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Anti-*N*-methyl-D-aspartate receptor encephalitis and Epstein-Barr virus: another tale on autoimmunity?

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Anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is characterized by psychiatric symptoms, movement disorders, autonomic dysfunction, seizures and abnormal level of consciousness [1]. It can be triggered by tumors or viral infections such as Herpes simplex virus-1(HSV-1) and Varicella zoster virus (VZV) encephalitis [2–4].

Anti-neuronal antibodies and herpes virus may coexist as 27–30% of patients with HSV-1 encephalitis harbor anti-neuronal antibodies [3,5]. Herein, we describe a patient with symptoms compatible with Epstein-Barr virus (EBV) primary infection who developed anti-NMDARE and positive cerebrospinal fluid (CSF) EBV-polymerase chain reaction (PCR).

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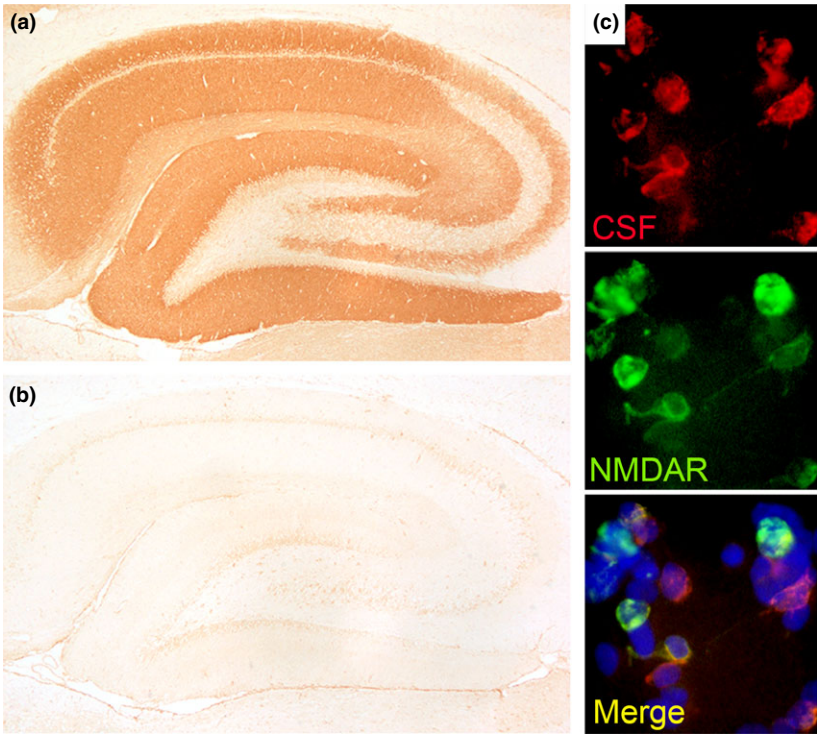

Figure 1 Detection of anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies in cerebrospinal fluid (CSF). Anti-neuronal surface antibody testing was performed with a tissue-based (in-house; avidin-biotin-peroxidase technique; rat brain) and a cell-based (in-house) assay. Tissue-based assay of the patient's CSF shows a strong neuropil staining of the hippocampus (a), whereas CSF of a healthy control is negative (b). (c) Cell-based assay: the patient's CSF strongly labels HEK293T cells transfected with the NR1 + NR2b NMDAR subunit (red, patient's CSF; green, commercial antibody to NMDAR; yellow, merge). Magnification: a and b, ×40; c, ×400.

Case report

A previously healthy 6-year-old boy presented with odynophagia, fever, headache and received antibiotics for suspected tonsillitis. After 2 weeks he developed irritability and agitation. Over the course of 2 days he presented seizures and decreased level of consciousness.

Neurological examination revealed somnolence, orofacial dyskinesia and choreoathetosis. Laboratory results showed normal leucocyte count without atypical lymphocytes, aspartate aminotransferase of 267, alanine transaminase of 290 and erythrocyte sedimentation rate of 69. Brain magnetic resonance imaging was normal and electroencephalography showed diffuse slow waves. CSF revealed 115 cells/mm^3, glucose 67 mg/dL, protein 82 mg/day and positive EBV-PCR.

The patient presented worsening of involuntary movements, dysautonomia and coma. CSF 5 days later showed 45 cells/mm^3 and negative EBV-PCR. Anti-*N*-methyl-D-aspartate receptor antibodies were detected in CSF (1:256) and serum (1:1600) (Fig. 1). After 3 weeks of symptoms, serum EBV IgG was positive and IgM was negative. Whole-body computed tomography scan and testicular ultrasound were normal.

The patient was started on steroids and intravenous immunoglobulin (IVIG) with partial improvement. He was switched to rituximab due to poor control of choreoathethosis and persistent

drowsiness. After 3 months, CSF EBV-PCR was negative and anti-*N*-methyl-D-aspartate receptor antibodies were 1:64. He presented full recovery after 5 months.

Discussion

Approximately 70% of patients with anti-NMDARE present prodromal symptoms such as fever, diarrhea or upper respiratory symptoms [2]; nonetheless, systemic infections were not clearly associated with autoimmune encephalitis (AIE). The most interesting finding of this report is the occurrence of anti-NMDARE 2 weeks after probable primary EBV infection. Although serum EBV IgM was negative, the patient presented the typical clinical picture and positive CSF EBV-PCR. Neurological symptoms evolved slowly in the recovering phase of the systemic illness, suggesting an immunological process rather than infectious encephalitis.

Viral neuroinfections are known triggers for AIE [3,4]. It is believed that virus-mediated cerebral tissue damage may lead to central nervous system antigen release that triggers the development of anti-neuronal antibodies [5]. Nonetheless, positive EBV-PCR has been reported in patients with anti-NMDARE without previous history of infectious (necrotizing) encephalitis [3]. The significance of this positivity remains uncertain, and may reflect a reactivation or shedding of viral DNA during the AIE [3]. Alternatively, EBV molecular mimicry or latently infected (autoreactive) B cells may initiate or contribute to a post-infectious autoimmune response after primary EBV infection [6]. Another possibility is that the EBV might have resulted in disruption of the blood–brain barrier that contributed to the development of AIE.

The clinical course of our patient, including normal magnetic resonance imaging, suggests that the anti-NMDARE resulted from a post-infectious autoimmune response. As EBV infection can mimic AIE (encephalitis, cerebellitis) and may also contribute to the development of autoimmunity, we suggest that patients with EBV neurological manifestation should be evaluated for anti-NMDARE in the appropriate clinical picture.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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