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CASE REPORT

Limbic encephalitis associated with systemic lupus erythematosus

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A 34-year-old woman with systemic lupus erythematosus (SLE) presented with general fatigue, seizures and memory loss. Magnetic resonance imaging of the brain showed a high signal area in the mesial temporal lobe bilaterally. Computed tomography scan of the chest and abdomen and ultrasound of pelvis detected no malignancy and tumour marker, antibodies to antineuronal antibodies (anti-Hu, anti-Ta and anti-Ma) and antibodies to voltage-gated potassium channels were all negative. The present case is limbic encephalitis (LE) associated with SLE and the pathogenesis may include autoimmunity shared. Our experience indicates that the immunologic spectrum of LE will expand to include additional immune mechanisms. *Lupus* (2009) **18**, 1316–1319.

Key words: limbic encephalitis; magnetic resonance imaging; systemic lupus erythematosus; voltage-gated potassium channel antibody

Introduction

Limbic encephalitis (LE) associated with malignancy was first described in 1968.¹ Subsequently, cases of LE associated with herpes simplex virus (HSV) infection² and heterogenous non-herpetic disorders such as non-herpetic viruses, Hashimoto's encephalopathy, central nervous system (CNS) lupus, Sjögren disease, relapsing polychondritis and paraneoplastic conditions have been reported.^{3–10} LE is clinically characterised by cognitive dysfunction including memory impairment, seizures and psychiatric features such as depression, anxiety and hallucinations.¹ The typical lesion on magnetic resonance imaging (MRI) is selective involvement of the limbic system, particularly the mesial temporal lobe. We report LE associated with systemic lupus erythematosus (SLE) that was successfully treated with steroids.

Case report

A 34-year-old woman presented with gradually worsening headaches, general fatigue, complex

partial seizure and memory impairment. Her medical history included a 3-year history of photosensitivity. She began behaving inappropriately at home and could not recall her trip to Spain 10 days before admission. Neurological examination at local hospital was normal, as were brain computed tomography (CT) and laboratory data. Three days after the onset of symptoms, the patient was transferred to our hospital for further assessment.

On physical examination, she had a low grade fever and butterfly rash on the face. Cognitive assessment showed disorientation in time, place and her age. There was severe anterograde and retrograde amnesia, extending for at least 10 years. Mini-Mental State Examination (MMSE) score was 20 points. Other findings of cognitive and neurologic examinations, including praxis and verbal output and understanding, were normal. T2-weighted, fluid-attenuated inversion recovery and diffusion-weighted MR images (apparent diffusion coefficient = $0.31 \times 10^{-3} \text{ mm}^2/\text{s}$) showed an area of increased signal intensity in the mesial temporal lobe bilaterally (Figure 1), which did not enhance after gadolinium administration. MR angiogram was normal. Electroencephalogram demonstrated bilateral temporal lobe epileptic activity. Laboratory studies showed antinuclear antibodies >1 : 160 with a homogenous pattern, and decreased complement levels (C3 = 77 mg/dl, C4 = 15 mg/dl).

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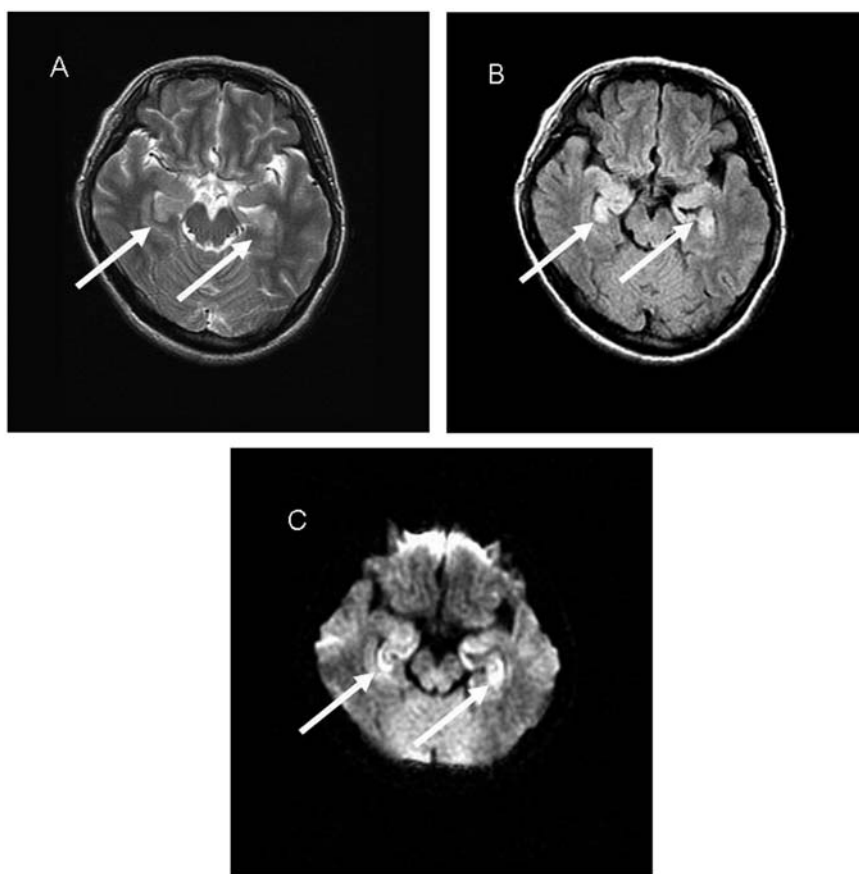


Figure 1 T2-weighted (A), fluid-attenuated inversion recovery (B) and diffusion-weighted (C) magnetic resonance images at midbrain level, obtained 3 days after the onset of symptoms, showed symmetric areas of increased signals in the bilateral mesial temporal lobe (arrows), which includes hippocampus and amygdala. Amnesic syndrome is usually secondary to bilateral lesions of the hippocampus and amygdala.

Anti-Sm, anti-RNP and anti-ribosomal-P antibodies were detected with high titres, but anti-ds DNA and anti-SSA and anti-SSB were negative. These results fulfilled the American College of Rheumatology revised criteria for the classification of SLE.¹¹ SLE disease activity was determined using systemic lupus erythematosus activity index (SLEDAI),¹² and the score was 21.

Cerebrospinal fluid (CSF) revealed 20 white cells/mm³ (predominantly lymphocytes), normal protein (36 mg/dl) and normal glucose (71 mg/dl). HSV, human herpes virus 6 (HHV-6), mumps virus, varicella-zoster virus and cytomegalovirus were not detected in serum and CSF by polymerase chain reaction. CSF on admission and that taken 2 weeks later were both negative for increased IgM and IgG antibody titres for HSV and HHV-6. CT scan of the chest and abdomen and ultrasound of pelvis detected no malignancy. Tumour marker (α -fetoprotein, carcinoembryonic antigen, Ca125,

Ca153, Ca199), anti-neuronal antibodies (anti-Hu, anti-Ta, anti-Ma), anti-thyroid antibodies (anti-TPO, anti-TG), anti-treponema antibodies (*Treponema pallidum* haemagglutination assay, rapid plasma reagent) and antibodies to voltage-gated potassium channels (VGKC-Ab) were all negative. Skin biopsy of the right cheek showed linear deposition of immunoglobulin and complexes (Ig-G, -A, -M, C3 and C1q) at the epidermal basement membrane.

Under the presumptive diagnosis of HSV encephalitis, acyclovir (30 mg/kg per day) was given for 9 days, during which the patient's neurological condition did not change. On day 10, we started oral methylprednisolone (1 mg/kg per day) and noted improvement in her memory and orientation, as well as low grade fever, headaches and seizures. Serial MMSE scores improved from 20 to 25 (day 20), 27 (day 50) points, and SLEDAI also ameliorated from 21 to 10.

Discussion

LE was initially described as a paraneoplastic syndrome characterised by rapid development of confusion, seizures and short-term memory loss.⁸ The concept of LE expanded with the description of patients with otherwise classic LE in association with VGKC-Ab and potentially reversible nonparaneoplastic encephalitis.^{13–15} More recently, a new encephalitis called ‘anti-*N*-Methyl-D-Aspartate (NMDA) receptor encephalitis’, was described with ovarian teratoma and most patients recovered after immunotherapy and tumour removal.¹⁶ In our case, the diagnosis of LE associated with SLE was based on clinical presentation, signal abnormalities on MRI of the mesial temporal lobe and increased white cells in the CSF. Her amnesic syndrome recovered gradually after administration of methylprednisolone. Her clinical course, as well as the absence of other abnormalities in CT scans, ultrasound, tumour markers and anti-neuronal antibodies did not support the diagnosis of paraneoplastic and VGKC-Ab-associated LE. Amnesic syndrome consisting of severe anterograde and retrograde amnesia is usually secondary to either bilateral lesions of the hippocampus, amygdala and their projections, or a lesion involving the septal area, mamillary bodies, mamillothalamic tracts, anterior and dorsomedial nuclei of the thalamus, cingulate gyrus and cingulum. Stübgen reported a case of LE associated with SLE treated with intravenous cyclophosphamide pulse (350 mg/m²), but the patient had a severe short-term memory deficit even after treatment.⁷

The pathogenesis of LE associated with SLE is not fully understood.⁵ One hypothesis entertained that the cause is autoimmune cerebral vasculitis with or without immune complex deposition.⁹ Cerebral vasculitis, however, was unlikely in the present case because it usually produces multifocal MRI changes and no such symmetric lesions was seen in this case. The normal MR angiogram is not unusual as the vascular disease in neuropsychiatric SLE is typically a microangiopathy and hence not detectable with MR angiogram. The other hypothesis considered is antineuronal antibody-mediated mechanisms.⁶ Gultekin, *et al.*⁸ reported that 30 of 50 patients with paraneoplastic LE had anti-neuronal antibodies. Earlier report has shown that a subset of lupus antibodies can cross-react with the NR2A and NR2B subunits of the NMDA receptor. This receptor is expressed in neurons throughout the brain but is of highest density within cells of

the hippocampus, amygdala and hypothalamus. The neurons in the CNS are normally protected from brain-reactive antibodies by the blood–brain barrier (BBB), but a breach in the barrier’s integrity exposes neurons to potentially pathogenic antibodies.¹⁷ Steroid therapy is known to reduce BBB leakage,¹⁸ thereby permeability of a subset of lupus antibodies are blocked and the patient’s amnesic syndrome might have recovered gradually.

Experience suggests that up to 40% of patients with LE do not have classic anti-neuronal or VGKC-Ab and absent serum VGKC-Ab and distinct immunology in patients without the paraneoplastic form of LE were reported.^{19,20} Samarasekera, *et al.*²⁰ reported the cases of four patients with negative VGKC-Ab and provided no evidence of cancer, and all patients made some recovery.

Our experience and earlier reports indicate that immunologic spectrum of LE will expand to include additional immune mechanism. Further immunological studies on patients with LE and SLE and those with SLE without LE are required to support this hypothesis.

Acknowledgements

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