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Case Report

LGI1-antibody encephalitis with subsequent rapid progression of diffuse cerebral atrophy: a case report

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Abstract: Brain lesions due to leucine-rich glioma-inactivated 1 (LGI1)-antibody encephalitis are usually limited to the medial temporal lobe, including the abnormal signal and variable degrees of atrophy. Cases of diffuse cerebral atrophy subsequent to LGI1-antibody encephalitis are rare. Here we report a 74-year-old male patient who developed LGI1-antibody encephalitis, and subsequently with rapid and extensive cerebral atrophy within 4 months of disease onset. The atrophy region included the bilateral hippocampus, frontal lobe, temporal lobe, parietal lobe, brain stem, and cerebellum, which is atypical of this disorder. We discuss the probable pathogenesis of cerebral atrophy and the relationship between atrophy and prognosis.

Keywords: Anti-LGI1 antibodies, limbic encephalitis, cerebral atrophy

Introduction

Voltage-gated potassium channel (VGKC) complex antibody-associated encephalitis is characterized by seizures, behavioral disorders and dysmnesia. Currently, leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) and, less frequently, contactin-associated proteinlike 2 (contactin-2) are categorized as the specific targets of VGKC complex antibodies [1]. The majority of patients with limbic encephalitis and temporal lobe epilepsy exhibit antibodies to LGI1 [2]. LGI1-antibody encephalitis is characteristic by faciobrachial dystonic seizures (FBDS), hyponatremia, a weak association with tumor and a good response to immunotherapy, which is different from other kinds of limbic encephalitis [1]. Brain lesions resulting from LGI1-antibody encephalitis are usually limited to the medial temporal lobe, with brain MRI typically revealing abnormally high signal on FLAIR sequences or T2 sequences, which partially or fully resolve after immunotherapy, but with variable degrees of hippocampal atrophy [3]. Cases of diffuse cerebral atrophy subsequent to LGI1-antibody encephalitis are rare. Herein, we describe a patient with LGI1-antibody encephalitis who quickly developed diffuse cerebral atrophy, including the bilateral hippocampus, frontal lobe, temporal lobe, parietal lobe, brain stem, and cerebellum.

Case report

A 74-year-old male patient was hospitalized because of sudden dysmnesia for two weeks, particularly to his short-term memory, which aggravated and accompanied by disorientation for another week. He exhibited poor temporal and spatial orientation, while his calculation and perceptivity skills were normal. The mini-mental state examination (MMSE) score was 19 when the patient was admitted. Fever, headache or convulsion did not occur. The patient had a history of high blood pressure and ischemic cerebrovascular disease.

Initial brain MRI (received on 12/15/2013) revealed a low signal on T1 sequences, and high signal on both T2 sequences and FLAIR sequences, on both sides of the hippocampus, which were swollen (**Figure 1A**). Electroencephalogram (EEG) showed low to moderate slow waves of all leads without epilepsy wave (**Figure 1E**). Lumbar puncture indicated a cerebrospinal fluid (CSF) pressure of 50 mm H_2O, without leucocytes or red blood cells. The levels of CSF

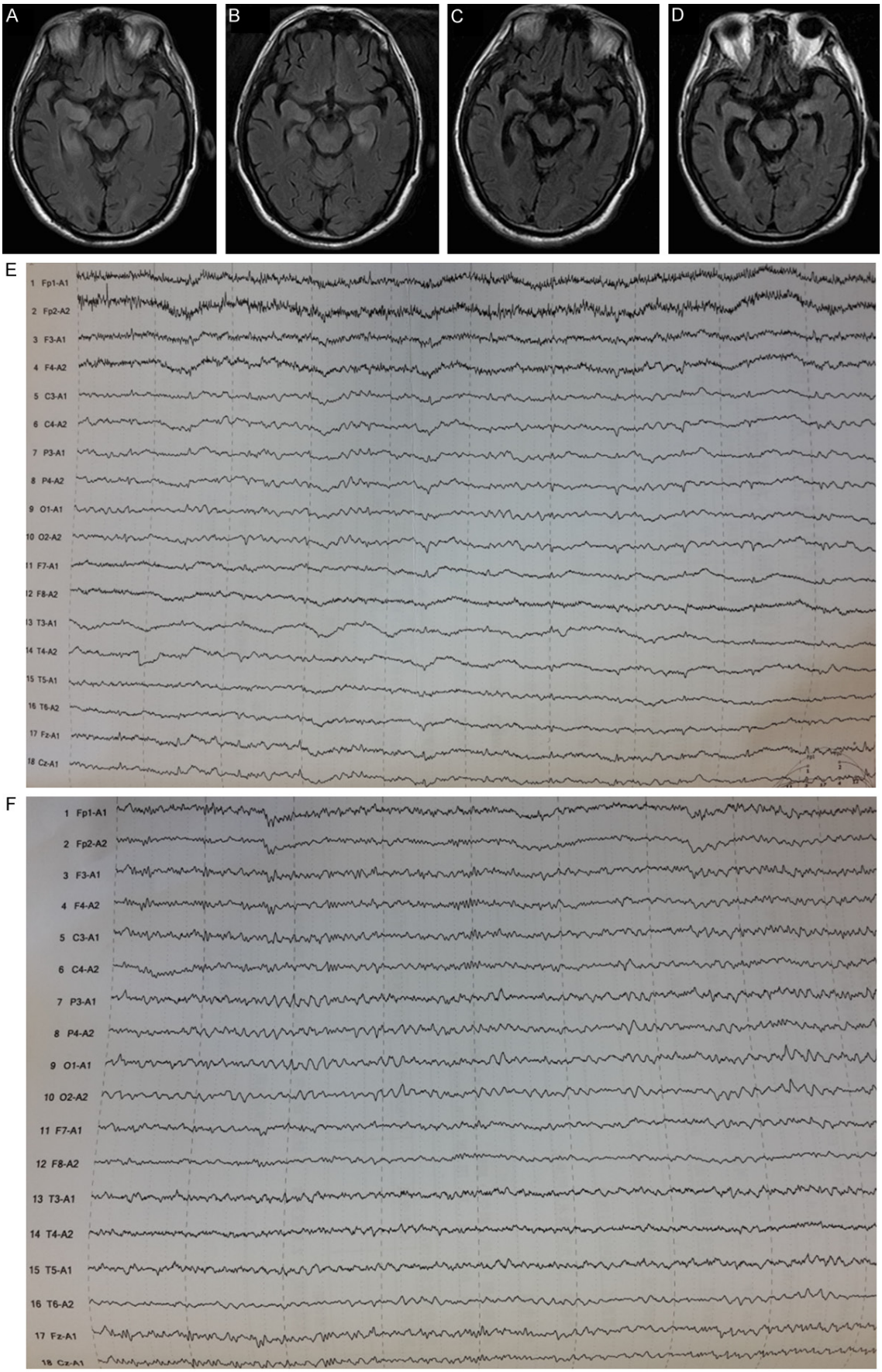
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Figure 1. A. Brain MRI (performed at 12/15/2013) showing high FLAR signal in the bilateral hippocampus, and swelling of the hippocampus. B. Brain MRI (performed at 1/10/2014) showing high FLAR signal in the bilateral hippocampus, particularly on the left side. C. Brain MRI (performed at 3/21/2014) showing that the high FLAIR signal was partially alleviated in the bilateral hippocampus. D. Brain MRI (performed at 4/15/2014) showing apparent atrophy in the medial temporal lobe, and enlargement of the cisterna ambiens and cornu temporale ventriculi lateralis. E. EEG showing low to moderate slow waves in all leads. F. EEG showing slower physiological frequencies.

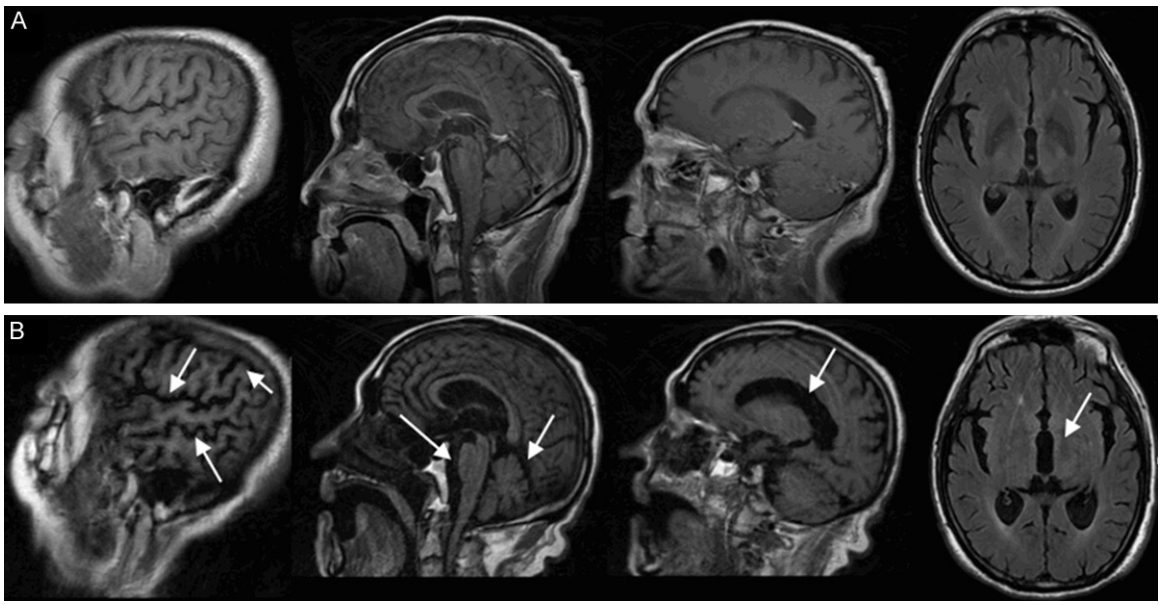

Figure 2. A. Brain MRI FLAIR sequences performed at 12/15/2013. B. Brain MRI FLAIR sequences performed at 4/15/2014. Arrows indicated atrophy in the frontal lobe, temporal lobe, parietal lobe and brain stem, as well as enlargement in the 3rd ventricle and lateral fissure.

protein, chloride and glucose were 52 mg/dl, 108 mmol/l and 3.37 mmol/l, respectively. CSF and blood tests showed that he was negative for herpes simplex viruses (including both type-1 and type-2), herpes zoster virus, cytomegalovirus, anti-Hu antibody, anti-Yo antibody, anti-Ri antibody, anti-NMDAR antibody or anti-CASPR2 antibody. However, his CSF and blood were positive for the LGI1 antibody.

Testing for human immunodeficiency virus, syphilis, systemic vasculitis, thyroid autoantibodies, biological tumor markers and chest CT scan were normal or negative. The blood sodium level was 130 mmol/L. Chest and abdomen single photon emission computed tomography (SPECT) scan revealed active glucose metabolism in the stomach, while gastroscopy biopsy showed severe and active chronic inflammation.

The patient was clearly diagnosed with LGI1-antibody encephalitis based on his clinical symptoms of cognitive disorder, the imaging lesions in the bilateral temporal lobes, the positive LGI1 antibody in blood and CSF and exclusion of virus infection and other antibody-associated limbic encephalitis. The patient was initially treated with corticosteroid therapy on day 23 after onset of the disease. His cognitive disorder was not improved compared with pretreatment. Subsequent brain MRI (received on 1/10/2014) still revealed a high signal on FLAIR and T2 sequences in the bilateral hippocampus, specifically on the left side (**Figure 1B**). The patient had a seizure on day 33 after disease onset, with manifestations of sudden loss of consciousness and limb convulsion. EEG results did not catch the epileptic waves. Application of anti-seizure medicines did not improve the condition. The patients' cognitive disorder aggravated after the epileptic seizure, and he was gradually unable to communicate with others, and lost capacity for daily living on month 2.5 after the onset of disease. The LGI1-antibody was still positive on follow-up CSF test. The patient received IVIg therapy (0.4 mg/kg/d for 5 d) on days 94 after disease onset. However, his clinical conditions were not

improved. Subsequent brain MRI revealed that the abnormal high signals were partially alleviated in the bilateral hippocampus. However, the atrophy was apparent in the hippocampus, and the cisterna ambiens and cornu temporale ventriculi lateralis were both enlarged (**Figure 1C**, **1D**). Subsequent EEG exhibited frequency slowing of the physiological waves compared with prior EEG (**Figure 1F**). The follow-up lasted for 1 year, and the patient had significant poor prognosis with a modified Rankin Score (mRS) of 5.

During the 4 months from the onset of the disease, the patient exhibited rapid development of extensive cerebral atrophy on MRI, including the frontal lobe, temporal lobe, parietal lobe, brain stem and cerebellum, and medial temporal lobe. The occipital lobe did not develop atrophy. These changes were also accompanied by enlargement of both sides of the lateral ventricles, the 3rd ventricle, the 4th ventricle, cisterna ambiens and the lateral fissure (**Figure 2**).

Discussion

LGI1-antibody encephalitis typically invades the medial temporal lobe, resulting in dysmnesia and seizure. Chan et al. reported a series of MRI study of patients with VGKC-Ab associated encephalitis, with abnormal high signal in the unilateral or bilateral medial temporal lobe on FLAIR and T2 sequences at the time of the initial imaging, which could be fully or partially resolved after immunotherapy, but with a degree of medial temporal lobe atrophy [3]. Urbach et al. reported that the majority of limbic encephalitis patients exhibited gradual progression of atrophy in the medial temporal lobe, with significant atrophy visible by approximately 1 year after disease onset [4]. MRI in our patient revealed a low signal on T1 sequences and high signal on T2 and FLAIR sequences in the bilateral hippocampus, which was also swollen at the time of initial imaging, consistent with imaging characteristics of LGI1-antibody encephalitis. During 4 months after the onset, subsequent MRI revealed partial resolution of the abnormal high signal in the bilateral hippocampus, accompanied by atrophy, and the atrophy in the frontal lobe, temporal lobe, parietal lobe, brain stem and cerebellum rapidly progressed. Enlargement was also observed in ventricle. These findings are different from reported cases previously. His aggravated clinical symptoms and continuous positive LGI1 antibody, suggest that the abnormal immune responses mediated by the pathogenic antibodies continued to damage his brain, which may have contributed to rapid progression of diffuse cerebral atrophy.

The relationship between atrophy and prognosis in patients with LGI1-antibody encephalitis remains controversial. Chan et al. [3] and Vincent et al. [5] both reported that patients who developed VGKC-Ab associated encephalitis with subsequent medial temporal atrophy could achieve varying degrees of clinical recovery after immunotherapy. Scott et al. [6] also reported a VGKC-Ab associated encephalitis patient with profound cerebral cortex atrophy who recovered after plasma exchange, except for retrograde amnesia. Further studies are required to investigate the relationship between atrophy and prognosis in LGI1-antibody encephalitis patients.

The mechanism underlying atrophy in LGI1-antibody encephalitis patients remains unclear, and it is not known whether atrophy is an imaging characteristic of the disease or a result of the frequent seizures. The unique aspect of our patient was that, in addition to his obvious medial temporal lobe atrophy, the diffuse atrophy in frontal lobe, temporal lobe, parietal lobe, brain stem and cerebellum progressed rapidly. Such rapid progression could not be explained by the physiological aging process, and is most likely due to pathological effects of the abnormal immune reaction mediated by the LGI1 antibody in the brain. Future clinical studies and animal models are needed to understand the mechanisms underlying cerebral atrophy in LGI1-antibody encephalitis patients.

Disclosure of conflict of interest

None.

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