Clinical characteristics and elevated ProGRP and positive oligoclonal bands of 13 Chinese cases with anti-GABABR encephalitis

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Abstract
Objective: To improve the clinical understanding of anti-gamma-aminobutyric-acid B receptor encephalitis (anti-GABABR encephalitis) by analyzing 13 cases.

Methods: We retrospectively studied demographic and clinical features including clinical symptoms, serum/cerebrospinal fluid (CSF) laboratory findings (including antibody test), brain magnetic resonance imaging (MRI), electroencephalogram (EEG), treatment plan, and treatment effect for 13 patients with a definitive diagnosis of anti-GABABR encephalitis.

Results: Seven patients (53.8%, 7/13) were complicated with lung cancer. Epileptic seizures were the most common symptoms at onset in 11 patients (84.6%, 11/13). All patients had seizures in the course of the disease. Abnormalities in craniocerebral MRI examination, including hippocampus, occipital lobe, insular lobe, were found in six of nine tested patients, and EEG abnormalities were found in seven out of nine tested patients. Elevated pro-gastrin releasing peptide (ProGRP) levels were found in 70% of patients with a median value of 490.10 pg/ml; and CSF oligoclonal bands were positive for 4 of 10 tested cases. However, there were no significant differences in modified Rankin Scale (mRS) between the ProGRP or CSF oligoclonal band positive and negative groups at admission and follow-up (p > .05). The value between SCLC and non-SCLC subgroup was significantly different (p < .05). Ten patients received immunotherapy (three patients refused treatment). After immunotherapy, the frequency of seizures was significantly reduced. There was a significant difference

Abbreviations: anti-AMPA, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; anti-GABABR encephalitis, anti-gamma-aminobutyric-acid B receptor encephalitis; anti-NMDAR, anti-N-methyl-D-aspartate receptor; A-TG, anti-thyroglobulin antibodies; A-TP, anti-thyroid peroxidase antibody; CA-724, carbohydrate antigen; CEA, carcinoembryonic antigen; CSF, cerebrospinal fluid; CYFRA21-1, cytokeratin fragment antigen 21–1; EEG, electroencephalogram; EP, epilepsy; FBDS, faciobrachial dystonic seizures; GTCS, generalized tonic–clonic seizures; Hu, anti-Hu antibody; LEV, levetiracetam; LGI1, leucine-rich glioma-activated 1; LUAD, lung adenocarcinoma; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OB, oligoclonal band; OXC, oxcarbazepine; ProGRP, pro-gastrin releasing peptide; SCLC, small-cell lung cancer; SE, status epilepticus; TPM, topiramate; VPA, valproate acid; WBS, white blood cell; Yo, anti-Yo antibody.
INTRODUCTION

Autoimmune encephalitis was first described only 20 years ago (Corsellis et al., 1968; Goodfellow & Mackay, 2019). The incidence of autoimmune encephalitis (0.8 per 100,000) is 1 per 100,000, and this is increasing along with increasing physician awareness of the disease and with improvements in diagnostic methods (Dubey et al., 2018). Anti-GABABR encephalitis was first reported in 2010 (Eric et al., 2010). It accounts for about 5% of all autoimmune encephalitis (Eric et al., 2011; Romana et al., 2013). The main clinical manifestations of anti-GABABR encephalitis include seizures, memory deficit, and psychiatric disorders (Romana et al., 2013). This encephalitis is responsive to immunotherapy, but typically evolves with bad prognosis associated with senior age at onset, co-morbidity with tumors, numerous complications, and deep venous thrombosis (Romana et al., 2013; Jingfang et al., 2019).

In our study, we retrospectively analyzed 13 patients with anti-GABABR encephalitis to improve the clinical understanding of anti-GABABR encephalitis.

PATIENTS AND METHODS

Thirteen patients of anti-GABABR encephalitis admitted to Qilu Hospital, Cheeloo College of Medicine, Shandong University between May 2013 and January 2019 met the diagnostic criteria for autoimmune encephalitis and presence of anti-GABABR antibodies in the serum and/or CSF (Neurology Branch of Chinese Medical Association, 2017).

The clinical symptoms, serum/CSF laboratory findings (including antibody tests), brain MRI, EEG, treatment plan, and treatment efficacy were collected. The patients were followed up in outpatient or by telephone. The mRS was used to evaluate the severity of the patients. The criteria for recurrence are based on the consensus of the following conditions: patients with recurrent symptoms or worsen symptoms are regarded as relapse (Neurology Branch of Chinese Medical Association, 2017).

RESULTS

Clinical features and auxiliary examination results (Table 1)

There were 13 cases of anti-GABABR encephalitis (males: 10; female: 3; range: 28–74 years; Median age: 65 years;
**TABLE 1**  Clinical features and auxiliary examination results

| Patients | Sex | Age (years) | First symptom | EP            | Syndromes                                      | Memory disorders | Cognitive impairment | Sleep disorder | Consciousness decreased | Abnormal mental behavior | Involuntary movement | Speech disorder | Dyskinesia | Autonomic nervous dysfunction | Tumor   |
|----------|-----|-------------|---------------|---------------|------------------------------------------------|------------------|-----------------------|----------------|-------------------------|------------------------|----------------------|-----------------|-----------|--------------------------------|--------|
| 1        | M   | 28          |               | EP            | Automatism of focal origin                        | N                | Y                     | N             | N                       | N                      | N                    | N               | N         | N                               | N       |
| 2        | M   | 54          |               | EP            | GTCS + Automatism of focal origin                  | Y                | N                     | N             | N                       | Y                      | Y                   | N               | N         | N                               | SCLC    |
| 3        | F   | 70          |               | EP            | GTCS                                              | Y                | Y                     | Y             | Y                       | Y                      | N                   | Y               | Y         | N                               | N       |
| 4        | M   | 67          |               | EP            | GTCS                                              | Y                | Y                     | N             | Y                       | N                      | N                   | N               | N         | N                               | N       |
| 5        | M   | 65          |               | EP            | GTCS + SE                                         | Y                | Y                     | Y             | Y                       | Y                      | N                   | N               | N         | N                               | SCLC    |
| 6        | M   | 69          |               | EP            | GTCS + Automatism of focal origin                  | Y                | Y                     | Y             | Y                       | N                      | N                   | N               | N         | N                               | N       |
| 7        | F   | 62          | Memory disorder| GTCS         |                                                  | Y                | N                     | N             | N                       | N                      | N                   | N               | N         | N                               | SCLC    |
| 8        | M   | 66          |               | EP            | GTCS + FBDS                                       | Y                | Y                     | Y             | N                       | Y                      | Y                   | N               | N         | N                               | SCLC    |
| 9        | M   | 64          | Headache      | GTCS         |                                                  | Y                | Y                     | N             | Y                       | Y                      | N                   | N               | N         | Y                               | N       |
| 10       | F   | 60          |               | EP            | GTCS                                              | Y                | Y                     | N             | Y                       | N                      | N                   | N               | Y         | N                               | SCLC    |
| 11       | M   | 70          |               | EP            | GTCS + Automatism of focal origin                  | Y                | Y                     | Y             | Y                       | Y                      | N                   | N               | N         | N                               | SCLC    |
| 12       | M   | 62          |               | EP            | GTCS                                              | Y                | Y                     | Y             | Y                       | N                      | N                   | N               | N         | N                               | LUAD    |
| 13       | M   | 74          |               | EP            | GTCS                                              | N                | N                     | Y             | N                       | N                      | N                   | N               | N         | N                               | N       |

Abbreviations: EP, epilepsy; F, female; GTCS, generalized tonic–clonic seizures; LUAD, lung adenocarcinoma; M, male; N, no; SCLC, small-cell lung cancer; SE, status epilepticus; Y, yes.
age: 61.60 ± 11.58 years). Seven patients (53.8%, 7/13) were found with lung cancer, including one case of lung adenocarcinoma and six cases of small-cell lung cancer (SCLC). Eleven patients were initially presented with epileptic seizures (84.6%, 11/13). All patients had seizures (100%, 13/13), including one case of FBDS. The other symptoms included memory disorders (84.6%, 11/13), cognitive impairment (76.9%, 10/13), sleep disorders (61.5%, 8/13), consciousness disorder (53.8%, 7/13), abnormal psychiatric behavior (46.2%, 6/13), involuntary movement (23.1%, 3/13), speech disorder (15.4%, 2/13), dyskinesia (15.4%, 2/13), and autonomic nervous dysfunction (7.7%, 1/13). The average mRS at admission was 3.69 ± 0.63 (Table 3).

### 3.2 Serum and CSF examination (Table 2)

Serum anti-GABABR antibodies were positive in 13 cases (100%, 13/13). Nine of 11 cases with CSF autoimmune encephalitis antibody detection were positive (81.8%, 9/11). Antibodies were positive in one relapsed patient after an interval of 15 months was 1:10 in serum and 1:1 in CSF; at the time of first diagnosis these values were 1:320 in serum and 1:32 in CSF, respectively. Serum paraneoplastic antibodies were detected in six patients, one case had anti-Hu antibody (16.7%, 1/6), one case had anti-Hu antibody and anti-Yo antibody (16.7%, 1/6).

Serum electrolyte examination has been taken in 12 patients. Two cases (16.7%, 2/12) showed hyponatremia, three cases showed hypokalemia (25.0%, 3/12), and three cases (25.0%, 3/12) showed hypochloremia. Serum tumor markers were examined in 12 cases: 8 cases exhibited abnormal elevated tumor markers with ProGRP in 7 cases among 10 tested patients for ProGRP (70%, 7/10), carbohydrate antigen-724 in 3 cases (25%, 3/12), carcinoembryonic antigen in 1 case (8.3%, 1/12), non-small-cell lung cancer-associated antigen in 1 case (8.3%, 1/12), and ferritin in 1 case (8.3%, 1/12). The range of serum ProGRP was 19.66-4957.45 pg/ml, and the median was 490.10 pg/ml (normal<63 pg/ml). The value between SCLC and non-SCLC subgroup was significantly different (p < .01). The average mRS at admission was 3.69 ± 0.63 (Table 3).

### 3.3 MRI and EEG (Table 2)

Abnormal craniocerebral MRI examination was found in six of nine patients (66.7%, 6/9), including hippocampus, occipital lobe, and insular lobe (Figure 2). One relapsed patient showed an abnormal signal in the right temporal lobe, while the original abnormal signal in the left hippocampus and insular lobe had disappeared by this point.

EEG abnormalities were found in 8 of the 9 patients (88.9%, 8/9). Among the eight patients, epileptiform discharge occurred in five cases (55.6%, 5/9). The aforementioned relapsed patient showed a marginal state at the time of recurrence, and had a sharp-slow wave and spike wave in the EEG at the initial diagnosis time.

Figure 2 There was significant difference between SCLC and no-SCLC subgroup. **p < .01.

Figure 2 Hippocampal involvement is a typical imaging manifestation of anti-GABABR encephalitis. T2 (A), T2-flair (B), and DWI (D) showing hyperintensity and T1 (C) with hypointensity in the bilateral hippocampus.

### 3.4 Treatment and follow-up (Table 3)

Ten patients received immunotherapy except three patients with malignant tumor, including methylprednisolone combined with immunoglobulin intravenous drip in six cases, dexamethasone combined with immunoglobulin intravenous drip in three cases, and dexamethasone intravenous drip in one case. Three cases received antiepileptic drugs prior to admission. After admission, 11 patients with antiepileptic treatment, including levetiracetam, sodium valproate, oxcarbazepine, and topiramate. After receiving immunotherapy, the frequency of seizures was significantly reduced. The average mRS at discharge was 2.61 ± 0.65. There was a significant difference in mRS between admission and after treatment (p < .05).

Eleven patients were followed up with for 3-31 months, with a median follow-up time of 26 months. The mRS of all follow-up cases was 3.72 ± 2.76. Among the six deceased patients, four patients died of tumor (66.6%, 4/6) and two patients without tumor died of pulmonary infection (33.3%, 2/6). The average survival time after onset was 27.7 months. The average mRS for the five surviving patients was 1.0 ± 1.41. There was a significant difference in mRS between admission and follow-up for the surviving cases (p < .05). Two cases were treated with oral corticosteroids and two cases with antiepileptic drugs. One case still had seizures and two cases had memory impairment. One case recurred 15 months after the first onset and 6 months after cessation of hormone treatment.

### 4 DISCUSSION

Anti-GABABR encephalitis is a disorder characterized by seizures and in some patients associated with small-cell lung...
| Patients | Potassium (3.5–5.3 mmol/L) | Sodium (137–147 mmol/L) | Chloride (99–110 mmol/L) | Tumor markers | Thyroid function (IU/ml) | Anti-GABABR sAb | Other Ab | WBS (<5/m3) | Glucose (2.5–4.5 mmol/L) | Protein (0.15–0.45 g/dl) | CSF Protein | WBS | EEG | MR |
|----------|---------------------------|------------------------|-------------------------|---------------|-------------------------|-------------------|----------|-------------|-------------------------|---------------------------|-------------|----|-----|-----|
| 1        | 4.23                      | 145                    | 106                     | -/ProGRP (N)  | N                       | 1 : 10            | N        | –           | 3.37                    | 0.68                      | –           | –       | Slow and sharp-slow waves | Left hippocampus |
| 2        | N                         | N                      | N                       | N             | –                       | 1 : 32            | N        | +           | 4.65                    | 0.24                      | –           | 1 : 10   | N       | N    |
| 3        | 3.90                      | 141                    | 105                     | ProGRP 19.66 pg/ml | A-TG 24.15, A-TP 509.89 | 1 : 320          | N        | –           | 3.25                    | 0.70                      | –           | 1 : 32   | N       | N    |
| 4        | 3.58                      | 146                    | 105                     | CYFRA21–1 4.22 ng/ml, ProGRP 65.45 pg/ml | –                       | 1:32             | N        | +           | 3.3                     | 0.42                      | –           | 1 : 3 2 | Slow and sharp-slow waves | N           |
| 5        | 3.19                      | 139                    | 97                      | ProGRP 886.35 pg/ml, CEA 5.37 ng/ml | –                       | +                 | N        | –           | 3.82                    | 0.44                      | +           | +       | N       | –    |
| 6        | 3.47                      | 135                    | 95                      | -/ProGRP (N)  | –                       | 1:32             | Hu       | +           | 5.8                     | 0.62                      | –           | 1 : 10   | Slow and spike-slow waves | –           |
| 7        | 4.55                      | 142                    | 106                     | ProGRP 444.66 pg/ml, CA-274 22.13 | –                       | 1:32             | N        | +           | 4.1                     | 0.35                      | +           | 1 : 1    | Slow wave Bilateral hippocampus | Left hippocampus |
| 8        | 3.97                      | 146                    | 105                     | ProGRP 554.48 pg/ml | –                       | 1:32             | –        | –           | 3.92                    | 0.33                      | –           | 1 : 32   | Marginal state | Left hippocampus |
| 9        | 3.20                      | 123                    | 81                      | ProGRP 48.9 pg/ml | –                       | 1:320 and relapse with 1:10 | –        | +           | 3.97                    | 0.29                      | +           | 1:32 and relapse with 1:1 | Spike and sharp-slow waves and relapse with marginal state | Left cingulate gyrus, hippocampus, insular lobe, and relapse with right temporal lobe |
| 10       | 3.98                      | 140                    | 103                     | ProGRP 4,957.45 pg/ml, A-TG 68.75, A-TP 7.38 | 1:100                  | Hu and Yo        | N        | N           | N                       | N            | N           | N       | Slow and spike-slow waves | –           |
| 11       | 3.73                      | 138                    | 103                     | ProGRP 596.68 pg/ml | –                       | +++               | N        | +           | 3.37                    | 0.84                      | +           | N       | N       | N    |
| 12       | 3.93                      | 144                    | 111                     | ProGRP 535.25 pg/ml, Ferritin 970.2 ng/ml | –                       | ++                | –        | –           | 3.62                    | 0.76                      | –           | +++     | Slow waves Bilateral hippocampus | Bilateral occipital lobe |
| 13       | 4.58                      | 142                    | 103                     | ProGRP 29.62 pg/ml, CA-724 10.1 U/ml | –                       | 1:10              | –        | –           | 3.76                    | 0.45                      | –           | –       | Marginal state | Bilateral occipital lobe |

Abbreviations: Ab, antibody; A-TG, anti-thyroglobulin antibodies; A-TP, anti-thyroid peroxidase antibody; CSF, Cerebrospinal fluid; CA-724, carbohydrate antigen; CEA, carcinoembryonic antigen; CYFRA21-1, Cytokeratin Fragment Antigen 21-1; EEG, electroencephalography; GABA, gamma-aminobutyric acid; Hu, anti-Hu antibody; MRI, magnetic resonance imaging; N, no; OB, oligoclonal band; ProGRP, pro-gastrin-releasing peptide; WBS, white blood cell; Yo, anti-Yo antibody; –, negative; +, positive.
cancer (Eric et al., 2010). Its mechanism is not clear. It is well-established that GABAB receptors are mainly distributed in the cerebral cortex, hippocampus, thalamus, and cerebellum (Fritschy et al., 1999). It can mediate synaptic inhibition to suppress neural activity (Benarroch Eduardo, 2012; Eric et al., 2010; Schuler et al., 2001). With improvements in clinical understanding, more and more anti-GABABR encephalitis cases have been diagnosed.

The values detected in our study for onset age, sex ratio, and co-morbidity with lung cancer are consistent with previous studies (Eric et al., 2010; Romana et al., 2013). In all forms of autoimmune encephalitis, increased prevalence in males also occurs in anti-leucine-rich glioma-activated 1 (anti-LGI1) encephalitis, whereas anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR) encephalitis are more prevalent in females (Wei et al., 2020; Zhang et al., 2016). It may suggest that sex hormones play a potential role in autoimmune encephalitis.

Seizures (13/13, 100%), including one case of FBDS, were the most common and initial symptom in our cases. It may be related to the antigenic function of mediating encephalitis (Eric et al., 2010; Carsten et al., 2017). FBDS found in our study has not been reported before in patients with anti-GABABR antibodies. Lesion of FBDS-related pathways may be the etiology of FBDS in anti-GABABR encephalitis. Immunotherapy delay was associated with the development of epilepsy in anti-GABABR encephalitis (Shen et al., 2020). Antiepileptic drugs alone usually can relieve seizures (De Bruijn et al., 2019; Maureille et al., 2019). In our study, seizures were relieved after immunotherapy. Four of five surviving patients still continued taking antiepileptic drugs or hormone therapy to help control seizures, it indicating that anti-GABABR encephalitis may cause permanent damage.

About 60% of patients with anti-GABABR encephalitis had abnormal EEG examination (McKay Jake & Dimberg Elliot, 2019; Xiu-He et al., 2020). Our study showed more abnormality in EEG with 88.9% patients. It may be related to the different periods and the duration of EEG examination (Retnaswami & Seshadri Roopa et al., 2014), and another possible explanation could be limitation and bias of numbers of cases. Lancaster et al showed that anti-GABABR encephalitis involves the medial temporal lobe and the corpus callosum (Eric et al., 2010). But, in our study, the insular lobe and occipital lobe were mainly located outside the temporal lobe.

ProGRP is the precursor protein of the bombesin-like peptide, a neuropeptide and autocrine growth factor expressed in nerve fibers, gastric tissue, pulmonary carcinoid, and SCLC.

**TABLE 3** Treatment and prognosis

| Patients | mRS on admission | Immunotherapy | Antiepileptic therapy | mRS at discharge | Follow-up time (months) | Last mRS |
|----------|------------------|---------------|-----------------------|------------------|------------------------|----------|
| 1        | 3                | Methylprednisolone + immunoglobulin | LEV            | 2                | 5                      | 0        |
| 2        | 4                | Dexamethasone + immunoglobulin      | LEV            | 2                | 18                     | 6        |
| 3        | 4                | Dexamethasone + immunoglobulin      | LEV + VPA      | 3                | 21                     | 3        |
| 4        | 3                | Methylprednisolone + Dexamethasone  | LEV + VPA      | 2                | 31                     | 6        |
| 5        | 2                | Methylprednisolone + immunoglobulin | LEV            | 2                | 31                     | 6        |
| 6        | 3                | Methylprednisolone + immunoglobulin | VPA            | 2                | 26                     | 6        |
| 7        | 3                | N               | N                     | 3                | N                      | N        |
| 8        | 3                | N               | LEV + OXC            | 3                | 20                     | 0        |
| 9        | 3                | Methylprednisolone + immunoglobulin | LEV + VPA      | 4                | 30                     | 2        |
| 10       | 4                | N               | VPA + TPM            | 3                | N                      | N        |
| 11       | 3                | Dexamethasone    | N                     | 3                | 30                     | 6        |
| 12       | 4                | Dexamethasone + immunoglobulin      | VPA + TPM      | 3                | 30                     | 6        |
| 13       | 3                | Methylprednisolone + immunoglobulin | LEV + VPA      | 2                | 3                      | 0        |

Abbreviations: LEV, levetiracetam; mRS, modified rankin scale; N, no; OXC, oxcarbazepine; TPM, topiramate; VPA, valproate acid.

![ProGRP in SCLC and NSCLC Groups](image-url)
The specificity and sensitivity of ProGRP for lung cancer were 93.2% and 78.5%, respectively (Aoran et al., 2019). Anti-GABABR encephalitis is not a completely curable autoimmune disease, and a considerable number of patients have a poor prognosis. Meanwhile, 50% of patients with anti-GABABR encephalitis are also diagnosed with SCLC (Romana et al., 2013). Therefore, early recognition of anti-GABABR encephalitis, especially anti-GABABR encephalitis with SCLC, is of great significance to predict prognosis. Interestingly, our study found that the level of serum ProGRP was higher in anti-GABABR encephalitis patients than in normal population. It has not been reported before. Deeply, the level of serum ProGRP showed significant difference between SCLC and non-SCLC subgroup \((p < .05)\). So, we think that the high level of ProGRP in patients is related to anti-GABABR encephalitis with SCLC. In other subtype, incidence of autoimmune encephalitis with tumors is different. Rare anti-LGI1 encephalitis patients are associated with tumors, while very few patients suffer from thymoma (<5%). In anti-NMDAR encephalitis, about half of patients have teratomas (Josep et al., 2018). As ProGRP is a sensitive, specific, and reliable tumor marker with SCLC (Ying et al., 2011), we infer the ProGRP test in the anti-GABABR encephalitis population can initially suggest whether the patient has SCLC, in order to expect early detection of potential tumors and timely treatment. It is pity that we did not test ProGRP during the follow-up. There are few patients because of the lower incidence, the sensitivity and specificity of ProGRP cannot be obtained at present.

Besides, four patients showed positive CSF oligoclonal bands, and the highest titer of CSF antibody was 1:32, which was lower than serum samples at the same time. At present, there are few studies on CSF oligoclonal bands in autoimmune encephalitis. Our observations support the inference that there is intrathecal synthesis of autoantibodies against anti-GABABR encephalitis, but it is not clear how the positive rate for oligoclonal bands is relatively low. There was no significant difference in mRS between the CSF oligoclonal band positive and negative groups at admission and follow-up \((p > .05)\), so we infer that CSF oligoclonal band status has no correlation with anti-GABABR encephalitis prognosis.

In this study, two patients with anti-GABABR encephalitis were complicated with anti-Hu and/or anti-Yo antibodies. At present, positive with two different types of autoimmune encephalitis antibodies at the same time has been reported in anti-contactin-associated protein-like 2 antibody and anti-LGI1 antibody (Avi et al., 2017; Meizan et al., 2010). Anti-AMPAR with paranoeplastic antibody or anti-GABABR antibody or anti-NMDAR antibody have been reported, too (Josep et al., 2018). A review of 94 cases with anti-GABABR encephalitis showed that commonly reported autoantibodies associated with GABABR
autoimmune disease were anti-Hu (10.8%, 9/83), anti-SRY-Related HMG-Box Gene 1 (10.8%, 9/83), glutamic acid decarboxylase-65 (8.5%, 8/94), and N-type voltage gated calcium antibodies (4.8%, 4/83) (McKay Jake & Dimberg Elliot, 2019). The positive rate of serum paraneoplastic antibodies may be related to the presence of tumors, but paraneoplastic antibodies were not found in all of the patients with tumors. Further study is needed to determine whether the intracellular and surface antibodies play a role in the anti-GABABR encephalitis disease process.

Previous studies have shown that the response rates of anti-GABABR encephalitis to immunotherapy were low (Romana & van Sonderen Agnes et al., 2015), but early immunotherapy was linked to good prognosis (Tae-Joon et al., 2014; Serafini Anna et al., 2016). In a nonrandomized control trial, therapeutic plasma exchange might be an effective rescue therapy associated with rapid functional improvement in patients (Zhang et al., 2021). In this study, all 10 cases responded to immunotherapy. A decrease in anti-GABABR antibodies titer was also observed in another study (Jia et al., 2018). Links between antibody titers and symptom improvement are controversial. The data of this study showed that there was no significant correlation between serum/CSF antibody titer and mRS score (or its improvement). Early immunotherapy can help to achieve a good prognosis for patients without tumors (Wei et al., 2020). In our study, there were four deaths in seven patients (57.1%) with tumor, and two deaths in five patients (40%) without tumor. The average mRS score of the five surviving patients was 1.

In this study, the recurrence rate was 9% (1/11). Its lower recurrence may be related to the high mortality rate. In addition, we observed that the clinical symptoms of the patient’s recurrence were less severe than the first onset. Recurrence often occurs when immunotherapy is withdrawal or stopped (Avi et al., 2017). In this study, one patient relapsed after stopping hormone administration due to gastrointestinal perforation. Rituximab is increasingly widely used as the initial treatment according to some studies (Margherita et al., 2015; Titulaer Maarten et al., 2013).

More data need to be collected to get more accurate statistics due to the lower incidence of anti-GABABR encephalitis and fewer patients.

5 | CONCLUSION

Epilepsy is the most common clinical manifestation of anti-GABABR encephalitis. The prognosis of anti-GABABR encephalitis is poor. Section of anti-GABABR encephalitis patients have higher level of serum ProGRP and positive GSF oligoclonal bands. Elevated ProGRP or positive CSF oligoclonal bands with classic clinical features can potentially help to improve early recognition of anti-GABABR encephalitis. The elevated ProGRP and positive CSF oligoclonal bands have no direct correlation with patient prognosis. But early recognition of anti-GABABR encephalitis and standardized immunotherapy could improve prognosis. Bias existed due to limitation of limited number of cases, and more data need to be collected.
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