of MS, although encephalopathy could occur in MS [5–7]. On the other hand, the absence of oligoclonal bands in CSF in acute stages and predominant involvement of the cortices and subcortical white matter without periventricular involvement may be more characteristic of ADEM [5,7–11]. Pathologically, perivenous demyelination and discrete confluent demyelination have been regarded as the hallmark of ADEM and MS respectively [3]. The brain biopsy of our patient, taken from the active lesion identified on MRI, revealed both patterns. Furthermore, the inflammatory cell infiltration of the leptomeninges consisting of T and B-lymphocytes was evident, which is very similar to those previously reported in a patient with MS with cortical demyelination and in secondary progressive MS, although B cell follicular structures as reported in the latter could not be found. Meningeal inflammation associated with cortical demyelination with a possible pathogenetic role of B cells has been recently reported in early and progressive stages of MS [12–15]. In this regard, it is noteworthy that an ADEM case with massive plasmacytosis in CSF has been reported [16]. Remarkable clinical and radiological recovery following steroid treatment in our patient suggests that the myelin sheath may have been the primary target of the immune attack, which seemed underscored by the presence of abundant reactive oligodendrocytes in the demyelinating lesions.

The present case showed large subcortical white matter lesions. A series of such intermediate cases with large demyelinating lesions with hybrid features between MS and ADEM were reported by Kepes [17] (later designated as tumefactive MS). Symptoms of tumefactive MS are generally atypical for MS and relate to the presence of focal mass lesions: focal neurological deficits, seizures, and various cortical symptoms including aphasia. Most patients with tumefactive MS respond favorably to corticosteroid therapy. The present case bears considerable clinical and radiological resemblance to tumefactive MS. Pathologically, the demyelinating lesions in tumefactive MS are indistinguishable from MS plaques [18]. In the present case, however, there was perivenular demyelinating lesions, a pathological hallmark of ADEM in addition to the confluent demyelinating foci characteristic of MS. Thus, the present case could be regarded as a clinicopathologically intermediate form of ADEM and tumefactive MS, suggesting that both disorders may share a common underlying pathogenesis of CNS demyelination. It should be noted, however, that heterogeneity of pathology of MS has recently been paid with particular attention that may reflect different underlying mechanisms of demyelination (reviewed by Lucchinetti et al. [14]).

Young et al. comparatively studied clinical features between those with and without perivenous demyelination using biopsy/autopsy materials. They found that perivenous demyelination is associated with a meningoencephalitic presentation and a monophasic course. However, among 13 patients with perivenous demyelination, three patients showed a pathologic overlap of both perivenous and confluent demyelination, two of them subsequently had relapsing attacks [3]. On the other hand, Lucchinetti et al. reported that 70% of patients with tumefactive MS developed definite MS at follow-up [18]. Therefore, despite that our patient did not relapse during the six years of clinically and radiological follow-up with brain MRI, the possibility of future relapse cannot be excluded.

The observation in the present case may have future therapeutic implications. Currently, intravenous high dose corticosteroid treatment is widely accepted as the first line of treatment of ADEM [8], although cases refractory to steroid therapy do exist [19,20]. It is possible that immunomodulatory treatments recently introduced for MS such as depletion of B cells using therapeutic monoclonal antibodies could also be useful in steroid resistant ADEM.

### Conflict of interest statement

The authors reports no conflicts of interests.

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