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ORIGINAL ARTICLE

Typical clinical and imaging manifestations of encephalitis with anti-γ-aminobutyric acid B receptor antibodies: clinical experience and a literature review

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Abstract

Objective To explore the clinical, imaging, and electroencephalogram (EEG) findings, as well as the treatment and prognosis of five patients with anti-γ-aminobutyric acid B receptor ($GABA_BR$) encephalitis and review the current literature to gain a deeper understanding and improve the clinical diagnostic ability of the disease.

Methods Clinical data such as blood examination, imaging, computed tomography (CT), EEG, and magnetic resonance imaging (MRI) findings from five patients with anti-$GABA_BR$ encephalitis were retrospectively analyzed.

Results Based on the imaging data, autoimmune encephalitis with anti-$GABA_BR$ antibodies displayed subacute onset of episodic memory loss, seizures, and confusion, in addition to signal changes in the medial temporal lobe and/or hippocampus. Anti-$GABA_BR$ antibodies were found in blood and cerebrospinal fluid (CSF) in all five patients, although the CSF leukocyte count and the levels of protein, sugar, and chloride showed no obvious abnormalities. On MRI, only two patients presented with abnormal signals in the medial temporal lobe and/or hippocampus. The EEG showed a slow wave rhythm in all five patients. After treatment with methylprednisolone pulse therapy combined with antiepileptic treatment, all five patients recovered well, without any complications.

Conclusions Autoimmune encephalitis with anti-$GABA_BR$ antibodies may be a severe and refractory disease. Anti-$GABA_BR$ antibodies tested in CSF and serum play a crucial role in the definitive diagnosis and treatment of autoimmune encephalitis. Early treatment is of vital importance to avoid serious complications and neurological sequelae.

Keywords Anti-$GABA_BR$ antibodies · Autoimmune encephalitis · Seizure · Early diagnosis · Autoantibodies

Introduction

An increasing number of noncommunicable diseases, mainly autoimmune encephalitis, have been identified in the last decade [1]. Autoimmune encephalitis is a set of syndromes involving memory impairment, subacute onset of amnesia, and recurrent seizures [, 2]. The rarity of autoimmune encephalitis and its association with autoantibodies that directly target cell surface antigens of neurons or synaptic proteins have been well established [3]. Autoimmune encephalitis can induce a broad range of neuropsychiatric symptoms [4]. Sensitive and specific diagnostic tests, such as cell-based assays, are vital not only for detecting neuronal cell surface antibodies in serum or cerebrospinal fluid (CSF) but also for determining patients' treatments and follow-ups [5].

The γ-aminobutyric acid (GABA), which is the main inhibitory neurotransmitter in the central nervous system, inhibits neuronal activity by binding ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors [6–8]. In recent years, neurologists have described encephalitis with anti-γ-aminobutyric acid B receptor (anti-$GABA_BR$) antibodies [9, 10]. In some patients with autoimmune encephalitis, anti-$GABA_BR$ antibodies were

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highly sensitive and specific diagnostic biomarkers and causative autoantibodies [11–13].

In the present study, we described the typical clinical and imaging manifestations of five patients diagnosed with anti-$GABA_BR$ encephalitis. In addition, we retrospectively analyzed the patients' laboratory and imaging findings, presentations, and therapeutic strategies. Furthermore, we reviewed the relevant literature to deepen our understanding of this disease.

Methods

Ethics statement

The data collection and review were approved by the ethics committee of Shandong Provincial Qianfoshan Hospital, China, and signed informed consent was obtained from the patients. This research involved only a retrospective review of the imaging data.

Basic data

Patient 1 A 47-year-old male who had an intermittent mental disorder characterized by visual hallucinations and ramblings was admitted for seizures. The seizures had started 45 days earlier and recurred the previous day. On admission, the patient expressed feelings of fear and reported excessive daytime sleepiness. The cause of the patient's mental disorder could not be identified.

Patient 2 A 77-year-old male was admitted to our department with paroxysmal confusion, a 2-year history of progressive memory loss, and a 5-day history of aggravated and mental impairment, which manifested as visual hallucinations, ramblings, and sleep loss. He had no history of inflammation, infections, psychiatric disease, or medication use. On admission, the patient's body temperature was normal. The patient's advanced neurological functions (including hippocampal function) and muscle strength of both lower limbs (IV grade) were decreased. The findings of a general examination and other physical neurological examinations were unremarkable.

Patient 3 A 22-year-old female was hospitalized due to "no words and abnormal behavior for 6 days, and seizures caused loss of consciousness and limb convulsions for 1 day." On the previous day, the patient had experienced seizures, causing loss of consciousness and limb convulsions. After admission, the patient continued to experience recurrent loss of consciousness and limb convulsions. The patient was treated with an intravenous injection of diazepam, acyclovir (0.5 g, q8h), and methylprednisolone (1 g, qd), in addition to oral administration of levetiracetam (0.5 g, bid) and oxcarbazepine (0.3 g, bid) every 3 days, followed by a half dosage for 5 days. However, the onset of loss of consciousness, limb twitching, and emotional disorders (e.g., mania, delirium, and unresponsiveness) continued to recur, and advanced neurological function decreased significantly. After 5 days of the intravenous infusion of albumin globulin (22.5 g), there was no recurrence of the mental impairment. The patient made a full recovery and was discharged 1 month after admission.

Patient 4 A 33-year-old female was hospitalized with abnormal behavior for 10 days and seizures caused loss of consciousness and limb convulsions for 6 days. After admission, the patient experienced frequent tonic spasm attacks and was treated with the intravenous infusion of acyclovir (0.5 g, q8h) and intramuscular injection of methylprednisolone (500 mg) as shock treatment. After 3 days of treatment, the severity of the seizures was significantly controlled. However, the patient continued to exhibit abnormal behavior, manifested as childish behavior and repetitive speech. After continuous treatment for 20 days, the abnormal behavior was resolved, and the patient was discharged.

Patient 5 A 27-year-old male was hospitalized with abnormal behavior for 10 days, together with seizures caused loss of consciousness and limb convulsions for 1 day. The patient's advanced neurological function was also markedly decreased. After admission, the patient was given a strong antiemetic injection of 500 mg. Three days after the semi-reduction for 1 week, the patient's mood and behavioral abnormalities began to improve. The patient made a full recovery and was discharged 1 month after admission.

Diagnostic indexes

Complete blood examinations, comprising routine tests to assess electrolytes, liver and renal functions, vitamin B1 and B12, autoimmune-related antibodies, tumor markers, and intracellular autoantibodies (anti-Hu, anti-Yo, anti-Ri, anti-Ma2/Ta, and anti-amphiphysin) were performed in all five patients.

The patients' CSF was also examined, including CSF pressure and white blood cell (WBC) count, in addition to glucose, lactate, and protein levels. Autoantibodies in cells were also detected.

Malignant neoplasms were excluded using abdominal and chest computed tomography (CT) examinations.

Magnetic resonance imaging (MRI) was performed in all five patients to analyze signal intensities on T1- and T2-weighted images in the left temporal lobe and hippocampus and to analyze frequency differences of electroencephalogram (EEG).

Variables

The following data were collected from the patients: fluid-attenuated inversion recovery (FLAIR) imaging, cranial MRI, diffusion-weighted imaging (DWI), and video-EEG.

Results

Results of blood examinations and laboratory tests

The results of full blood examinations revealed that all the test results were within normal ranges. In all five patients, both CSF pressure and WBC counts were normal. Laboratory tests indicated that glucose, lactate, and protein levels in the CSF were in the normal range.

There was no evidence of herpes simplex virus type 1 or 2, *Treponema pallidum,* or *Borrelia burgdorferi* in the CSF or blood samples. However, CSF and sera were strongly positive for anti-$GABA_BR$ antibodies and negative for the following antibodies: anti-Hu, anti-Yo, anti-Ri, anti-Ma, anti-N-methyl-D-aspartate receptor (NMDAR), anti-glioma inactivated 1 (LGI1), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 (AMPAR1), anti-AMPAR2, and anti-contactin-associated protein 2 (Caspr2). Malignant tumors were excluded by abdominal and chest CT examinations.

Results of imaging examinations

In patient 1, cranial MRI and FLAIR imaging showed a low signal on T1-weighted images and a high signal on T2-weighted images in the right hippocampus but no contrast enhancement. On DWI, the right hippocampus revealed a normal signal (Fig. 1). Video-EEG did not detect epileptiform paradoxical discharge (Fig. 2).

In patient 2, cranial MRI showed abnormal signals in the left medial temporal lobe and hippocampus, which showed a low signal on T1-weighted images and a high signal on T2-weighted images, without contrast enhancement, in a manner similar to those observed in patient 1. On DWI, the left medial temporal lobe showed a slightly higher signal (Fig. 3). Video-EEG suggested paroxysmal slow waves on the left lines, with a frequency of 4–6 Hz (Fig. 4).

In patient 3, video-EEG showed paroxysmal slow waves, with a frequency of 6–7 Hz. No abnormality was shown in the brain MRI.

In patient 4, the EEG revealed a wide range of multi-spine slow complex composite waves and the front head leading was the most significant.

Patient 5 refused the EEG examination, and an MRI revealed no brain abnormality, as seen in patient 3.

Diagnostic results

Some of the patients with seizures showed refractory status epilepsy, displaying a poor response to treatment with antiepileptic drugs. Most importantly, anti-$GABA_BR$ antibodies were found in the blood and CSF of all five patients, despite their CSF leukocyte counts and protein, sugar, and chloride levels showed no obvious abnormalities. In the MRI examinations, abnormal signals at the medial temporal lobe and/or hippocampus were detected in only two patients. The EEG showed a slow-wave rhythm. The subacute or acute onset of epileptic seizures, mental disorder, confusion, and memory impairment that were observed in some of the cases indicated the occurrence of autoimmune encephalitis. Based on these findings, all five patients were diagnosed with anti-$GABA_BR$ encephalitis, accompanied by clinical manifestations (including mental disorders and seizures).

Discussion

It is well known that autoimmune encephalitis is a kind of neurological inflammation, which is accompanied by the subacute onset of epilepsy, context-dependent memory deficiency, confusion, mental impairment, and signal changes in the medial temporal lobe and hippocampus, as shown by imaging studies [14]. Recently, the mechanisms of autoimmunity and immune dysregulation in autoimmune encephalitis have been determined [15]. In autoimmune encephalitis, antibodies bind to targets, including neuronal cell surface antigens, which play a significant role in synaptic plasticity and transmission that are essential for learning, memory, and cognition [,]. Synaptic plasticity is dependent upon the activation of synaptic receptors and ionic channels, including excitatory glutamate NMDARs, AMPARs, and inhibitory $GABA_BR$ [16, 17]. In animal models, pharmacological or genetic disruption of these receptors led to the development of epilepsy and changes in learning and memory behaviors [18]. Immune responses against these receptors might lead to similar symptoms. Recently, an increasing number of autoantibodies targeting the NMDARs, leucine-rich LGI1, $GABA_BR$, and CASPR2 have been identified [19–23]. GABARs are located widely in the brain, predominantly in the presynaptic and postsynaptic regions of the hippocampus, thalamus, and cerebellum, as well as in the medulla spinalis [16]. The primary role of GABARs is inhibition of the activities of neurons [21, 22, 24, 25]. GABA acts mainly as an inhibitory neurotransmitter in the central nervous system, inhibiting neuronal activity by binding both $GABA_A$ and $GABA_B$ receptors [26].

The $GABA_BR$ is a G protein-coupled receptor that consists of two subunits, $GABA_B1$ and $GABA_B2$. It is activated by G-proteins, which promotes potassium influx and calcium channel inhibition, resulting in inhibition of neuronal activity. The inhibition of neuronal activity by $GABA_BR$ activation is slower [14, 18, 27–29]. The autoantibody anti-$GABA_BR$ was first described by Lancaster et al. in 2010 [11]. In 15 patients with epilepsy and encephalitis, Lancaster et al. reported the primary involvement of hippocampal and temporal lobe, accompanied by the clinical symptoms of refractory epilepsy consisting of recent memory loss, abnormal behavior, and mental impairment.

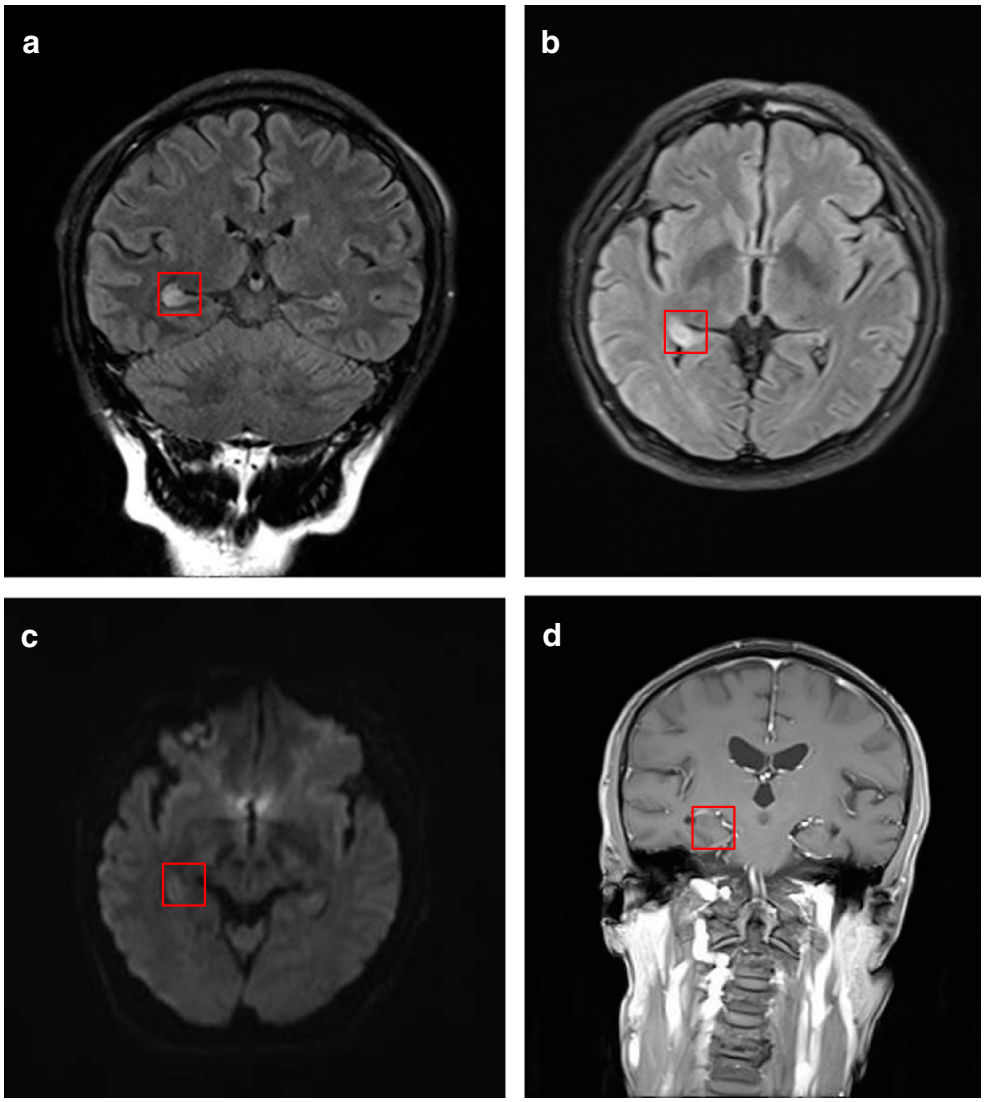

Fig. 1 Fluid-attenuated inversion recovery (FLAIR) imaging and diffusion-weighted imaging (DWI) of patient 1. A high signal on FLAIR imaging (**a**, **b**) and a normal signal on DWI (**c**) in the right hippocampus, without contrast enhancement (**d**). The areas shown in the red box are the right hippocampus

In patients with anti-NMDAR encephalitis, psychomotor symptoms and clinical manifestations change over time []. These include early manifestations of anxiety, insomnia, and irritability, leading to muscle dystonia and limb movement disorders [30, 31]. The presence of anti-$GABA_BR$ antibodies in autoimmune encephalitis is less common than that of anti-NMDAR antibodies. Since the first report in 2010, only a few cases have been reported. Affected sites in anti-$GABA_BR$ encephalitis include the hippocampus and edge of the leaf, and the clinical manifestations are similar to those observed in other marginal types of encephalitis [32]. Most patients with anti-$GABA_BR$ antibodies develop autoimmune encephalitis, showing severe epilepsy that is usually refractory to multiple antiepileptic agents and unresponsive to immunotherapy [11, 12]. Anti-$GABA_BR$ encephalitis involving the cerebellum is accompanied by ataxia and oblique eye muscle clonus. A previous study reported a case of an elderly male with post-operative cerebellar ataxia not associated with epilepsy, where the serum was positive for anti-$GABA_BR$ antibodies [14]. Another study reported a case of a 3-year-old child with the onset of oblique eye muscle clonus and ataxia, as well as the presence of anti-$GABA_BR$ antibodies in CSF and serum, without a tumor or progressive immune response [33]. Taken together, these findings suggest the apparent diversity in clinical manifestations of anti-$GABA_BR$ encephalitis. In addition to the well-known clinical manifestations of peripheral leaf encephalitis, other disease-related indicators include cerebellar ataxia and dystonia. Prompt evaluation and treatment can improve the prognosis of patients with autoimmune encephalitis. Therefore, this disease should be detected by a routine examination of nerve antibodies.

As mentioned above, antibodies in CSF and serum play an important role in the diagnosis of autoimmune encephalitis [34]. Anti-$GABA_BR$ encephalitis may also be detected by the positivity for other antibodies in serum or CSF, such as anti-glutamic acid decarboxylase (GAD), anti-SRY-box containing gene 1 (SOX1), anti-NMDAR, and anti-Hu [11, 25, 35]. In the present study, the sera and CSF were strongly

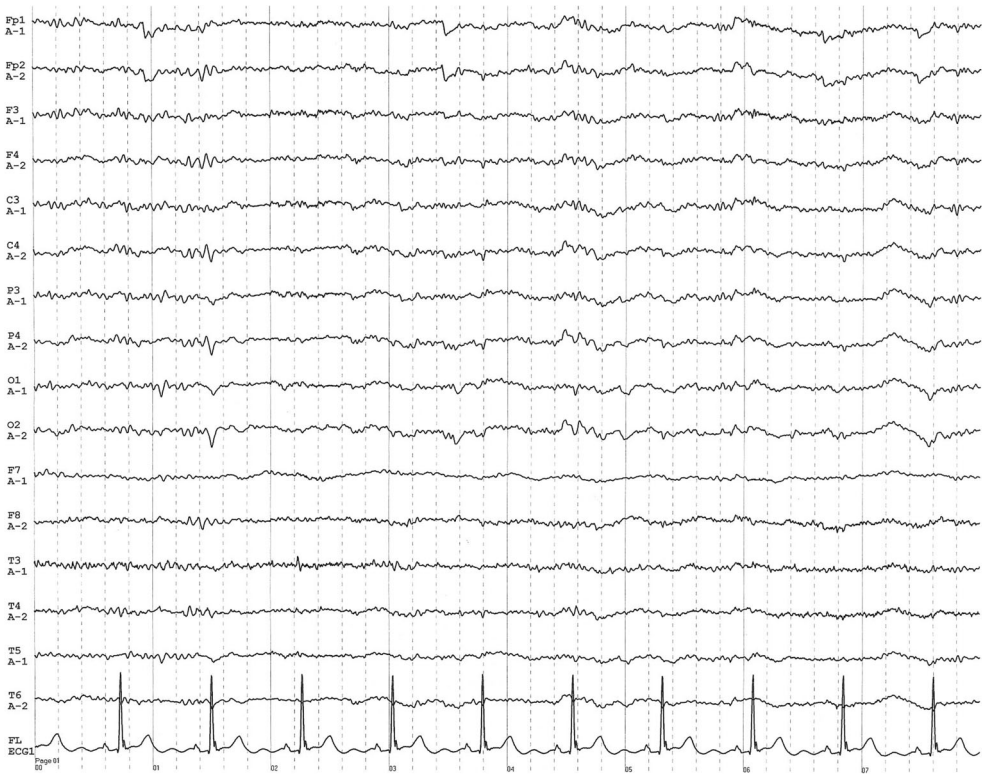

Fig. 2 Video-electroencephalogram (EEG) of patient 1

positive for anti-$GABA_BR$ antibodies in all five patients, and the presence of these antibodies was crucial for the diagnosis. The clinical manifestations and prognosis of anti-$GABA_BR$ encephalitis might be associated with the antibody expression []. Hoftberger et al. [12] reported that five out of 20 patients with anti-$GABA_BR$ encephalitis had anti-amphiphysin and anti-SOX1 antibodies and small cell lung cancer (SCLC); SCLC patients develop additional paraneoplastic neurological syndromes, such as polyneuropathy, usually leading to a poor response to immunotherapy and a poor prognosis [25, 36]. As reported, the titers of anti-$GABA_BR$ antibodies in patients with anti-$GABA_BR$ encephalitis varied from 1:10 to 1:240; however, antibody titers were not associated with disease severity [33, 34].

A number of studies reported that paraneoplastic encephalitis was associated with positivity for intracellular antigen and antigen antibodies, and 16.2% of patients with paraneoplastic syndrome had low titers of anti-Hu antibodies, with manifestations of multiple sensory neuropathies []. Studies have shown that anti-$GABA_BR$ encephalitis is relatively rare, with the symptoms being extremely mild and even stable without any treatment [27, 37]. However, in some cases, it may be potentially fatal and requires immediate hospitalization in the intensive care unit [18]. Therefore, the disease severity in anti-$GABA_BR$ encephalitis appears to vary. Previous studies reported high CSF pressure and elevated WBC counts and protein concentrations in some patients with anti-$GABA_B$ receptor encephalitis. However, others found no such changes in CSF [38]. In the present study, all the test results were within normal ranges.

It has been reported that using conventional MRI, a high T2/FLAIR signal was present in unilateral or bilateral middle temporal lobes in the majority of patients with anti-$GABA_BR$ encephalitis, whereas the signal was normal in the temporal lobe, cortex, and subcortex in a few cases [24, 36]. In a follow-up of 10 patients with anti-$GABA_BR$ encephalitis, five of the patients showed progressive hippocampal atrophy on MRI, with a high T2/FLAIR signal, indicating the occurrence of hippocampal sclerosis [36]. Besides, T1-weighted images revealed a low signal in the hippocampal horn, indicating necrosis of neurons and astrocytes, which might be associated with seizures, cerebral ischemia, and hypoxia []. It is well-know that ^{18}F fluorodeoxyglucose positron emission tomography (FDG-PET) can detect ^{18}F-FDG in lesional site, illuminating the metabolic state and function of the lesion. FDG-PET has been used to screen tumors in patients with borderline encephalitis. Some researchers detected metabolic changes in the acute phase of anti-$GABA_BR$ encephalitis using FDG-PET [39]. Besides, a significant correlation was found between metabolic changes detected by FDG-PET and autoantibody types in CSF [40]. In patients with anti-$GABA_BR$ encephalitis and positive for intracellular antigens and antibodies, metabolic abnormalities were detected in the medial temporal lobes of all five patients and cell antigen antibodies were observed in two of the patients [40].

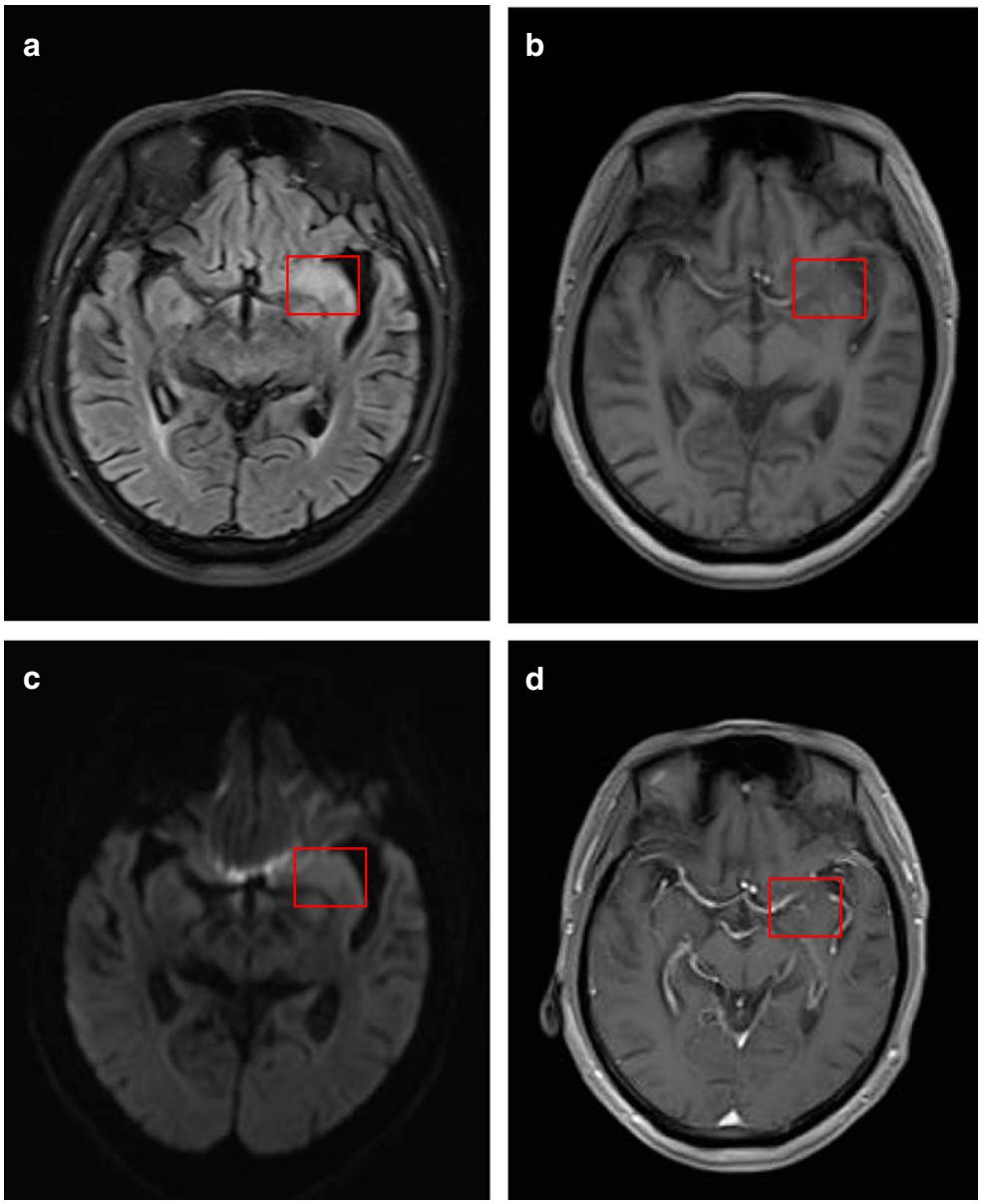

Fig. 3 Fluid-attenuated inversion recovery (FLAIR) imaging and diffusion-weighted imaging (DWI) of patient 2. A high signal on FLAIR image (**a**), a low signal on a T1-weighted image (**b**), and a slightly higher signal on DWI (**c**) in the left medial temporal lobe, without contrast enhancement (**d**). The areas shown in the red box are the left medial temporal lobe

In the present study, in addition to analyzing the characteristic clinical symptoms and cranial MRI findings of patients with anti-$GABA_BR$ encephalitis, the video-EEG was also performed. As shown by the analysis of EEG features in each disease stage, the background period of the ascending phase and lag phase mostly consisted of slow waves, with a relatively wide range. The distribution range of slow wave activity was reduced in the recovery period, suggesting that the distribution range of slow wave activity reflects the severity of anti-$GABA_BR$ encephalitis. Taken together, early EEG background activity may be related to disease recurrence. Thus, more attention should be paid when finding a mismatch between EEG patterns and head MRI findings in patients with neuronal surface antibody-related encephalitis. Given the small sample size in the present study, we used a descriptive, not statistical, analysis to identify the possible trends in EEG changes. Therefore, we did not include the potential impact of confounding factors. Notably, paroxysmal slow waves and epileptiform paradoxical discharges were observed in all five patients with anti-$GABA_BR$ encephalitis. Although this study cannot reach a definitive conclusion, it provides a new thought for further research.

Currently, there are no uniform diagnostic criteria for encephalitis with anti-$GABA_BR$ antibodies. The diagnosis is generally based on clinical and imaging evidence of typical marginal system involvement, in addition to positive anti-$GABA_BR$ antibodies in CSF and/or serum. The differential diagnosis is required for the distinguishing of viral encephalitis from metabolic encephalopathy; cranial MRI and CSF-related tests are used to support the diagnosis.

Reports of effective treatments for autoimmune encephalitis are scarce [41, 42]. According to our current

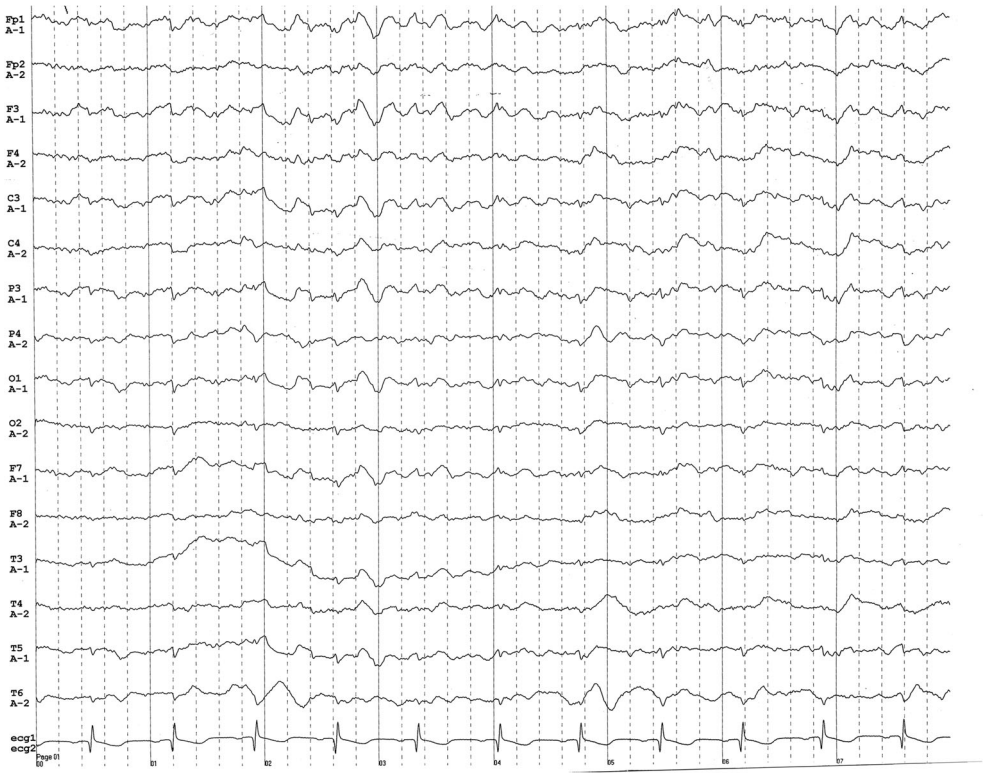

Fig. 4 Video-electroencephalogram (EEG) of patient 2

clinical experience, the primary treatment involves removal of the tumors in patients with malignancies and first-line immunotherapy; the majority of patients with anti-$GABA_BR$ encephalitis achieved complete or partial neurological relief in response to immunotherapy, whereas patients with lung cancer had a poor response to immunotherapy. At present, first-line immunotherapy consists of methylprednisolone pulse therapy, intravenous immunoglobulin, plasma replacement therapy, and a combination of the above treatments [12]. The clinical symptoms of the five patients described herein were markedly improved after methylprednisolone pulse therapy combined with antiepileptic treatment, and none of the patients experienced any further epileptic seizure, thereby confirming the efficacy of the immunotherapy. According to our previous experience, autoimmune encephalitis might recur; therefore, we suggest the treatment with oral administration of prednisolone for a period after methylprednisolone pulse therapy.

In conclusion, anti-$GABA_BR$ encephalitis is a comparatively rare but manageable autoimmune disease. In patients who present with mainly limbic encephalitis symptoms, the differential diagnosis should be taken for anti-$GABA_BR$ encephalitis. This study deepens our understanding of typical clinical and imaging manifestations of anti-$GABA_BR$ encephalitis, thereby contributing to the treatment of the disease.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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