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Letter to the Editor

Adult-onset Rasmussen's encephalitis with persistent infection of herpes simplex virus

Dear Editor,

Rasmussen's encephalitis (RE) is a chronic progressive inflammatory refractory disease that usually begins in childhood. It manifests as epilepsia partialis continua and finally results in unilateral paralysis and cognitive disturbance. Whether autoimmunity causes RE or not remains controversial; some studies have reported that RE may be caused by autoantibodies such as GluR3, alpha-7 nicotinic acetylcholine receptor, and Munc18-1 [1–3]. Here we report a case of adult-onset RE, with elevated levels of cerebrospinal fluid (CSF) anti-*N*-methyl-D-aspartic acid (NMDA) receptor antibodies and serum herpes simplex virus (HSV)-IgM, successfully treated with steroid administration.

A 42-years old Japanese man with no prior medical history, initially experienced right hand numbness 14 months before admission. Gradually, he began having difficulty with movement of his right hand, walking, and recalling words. Eleven months before admission, he became depressed and quick-tempered. Nine months prior to being admitted, he reported occasional loss of consciousness. Three months before being admitted, he could not walk and was restricted to a wheelchair. Subsequently, he was admitted to our hospital for dexterity movement disorders, gait disturbance, mental disorder, and cognitive dysfunction. His Mini-Mental State Examination score (MMSE) was 23 points and Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Full scale IQ (FIQ) was 56 points.

Brain Magnetic Resonance Imaging (MRI) on admission revealed high T2/FLAIR signal intensity of the white matter of the left parietal lobe, these lesions were not enhanced by gadolinium DTPA. The surrounding cortical area had atrophied, but did not showed high T2/FLAIR signal intensity. (Fig. 1).

White matter of the left parietal lobe showing high FLAIR signal intensity. These lesions were not enhanced by gadolinium DTPA. The surrounding cortical area is atrophied, but does not show high T2/FLAIR signal intensity.

SPECT showed decreased flow which corresponded with the left parietal atrophied brain on the MRI. Serum autoimmune antibodies such as anti-nuclear antibody, anti-double stranded antibody, anti-SS-A, B antibody, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibody, and anti-neutrophil cytoplasmic antibody were negative. Serum HSV-IgG and HSV-IgM levels were elevated. CSF analysis showed normal cell counts of 2/μl, and elevated protein level of 98 mg/dl. CSF HSV-IgG level was elevated, but CSF HSV-IgM was not detected. CSF anti-NMDA receptor (GluN2B-NT, GluN2B-CT, GluN1-NT, GluD2-NT) antibodies detected by ELISA were positive.

Although the patient's electroencephalogram was normal, he presented with progressive unilateral cortical deficits and unihemispheric focal cortical atrophy. He fulfilled the part B criteria of RE proposed by Bien [4]; therefore, he was diagnosed as RE. Intravenous methylprednisolone (1000 mg/day for 4 days) was administered and followed with oral PSL (50 mg/day) tapering off gradually. One month later, he was able to move his hands, and walk.

Discussion

This case involving a 42-year-old patient having satisfied the criteria of RE is considered to be one of the adult-onset RE cases with the oldest reported patient. While he responded to corticosteroid therapy and his symptoms mitigated, elevated serum HSV-IgG and HSV IgM titer persisted for over 6 months from admission. It has been reported that compared to childhood-onset RE, the clinical course of adult-onset RE is slower and the symptoms are milder. Adult-onset RE shows good response to immunomodulatory treatment. However, there are many cases that resisted various immunomodulatory treatments such as corticosteroids, intravenous immunoglobulins, tacrolimus, azathioprine, and plasmapheresis [5–8]. The natural clinical course of RE is divided into 3 stages: the first stage is the prodromal stage with infrequent seizures; the second, is the acute stage with frequent drug-resistant seizures; the third, is the stable residual stage with fixed neurological deficit [9]. In comparison with previously reported RE cases showing immune resistance, the duration of the prodromal and acute stage in this case was only one year and remarkably shorter. Intravenous methylprednisolone administration was effective partially because immunotherapy was carried out in the relatively early stage of RE.

Though cytotoxic T lymphocytes are considered to play a major part in the pathogenesis of RE, the detailed mechanisms are unknown.

Herpes simplex virus along with Epstein-Barr and cytomegalovirus were detected in the patient's brain tissue, and various autoimmune antibodies including anti-NMDA receptor antibodies were produced. HSV itself does not have cross antigenicity. It is considered that chronic central nervous system inflammation is triggered by viral infection, and various autoimmune antibodies are induced that cause RE.

In some patients with HSV encephalitis, while the symptoms disappeared, the neurological signs had worsened a few months later. These cases with relapsed encephalitis had partially presented positive anti-NMDA receptor antibodies.

These patients showed persistent elevation of CSF T-helper-1 (chemokine [C-X-C motif] ligand 9 [CXCL 9], CXCL 10), and B cell (CXCL 13, CCL 19, a proliferation-inducing ligand [APRIL])-mediated cyto-/chemokines, and interferon-α. A chronic post-HSV encephalitis patient who relapsed showed persistent elevation of CSF CXCL9, CXCL10, and interferon-α [10].

As CSF HSV-DNA PCR was negative, no active HSV infection was found in our patient. However, serum HSV-IgM persisted to be positive for over 6 months. Long-standing non-viral autoimmune inflammation associated with anti-NMDA receptor antibodies could be induced by persistent HSV infection and finally result in RE.

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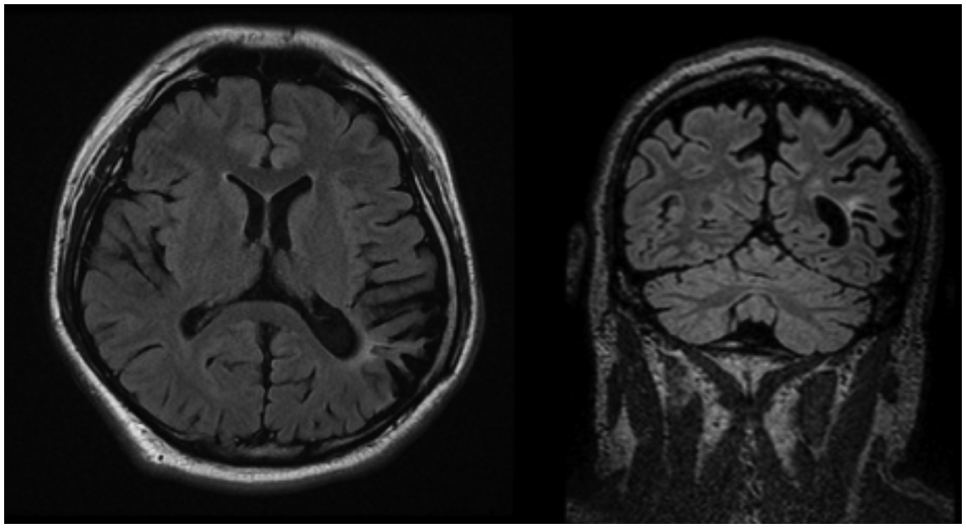

Fig. 1. Magnetic Resonance Imaging (axial and coronal view).

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Declaration of Competing Interest

None.

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