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LETTER TO THE EDITOR

Herpes simplex encephalitis relapse associated with positive *N*-methyl-D-aspartate receptor antibodies

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Sir,

Autoimmune encephalitis (AE) occurring following a neuroinfectious event is an uncommon event, representing a diagnostic challenge. Although NMDA-R antibodies can occur both in patients' serum and/or cerebrospinal fluid (CSF) during the course of herpes simplex virus encephalitis (HSE), their presence is not equivalent to the diagnostic of AE [1]. We present the case of *N*-methyl-D-aspartate receptor (NMDA-R) antibody-associated AE following HSE, an emerging clinical entity.

A 35-year-old male, with no previous medical history, was admitted to the emergency room for altered general status and unusual headache in the absence of fever. Neurological examination, brain magnetic resonance imaging (MRI), MR angiography, blood work-up, and electroencephalogram were normal. He was discharged with symptomatic treatment. At day 4, he was readmitted with altered consciousness, fever, aphasia, irritability, and aggressivity. A second cerebral MRI showed a left infiltrative temporal lesion upon axial fluid-attenuated inversion recovery sequences, without contrast enhancement (Fig. 1a). Polymerase chain reaction (PCR) on the CSF was positive for HSV. The patient was put on acyclovir (3 × 10 mg/kg/day). At day 24, HSV-PCR on CSF was negative. Brain MRI showed a very large lesion of the left temporal lobe, and T1-weighted sequence with gadolinium showed surrounding vasogenic edema and contrast enhancement (Fig. 1b). At day 26, the patient developed headache, confusion, and worsening-aphasia. The same day CSF analysis showed again pleocytosis, increased protein content and PCR for HSV was again positive. A second 10-day course of acyclovir was, therefore, administered in association with intravenous methylprednisolone at the dose of 1 g/day for 5 days. Brain MRI did not show any change at day 33. Retrospectively, 1 month later, NMDA-R antibodies were found positive in the CSF, but not in the serum. No onconeural antibodies or antibodies against other specific synaptic surface proteins were detected. A full oncological check-up was made including PET scan and was negative. At month 3, the patient was oriented again; his aphasia had improved as well as his behavior. 3 weeks later, his behavior deteriorated and confusion increased. The next day, he was readmitted for recurrent generalized seizures, despite the first-line anti-epileptic treatment. The lumbar puncture showed no sign of HSV reactivation, but NMDA-R antibodies were still detectable. The diagnosis of relapsing AE was suspected and methylprednisolone was administered as well as five rounds of plasmapheresis. The temporal lobe lesion was stable on brain MRI and there was regression of contrast enhancement (Fig. 1c). To consolidate the remission of AE, a treatment by cyclophosphamide was chosen (600 mg/m^2/month for 6 months), as rituximab was not available. 10 months after the initial episode, the patient was able to return home, but he still presented memory deficits and behavioral trouble. Brain MRI at 10 months showed an extension of white matter and cortical damage, without contrast enhancement (Fig. 1d).

HSE can still be fatal even if its prognosis has improved since the availability of acyclovir [2]. In 2012, Pruss et al. suggested that some clinical features of HSE might be related to a secondary autoimmune phenomenon related to the presence of NMDA-R antibodies and that patients might benefit from immunotherapy [1]. A prospective study on post-HSV AE suggested that children presented more frequently with choreoathetosis and altered consciousness resulting in shorter time to diagnosis and treatment in

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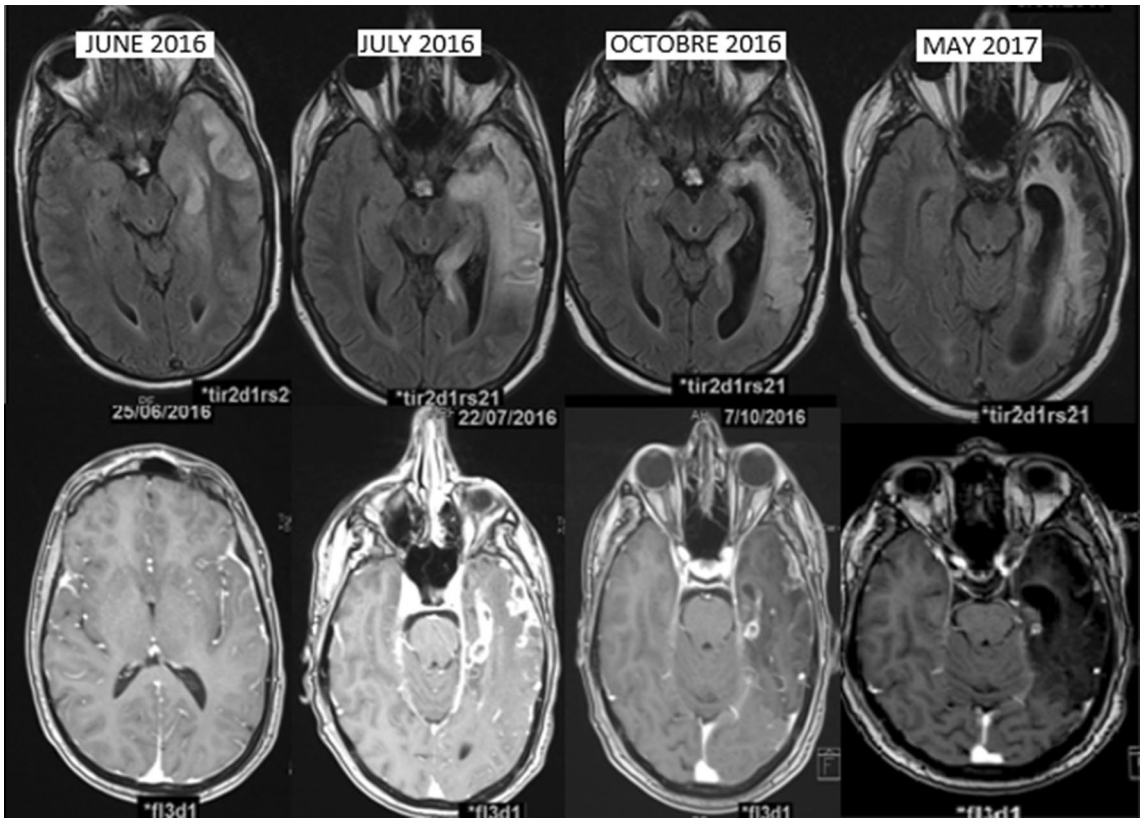

Fig. 1 Brain MRI evolution. **a** June 2016. Proven HSV type 1 encephalitis. (FLAIR) (upper panel) image showing a left temporal lesion, with no contrast enhancement (axial T1-weighted image with gadolinium (Gd) in the lower panel). **b** July 2016, 3 days before the recurrence of HSE, following the first course of Acyclovir treatment: FLAIR image shows an increase in size of the left temporal infiltrative lesion (upper panel); T1-weighted sequence with Gd shows surrounding vasogenic edema and contrast enhancement (lower panel). **c** October 2016. Stability of the temporal lesion on axial FLAIR imaging (upper panel), and regression of contrast enhancement on T1-weighted image with Gd (lower panel). **d** May 2017. Following the 6th cyclophosphamide administration, extensive white matter and cortical damage on axial FLAIR sequence (upper panel) without contrast enhancement on T1-weighted image with Gd (lower panel)

comparison to adults and teenagers [3]. It was observed that patients presenting NMDA-R antibodies during the course of HSE are less likely to be immunocompromised; they tend to have longer intervals between the first prodromal signs and clinical admission and that relapsing symptoms do not respond to acyclovir but to immunotherapy [1, 4, 5]. There is currently no way to predict which patients are at risk of developing post-HSV AE. In patients with anti-NMDA-R antibodies, it remains difficult to determine whether symptomatic worsening post-HSE is due to antibody-mediated AE or whether it is attributed to fluctuations in residual deficits. In our case, positivity of anti-NMDA-R antibodies was already present at the time of HSE reactivation and remained positive afterwards. Careful clinical evaluation, complemented by imaging and CSF analysis (including PCR and antibody testing), remains crucial to decide whether to initiate or not immunotherapy in this setting. Further studies are necessary to guide professionals in the choice of the timing, duration, and nature of prolonged and sometimes aggressive immunotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The patient informed consent has been obtained.

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