

# Clinical characteristics, long-term functional outcomes and relapse of anti-LGI1/Caspr2 encephalitis: a prospective cohort study in Western China

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## Abstract

**Objective:** To study the clinical characteristics of anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis and anti-contactin-associated protein-like 2 (Caspr2) encephalitis and to investigate factors associated with poor long-term neurological functional outcomes and relapse among patients in western China.

**Methods:** In this single-center prospective cohort study, we consecutively enrolled patients with anti-LGI1 encephalitis and anti-Caspr2 encephalitis from April 2014 to February 2021. Patient outcomes were assessed using the modified Rankin scale. Predictors of long-term functional outcomes and relapse were analyzed.

**Results:** Forty-four anti-LGI1 encephalitis patients [median age: 44 years, range: 18–82 years; females: 25 (56.8%)], 35 anti-Caspr2 encephalitis patients [median age: 43 years, range: 14–80 years; females: 19 (54.3%)], and 5 dual-positive patients [median age: 44 years, range: 36–58 years; females: 5 (100%)] were enrolled. Overall, 86.4% anti-LGI1 encephalitis patients and 80% anti-Caspr2 encephalitis had a favorable neurological functional outcome (mRS 0–2). Tumor occurrence and weight loss were associated with poor long-term functional outcomes in anti-LGI1 encephalitis, whereas in anti-Caspr2 encephalitis, predictors included behavioral disorder at acute phase, abnormalities in brain magnetic resonance imaging, higher modified Rankin scale scores at onset, poor response to the initial immunotherapy at 4 weeks, age at onset <30 years, and relapse ( $p < 0.05$ ). Overall, 13.6% of anti-LGI1 encephalitis patients and 20% of anti-Caspr2 encephalitis patients had at least one relapse. Sleep disorder at the acute phase was the risk factor of relapse in anti-LGI1 encephalitis, while female, age at onset <30 years, and behavioral disorder at acute phase were the risk factors of relapse in anti-Caspr2 encephalitis (log rank  $p < 0.05$ ).

**Conclusion:** The clinical characteristics such as age, gender, and tumor occurrence rates of anti-LGI1 encephalitis and anti-Caspr2 encephalitis in western China are different from those in the Western countries. Most patients in our study had favorable long-term functional outcomes. The relapse rates are still high in both types of encephalitis, which warrants caution.

**Keywords:** Caspr2, LGI1, Autoimmune encephalitis, Prospective, Cohort studies

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## Introduction

Anti-leucine-rich glioma-inactivated 1 (LGI1) antibodies and anti-contactin-associated protein-like 2 (Caspr2) antibodies are antibodies against

voltage-gated potassium channels (VGKCs), which were recently identified by Irani *et al.* in 2010.<sup>1</sup> This discovery updated our understanding of the clinical significance of VGKC antibodies.

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Nowadays, evidence showing a positive VGKC antibodies result by itself is insufficient to diagnose autoimmune encephalitis.<sup>2</sup> VGKC antibody-positive patients should be distinguished into three different subgroups: anti-LGI1 antibody-positive patients, anti-Caspr2 antibody-positive patients, or VGKC antibody-positive patients lacking both anti-LGI1 and anti-Caspr2 antibodies.<sup>3</sup> LGI1 is a secreted neuronal protein forming a trans-synaptic complex which includes the presynaptic protein – a disintegrin and metalloproteinase 23 (ADAM 23), which interacts with VGKC Kv1, and the postsynaptic protein ADAM 22, which interacts with  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). Caspr2, which is an associated protein of VGKC Kv1, forms a trans-membrane axonal complex together with contactin-2.<sup>4</sup> Although both anti-LGI1 and anti-Caspr2 antibodies recognize VGKC Kv1-related proteins, the clinical profiles of anti-LGI1 encephalitis and anti-Caspr2 encephalitis are not exactly the same.

Previous reports had described the clinical characteristics, concomitant tumors, and clinical characteristics of relapse of the diseases in Western countries as the following. Anti-LGI1 encephalitis was reported to usually present with typical limbic encephalitis, which could be characterized by subacute and progressive disturbance in cognitive symptoms, seizures, and sleep disorder.<sup>5</sup> Faciobrachial dystonic seizures (FBDS) as one subtype of seizures was regarded as a specific symptom for anti-LGI1 encephalitis.<sup>5</sup> Compared with anti-LGI1 encephalitis, the clinical manifestations of anti-Caspr2 encephalitis could be more diverse because both the central nervous system (CNS) and peripheral nervous system (PNS) might be involved. Patients with anti-Caspr2 encephalitis may develop limbic encephalitis, neuromyotonia, cerebellar ataxia, or Morvan syndrome.<sup>5</sup> Compared with anti-LGI1 encephalitis, tumors are more frequently found in anti-Caspr2 encephalitis patients (anti-LGI1 encephalitis: ~10% versus anti-Caspr2 encephalitis: 20–30%), especially thymoma.<sup>5</sup> Relapses occurred in about 14–35% of anti-LGI1 encephalitis and 25–38% of anti-Caspr2 encephalitis patients.<sup>6–12</sup>

However, our previous studies suggested that autoimmune encephalitis, such as anti-N-methyl-D-aspartate receptor (NMDAR) and anti-gamma-aminobutyric-acid type B receptor (GABA<sub>B</sub>R) encephalitis, has significant differences with studies of Western countries regarding gender ratio

and the proportion of combined tumors, which indicate the heterogeneity caused by different genetic backgrounds. For example, our studies showed a higher proportion of male patients and a lower tumor frequency in Chinese anti-NMDAR encephalitis patients compared with Western countries.<sup>13,14</sup> Therefore, the clinical information of patients in different populations is valuable. So far, large prospective cohort studies on the long-term functional outcomes and relapse among anti-LGI1 or anti-Caspr2 encephalitis and on the factors associated with them in western China are still lacking.

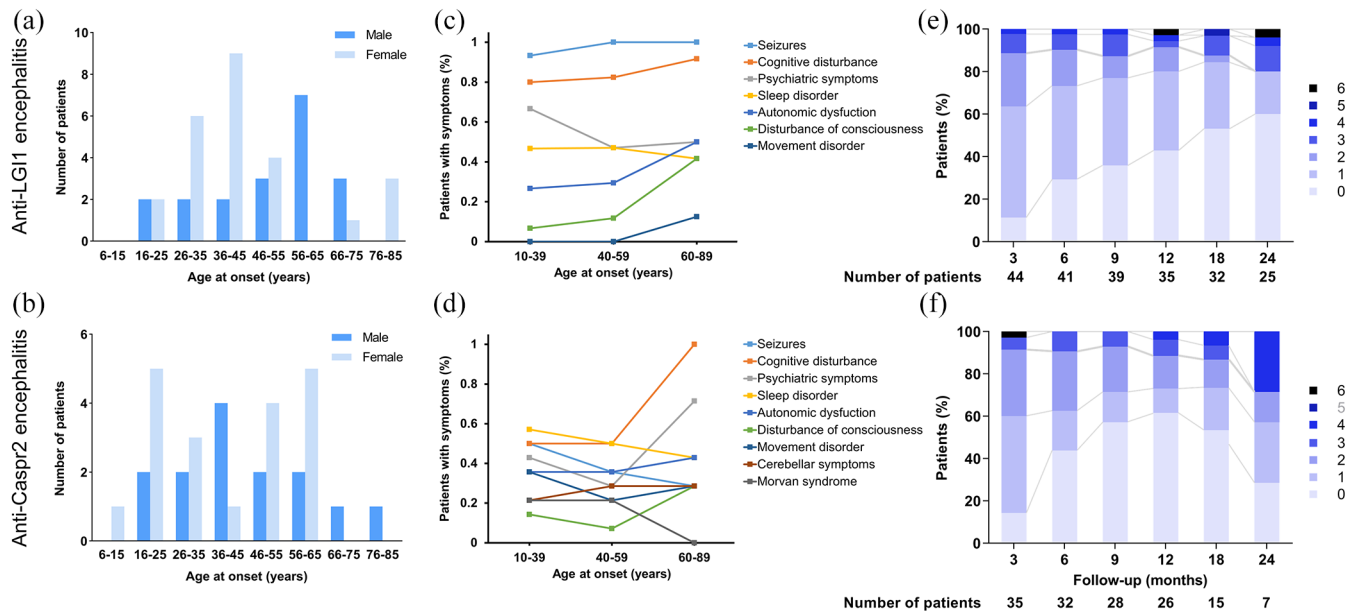
As far as we know, up to date, the present single-center cohort study is the largest cohort with the longest follow-up in western China, which is also the first prospective study. The differences in clinical characteristics, prognosis, and relapse rate of anti-LGI1 encephalitis and anti-Caspr2 encephalitis in western China from Western countries were revealed and compared. In addition, we focused on patient long-term functional outcomes, relapse and also investigated factors that may predict a poor functional outcome or a relapse disease course of the two types of autoimmune encephalitis.

## Methods

### Patients

This study was registered (registration number: ChiCTR1800019762) on the World Health Organization international clinical trial registry platform. For more details on the study, please see our previous research.<sup>14–17</sup> In the present study, we recruited patients with definitive diagnosis of anti-LGI1 encephalitis or anti-Caspr2 encephalitis who were admitted to the Department of Neurology, West China Hospital between April 2014 and February 2021. Observational data (e.g. demographic information, clinical features, laboratory tests, auxiliary examinations, treatments, and functional outcomes) were collected prospectively.

Patients were included when they met the following criteria:<sup>4,18</sup> (1) subacute onset (rapid progression of fewer than 3 months) of one or more of the following 10 major groups of neurological symptoms: seizures, memory deficit, psychosis, movement disorder, disturbance of consciousness, autonomic dysfunction, sleep disorders, cerebellar ataxia, and Morvan syndrome; (2) serum and/or



**Figure 1.** Demographic, clinical manifestations, and functional outcomes evaluated at different follow-up points (3, 6, 9, 12, 18, 24 months after disease onset) of patients with anti-LGI1 encephalitis and anti-Caspr2 encephalitis. The distributions of patients by age and sex in anti-LGI1 encephalitis (a) and anti-Caspr2 encephalitis (b). The proportions of anti-LGI1 encephalitis patients (c) and anti-Caspr2 encephalitis patients (d) with cumulative clinical symptoms stratified by different ages at onset. The modified Rankin scale scores at different follow-up points in patients with anti-LGI1 encephalitis (e) and anti-Caspr2 encephalitis (f).

cerebrospinal fluid (CSF) testing positive for anti-LGI1 antibodies and/or anti-Caspr2 antibodies based on cell-based assay (CBA); (3) reasonable exclusion of other disorders.

The exclusion criteria were as follows: (1) patients with follow-up < 3 months; (2) patients with positive serum and/or CSF test results for other autoimmune encephalitis antibodies or paraneoplastic autoantibodies; (3) patients with a medical history of other neurological or psychological diseases before the onset of autoimmune encephalitis; and (4) patients lacking essential clinical data.

### Data collection

The standardized data of patients in the acute stage were obtained from the hospital medical record system and face-to-face interviews conducted by experienced neurologists. The data collected included demographic data, clinical features, laboratory test results, auxiliary examination results including electroencephalogram (EEG), video EEG, electromyogram, and magnetic resonance imaging (MRI), treatment, and outcomes. The spectrum of antineuronal antibodies, including anti-NMDAR, anti-AMPA1 and 2, anti-Caspr2, anti-LGI1, and anti-GABA<sub>B</sub>R, were tested based

on a CBA (Euroimmun, Lübeck, Germany) in serum and CSF. Onconeural antibodies (anti-Hu, anti-Ri, anti-Yo, anti-CV2/CRMP5, anti-Ma2, anti-amphiphysin, anti-Tr, anti-GAD65, and PCA-2) were tested by immunoblot analysis (Euroimmun) in serum and CSF.

### Outcome assessment and definitions

Follow-up information was assessed every 3 months after the disease onset by trained neurologists. Relapse was defined as new onset or worsening of symptoms after an initial improvement or stabilization of at least 2 months.<sup>19</sup> For patients with relapse, extra data, including the frequency of relapses, time to relapse, clinical data, and treatment at relapse, were collected. Thorough clinical and laboratory examinations were conducted to confirm the diagnosis of relapse.

Experienced neurologists evaluated neurological functional outcomes after 4 weeks of initial treatments and every 3 months after disease onset through the modified Rankin scale (mRS). Patients with an mRS score < 3 at the end of follow-up were defined as a good outcome, otherwise defined as a poor outcome.<sup>19</sup> A poor response

to the initial therapy was defined as an mRS score  $\geq 4$  or no improvement in the mRS score for 4 weeks. Clinical improvement was defined as a decrease in the mRS score  $\geq 1$ .<sup>19</sup> A delay of initial immunotherapy was defined as it administered after 30 days of the first onset (for patients treated without immunotherapy, the delay time was defined as the duration from the first onset to the last follow-up).<sup>19</sup>

### Statistical analysis

All data were analyzed using SPSS version 25.0 (SPSS, Inc., IBM, Armonk, NY, USA). Continuous variables with normal distributions were shown as means  $\pm$  SD, otherwise as the medians with the interquartile range (IQR). Categorical variables were shown as frequencies (proportions). Demographic data, symptoms, auxiliary tests results, and univariate analysis of factors predicting poor functional outcomes were analyzed by independent sample *t* test or Mann-Whitney *U* test for continuous variables, while Pearson's  $\chi^2$  test,  $\chi^2$  analysis with continuity correction, or Fisher's exact test for categorical variables where applicable. Univariate analysis of factors predicting clinical relapse were analyzed by Cox regression for continuous variables, and the Kaplan-Meier method for categorical variables, respectively. Multivariate analysis was not available due to the small number of patients with poor outcomes or relapses. A *p* value of  $< 0.05$  was considered statistically significant.

## Result

### Demographic and clinical characteristics

Figure 1(a) and (b) shows the distributions of patients by age and sex in anti-LGI1 encephalitis and anti-Caspr2 encephalitis, respectively. A total of 84 patients were enrolled in this study, including 44 with anti-LGI1 encephalitis, 35 with anti-Caspr2 encephalitis, and 5 dual-positive patients. The median age at disease onset was 44 years (range: 18–82) in anti-LGI1 encephalitis patients and 43 years (range: 14–64) in anti-Caspr2 encephalitis patients. Twenty-five (56.8%) and 19 patients (54.3%) were female in anti-LGI1 encephalitis and anti-Caspr2 encephalitis, respectively.

Figure 1(c) and (d) shows the proportions of anti-LGI1 encephalitis patients and anti-Caspr2 encephalitis patients with different cumulative

symptoms stratified by age. Comparison of demographic data and clinical manifestation between anti-LGI1 encephalitis and anti-Caspr2 encephalitis are summarized in Table 1. All anti-LGI1 encephalitis patients developed a central manifestation as the initial symptom. However, five anti-caspr2 encephalitis patients (14.3%) presented non-CNS initial symptoms at onset ( $p = 0.034$ ). Seizures is the most common initial symptom in anti-LGI1 encephalitis (63.6%), which is more frequent compared with that in anti-Caspr2 encephalitis (25.7%,  $p = 0.001$ ).

During the acute phase, seizures were more common in anti-LGI1 encephalitis patients (97.7%) than in anti-Caspr2 encephalitis patients, regardless of the type of origin ( $p < 0.001$ ). FBDS were specific to anti-LGI1 encephalitis patients (45.5%;  $p < 0.001$ ). It should be noted that two anti-LGI1 encephalitis patients had pilomotor seizures, which is extremely rare.<sup>20</sup> Cognitive decline (84.1%;  $p = 0.016$ ) and memory deficit (77.3%;  $p = 0.002$ ) were more common in anti-LGI1 encephalitis compared with anti-Caspr2 encephalitis. Movement disorders occurred in more anti-Caspr2 encephalitis patients (20%,  $p = 0.003$ ). Cerebellar symptoms only occurred in anti-Caspr2 encephalitis patients (25.7%,  $p = 0.001$ ).

Six anti-LGI1 encephalitis patients (13.6%) and seven anti-Caspr2 encephalitis patients (20%) had peripheral manifestations. Neuropathic pain was complained of by six anti-Caspr2 encephalitis patients (17.1%), which did not occur in anti-LGI1 encephalitis patients ( $p = 0.015$ ). Six anti-Caspr2 encephalitis patients (17.1%) were also diagnosed with Morvan syndrome. Autonomic dysfunction was observed at a similar rate in 15 anti-LGI1 encephalitis (34.1%) and 12 anti-Caspr2 encephalitis patients (37.1%).

Considering total cancer including those prior to the onset of autoimmune encephalitis, three anti-LGI1 encephalitis patients (6.8%) and four anti-Caspr2 encephalitis patients (11.4%) had identified tumors. One anti-LGI1 encephalitis patient found lung cancer, and two anti-Caspr2 encephalitis patients found thymoma at the time of autoimmune encephalitis onset. One anti-LGI1 encephalitis patient confirmed CNS lymphoma, and one anti-Caspr2 encephalitis patient confirmed ovarian teratoma at relapse. One anti-LGI1 encephalitis patient had a history of thyroid

**Table 1.** Comparison of demographic data and clinical manifestation at acute phase between anti-LGI1 encephalitis and anti-Caspr2 encephalitis.

	LGI1 (n=44)	Caspr2 (n=35)	Dual-positive (n=5)	p value, LGI1 versus Caspr2
Demographic data				
Sex (female), n (%)	25 (56.8%)	19 (54.3%)	5 (100%)	0.822 <sup>a</sup>
Age at onset, y, median (range)	44 (18-82)	43 (14-80)	44 (36-58)	0.270 <sup>b</sup>
Initial symptoms, n (%)				
Prodromal symptoms	9 (20.5%)	9 (25.7%)	0	0.580 <sup>a</sup>
CNS symptoms	44 (100%)	30 (85.7%)	4 (80%)	<b>0.034<sup>c</sup></b>
Seizures	28 (63.6%)	9 (25.7%)	0	<b>0.001<sup>a</sup></b>
Cognitive disturbance	9 (20.5%)	7 (20%)	4 (80%)	0.960 <sup>a</sup>
Psychiatric symptoms	7 (15.9%)	10 (28.6%)	0	0.174 <sup>a</sup>
Cerebellar ataxia	0	3 (8.6%)	0	0.165 <sup>c</sup>
Others	0	1 (2.3%)	0	0.443 <sup>d</sup>
Non-CNS symptoms	0	5 (14.3%)	1 (20%)	<b>0.034<sup>c</sup></b>
Cumulative symptoms				
CNS manifestations, n (%)				
Seizures	43 (97.7%)	14 (40%)	4 (80%)	< <b>0.001<sup>a</sup></b>
Focal seizures	25 (56.8%)	8 (22.9%)	2 (40%)	<b>0.002<sup>a</sup></b>
Generalized tonic-clonic seizures	23 (52.3%)	6 (17.1%)	3 (60%)	<b>0.001<sup>a</sup></b>
FBDS	20 (45.5%)	0	1 (20%)	< <b>0.001<sup>a</sup></b>
Status epilepticus	2 (4.5%)	2 (5.7%)	0	1.000 <sup>c</sup>
Cognitive disturbance	37 (84.1%)	21 (60%)	5 (100%)	<b>0.016<sup>a</sup></b>
Memory deficit	34 (77.3%)	15 (42.9%)	5 (100%)	<b>0.002<sup>a</sup></b>
Behavioral disorder	20 (45.5%)	12 (34.3%)	3 (60%)	0.315 <sup>a</sup>
Psychiatric symptoms	24 (54.5%)	16 (45.7%)	3 (60%)	0.435 <sup>a</sup>
Depression/anxiety	7 (15.9%)	8 (22.9%)	1 (20%)	0.434 <sup>a</sup>
Hallucination	16 (36.4%)	11 (31.4%)	3 (60%)	0.646 <sup>a</sup>
Paranoia	4 (9.1%)	8 (22.9%)	1 (20%)	0.063 <sup>a</sup>
Sleep disorders	20 (45.5%)	18 (51.4%)	3 (60%)	0.598 <sup>a</sup>
Movement disorders	2 (4.5%)	10 (28.6%)	0 (20%)	<b>0.003<sup>a</sup></b>
Involuntary movements	1 (2.3%)	7 (20%)	0	<b>0.026<sup>c</sup></b>
Parkinsonism	1 (2.3%)	3 (8.6%)	0	0.452 <sup>c</sup>

*(Continued)*

Table 1. (Continued)

	LGI1 (n=44)	Caspr2 (n=35)	Dual-positive (n=5)	p value, LGI1 versus Caspr2
Disturbance of consciousness	8 (18.2%)	5 (14.3%)	1 (20%)	0.643 <sup>a</sup>
Cerebellar symptoms	0	9 (25.7%)	0	<b>0.001<sup>c</sup></b>
PNS manifestations, n (%)				
Peripheral involvement	6 (13.6%)	7 (20%)	2 (40%)	0.449 <sup>a</sup>
Neuropathic pain	0	6 (17.1%)	1 (20%)	<b>0.015<sup>c</sup></b>
Peripheral nerve hyperexcitability syndrome	1 (2.3%)	6 (17.1%)	0	0.056 <sup>c</sup>
Sensorimotor symptoms	5 (11.4%)	5 (14.3%)	2 (40%)	0.962 <sup>c</sup>
Autonomic nervous system, n (%)				
Autonomic dysfunction	15 (34.1%)	13 (37.1%)	1 (20%)	0.778 <sup>a</sup>
Hyperhidrosis	6 (13.6%)	8 (22.9%)	0	0.286 <sup>a</sup>
Tachycardia	7 (15.9%)	4 (11.4%)	1 (20%)	0.807 <sup>c</sup>
Urinary retention/hesitation	3 (6.8%)	1 (2.9%)	0	0.779 <sup>c</sup>
Constipation	1 (2.3%)	3 (8.6%)	0	0.452 <sup>c</sup>
Erectile dysfunction	1 (2.3%)	1 (2.9%)	0	1.000 <sup>d</sup>
Other symptoms, n (%)				
Weight loss	5 (11.4%)	8 (22.9%)	2 (40%)	0.171 <sup>a</sup>
Tumor, n (%)	3 (6.8%)	4 (11.4%)	0	0.751 <sup>c</sup>

CNS, central nervous system; FBDS, faciobrachial dystonic seizures; LGI1, leucine-rich glioma-inactivated 1; PNS, peripheral nervous system. Bold entries indicate  $p < 0.05$ .  
<sup>a</sup>Pearson's  $\chi^2$  test.  
<sup>b</sup>Student's  $t$  test.  
<sup>c</sup>Chi-square test with continuity correction.  
<sup>d</sup>Fisher's exact test.

cancer, and one anti-Caspr2 encephalitis patient had a history of ovarian cancer, and both of them had the tumor removed before onset.

#### Ancillary test results

Comparison of laboratory test and auxiliary examinations results between anti-LGI1 encephalitis and anti-Caspr2 encephalitis is summarized in Table 2. Among the 44 patients with anti-LGI1 encephalitis, 12 patients were positive for anti-LGI1 antibodies only in the serum, 14 were positive only in the CSF, and 18 were positive in both the serum and CSF. Among the 35 patients with

anti-Caspr2 encephalitis, 23 (including 5 diagnosed with Morvan syndrome) were positive for anti-Caspr2 antibodies only in the serum, 5 were positive only in the CSF, and 7 were positive in both the serum and CSF.

Hyponatremia occurred more often in anti-LGI1 encephalitis patients (38.6%) than in anti-Caspr2 encephalitis patients (11.4%;  $p = 0.007$ ). The frequencies of elevated intracranial pressure and abnormalities in CSF examinations, including pleocytosis and increased protein level, were unremarkable in 79.5% anti-LGI1 encephalitis patients and 77.1% anti-Caspr2 encephalitis patients.

**Table 2.** Comparison of laboratory test and auxiliary examinations results between anti-LGI1 encephalitis and anti-Caspr2 encephalitis.

	LGI1 ( <i>n</i> =44)	Caspr2 ( <i>n</i> =35)	Dual-positive ( <i>n</i> =5)	<i>p</i> value, LGI1 versus Caspr2
Anti-LGI1 (Caspr2) antibodies, <i>n</i> (%)				
Serum positive only	12 (27.3%)	23 (65.7%)	1 (20%)	
CSF positive only	14 (31.8%)	5 (14.3%)	1 (20%)	
Both positive	18 (40.9%)	7 (20%)	3 (20%)	
Na (serum), <i>n</i> (%)				
Hyponatremia	17 (38.6%)	4 (11.4%)	2 (40%)	<b>0.007<sup>a</sup></b>
CSF, <i>n</i> (%)				
Pleocytosis	4 (9.1%)	0	0	0.189 <sup>b</sup>
Increase protein concentration	6 (13.6%)	8 (22.9%)	0	0.286 <sup>a</sup>
Increase ICP	3 (6.8%)	2 (5.7%)	0	1.000 <sup>b</sup>
EEG abnormal findings, <i>n</i> (%)				
Nonspecific and irregular slowing	14/43 (32.6%)	7/32 (21.9%)	1/5 (20%)	0.308 <sup>a</sup>
General slowing	2/43 (4.7%)	1/32 (3.1%)	0	1.000 <sup>b</sup>
Focal slowing	10/43 (23.3%)	4/32 (12.5%)	0	0.237 <sup>a</sup>
Epileptic discharge	15/43 (34.9%)	4/32 (12.5%)	1/5 (20%)	<b>0.027<sup>a</sup></b>
Brain MRI with specific changes, <i>n</i> (%)				
Mesial temporal lesion	17/43 (39.5%); 6 unilateral and 11 bilateral	5/32 (15.6%); 5 bilateral	0	<b>0.024<sup>a</sup></b>
Basal ganglia lesion	3/43 (7.0%)	2/32 (6.3%)	0	1.000 <sup>b</sup>
EMG abnormal findings, <i>n</i> (%)				
Nerve conduction abnormalities	1/3 (33.3%)	1/7 (14.3%)	NA	1.000 <sup>c</sup>
Hyperexcitability	1/3 (33.3%)	6/7 (85.7%)	NA	0.183 <sup>c</sup>
CSF, cerebrospinal fluid; EEG, electroencephalogram; EMG, electromyogram; ICP, intracranial pressure; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging. Bold entries indicate <i>p</i> < 0.05. <sup>a</sup> Pearson's $\chi^2$ test. <sup>b</sup> Chi-square test with continuity correction. <sup>c</sup> Fisher's exact test.				

Brain MRI with specific changes was found in 21 of 43 (48.8%) anti-LGI1 encephalitis patients and 9 of 32 (28.1%) anti-Caspr2 encephalitis patients. Hyperintensity on T2 signal of mesial temporal lesions was more frequent in anti-LGI1 encephalitis patients (39.5%) than in anti-Caspr2 encephalitis patients (15.6%, *p*=0.024). In 8 of 43

anti-LGI1 encephalitis patients (18.6%), hyperintensities extended to the insula (*n*=4), amygdala (*n*=3), or striatum (*n*=1). Basal ganglia lesions were observed in 3 of 43 anti-LGI1 encephalitis patients (7.0%) and 2 of 32 anti-Caspr2 encephalitis patients (6.3%). Hyperintensity on T2 signal in other regions was observed in six anti-LGI1

encephalitis patients (two frontal lobe, two occipital lobe, and three cingulate gyrus) and five anti-Caspr2 encephalitis patients (five frontal lobe). (two frontal lobe, two occipital lobe, and three cingulate gyrus) into (one frontal lobe, one occipital lobe, one both frontal lobe and occipital lobe, and three cingulate gyrus). One patient with anti-Caspr2 encephalitis showed cerebellar atrophy.

#### Treatment and long-term outcomes

Details of treatment at onset and outcomes in all patients are summarized in Supplementary Table 1. First-line immunotherapy including IV methylprednisolone (1000 mg for 3–5 days), IVIg (0.4 g/kg/d for 5 days), or a combination of both was initiated in 43 (97.7%) anti-LGI1 encephalitis patients and 30 (85.7%) anti-Caspr2 encephalitis patients, both with a median delay of 1.5 months (IQR: 1–4.1 and 0.6–4.4, respectively). Two anti-LGI1 encephalitis patients and one anti-Caspr2 encephalitis patient also received second-line immunotherapy (two cyclophosphamide and one rituximab). Two anti-Caspr2 encephalitis patients found thymoma at onset also received removal surgery. Except for three anti-LGI1 encephalitis patients (7%) and three anti-Caspr2 encephalitis patients (10%), all patients had a good response to the initial immunotherapy. One anti-LGI1 encephalitis patient and three anti-Caspr2 encephalitis patients mainly had seizures refused immunotherapy and only received antiepileptic drugs. Two anti-Caspr2 encephalitis patients, one mainly had psychiatric symptoms, and another only had cerebellar ataxia refused any treatment. The median mRS score decreased from 3 at baseline to 2 at 4 weeks after initial therapy of each encephalitis.

The mRS scores evaluated over different follow-up points in anti-LGI1 encephalitis patients and anti-Caspr2 encephalitis patients are summarized in Figure 1(e) and (f), respectively. Overall, 86.4% anti-LGI1 encephalitis patients and 80% anti-Caspr2 encephalitis had a favorable neurological functional outcome (mRS 0–2) at the last follow-up. The median mRS score at final follow-up was 0 in both encephalitis, which is significantly decreased compared with the median mRS score of 3 at onset (Wilcoxon test:  $Z = -4.549$ ,  $p < 0.001$ ). One anti-LGI1 encephalitis patient died due to comorbidities of lung cancer, another died due to poor treatment response at relapse and CNS lymphoma progression. One anti-Caspr2

encephalitis patient died at the initial stage due to neurological disease progression and respiratory failure.

Follow-up  $\geq 1$  year was available in 35 anti-LGI1 encephalitis patients and 26 anti-Caspr2 encephalitis patients, with 44 and 18 months median follow-up, respectively. Comparisons among patients with  $\geq 1$ -year follow-up between favorable functional outcomes group and poor functional outcomes group in each encephalitis are summarized in Table 3. In univariate analysis, the factors associated with poor functional outcomes included weight loss ( $p = 0.002$ ) and the presence of tumor ( $p = 0.017$ ) among patients with anti-LGI1 encephalitis. Among anti-Caspr2 encephalitis patients, the factors associated with poor functional outcomes included age at onset  $< 30$  years ( $p = 0.013$ ), higher mRS scores at onset ( $p = 0.04$ ), behavioral disorder at acute phase ( $p = 0.018$ ), abnormal brain MRI ( $p = 0.045$ ), poor response to the initial immunotherapy ( $p = 0.04$ ), and occurrence of relapse ( $p = 0.028$ ). Multivariate analysis of independent predictors of poor functional outcomes is not available due to the limited number of cases.

In patients with  $\geq 1$ -year follow-up, residual symptoms were reported by 80% anti-LGI1 encephalitis patients and 38.5% anti-Caspr2 encephalitis patients at last follow-up. Among 35 anti-LGI1 encephalitis patients, a total of 77.1% of patients had memory deficits, and 71.4% of patients reported persistent amnesia for the disease period. Seizures were recovered within 3 months in 26 (76.4%) patients (including 13 with FBDS) who had seizures at onset, and 4 (11.8%) still had seizures (including 2 with FBDS) in the last year and were on antiepileptic drugs at last follow-up. Other residual symptoms included sleep disorder ( $n = 4$ ), psychiatric symptoms ( $n = 2$ ), and tremor ( $n = 1$ ). Among 26 anti-Caspr2 encephalitis patients, residual symptoms included memory deficits ( $n = 6$ ), psychiatric symptoms ( $n = 5$ ), sleep disorder ( $n = 3$ ), dystonia ( $n = 1$ ), cerebella ataxia ( $n = 1$ ), and neuropathic pain ( $n = 1$ ). None of these anti-Caspr2 encephalitis patients were still on antiepileptic drugs or having seizures in the last year at last follow-up.

#### Relapse

In total, six anti-LGI1 encephalitis patients (13.6%) and seven anti-Caspr2 encephalitis



**Table 3.** Comparison between good outcome group and poor outcome group in patients with follow-up  $\geq 1$  year.

Variables	LG11			Caspr2		
	Good outcomes (n = 30)	Poor outcomes (n = 5)	p value	Good outcomes (n = 20)	Poor outcomes (n = 6)	p value
Demographic						
Sex (female), n (%)	14 (46.7%)	4 (80.0%)	0.338 <sup>a</sup>	10 (50%)	6 (100%)	0.053 <sup>a</sup>
Age >40y (Caspr2: age <30 y)	16 (53.3%)	4 (80%)	0.365 <sup>a</sup>	2 (10%)	4 (66.7%)	<b>0.013<sup>a</sup></b>
Symptoms, n (%)						
Prodromal symptoms	8 (26.7%)	0	0.315 <sup>a</sup>	6 (30%)	0	0.280 <sup>a</sup>
Seizures	29 (96.7%)	5 (100%)	1.000 <sup>a</sup>	7 (35%)	1 (16.7%)	0.628 <sup>a</sup>
FBDS	12 (40%)	3 (60%)	0.631 <sup>a</sup>	0	0	1.000 <sup>a</sup>
Focal seizures	16 (53.3%)	3 (60%)	1.000 <sup>a</sup>	5 (25%)	1 (16.7%)	1.000 <sup>a</sup>
Generalized tonic-clonic seizures	18 (60%)	1 (20%)	0.156 <sup>a</sup>	2 (10%)	0	1.000 <sup>a</sup>
Status epilepticus	1 (3.3%)	1 (20%)	0.269 <sup>a</sup>	1 (5%)	0	1.000 <sup>a</sup>
Cognitive disturbance	27 (90%)	4 (80%)	0.477 <sup>a</sup>	12 (60%)	5 (83.3%)	0.380 <sup>a</sup>
Memory deficit	24 (80%)	4 (80%)	1.000 <sup>a</sup>	9 (45%)	3 (50%)	1.000 <sup>a</sup>
Behavioral disorder	15 (50%)	2 (40%)	1.000 <sup>a</sup>	5 (25%)	5 (83.3%)	<b>0.018<sup>a</sup></b>
Psychiatric symptoms	17 (56.7%)	4 (80%)	0.627 <sup>a</sup>	9 (45%)	4 (66.6%)	0.645 <sup>a</sup>
Depression/anxiety	4 (13.3%)	1 (20%)	0.561 <sup>a</sup>	3 (15%)	3 (50%)	0.112 <sup>a</sup>
Hallucination	12 (40%)	3 (60%)	0.631 <sup>a</sup>	7 (35%)	3 (50%)	0.644 <sup>a</sup>
Paranoia	3 (10%)	1 (20%)	0.477 <sup>a</sup>	5 (25%)	2 (33.3%)	1.000 <sup>a</sup>
Sleep disorder	14 (46.7%)	3 (60%)	0.658 <sup>a</sup>	13 (65%)	3 (50%)	0.644 <sup>a</sup>
Movement disorder	2 (6.7%)	0	1.000 <sup>a</sup>	3 (15%)	3 (50%)	0.112 <sup>a</sup>
Disturbance of consciousness	5 (16.7%)	3 (60%)	0.067 <sup>a</sup>	2 (10%)	1 (16.7%)	1.000 <sup>a</sup>
Cerebellar ataxia	0	0	1.000 <sup>a</sup>	5 (25%)	2 (25%)	1.000 <sup>a</sup>
Peripheral involvement	6 (20%)	0	0.561 <sup>a</sup>	7 (35%)	0	0.146 <sup>a</sup>
Neuropathic pain	0	0	1.000 <sup>a</sup>	6 (30%)	0	0.280 <sup>a</sup>
Peripheral nerve hyperexcitability	1 (3.3%)	0	1.000 <sup>a</sup>	6 (30%)	0	0.280 <sup>a</sup>
Sensorimotor symptoms	5 (16.7%)	0	1.000 <sup>a</sup>	5 (25%)	0	0.298 <sup>a</sup>
Autonomic symptoms	9 (30%)	3 (60%)	0.313 <sup>a</sup>	9 (45%)	1 (16.7%)	0.352 <sup>a</sup>
Hyperhidrosis	3 (10%)	1 (20%)	0.477 <sup>a</sup>	6 (30%)	0	0.280 <sup>a</sup>
Tachycardia	4 (13.3%)	1 (20%)	0.561 <sup>a</sup>	2 (10%)	1 (16.7%)	1.000 <sup>a</sup>

*(Continued)*

Table 3. (Continued)

Variables	LGI1			Caspr2		
	Good outcomes (n=30)	Poor outcomes (n=5)	p value	Good outcomes (n=20)	Poor outcomes (n=6)	p value
Urinary retention/incontinence	2 (6.7%)	1 (20%)	0.380 <sup>a</sup>	1 (5%)	0	1.000 <sup>a</sup>
Constipation	1 (3.3%)	0	1.000 <sup>a</sup>	0	0	1.000 <sup>a</sup>
Hyposexuality	1 (3.3%)	0	1.000 <sup>a</sup>	1 (5%)	0	1.000 <sup>a</sup>
Weight loss	0	3 (60%)	<b>0.002<sup>a</sup></b>	6 (30%)	1 (16.7%)	1.000 <sup>a</sup>
Tumor	0	2 (40%)	<b>0.017<sup>a</sup></b>	2 (10%)	2 (25%)	0.218 <sup>a</sup>
Auxiliary examinations, n (%)						
Hyponatremia	11 (36.7%)	1 (20%)	0.640 <sup>a</sup>	2 (10%)	0	1.000 <sup>a</sup>
CSF						
Pleocytosis	4 (13.3%)	0	1.000 <sup>a</sup>	0	0	1.000 <sup>a</sup>
Increase protein concentration	3 (10%)	0	1.000 <sup>a</sup>	2 (10%)	1 (16.7%)	1.000 <sup>a</sup>
Increase ICP	1 (3.3%)	0	1.000 <sup>a</sup>	2 (10%)	0	1.000 <sup>a</sup>
EEG abnormal findings	28/29 (96.6%)	4 (80%)	0.276 <sup>a</sup>	12/18 (66.7%)	1 (16.7%)	0.061 <sup>a</sup>
Brain MRI with specific changes	14/29 (48.3%)	2 (40%)	1.000 <sup>a</sup>	3/17 (17.6%)	4 (66.7%)	<b>0.045<sup>a</sup></b>
Titer of antibodies in serum			1.000 <sup>a</sup>			1.000 <sup>a</sup>
Negative	8 (26.7%)	1 (20%)		3 (15%)	1 (16.7%)	
≤1:32	11 (36.7%)	2 (40%)		14 (70%)	4 (66.7%)	
≤1:320	10 (33.3%)	2 (40%)		3 (15%)	1 (16.7%)	
>1:320	1 (3.3%)	0		0	0	
Titer of antibodies in CSF			0.301 <sup>a</sup>			1.000 <sup>a</sup>
Negative	11 (36.7%)	1 (20%)		13 (70%)	4 (66.7%)	
≤1:3.2	7 (23.3%)	0		2 (10%)	1 (16.7%)	
≤1:32	9 (30%)	4 (80%)		5 (25%)	1 (16.7%)	
>1:32	3 (20%)	0		0	0	
Treatments and outcomes						
Maximum mRS scores at onset (median, IQR)	3 (2-3)	4 (4-5)	0.63 <sup>b</sup>	3 (2-3)	4 (3-4)	<b>0.04<sup>b</sup></b>
First-line immunotherapy, n (%)			0.089 <sup>a</sup>			0.497 <sup>a</sup>
IV methylprednisolone alone	9 (30%)	0		6 (30%)	0	
IVIg alone	7 (23.3%)	2 (40%)		5 (25%)	2 (33.3%)	

(Continued)

**Table 3.** (Continued)

Variables	LGI1			Caspr2		
	Good outcomes (n=30)	Poor outcomes (n=5)	p value	Good outcomes (n=20)	Poor outcomes (n=6)	p value
IV methylprednisolone combined with IVIg	14 (46.7%)	2 (40%)		7 (35%)	3 (50%)	
None	0	1 (20%)		2 (10%)	1 (37.5%)	
Poor response to the initial immunotherapy, n (%)	2 (6.7%)	1/4 (25%)	0.322 <sup>a</sup>	0/18	2/5 (40%)	<b>0.04<sup>a</sup></b>
First immunotherapy day ≥ 30 d from onset, n (%)	18 (60%)	5 (100%)	0.141 <sup>a</sup>	12 (60%)	5 (83.3%)	0.380 <sup>a</sup>
Length of hospital stay at first onset (d, mean, ± SD)	16.3 ± 6.2	19 ± 7.3	0.392 <sup>c</sup>	14.0 ± 4.2	17.3 ± 6.5	0.291 <sup>c</sup>
Follow-up duration (mo, median, IQR)	56 (22.3-63.8)	24 (18-50)	0.395 <sup>b</sup>	17 (13.5-20.3)	24.5 (15.5-30.5)	0.232 <sup>b</sup>
ICU admission, n (%)	1 (3.3%)	0	1.000 <sup>a</sup>	0	0	1.000 <sup>a</sup>
Relapse, n (%)	4 (13.3%)	2 (40%)	0.195 <sup>a</sup>	3 (15%)	4 (66.7%)	<b>0.028<sup>a</sup></b>

CSF, cerebrospinal fluid; EEG, electroencephalogram; EMG, electromyogram; FBDS, faciobrachial dystonic seizures; ICP, intracranial pressure; ICU, intensive care unit; IQR, interquartile range; IVIg, IV immunoglobulin; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; SD, standard deviation.  
 Bold entries indicate  $p < 0.05$ .  
<sup>a</sup>Fisher's exact test.  
<sup>b</sup>Mann-Whitney  $U$  test.  
<sup>c</sup>Student's  $t$  test.

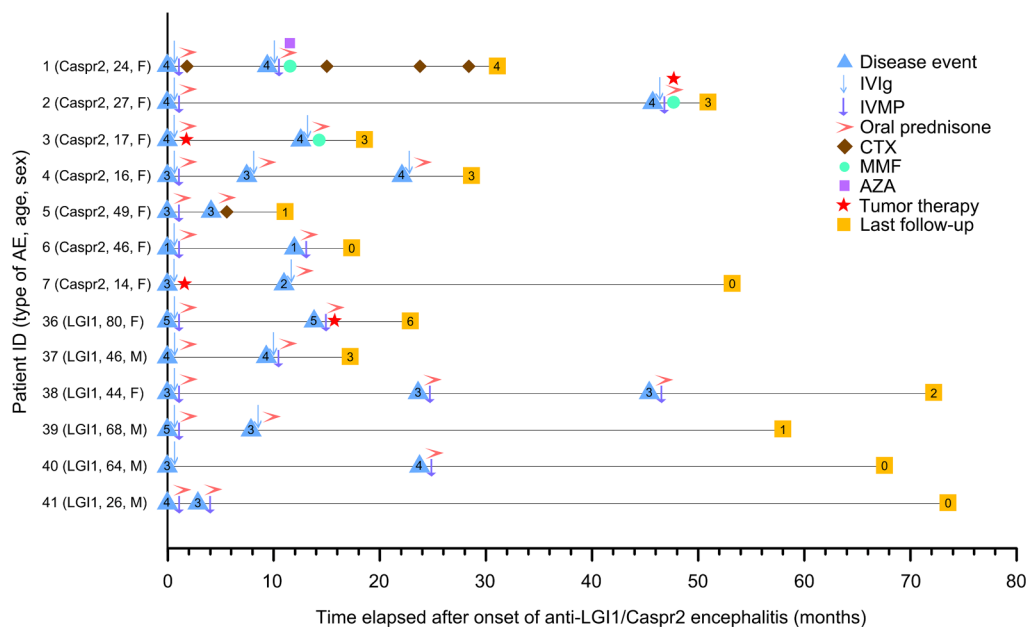
patients (20%) had at least one relapse at last follow-up. The details of disease course and treatment of each patient with relapse are shown in Figure 2. The median time from initial onset to the first relapse was 12.5 months (range: 3–24 months) and 12 months (range: 5–48 months), respectively. About half of these patients (53.8%) had the first relapse during the first year after the first onset. One anti-LGI1 encephalitis patient and one anti-Caspr2 encephalitis patient experienced a second relapse.

At relapse, six anti-LGI1 encephalitis patients and six anti-Caspr2 encephalitis patients had symptoms similar to those of the first episode. However, one anti-Caspr2 encephalitis patient developed severe dystonia, which did not occur during the first episode. Two patients had severer condition and higher mRS scores at relapse than that at the first onset. One anti-LGI1 encephalitis

patient found CNS lymphoma, and one anti-Caspr2 encephalitis patient found ovarian teratoma during the relapse.

The changes of antibody titers in relapse patients are shown in Supplementary Figure 1. All except one anti-LGI1 encephalitis patient had tested positive for the antibodies in the serum and/or CSF at relapse. In anti-LGI1 encephalitis patients with relapse, antibody titer changed in the CSF and the serum as expectation (decrease at remission after immunotherapy and increase at relapse) in two of five and three of five clinical changes, respectively. In anti-Caspr2 encephalitis patients with relapse, antibody titer changed in the CSF and the serum as expectation in two of seven and seven of seven clinical changes, respectively.

Except for one anti-Caspr2 encephalitis patient received only cyclophosphamide, all these patients



**Figure 2.** Disease and treatment courses in 13 patients with relapses. Each line shows the disease course and the treatment of the patient with relapse. The triangles represent disease events, which included the disease initial onset and relapse episode. The numbers in the triangles and squares represent the modified Rankin scale scores during the event and at the last follow-up, respectively. AZA, oral prednisone; Caspr2, contactin-associated protein-like 2; CTX, cyclophosphamide; IVIG, IV immunoglobulin; IVMP, IV methylprednisolone; LGI1, leucine-rich glioma-inactivated 1; MMF, mycophenolate mofetil.

had reinitiated first-line immunotherapy after the first relapse, and three anti-Caspr2 encephalitis patients also received second-line immunotherapy (one cyclophosphamide, azathioprine, and mycophenolate mofetil). The patient who found ovarian teratoma at relapse also underwent a tumor removal surgery. Except for one anti-LGI1 encephalitis patient and one anti-Caspr2 encephalitis patient, all these patients had improved after the treatment.

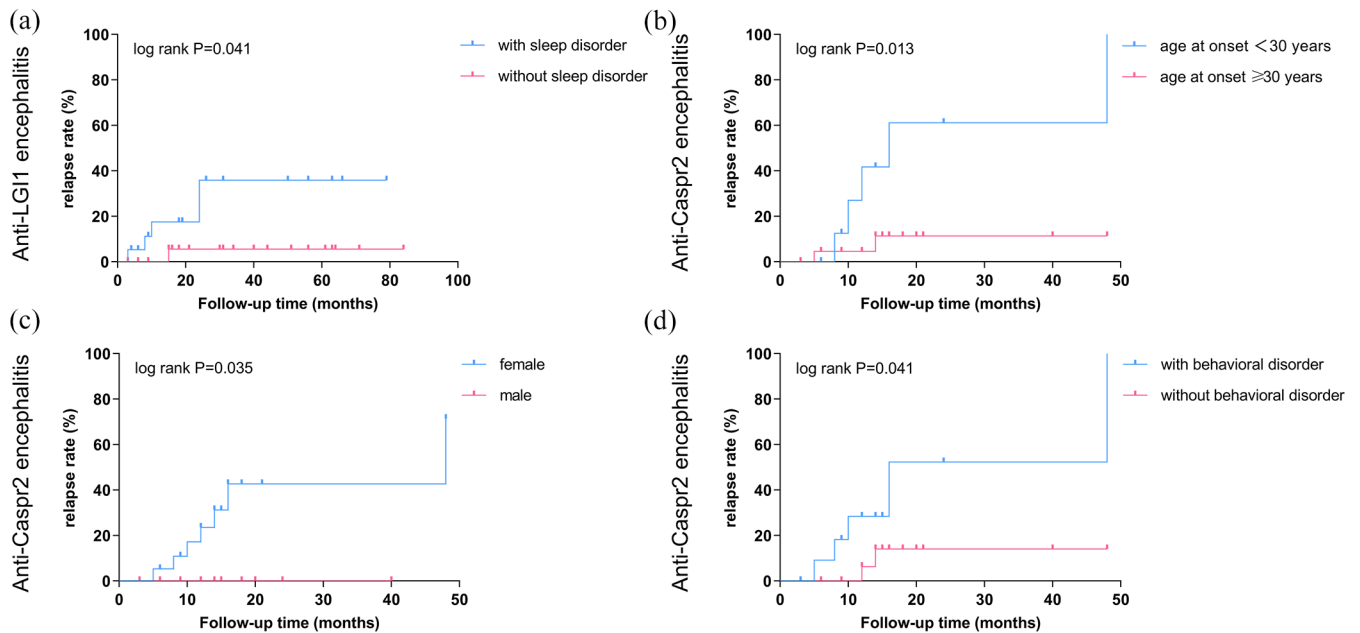
Univariate analyses of risk factors of relapse with the Kaplan–Meier method are shown in Supplementary Table 2. One anti-LGI1 encephalitis patient and one anti-Caspr2 encephalitis patient who died before the first relapse were excluded. The results suggested that anti-LGI1 encephalitis patients with sleep disorders at the acute phase had a higher risk of relapse (log rank  $p=0.041$ ). Female (log rank  $p=0.035$ ), age at onset  $<30$  years (log rank  $p=0.013$ ), and behavioral disorder at acute phase (log rank  $p=0.041$ ) were the risk factors of relapse in anti-Caspr2 encephalitis patients (Figure 3). Multivariate analyses of independent predictors of relapse were not available due to the limited number of cases.

## Discussion

This prospective cohort study first provided the detailed clinical character of anti-LGI1 encephalitis patients and anti-Caspr2 encephalitis patients in western China. The long-term functional outcomes and relapses and the predictors of poor long-term functional outcomes and relapse were also reported.

To better demonstrate the results of this study, we compared the demographic characteristics, disease characteristics, and prognosis of patients in western China of this study with those in other regions. The representative studies are summarized in Supplementary Tables 3 and 4.

In our study, the proportions of female patients are higher than that of male patients, while the ages at onset are younger, both in anti-LGI1 encephalitis and anti-Caspr2 encephalitis, which were different from most studies of Western countries.<sup>1,6–10,11,12,21–23</sup> The differences in age and gender distribution may be due to the varied genetic background and the small number of each cohort.



**Figure 3.** Kaplan–Meier curves showing the relapse rate over time in patients with anti-LGI1 encephalitis and anti-Caspr2 encephalitis. Kaplan–Meier curve shows that anti-LGI1 encephalitis patients with sleep disorder (log rank  $p=0.041$ ) had an increased risk of relapse (a). Kaplan–Meier curves show that anti-Caspr2 encephalitis patients with behavioral disorder (log rank  $p=0.041$ ), age at onset  $<30$  years (log rank  $p=0.013$ ), and female patients (log rank  $p=0.035$ ) had an increased risk of relapse (b–d).

In general, the main symptoms of anti-LGI1 encephalitis in our cohort are comparable with the previous study.<sup>12</sup> In this study, the most common symptoms of anti-LGI1 encephalitis were seizures (97.7%) and cognitive disturbance (84.1%). FBDS, a highly specific focal seizure semiology associated with anti-LGI1 encephalitis, was observed in 45.5% of anti-LGI1 encephalitis patients in our study, comparable with 34–53% reported by previous studies in Western countries.<sup>7–9,21,22</sup> Among 15 patients with  $\geq 1$ -year follow-up with FBDS, cessation of FBDS was observed in 13 (86.7%) of them 3 months after initial immunotherapy, which is close to that reported by Thompson *et al.*<sup>24</sup> As it has been proved that expedited immunotherapy can reduce the long-term disability associated with cognitive impairment caused by FBDS, timely recognition of FBDS and immunotherapy are necessary for clinical practice.<sup>24</sup>

Unlike LGI1, Caspr2 is not only present in the CNS, but also widely expressed in the PNS, forming a transmembrane axonal complex.<sup>4</sup> Therefore, compared with anti-LGI1 encephalitis, the symptoms of anti-Caspr2 encephalitis are more various, and some patients may have

peripheral involvement. In our cohort, 40% of patients had seizures and 60% of patients had cognitive disorders, which is comparable with the previously reported incidences of 20–89% and 39–94%, respectively.<sup>1,10,11,21,23,25</sup> In total, 17.1% anti-Caspr2 encephalitis patients were diagnosed Morvan syndrome, which is lower than the reported incidence of 29% and 53% by van Sonderan *et al.*<sup>11</sup> and Irani *et al.*,<sup>1</sup> but higher than the incidences of 9% and 16% reported by Bien *et al.*<sup>23</sup> and Qin *et al.*,<sup>25</sup> respectively. The different incidences of Morvan syndrome may be due to the diverse awareness of the disease and the small sample of each cohort. It was worth noting that five of them had peripheral neurological symptoms (four neuropathic pain, three myokymia, and one muscle cramps) as the initial symptom, which is more frequent than patients who have not diagnosed with Morvan syndrome (83.3% *versus* 0,  $p<0.001$ ). Joubert *et al.*<sup>10</sup> suggested that autoimmune reaction is strictly developed outside of the CNS in patients with Morvan syndrome or neuromyotonia as anti-Caspr2 antibodies were always undetectable in the CSF among these patients. However, one patient diagnosed with Morvan syndrome in our cohort found anti-Caspr2 antibodies in both the CSF and the

serum, indicating the autoimmune reaction may also develop in CNS in Morvan syndrome. Recently, the addition of paroxysmal cerebellar ataxias to the spectrum of the anti-Caspr2 antibody-related neurological syndrome was proposed.<sup>26</sup> However, the cerebellar ataxia was persistent in all the nine anti-Caspr2 encephalitis patients with cerebellar symptoms in our cohort. As paroxysmal symptoms are easier to be ignored in clinical observation and may cause omission, a longer and detailed follow-up may be necessary to observe this newly described anti-Caspr2 antibody syndrome.

Tumor is a common comorbid to autoimmune encephalitis. However, the incidence of tumor occurrence in anti-LGI1 encephalitis was relatively lower than other types of autoimmune encephalitis.<sup>19,27,28</sup> The tumor occurrence rate in anti-LGI1 encephalitis was 6.8% in our cohort, which is comparable with the reported incidences of 0–13% in the previous studies of Western countries.<sup>1,6–9,12,21,22</sup> Compared with anti-LGI1 encephalitis, tumor occurrence is more frequent in anti-Caspr2 encephalitis in our cohort with a rate of 11.4%, which is relatively lower than most previous studies in Western countries.<sup>1,10,11,21</sup> The differences could be due to the limited number of cases and relatively short follow-up for some patients. However, we also could not ignore the differences in genetic background characteristics because previous cohort studies of anti-NMDAR encephalitis and anti-GABA<sub>B</sub>R encephalitis by our team also revealed lower incidences of tumor occurrence compared with European and American case series.<sup>13,14</sup> Notably, two patients in our cohort found tumors at relapse although they already went through a thorough tumor screening at the first onset. It suggested that tumor could trigger autoimmune encephalitis both in first onset and relapse, which highlighted the importance of comprehensive tumor screening at relapse.

Most patients in our cohort showed improvement after the first-line immunotherapy (IVIg, IV corticosteroids, or a combination of both). Among patients who received first-line immunotherapy, only 7% anti-LGI1 encephalitis patients and 10% anti-Caspr2 encephalitis patients had poor response to the initial immunotherapy at 4 weeks, which is in agreement with that reported by van Sonderen *et al.*<sup>11,12</sup> The symptom improvement rate within 4 weeks after immunotherapy was higher compared with 53% in anti-NMDAR

encephalitis.<sup>19</sup> Second-line immunotherapy was only applied in three of all patients at the first onset. It has been considered that both anti-LGI1 and anti-Caspr2 encephalitis show good responses to immunotherapies, especially in nonparaneoplastic conditions.<sup>1</sup> However, the responses to immunotherapies showed no significant differences between paraneoplastic and nonparaneoplastic conditions in our cohort, which might be due to a few numbers of tumor patients. In general, our cohort showed good long-term neurological functional outcomes and low mortality rates in both anti-LGI1 encephalitis and anti-Caspr2 encephalitis. Among patients with follow-up  $\geq 1$  year, 85.7% of anti-LGI1 encephalitis patients and 76.9% of anti-Caspr2 encephalitis patients had good neurological functional outcomes (mRS  $\leq 2$ ). The mortality rate in all patients was 4.5% in anti-LGI1 encephalitis and 2.9% in anti-Caspr2 encephalitis at the last follow-up, which was slightly lower than that reported in our previous study on anti-NMDAR encephalitis.<sup>14</sup> Cohort studies in a larger sample size with longer follow-up are needed to confirm these findings.

At final follow-up, 13.6% of anti-LGI1 encephalitis patients and 20% of anti-Caspr2 encephalitis patients had a relapse, which is in agreement with the previous cohort study (Supplementary Tables 3 and 4). Considering some of the relapses may occur years after the first onset, the relapse rate might be underestimated.<sup>12</sup> The relapse rates of both types of autoimmune encephalitis did not show a significant difference between different immunotherapy strategies in our study, which does not agree with Zhao *et al.*<sup>29</sup> Further trial studies are needed to evaluate the correlation between relapse and immunotherapy strategy. Recently, a study in anti-NMDAR encephalitis indicated that clinical relapses and remissions are correlated with antibody titers.<sup>30</sup> We also observed this correlation in patients with anti-LGI1 or anti-Caspr2 encephalitis. Given the limited sample size, these findings require more extensive cohort studies to verify. We also found that sleep disorder at acute phase (log rank  $p=0.041$ ) was the predictors of relapse in anti-LGI1 encephalitis, whereas in anti-Caspr2 encephalitis, the predictors including age at onset  $<30$  years (log rank  $p=0.013$ ), female (log rank  $p=0.035$ ), and with behavioral disorders at acute phase (log rank  $p=0.041$ ). Although these predictors were easily interfered with by the follow-up time, sample

size, and evaluation methods, aggressive therapy may benefit these patients.<sup>27</sup>

Our study has several limitations. First, multivariate analyses of the predictors of poor long-term functional outcomes and relapse could not be performed due to the limited cases in our cohort. Second, only a few patients received second-line immunotherapy, therefore the efficacy of second-line immunotherapy could not be further evaluated. Third, as discussed in a recent study that the mRS might be insensitive to fully reflect the neurological recovery in anti-LGI1/Caspr2 encephalitis,<sup>31</sup> more distinct scales should be designed to evaluate the neurological improvements in these patients. Finally, the follow-up time of anti-Caspr2 encephalitis patients is relatively short.

### Conclusion

Different characteristics of patients with anti-LGI1 encephalitis or anti-Caspr2 encephalitis in western China were revealed and compared with other populations in the study. Compared with the previous studies in Western countries, patients in western China are younger and female predominant in both anti-LGI1 encephalitis and anti-Caspr2 encephalitis. Besides, there are fewer anti-Caspr2 encephalitis patients with Morvan syndrome and tumors. While similar to the previous reports, most patients with anti-LGI1 encephalitis or anti-Caspr2 encephalitis in western China had a good response to immunotherapy and a favorable long-term neurological functional outcome. The relapse rates are still high in both encephalitis, which should not be ignored.

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### Author contributions

**Kundian Guo:** Major role in the acquisition of data; analyzed the data; drafted the manuscript.

**Xu Liu:** Major role in the acquisition of data; analyzed the data.

**Jingfang Lin:** Collected clinical information.

**Xue Gong:** Collected clinical information.

**Aiqing Li:** Collected clinical information.

**Yue Liu:** Collected clinical information.

**Dong Zhou:** Revised the manuscript for intellectual content.

**Zhen Hong:** Design and conceptualized study; revised the manuscript for intellectual content.

### Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


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### Ethics statement

This study was approved by the Research Ethics Committee of West China Hospital of Sichuan University (approval number: 292). All participants provided written informed consent for the use of their medical records. All patient data were kept strictly anonymous.

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### Data availability

The data from this study are available from the corresponding author upon reasonable request.

### Supplemental material

Supplemental material for this article is available online.

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