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Anti-N-methyl-D-aspartate receptor encephalitis associated with acute Epstein–Barr virus infection: A case report

Xiang-Dong Zeng *MM*, Wen-Guang Hu *MM*

Department of Pediatric Neurology, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Abstract

Epstein-Barr virus (EBV) infection is associated with some autoimmune diseases. We report here a 32 months old girl with fever, isthmitis, lymphadenectasis, and excessive atypical lymphocytes, who developed seizures, personality and behavior changes, with positive anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibody and EBV-early antigen (EA)-IgG antibody in cerebrospinal fluid (CSF), which suggested the possibility that the acute EBV infection have triggered the anti-NMDAR encephalitis, which has not been reported previously.

Keywords: Anti-NMDA receptor encephalitis; Epstein-Barr virus infection; Children.

INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was first described in a young woman with ovarian teratoma, and was later also found to be associated with thymomas and other tumors. However, in the pediatric population, the condition is more commonly diagnosed in the absence of tumors.[1] Epstein-Barr virus (EBV) infection is associated with some autoimmune diseases.[3,4] We describe here the clinical course and management of a pediatric case with anti-N-NMDA receptor encephalitis induced by acute EBV infection.

CASE REPORT

A 32-month-old female child was admitted to our hospital with fever, accompanied by pharyngeal pain and a lump in the neck. Physical examination upon admission was normal except for the bilateral grade II tonsil with visible white exudate and a lymph node of about 1 cm × 1.5 cm was palpable in the left neck. The complete blood cell count test showed all components to be within normal range, with the exception of increased atypical lymphocytes (10%). Serological testing for pathogens showed positive EBV-capsid antigen (CA)-IgM antibody and negative EBV- CA-immunoglobulin (Ig)G antibody. Chest x-ray and abdominal ultrasonography examinations were normal. We made the diagnosis of infectious mononucleosis, and started her with acyclovir (10 mg/kg once every 8 hour).

During the hospitalization, she had repeated seizures, and progressed to behavior changes of agitation, irritability, aggressive behavior, and involuntary movements. Repeat serum test for EBV- CA-IgG was positive and that for EBV-CA-IgM became negative. Cerebral spinal fluid (CSF) analysis showed 12 × 10^6/L lymphocytes (reference value: < 15 × 10^6/L), normal glucose and protein levels. CSF investigations for pathogens (HSV, cytomegalovirus, and Japanese encephalitis virus) were negative. CSF EBV-early antigen (EA)-IgG, EBV-EA-IgA and EBV-CA-IgA antibodies were positive. CSF polymerase chain reaction was negative for EBV. Anti-NMDA receptor antibody (1:10 titer) was positive in the CSF (Figure 1). Video electroencephalography (VEEG) demonstrated 2-3 Hz δ-slow wave in bilateral occipital area and spike waves in bilateral occipital area (Figure 2A-C). Cranial magnetic resonance imaging (MRI) scan showed no abnormality. She was diagnosed with anti-NMDA receptor encephalitis associated with acute EBV infection, and was subsequently treated with IVIG (2 g/kg over 2 days) and glucocorticoid (intravenous injection of methylprednisolone at 20 mg/kg/d × 5 days, followed by oral prednisone at 2 mg/kg/d with tapering decrease in dose). The acyclovir treatment was continued for 2 weeks.

Address correspondence to: Xiang-Dong Zeng, Department of Pediatric Neurology, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, No. 1617, Riyue Avenue, Chengdu 611731, China. Tel: +86-18080861285, +86-02861866046. E-mail: zengxiangdong333@163.com

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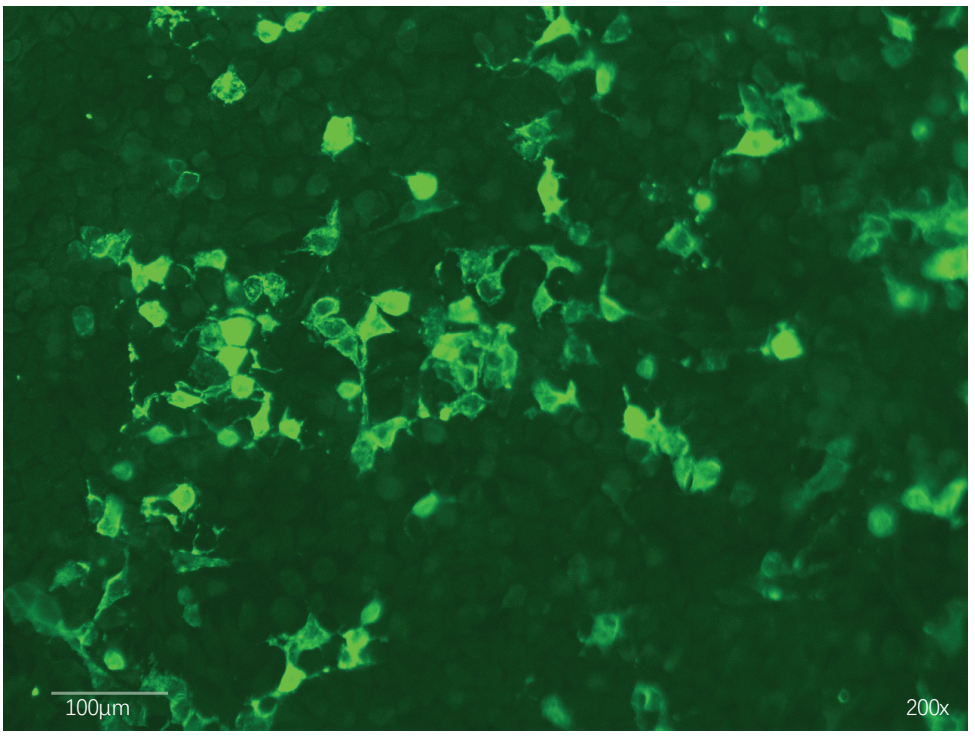


Figure 1. Cell transfection assay detected anti-NMDA receptor-IgG (green) in the patient's cerebral spinal fluid. Ig: Immunoglobulin; NMDA: N-methyl-D-aspartate.

A

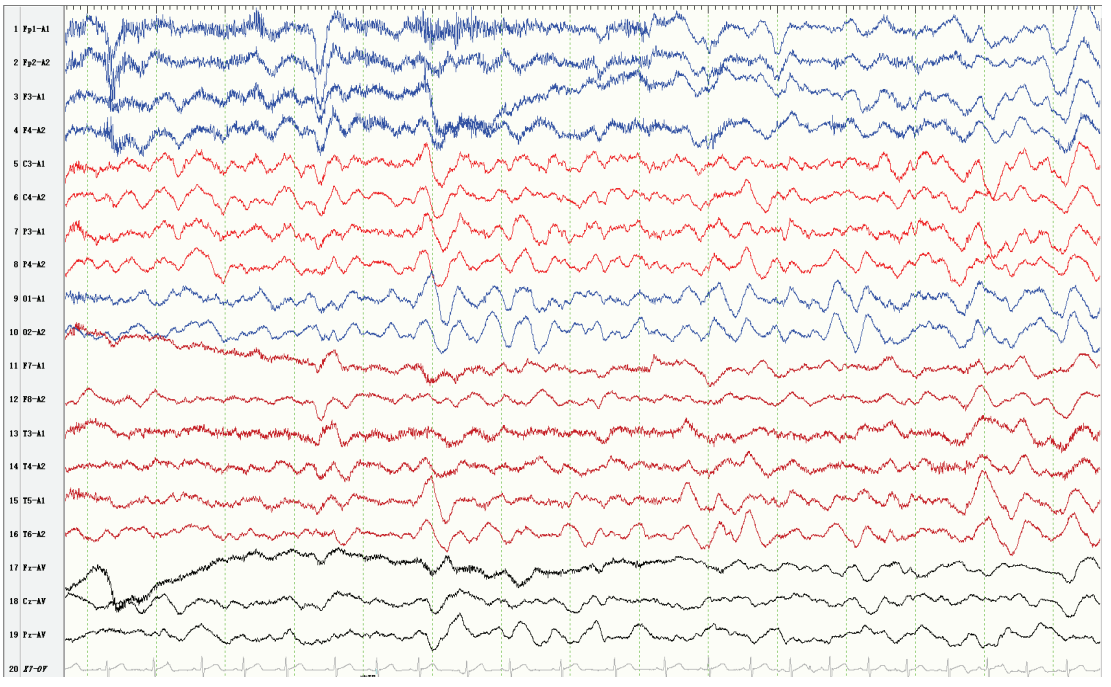
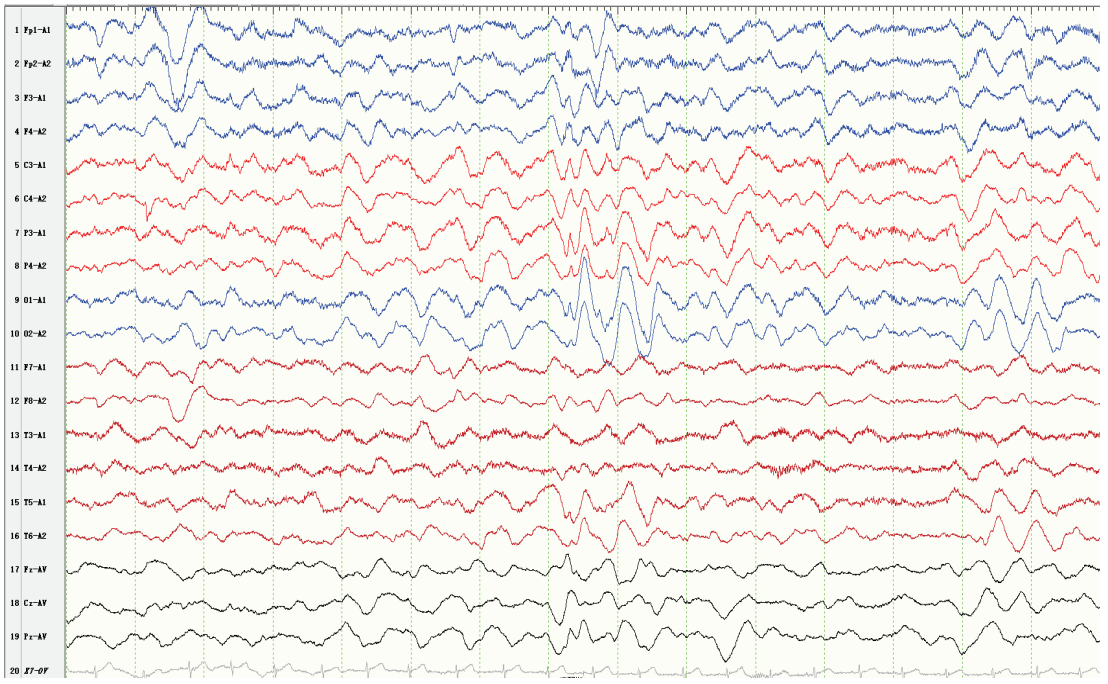


Figure 2. Video electroencephalography findings. A-F: At the initial presentation of the disease (A-C) and 2 mo later (D-F), 2-3 Hz δ-slow wave activity was found in the bilateral occipital area (A, D) and sharp-and-slow wave complex in the bilateral occipital and parietal area (B, C, E, F); (G) At 6 mo later, 3-4 Hz slow wave activity was found in the bilateral occipital, parietal and posterior temporal area.

B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9 O1-A1
10 O2-A2
11 F7-A1
12 F8-A2
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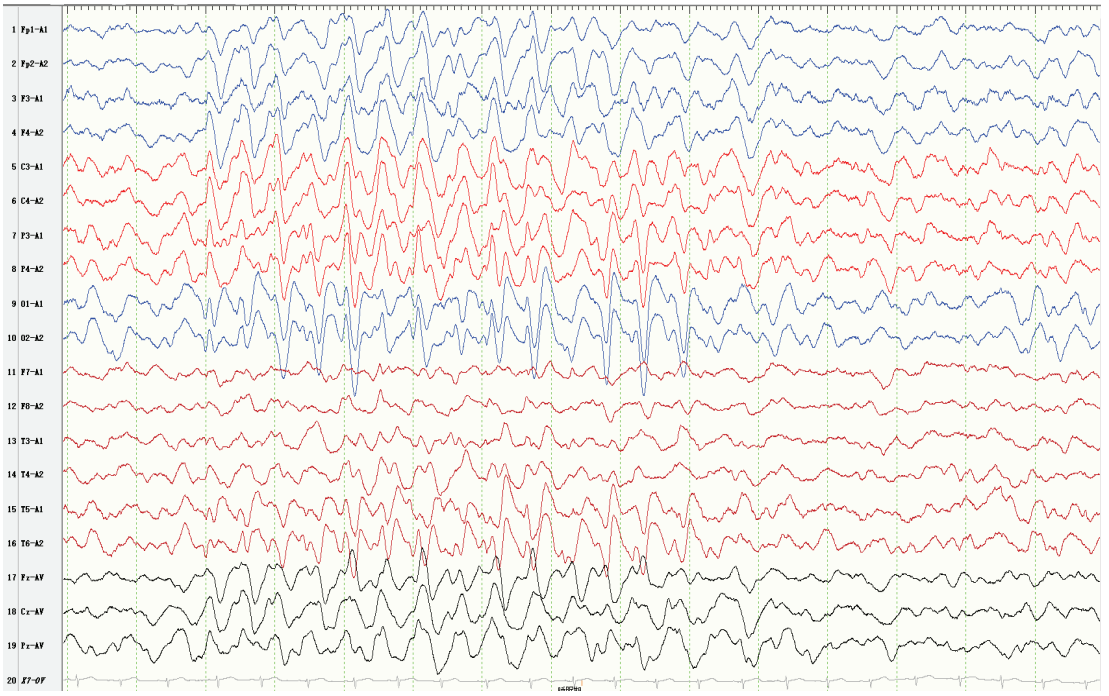
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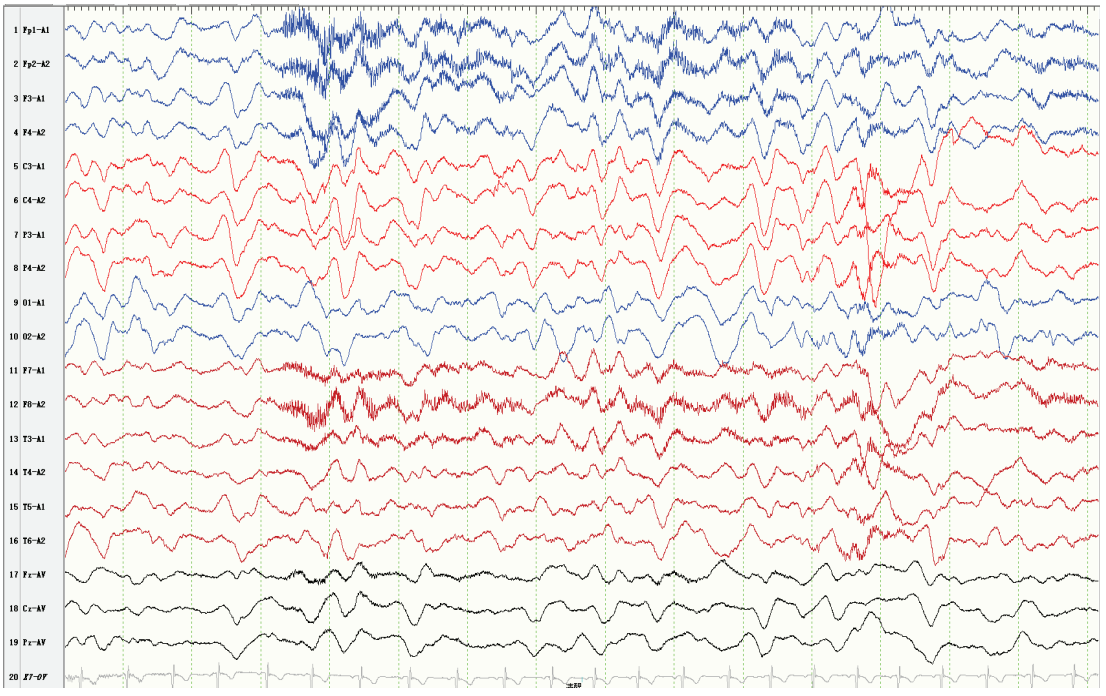
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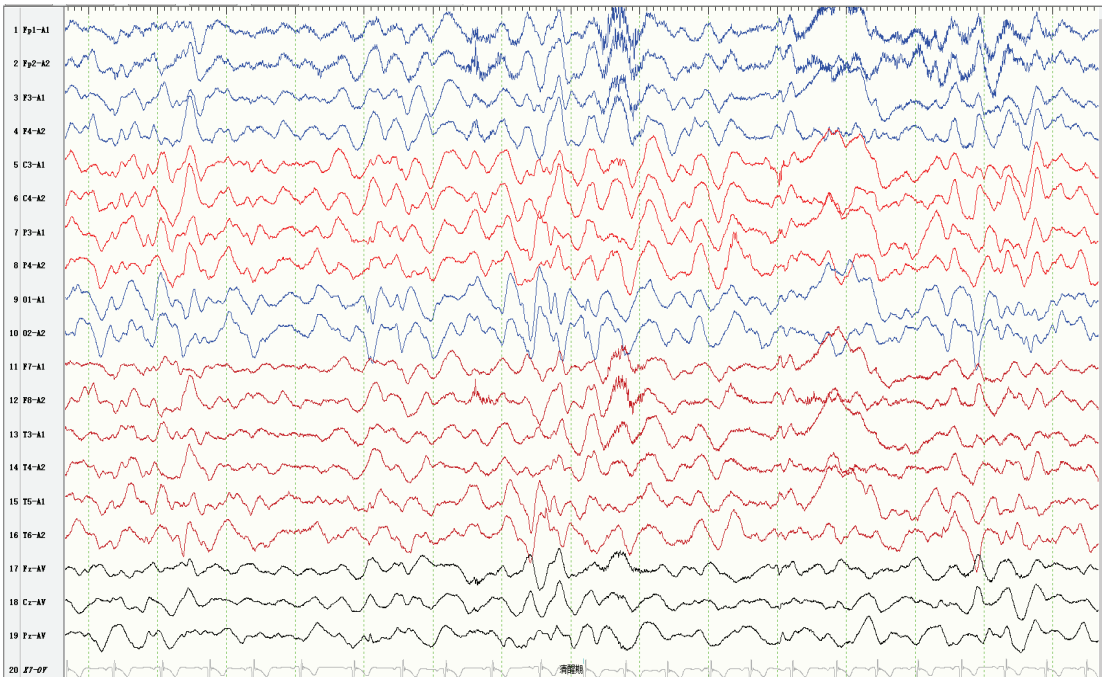
E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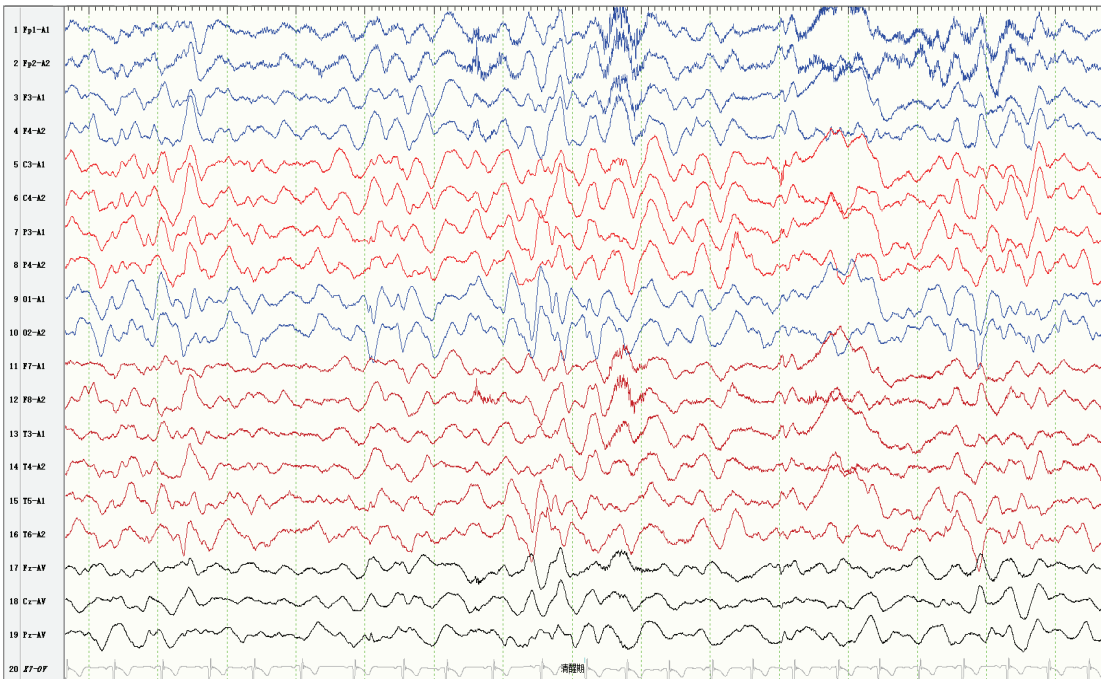
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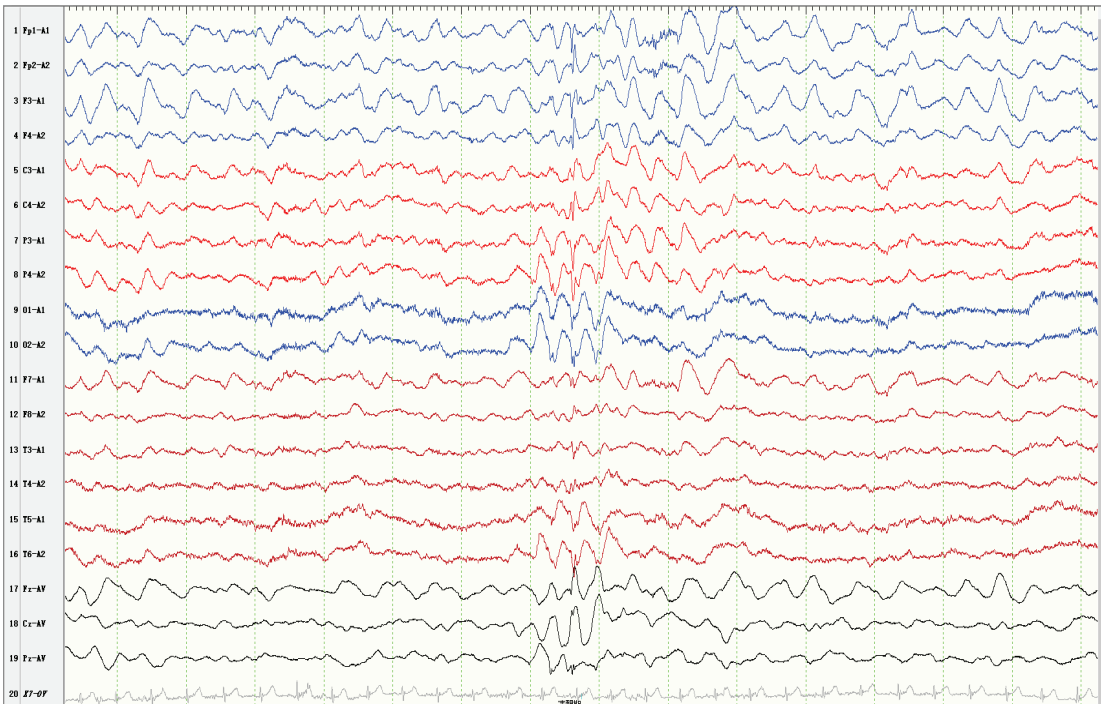
G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18 Cz-AV
19 Pz-AV
20 X7-OF

Oxcarbazepine was given to treat the seizures. She showed substantial improvement and was discharged home.

At 2 months after discharge, she developed dyskinesia manifesting as right leg stiffness and unwillingness to walk and stand, speech impairment manifesting as exclusive use of simple words and sleep disorder. She was readmitted and the physical examination revealed decreased muscle strength of the right lower limbs (*i.e.* left limbs and right upper limb V, right lower limb III) and positive right ankle clonus. Repeat CSF showed increased anti-NMDA receptor antibody titer (1:32). Repeat MRIs showed normal brain and spinal cord. Repeat VEEG showed no significant change from the previous findings (Figure 2D-F). She was treated with rituximab at 375 mg/m^2 once a week for 4 weeks. After rituximab treatment, the patient was followed up for 2 months. At the last follow up 6 months since the onset of the neurological symptom, , she was clinically normal, with repeat VEEG showed only localized slow waves (Figure 2G). The CSF anti-NMDA receptor antibody titer is now (1:3.2), decreased from a peak of (1:32) four months ago.

DISCUSSION

Previous studies have suggested that anti-NMDA receptor encephalitis might be associated with postinfectious immune response.[1,4] It has also been reported that this disease can be associated with acute HSV, mycoplasma, influenza infections, and vaccines.[5-8] EBV infection is also associated with some autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis.[2,9] In our case, the clinical manifestations and laboratory results supported the diagnoses of anti-NMDA receptor encephalitis associated with acute EBV infection. EBV encephalitis is unlikely here because the patient's CSF leukocyte count, glucose and protein levels were near to normal, EBV-PCR of CSF was negative, and cranial MRI studies were normal. We found anti-NMDA receptor antibody and EBV-EA-IgG antibody positivity in CSF, which suggested the possibility that EBV infection may have triggered the anti-NMDA receptor encephalitis. The possible mechanism may involve the virus infection having damaged the blood–brain barrier, invaded the central nervous system, destroyed the neurons, and then initiated a primary autoimmune response against the NMDA receptor by presenting tissue which is normally shielded from systemic immunity.[8] Future research should clarify the possible association between anti-NMDA receptor encephalitis and acute EBV infection through clinical trials. Results from such studies may clarify the potential benefit of immunotherapy combined with antiviral therapy to patients with anti-NMDA receptor encephalitis that is provoked by viral infection.

DISCLOSURE

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Conflict of Interest: None

REFERENCES

1. Ryan N. Anti-N-methyl-D-aspartate receptor-mediated encephalitis: recent advances in diagnosis and treatment in children. *Curr Probl Pediatr Adolesc Health Care* 2016;46:58-61.
2. Laurence M, Benito-León J. Epstein-Barr virus and multiple sclerosis: updating Pender's hypothesis. *Mult Scler Relat Disord* 2017;16:8-14.
3. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. *Clin Dev Immunol* 2013;2013:535738.
4. Armangue T, Titulaer MJ, Málaga I, *et al*. Pediatric anti-N-methyl-D-aspartate receptor encephalitis clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162:850-6.
5. Wang H. Anti-NMDA receptor encephalitis and vaccination. *Int J Mol Sci* 2017;18:193-202.
6. Baltagi S, Shoykhet M, Felmet K, Kochanek PM, Bell MJ. Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. *Ped Crit Car Med* 2010;11:179-84.
7. Gable SM, Gavali S, Radner A, *et al*. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis* 2009;28:1421-9.
8. Pruss H, Finke C, Holtje M, *et al*. N-Methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012;16:902-11.
9. Blaschke S, Schwarz G, Moneke D, Binder L, Mller G, Reuss-Borst M. Epstein-Barr virus infection in peripheral blood mononuclear cells, synovial fluid cells, andsynovial membranes of patients with rheumatoid arthritis. *J Rheumatol* 2000;27:866-73.