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Anti-leucine-rich glioma inactivated-1 autoimmune encephalitis: A review of diagnosis and treatment

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Abstract

Anti-leucine-rich glioma inactivated-1 (LGI1) autoimmune encephalitis is the second most common autoimmune encephalitis, usually with acute or subacute onset. The rates of misdiagnosis and missed diagnosis are high because of its insidious onset. We review the pathogenesis, clinical manifestations, differential diagnosis, treatment, and prognosis of anti-LGI1 autoimmune encephalitis, so as to provide references for clinicians to understand this disease. This disease presents with a variety of clinical manifestations, including faciobrachial dystonic seizure (FBDS), cognitive impairment, hyponatremia, hyperkinetic movements (HMs), and mental impairment. ^{18}F-fluorodeoxyglucose position emission tomography (^{18}F-FDG PET) has higher sensitivity than magnetic resonance imaging (MRI) and can be used to measure disease activity and assess patient response to treatment. The detection of LGI1 antibodies in cerebrospinal fluid or serum is a confirmatory test. The rapid initiation of immunotherapy after diagnosis can significantly improve the prognosis of patients.

Keywords: Autoimmune encephalitis; Leucine-rich glioma-inactivated-1; Faciobrachial dystonic seizure; Immunotherapy

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1. Introduction

Autoimmune encephalitis (AE) generally refers to a type of encephalitis that is mediated by autoimmune mechanisms. AE can be divided into three main types according to different anti-neuronal antibodies and their corresponding clinical syndromes: anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, limbic encephalitis (including anti-leucine-rich glioma inactivated-1 [LGI1] antibody, anti-γ-aminobutyric acid type B receptor [$GABA_BR$] antibody, and anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR] antibody-related encephalitis), and other AE syndromes[1]. LGI1 is a neuronal secretory glycoprotein, mainly expressed in the hippocampus and temporal lobe cortex. It participates in the development and physiological function of the central nervous system[2]. LGI1 antibody-associated limbic encephalitis was discovered by Irani *et al*. in 2010, accounting for about 25% of autoimmune encephalitis[2]. It is common in

the elderly, affecting more males than females. Its clinical manifestations are characterized by faciobrachial dystonic seizure (FBDS), cognitive disorders, mental disorders, and refractory hyponatremia.

2. Etiology and pathogenesis

LGI1 is a glycoprotein secreted by the presynaptic membrane. It is mainly expressed in the hippocampus and temporal cortex but is also weakly expressed in the basal ganglia and the inner cerebral cortex[3,4]. It connects presynaptic voltage-gated potassium channels (VGKC) and postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)[5,6]. LGI1 antibody inhibits the binding of LGI1 protein to A Disintegrin And Metalloproteinase 22/23 (ADAM22/23)[7], a metalloproteinase in the synaptic space, through its epitempin (EPTP) domain, and reduces the AMPAR function of inhibitory interneurons. In the hippocampus, inhibitory interneurons constitute a strong feedback or feed forward inhibition loop; thus, the decreased activity of inhibitory interneurons may lead to over-excitation of the whole network[8], resulting in the occurrence of FBDS. It has been found[5] that the knockout of LGI1 gene may cause autosomal dominant lateral temporal epilepsy (ADLTE)[9,10].

Fukata *et al.*[11] showed that the LGI1-ADAM22 complex can form a cross-synaptic heterodimer complex, which is composed of three major parts: the presynaptic part, which includes ADAM23 and the Kv1 channel; the synaptic cleft part, which includes LGI1 protein; and the postsynaptic part, which includes ADAM22, postsynaptic density protein 95 (PSD-95), regulatory protein Stargazin, and AMPAR (Figure 1)[12]. In the physiological state, the Kv1 channel that is located in the presynaptic membrane is activated at the membrane potential near the discharge threshold of neuron[13], which limits and delays the discharge of neuron, thus inhibiting the secretion of the excitatory neurotransmitter glutamate. Glutamate activates AMPAR in the postsynaptic membrane, and the opening of the sodium (Na^+) influx channel mediates postsynaptic excitatory current[14]. Several studies have shown that the loss of LGI1 increases excitatory synaptic transmission, whereas the overexpression of LGI1 decreases glutamate synaptic transmission[15-17]. In a study, Schulte *et al.* transfected oocytes with plasmids expressing Kv1.1, Kv1.4, and Kvβ1 channels and electrophysiologically recorded potassium currents in the presence of endogenous LGI1. They observed that LGI1 prevented the rapid inactivation of Kv1.1 channel via the Kvβ1 subunit. Therefore, it was speculated that LGI1 antibody may mediate the rapid inactivation of Kv1 channel. Lancaster *et al.* have also demonstrated that independent ADAM22 alone had no effect on Kv1.1 current, while the presence of LGI1

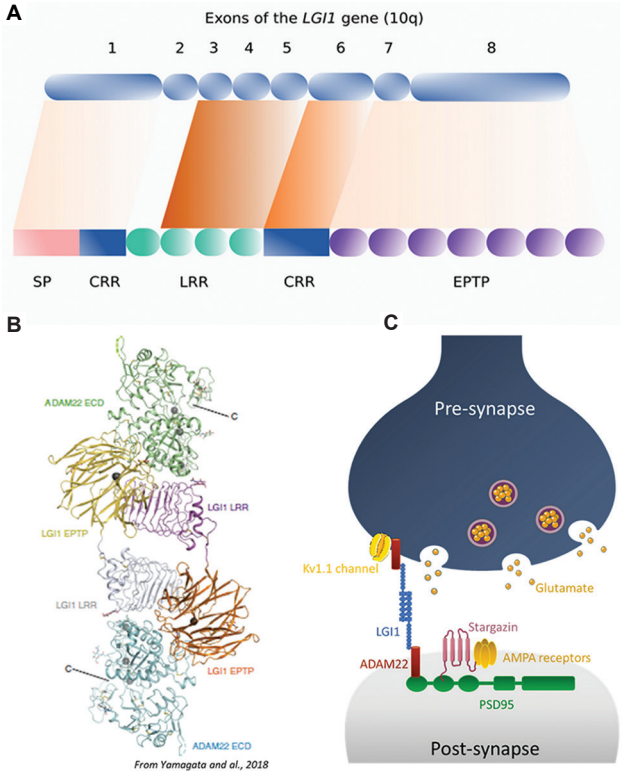

Figure 1. (A-C) *LGI1* gene structure and interaction. (Adapted from Fels *et al.*, 2021, Role of LGI1 protein in synaptic transmission: From physiology to pathology, *Neurobiol Dis*, 160: 105537. http://doi.org/10.1016/j.nbd.2021.105537).

and ADAM22 increased Kv1.1 current[18]. In addition, it has been shown that LGI1 antibodies can induce the internalization of Kv1 channel and its protein complex[19]. These may be the possible mechanisms of FBDS in patients with antibody-LGI1 autoimmune encephalitis (anti-LGI1 AE).

Multiple studies have shown that anti-LGI1 AE is related to human leukocyte antigen (HLA)[20-25], and Ding *et al.* have reported a familial case supporting this genetic association[26]. To date, several studies have conducted HLA genotyping and genome-wide association studies (GWAS) on anti-LGI1 AE patients in different populations, including the Caucasian population[22,23,25,27], Korean population[24], and Southwest Han population[21], revealing significant associations between unique HLA subtypes and anti-LGI1 AE. A genome-wide association study (GWAS) that was conducted in Germany[23] has found that anti-LGI1 AE is associated with 27 single nucleotide polymorphisms (SNPs) that are located in the major histocompatibility complex II (*MHC II*) gene region (between *HLA-DRB1* and *HLA-DQA1*) and that *DRB1*07:01* and *DQA1*02:01* always appeared in all patients. In addition, a study in South Korea has found a high frequency of *B*44:03* and

*C*07:06 HLA I* alleles in patients with anti-LGI1 AE, suggesting that the pathogenesis of this disease may also be related to *HLA I* genes[24]. A French study that performed HLA genotyping in patients with anti-LGI1 AE[27] has found that 88% of patients carried *DRB1*07:01*, with noncarriers being more likely to be young women and less likely to have psychiatric symptoms. It may be that estrogen can alter the expression of HLA[28]. However, the only study in the Chinese Han population has shown no evidence of association between *DRB1*07:01~DQB1*02:02* haplotypes and this disease[21]. These inconsistent results may be due to the fact that the study populations are of different races; thus, it is speculated that genetic factors may play an important role in the etiology of this disease. Future studies with larger samples and more races are needed to verify this hypothesis.

In recent years, several literatures have reported that anti-LGI1 AE may be a rare complication of coronavirus disease (COVID-19) vaccination[29,30], with a strict time relationship between the onset and vaccination (about 2 weeks from vaccination to disease onset). Molecular mimicry and immune cross reaction may be involved in its pathogenesis. Asioli *et al.* have reported four patients who developed anti-LGI1 AE after receiving two different messenger ribonucleic acid (mRNA) vaccines, with one patient vaccinated with a viral vector vaccine. However, since there are too few reported cases of vaccination-related anti-LGI1 AE, it is not possible to determine whether the cause of the disease is related to specific types of COVID-19 vaccines.

3. Clinical manifestations

Most patients have an acute or subacute onset, with the most prominent manifestation being FBDS. Other manifestations include cognitive disorders (mainly recent memory loss), hyponatremia, hyperkinetic movements (HMs), psychiatric disorders, as well as mood and sleep disorders.

3.1. Faciobrachial dystonic seizure (FBDS)

FBDS is highly specific, with a positive rate of approximately 20 – 40%[31,32]. It often occurs as the initial symptom of anti-LGI1 AE[31,33]. FBDS is a frequent and transient involuntary movement like dystonia, which often involves unilateral upper limbs, face, and even lower extremities. Its attacks are usually short, lasting only few seconds, but the frequency of attacks may reach dozens of times a day[1]. Traumatic falls may occur when it manifests as FBDS of the lower limbs. The results of previous studies have indicated that antiepileptic drugs (AEDs) alone are ineffective for FBDS, but the use of immunotherapy can significantly reduce or even eliminate FBDS[32,34-39]. In a study conducted by Thompson *et al.*[31], FBDS ceased in only 10% of anti-LGI1 AE patients who took AEDs alone; in contrast, the cessation of FBDS was observed 30 days after immunotherapy in 51% of patients and even earlier in cognitively normal patients. The current findings on the origin of FBDS and whether it should be regarded as an epileptic seizure are controversial[40]. Some scholars call it a seizure-like episode[41]. In a study, Liu *et al.*[42] divided LGI1 AE patients into two groups, the FBDS group and the non-FBDS group. ^{18}F-fluorodeoxyglucose position emission tomography (^{18}F-FDG-PET) results showed that basal ganglia (BG) hypermetabolism was detected in seven patients (44%) in the FBDS group but in only one patient (7%) in the non-FBDS group. It has been hypothesized that BG abnormalities may be involved in the etiology of FBDS and LGI1-associated FBDS is more likely a dyskinesia rather than an epileptic disease. However, in another study by Liu *et al.*[43], anti-LGI1 AE patients initially presented with FBDS, followed by classic limbic epilepsy or ipsilateral tonic-clonic seizures (TCS), and electroencephalogram (EEG) recorded changes in cortical potentials. These specific, stereotyped clinical presentations and EEG changes reflected both cortical and subcortical network involvement rather than a single site. They therefore speculated that FBDS is more likely to be a part of epileptic motor events.

3.2. Cognitive disorders

The majority of patients have rapidly progressive memory impairment, short-term memory loss, and impaired orientation. Other clinical manifestations include language ability deficits, impaired executive function, impaired visuospatial ability, and calculation disturbance[44]. Brain magnetic resonance imaging (MRI) examination shows that the hippocampus, temporal lobe, and basal ganglia are the main lesion sites[37,45,46-49]. At present, it is believed that inflammation in the acute phase is associated with atrophy in the recovery stage, which may be the cause of persistent cognitive impairment in patients with anti-LGI1 AE. Studies by Thompson *et al.*[31] have shown that patients with both cognitive impairment and FBDS have more abnormal examination results than patients with FBDS alone. Abnormal findings of brain MRI and electroencephalogram and hyponatremia were almost exclusively observed in patients with cognitive impairment. There is evidence that cognitive impairment can be prevented by early termination of FBDS[31].

3.3. Hyponatremia

Hyponatremia is another prominent feature of anti-LGI1 AE. As shown in the previous studies, 60% of patients developed hyponatremia after early treatment of the

disease[50]. The pathogenic mechanism of hyponatremia is likely associated with the syndrome of inappropriate antidiuretic hormone secretion caused by the simultaneous expression of LGI1 by the hypothalamus and the kidney[51]. Sometimes, severe hyponatremia can be seen as a precursor to anti-LGI1 AE. The serum sodium concentration of patients with refractory hyponatremia who have been receiving continuous intravenous and oral sodium supplementation can no longer be maintained at the normal level. As a result, they need to take concentrated sodium for a long time and recheck their serum sodium concentration regularly after being discharged from the hospital.

3.4. Hyperkinetic movements (HMs)

In contrast to the extensive discussion on FBDS, HMs have been overlooked in the past. HMs are characterized as a group of jerk-like or twisting movements[43]. This type of manifestation has only been described in a few case reports[43,52-54]. HMs may occur when the patient is asleep or awake, and they do not interrupt the patient's autonomous movements. As a result, only a small number of patients would notice such symptoms and inform the doctor at the time of admission. According to Liu *et al.*[43], HMs are very common in anti-LGI1 AE and can be promoted by sleep. Therefore, it is inferred that HMs are the result of the imbalance of the motor cortex, basal ganglia, thalamus, and substantia nigra/red nucleus. HMs may also be the potential cause of sleep disorders.

3.5. Psychiatric disorders

Results from the previous studies have shown that the incidence of psychiatric symptoms in patients with anti-LGI1 AE is significant. The main manifestations are personality and behavioral disorders, irritability, anxiety, impulsive behavior, hallucinations, delusions, and coma[50,51]. In a South Korean study by Jang *et al.*[55], 62.5% of patients with anti-LGI1 AE developed psychiatric symptoms that were associated with mood, with depressed mood being the most common symptom, while others such as irritability, self-injurious behavior, and emotional instability were also observed. These mood-related symptoms may mislead patients and their clinicians into considering the illness as a psychiatric disorder, such as geriatric depression, early behavioral and psychological symptoms of dementia (BPSD), or epilepsy-related psychosis. As a result, a considerable number of patients may visit the psychiatric department first, thus precluding the early diagnosis of anti-LGI1 AE. Among the various sleep disorders, insomnia is the most common. Insomnia is characterized by difficulty in falling asleep or lack of sleep caused by frequent waking. These symptoms are mainly related to hippocampal and amygdala impairment[56]. These symptoms can reflect the severity of the disease and the effectiveness of treatment to a certain extent.

4. Supplementary examination

4.1. Cerebrospinal fluid examination

Cerebrospinal fluid examinations of patients with anti-LGI1 AE are often non-inflammatory and without any apparent specificity. Lumbar puncture pressure can be normal or slightly increased, and the white blood cell count in cerebrospinal fluid can also be normal or slightly increased, especially lymphocytes[1,51,57]. Cerebrospinal fluid routine biochemical examinations are usually normal. However, few patients may show slightly increased cerebrospinal fluid protein and glucose[58], with positive oligoclonal bands[59].

4.2. Brain magnetic resonance imaging (MRI)

Brain MRI is the first choice for an early diagnosis of anti-LGI1 AE. In most patients, brain MRI shows unilateral or bilateral medial temporal lobes (amygdala and hippocampus) with long T1 and long T2 signals in the acute phase, and slightly higher signals can be seen on diffusion-weighted imaging (DWI) sequence. T2-fluid-attenuated inversion recovery (FLAIR) hyperintensity can be seen on both plain and enhanced MRI[58]. Amygdaloid hypertrophy, which is sensitive to FLAIR sequence, can be found in some patients. Abnormal signals in basal ganglia can also be observed in the brain MRIs of some patients. However, the brain MRIs of some patients may be normal. Significant reductions in brain connectivity involving inferior frontal gyrus, anterior and posterior cingulate gyri, several regions of the default mode network (DMN), and higher visual networks have been demonstrated in patients with anti-LGI1 AE using resting-state functional MRI (fMRI)[3]. Irani *et al.*[38] have shown that the hippocampal volume of patients was significantly smaller than that of matched normal controls during the follow-up period after recovery, although the brain MRIs revealed no abnormal signals in their hippocampus in the acute phase, thus suggesting that anti-LGI1 AE may be caused by brain atrophy.

4.3. ^{18}F-fluorodeoxyglucose position emission tomography (^{18}F-FDG PET)

According to current research, ^{18}F-FDG-PET is considered to be more sensitive than MRI in the diagnosis of anti-LGI1 AE[42,60]. Parietal and frontal cortex hypometabolism and medial temporal lobe (MTL), basal ganglia (BG), and occipital lobe hypermetabolism can be detected by ^{18}F-FDG PET in patients with anti-LGI1 AE[42]. The hypometabolism may be a result of functional impairment propagated along cortical and subcortical networks, arising from the sites of primary abnormalities in MTL and BG[3]. Occipital

hypermetabolism, on the other hand, may be a compensatory mechanism during the acute/early phase of the illness. In the acute phase of the disease, FDG uptake shows a significant increase, followed by a gradual decrease, which eventually returns to normal after treatment[46,61]. Therefore, ^{18}F-FDG PET can be used as a tool to measure disease activity and evaluate patients' responses to treatment.

4.4. Electroencephalogram (EEG)

The proportion of abnormal EEG during FBDS attacks is only 21% to 30%. During the interictal period of FBDS, mild diffuse slow wave or bilateral frontotemporal slow wave can be seen, or the EEG may also be completely normal[37]. Navarro *et al*. have found that FBDS originates from the primary motor cortex (M1)[35]. Before muscle contraction, EEG shows focal, contralateral, and frontal slow waves. The previous studies have demonstrated the superiority of long-lasting EEG monitoring over short-lasting routine EEG in revealing subclinical and recurrent seizures[62,63], which enables clinicians to adjust the treatment plan in time.

4.5. Antibody detection

Anti-LGI1 antibodies in serum and/or cerebrospinal fluid are positive. It is worth noting that the detection of LGI1 antibodies in the serum seems to be more sensitive than that in cerebrospinal fluid compared to other types of autoimmune encephalitis[20,32,54]. Therefore, it is important to detect both types of samples when anti-LGI1 AE is clinically suspected[27]. According to Zhong *et al.*[64], the concentration of LGI1 antibody in the cerebrospinal fluid is related to the probability of recurrence of anti-LGI1 AE, in which the higher the concentration, the greater the probability of recurrence.

4.6. Tumor markers

According to the previous studies, the incidence of tumors in anti-LGI1 AE patients was found to be 0% to 13%[43], which was comparatively less than other types of autoimmune encephalitis[65,66]. In addition, the serum tumor markers of anti-LGI1 AE patients are often negative. Due to the lack of specific recommendations for tumor screening in anti-LGI1 AE, the tumor screening methods for paraneoplastic syndromes (PNS)[67] can be referenced: a second screening shall be repeated after 3–6 months, followed by regular screening every 6 months for 4 years. Patients with concurrent neoplasia may seek chemotherapy, radiotherapy, and/or surgery after AE is controlled.

5. Differential diagnosis

Anti-LGI1 AE needs to be differentiated from central nervous system infection (such as herpes simplex virus meningitis), metabolic encephalopathy, toxic encephalopathy (such as Wernicke's encephalopathy, hepatic encephalopathy, and pulmonary encephalopathy), Hashimoto's encephalopathy[68], central nervous system neoplasms (such as cerebral gliomatosis, primary central nervous system lymphoma, and metastatic cancer), hereditary diseases (such as mitochondrial encephalopathy, methylmalonic acidemia, and adrenoleukodystrophy), and neurodegenerative diseases (such as Creutzfeldt-Jakob disease, Lewy body dementia, multiple system atrophy, and hereditary cerebellar degeneration).

6. Treatment and prognosis

Early identification, diagnosis, and rapid initiation of immunotherapy are all very important to improve the prognosis of patients with anti-LGI1 AE[31,38]. However, the median time from onset to diagnosis of patients with anti-LGI1 AE in China is about 2 months[69], indicating that many patients would have had missed the best opportunity for diagnosis and treatment.

First-line immunotherapy, including glucocorticoids, intravenous immunoglobulin (IVIg), and plasma exchange, is the preferred treatment. The previous studies have shown that immunotherapy is particularly effective in achieving control of FBDS and other seizures. Patients who receive glucocorticoids (intravenous, oral, or both) tend to have better short-term prognosis than those receiving IVIg alone. This may be due to the fact that LGI1 antibodies mainly belong to the IgG4 subclass, which cannot activate complements; thus, steroids have a stronger immunosuppressive effect on these antibodies, while IVIg has a lower efficacy in these diseases[70,71]. The side effects of glucocorticoid therapy are common, especially those affecting the musculoskeletal system (myopathy, tendon rupture, and osteoporosis). Other rare but serious complications include acute respiratory distress syndrome (ARDS), septicemia, and pulmonary embolism (PE)[31]. Zhang *et al.*[72] have demonstrated that plasmapheresis can promptly relieve the symptoms of patients without fatal adverse events. However, it is more suitable for the emergency treatment of critically ill patients so as to achieve faster remission in view of its high treatment cost and less trauma.

Second-line therapeutic agents include rituximab and IV cyclophosphamide[1]. They are mainly used for patients with poor effect of first-line immunotherapy (Figure 2)[73], which account for 10% to 15% of all anti-LGI1 AE patients. Rituximab can be used when the patient's condition has not significantly improved or is aggravated after 2 weeks of treatment with more than two kinds of first-line immunotherapies. Cyclophosphamide may be used when rituximab is not available or contraindicated. Rituximab is

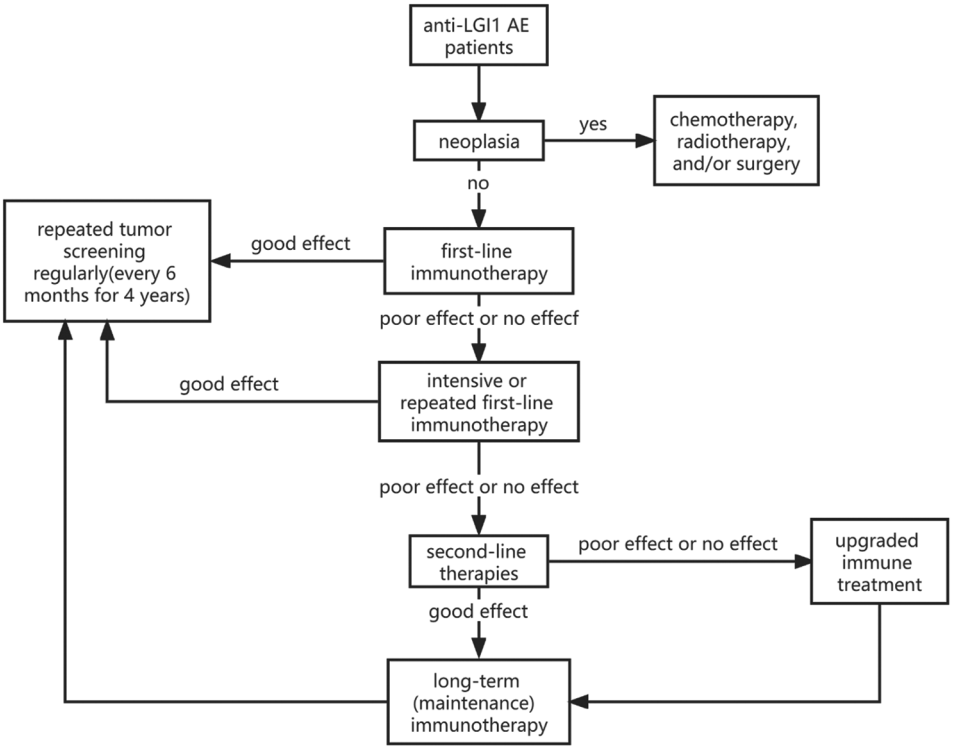

Figure 2. Immunotherapy flow chart for anti-leucine-rich glioma inactivated-1 (LGI1) autoimmune encephalitis.

prescribed at 375 mg/m^2 (up to 1 g) once weekly for four consecutive weeks[1]. It has been found that rituximab is effective in anti-LGI1 AE patients and well-tolerated in elderly patients[74,75]. Common adverse reactions of rituximab include infusion-related reactions (IRRS), pneumonia, severe sepsis, and so on[44].

The overall effect of antiepileptic drugs (AEDs) is limited, and immunotherapy is more effective in controlling FBDS and seizures, so AEDs are only used as an add-on therapy to immunotherapy. Immunotherapy is viewed as an etiological treatment, whereas antiepileptic therapy is a symptomatic approach. A nationwide cohort study from the Netherlands has suggested that sodium channel blockers (carbamazepine, oxcarbazepine, *etc.*) may be more effective in patients with anti-LGI1 AE[76]. The study, which included 53 patients, showed that carbamazepine was more effective than levetiracetam in reducing seizures. Compared to patients with other types of AE, those with anti-LGI1 AE have been reported to have a higher incidence of adverse reactions to AEDs. Marienke *et al.* have reported in their study that one-third of patients who were prescribed with carbamazepine developed rash. A possible reason for that was the rapid increase in the dose of carbamazepine due to frequent drug-resistant seizures. Therefore, caution must be exercised when increasing the dose of AEDs. IV bolus diazepam or intramuscular midazolam can be administered to terminate status epilepticus (SE).

At present, there are very few studies on the effect of drug therapy on cognitive impairment. An early initiation of immunotherapy will not only help control the onset of FBDS, but also improve the cognitive function of patients. Both donepezil and memantine are classic cognitive-improving agents for Alzheimer's disease, but there is no literature to report the efficacy of these agents in patients with anti-LGI1 AE.

A recent large cohort study of the recurrence rate of anti-LGI1 AE in western China population[77] has shown that the recurrence rate of anti-LGI1 AE patients is 13.6%. According to another study in northeast China[64], the recurrence rate is 28.6%. The recurrence rate varies from study to study, indicating that there is heterogeneity in anti-LGI1 AE in different ethnic populations. In addition, considering that relapses may occur in several years after the initial onset, the recurrence rate may be underestimated. Inadequate dose and duration of the drug may be the cause of recurrence[32]. Some scholars believe that acute sleep disorders are risk factors for the recurrence of anti-LGI1 AE[77]. In a study using ^{18}F-FDG-PET, the recurrence rate of patients with high metabolism of BG alone or both BG and MTL was lower than that of patients with high metabolism of MTL alone[42]. Overall, a consensus on the factors affecting recurrence has not been achieved; hence, more long-term follow-up

studies are required to further determine the causes of recurrence.

A mortality rate of 6% has been reported in patients with anti-LGl1 AE[78]. Persistent cognitive impairment is a long-term sequela of patients with anti-LGl1 AE, especially in the absence of early and appropriate immunotherapy. This irreversible cognitive impairment in patients may be due to high levels of LGI1 antibody in their cerebrospinal fluid, followed by complement deposition and hippocampal atrophy[49,78-80]. Thompson *et al.*[31,78] have emphasized the importance of early and effective immunotherapy for patients. For each week of delay in immunotherapy, the possibility of FBDS resolution decreases by 5%. If FBDS persists for more than 90 days, more than half of the patients will develop cognitive impairment. The time needed to recover from cognitive impairment is associated with the time immunotherapy is initiated. Early initiation of immunotherapy may reduce FBDS and, more likely, prevent long-term cognitive impairment.

In addition, the prognosis of a patient is largely affected by the occurrence of tumor. A study in the Netherlands has found that non-neoplastic anti-LGI1 AE is strongly associated with *HLA-DR7* and *HLA-DRB4*, suggesting that *HLA-DR7* or *HLA-DRB4* gene deletion may increase the incidence of tumors[25]. Therefore, the researchers have recommended intensive tumor screening and long-term follow-up in patients without *HLA-DR7* or *HLA-DRB4*. In contrast, a British study has shown that HLA is not associated with tumors in anti-LGI1 AE[22]. Considering the incongruity, there is an urgent need for more research on HLA and tumors of these patients to guide clinical diagnosis and treatment.

7. Conclusions

Anti-LGI1 AE is a rare condition, and because it often occurs with recent memory loss or mental and behavioral disorders, diagnosis and treatment are often delayed, thus increasing the risk of poor prognosis. The diagnosis of anti-LGI1 AE mainly depends on the history, clinical manifestations, positive results of cerebrospinal fluid or serum LGI1 antibody spectrum tests, and characteristic brain MRI and ^{18}F-FDG PET results. Patients with anti-LGI1 AE require early diagnosis, while missed diagnosis or misdiagnosis should be prevented. An early initiation of immunotherapy can effectively reduce mortality, seizures, and the incidence of long-term sequelae; it can also prevent borderline encephalitis and long-term cognitive impairment. More prospective studies are needed in the future since the majority of existing studies are retrospective studies. The review of relevant literature may help improve clinicians' understanding of the characteristic manifestations of the disease.

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Conflict of interest

The authors report no conflict of interest.

Author contributions

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Consent for publication

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Availability of data

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