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REVIEW ARTICLE

Seizures in steroid-responsive encephalopathy

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Abstract

Steroid-responsive encephalopathy is a general term for diseases that are characterized by diffuse brain injury and respond well to corticosteroids or immunosuppressive agents, including Hashimoto's encephalopathy (HE), limbic encephalitis (LE), systemic lupus erythematosus encephalopathy (SLEE), antineutrophil cytoplasmic antibodies (ANCA)-associated systemic vasculitis encephalopathy (AASV), viral encephalitis (VE), and primary central nervous system lymphoma (PCNSL). Epilepsy and status epilepticus are the main manifestations of steroid-responsive encephalopathy. The spectrum of "autoimmune epilepsy" diseases, which has been approved by the epilepsy diagnostic recommendations of the International Antiepileptic League, is characterized by a high prevalence of epilepsy in central nervous system (CNS) autoimmune diseases and a variety of neuron-specific autoantibodies. Steroid-responsive encephalopathy with different causes may have different pathogeneses and has been suggested to be associated with some internal commonality producing seizure as the main symptom. Determining the regularity of seizures caused by steroid-responsive encephalopathy and implementing appropriate measures will help us improve the prognosis of patients. This paper summarizes the epidemiology, seizure onset, seizure type, and other characteristics of seizures in steroid-responsive encephalopathy (including HE, LE, SLEE, ANCA-associated systemic vasculitis encephalopathy, VE, and PCNSL) and then discusses the use of antiepileptic drugs to treat steroid-responsive encephalopathy.

Keywords Steroid-responsive encephalopathy · Seizure · Status epilepticus · Central nervous system · Autoimmunity

Historical development

The relationship between epilepsy and the autoimmune response has long been recognized. In 1966, Brain et al. first described a possible link between the CNS and the autoimmune response, proposing Hashimoto's encephalitis, later known as steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT), in which seizures may complicate the systemic autoimmune disorder [1]. In 1968, Corsellis et al. reported the first case of LE, with cognitive decline, behavioral changes, and seizures as the primary manifestations, and they considered it to be a tumor-associated disease [2]. Therefore, tumors and encephalitis have been suggested to have autoimmune associations to some extent. The increased frequency of seizures in systemic autoimmune diseases, such as systemic lupus erythematosus, provides further evidence for the link between autoimmune responses and epilepsy [3]. In 1999, the American College of Rheumatology (ACR) named the formal unification of neuropsychiatric manifestations of systemic lupus erythematosus as neuropsychiatric lupus erythematosus (NPSLE), with 19 recognized NPSLE syndromes. Clinically referred to as SLEE, seizure is one of the core manifestations [4]. In 1999, Arbusow and Samtleben first described the neurological complications of ANCA-associated vasculitis as ANCA-associated vasculitis encephalopathy [5]. In 2001, Thajeb et al. reported that seizures were the major clinical manifestation [6]. In 1945, for the first time, some scholars reported the emergence of VE in the Journal of Science [7]. Seizures are a common clinical manifestation of VE and are often difficult to control [8]. In 1966, the Japanese scholar Kawafuchi et al. first described the clinical symptoms of two patients with CNS lymphoma who suffered from associated seizures [9].

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Characteristics of seizures in different types of steroid-responsive encephalopathy

The clinical features of steroid-responsive encephalopathy with seizure are summarized in Table 1.

HE

HE causes epileptiform/stroke attacks, mental disorders, and other clinical symptoms. Clinically, it has two forms, the vasculitis type characterized by multiple stroke-like symptoms and the diffuse progressive type characterized by dementia and mental symptoms. The two forms can produce epileptic seizures, myoclonus and tremors [10]. Epileptic seizures in patients with HE are common clinical manifestations. Epileptic seizures have been found in 47–66% of HE patients [10, 11]. Although most of the patients with HE have epileptic seizures, the incidence of epileptic discharge from EEG is very low. Laurent et al. studied 251 HE cases and found that 47% of the cases developed seizures and 14% of the patients had epileptic discharge from their EEGs [11].

The characteristics of seizures in HE

The types of seizures in patients with HE include generalized tonic–clonic seizures, focal aware seizures, focal impaired awareness seizures, myoclonus, and status epilepticus. These types of seizures can overlap in the same patient [12].

Generalized tonic–clonic seizures, focal aware seizures, and focal impaired awareness seizures Several scholars reported that the most common type of seizure in children and adults with HE is the focal to bilateral tonic–clonic seizures [12, 13]. Chong et al. reported 56 cases of HE patients with epilepsy, the seizures include all types, such as focal motor seizures and myoclonic [10]. Castillo et al. studied 56 HE patients with seizures who were 27–84 years old and found that 50% of them had generalized tonic–clonic seizures, 35% had focal aware seizures, and 5% exhibited two or more types of seizures [12].

Status epilepticus and others Chong et al. studied 85 patients with HE and found that 12% of them had status epilepticus [10]. Ferlazzo et al. reported one patient with HE who is insensitive to anticonvulsant drugs and then presented with refractory generalized convulsive status epilepticus [21]. Myoclonus can also occur in patients with HE. Chong et al. reported 38% patients with HE-developed myoclonus [10].

Treatment

HE responds well to corticosteroids and other immunomodulatory therapies. The use of immunotherapy in the acute stage of HE can effectively control seizures and help diagnose immune epilepsy. First-line treatment includes glucocorticoids and intravenous immunoglobulin (IVIG) [22]. In addition, plasma exchange (PLEX) treatment also resulted in a better prognosis in terms of neurological features [22]. Ferlazzo et al. reported a case of a patient with HE with status epilepticus as the first symptom. The patient had three episodes of generalized convulsive status epilepticus (GCSE) within 9 months. Steroids effectively controlled GCSE and prevented the recurrence of GCSE; however, diazepam was ineffective [21]. When the first-line treatment was ineffective, second-line treatment had significant effects when compared with patients who did not receive second-line treatment such as rituximab, cyclophosphamide, and other immunosuppressive agents [22]. Notably, some patients will have repeated seizures, especially when immunosuppressive therapy is gradually reduced. Therefore, maintenance immunotherapy is necessary for some patients. A retrospective analysis of 13 HE patients conducted by Olmez et al. found that the symptoms of 12 patients almost completely disappeared after maintenance treatment with rituximab, azathioprine, mycophenolate mofetil, and other drugs [19].

In addition, antiepileptic drugs have been reported to be used successfully. Wong et al. presented the cases of two female patients with HE complicated with diabetes (unable to receive steroids or immune therapy), and they were both successfully treated with levetiracetam [23]. In addition, difficulty finding words and dysarthria were also clearly improved. The levels of antithyroglobulin antibodies and thyroid peroxidase antibody were significantly reduced after 3 months of treatment, and epileptic discharges on EEG disappeared after 6 months [23]. Therefore, in addition to antiepileptic effects, levetiracetam can also exert anti-inflammatory effects through interleukin 1β and transforming growth factor-β 1 [68]. The dual anti-inflammatory and antiepileptic properties of levetiracetam suggest that it may be an effective alternative treatment for HE patients who are unresponsive to steroids or are unable to receive immune therapy [23].

LE

In 1968, the concept of LE was first defined by Corsellis and his colleagues, referring to an inflammatory disease of the CNS that mainly involved the limbic system [2]. It is also associated with tumors and called paraneoplastic LE (PLE) [2]. In 2001, the term "nonparaneoplastic LE (NPLE)" was coined. In recent years, neuronal surface antibody-associated LE has attracted a great deal of attention, the antigens of which are mainly receptors or synaptic proteins located on the surface of neurons [20]. LE has some common clinical manifestations, such as short-term memory loss, abnormal mental behavior, and seizures. In 2007, Dalmau et al. proposed that anti-NMDA receptor (NMDAR) encephalitis differs from classical LE because it has a diversity of clinical

Table 1 The clinical features of seizures in steroid-responsive encephalopathy

	Incidence of seizures	Characteristics of seizures of different etiologies			Possible mechanism	Treatment
		Seizure type	Seizure location	Frequency or association		
HE	47–66% [10, 11].	Generalized seizure [12, 13]; focal aware seizure [12]; focal impaired awareness seizure [13]; focal to bilateral tonic–clonic seizure [12, 13]; myoclonus [4]; status epilepticus [10] .	Auditory hallucination [14]; visual hallucination [15]; facio-brachial dystonia [16]; GTCS [12, 13].	3 times a day to once every few months [17, 18]	1. Antithyroid antibodies targeting alpha-enolase, dimethylargininase-I, and aldehyde reductase-I [19]; 2. Circulating immune complexes [17]; 3. Neuronal autoantibodies [20]; 4. Autoimmune vasculitis [17].	HE responds well to corticosteroids and other immunomodulatory therapies [21]/Seizures in HE can generally be controlled by corticosteroids [22]. Antiepileptic drugs have also been used successfully [23].
LE PLE	29–50% [24, 25].	Status epilepticus [24]; generalized seizure [24]; focal impaired awareness seizure [24]; psychomotor seizure and mixed type [25].	Stare [26]; hemifacial spasm [26]; GTCS [24].	Once in a few days to once in a few weeks [26]. The association of seizure is not clear.	1. Ma2 antibodies [25]; 2. Hu antibodies [24].	Commonly used first-line immunotherapy methods are corticosteroids, intravenous immunoglobulin, plasma exchange or a combination of these. The use of antiepileptic drugs is necessary, but they are not effective for reducing intrathecal antibody titers, and additional immunotherapy may be required [27].
Anti-GABA(B)receptor -associated LE	80–85% [28, 29].	Focal seizure [28]; generalized seizure [4]; status epilepticus [29].	Opsoclonus-myoclonus syndrome [28]; GTCS [4].	Lack of relevant reports, reports of 1–3 times within a month [30].	Antibodies against the GABA(B) receptor [29].	
GAD-LE	~ 100% [31].	Focal impaired awareness seizure [32]; generalized seizure [32]; and status epilepticus [32].	Facio-brachial dystonic seizures [33]; GTCS [32].	Rarely, once every few months [33].	Anti-GAD antibody [34].	
VGKC-LE	85–100% [35, 36].	Focal aware or impaired awareness seizure [4]; generalized seizure [4].	Typical manifestation is facio-brachial dystonic seizures [37].	7–8 times per day-once a month [38].	VGKC, which is composed of 3 subunits: contactin-associated protein-like 2 (CASPR 2), LGI1 and contactin-2 [37].	
LGI1-LE	65–82% [39, 40].	Focal aware seizures [41]; generalized seizure [41]; and special type [42].	Piloerection seizures [42]; facio-brachial dystonic [43]; GTCS [41].	The results are variable, a report indicates that the frequency is 27.5 times per day [44].	Antibodies against LGI1 [41].	
SLEE	7–84% [45].	Focal aware or impaired awareness seizure [46]; generalized seizure [47].	Mainly GTCS [47].	Lack of reports, autoimmune epilepsy is reported to result in daily seizures [48].	1. Anti-NR2 antibodies [49]; 2. TREX1 gene polymorphism [50]; 3. Genetic material located on chromosome 15 [51].	In patients with acute inflammatory changes with new seizure or concurrent lupus activity, consider using corticosteroids or immunosuppressive therapy [49, 52]. Long-term antiepileptic drugs should be considered for patients with recurrent seizures [52].
AASVE	Not reported.	Generalized seizure [53]; focal to bilateral tonic–clonic seizure [54]; focal seizures and status epilepticus [53].	Hemibody clonic jerks; horizontal nystagmus [55].	Seizures are reported to be frequent, usually several times a day [55]. Generalized seizure is reported to be related to intravenous lorazepam [55].	Further research is needed.	High-dose steroids, cyclophosphamide or rituximab combined with antiepileptic drugs [53].
VE	10–35% [8, 56].	Generalized seizures [8]; focal seizures [57]; focal to bilateral tonic–clonic seizures and status epilepticus [8].	Joint-trunk-hip joint rhythmic clonic seizure [57]; GTCS [8].	Seizures usually occur in the acute phase, single to several attacks in the first week [8].	1. HSV antigens [58]; 2. Interleukin-6 [59]; 3. Complement component [58].	HSV: early high-dose acyclovir, use corticosteroids when necessary [58]. VSV: Corticosteroid therapy is recommended [58].

Table 1 (continued)

	Incidence of seizures	Characteristics of seizures of different etiologies			Possible mechanism	Treatment
		Seizure type	Seizure location	Frequency or association		
						Antiepileptic drugs have long been controversial [60]. KD may be selected [61].
PCNSL	14% [62].	Generalized seizures [63], clonic seizures [63], myoclonic seizures [64], - status epilepticus, febrile seizures [63–65].	Mainly tonic–clonic seizure [63].	Two-thirds occurred at the time of initial presentation [66].	Not reported.	Using only dehydrating drugs is best to reduce intracranial pressure before diagnosis. PCNSL is sensitive to corticosteroids, chemotherapy, and radiation therapy [65]. For patients resistant to these methods, HDMTX combined with rituximab treatment may be selected [67].

VE viral encephalitis, *HSV* simple herpes virus, *VSV* vesicular stomatitis virus, *PLE* paraneoplastic limbic encephalitis, *LE* limbic encephalitis, *GABA* gamma-aminobutyric acid B receptor, *GAD* glutamic acid decarboxylase, *VGKC* voltage-gated potassium channel-complex, *LGI1* leucine-rich glioma inactivation gene 1, *GTCS* generalized tonic–clonic seizure, *HE* Hashimoto's encephalopathy, *SLEE* systemic lupus erythematosus encephalopathy, *AASVE* antineutrophil cytoplasmic antibodies (ANCA)-associated systemic vasculitis encephalopathy, *KD* ketogenic diet, *PCNSL* primary central nervous system lymphoma, *HDMTX* high-dose methotrexate

manifestations exceeding the "triple signs" of LE [69]. Therefore, in the classification of autoimmune encephalitis, anti-NMDAR encephalitis is classified as an independent type, which is distinguished from other forms of LE.

Characteristics of seizures caused by different types of LE

PLE PLE is a rare paraneoplastic syndrome of the nervous system and is also known as neoplasm-associated LE or paraneoplastic encephalitis. The disease is most common in small cell lung cancer patients and may occur before the lung cancer. With the development of immunology, the presence of specific neuronal antinuclear antibodies (anti-Hu) in the serum and cerebrospinal fluid of PLE patients has been discovered in recent years, providing a reliable basis for the early diagnosis of PLE [24]. The incidence of seizure in PLE patients was 29–50% [24, 25]. Most of these patients exhibit generalized seizures and focal impaired awareness seizures. Status epilepticus has also been reported, of which focal status epilepticus is the most common type [25].

Anti-GABA(B) receptor antibody-associated LE Several retrospective studies found that 80–85% of patients experienced seizures [28, 29]. Seizures are one of the most prominent clinical manifestations of LE [28]. Dogan Onugoren et al. reported findings in 10 anti-GABA(B) receptor antibody-associated LE patients and showed that generalized convulsive seizures constituted the initial clinical symptom in 8 patients, 2 of whom developed status epilepticus during hospitalization [29]. In addition, these patients also exhibited non-seizure symptoms such as memory deficits, confusion, apraxia, psychotic symptoms, and personality changes [29].

GAD antibody-associated LE The acute or chronic epilepsy experienced by patients with (GAD-LE) is mainly related to the temporal lobe. Epilepsy may be the first symptom or the only manifestation. During the course of the disease, epilepsy manifests in a variety of forms, mainly including focal impaired awareness seizures, generalized tonic–clonic seizures, and status epilepticus [70].

GAD antibody-positive lesions are located throughout the brain and are associated with a poor prognosis [34]. AEDs and immunosuppressants are insufficient to control the seizures [34]. Patients usually require a variety of immunosuppressive treatments, but the reduction in seizure frequency is only temporary. Therefore, patients with GAD-LE may need long-term immunosuppressive therapy [34].

Voltage-gated potassium channel antibody-associated LE VGKC-LE is one of the most common types of autoimmune-mediated LE [37]. The main manifestations of VGKC-LE are focal seizures (62%), followed by tonic–clonic seizures (19%) and a small number of subclinical

seizures (5.8%) that were characterized by epileptic form discharges on the EEG [37].

LGI1 antibody-associated LE It has been reported that 65–82% of LGI1-LE patients have epileptic seizures [39, 40]. Patients with LE can have generalized and focal seizures; piloerection seizures are a special type [42]. These rate autonomic seizures originate in the temporal lobe and are very difficult to diagnose. It takes an average of 5.2 years (range 2–14) from the onset of the disease to the diagnosis of piloerection seizures [42]. Therefore, when patients with LGI1-LE have autonomic symptoms, the doctor should carefully identify whether they have this special type of seizure.

Treatment of LE

The treatment is related to the primary disease. Immunotherapy is the most important treatment method. In some cases, tumor resection can be performed. Immunotherapy is divided into first-line therapy and second-line therapy according to the phase of the disease. In the acute phase, high-dose corticosteroid, IVIG, and PLEX are usually used as preferred first-line treatment. For some patients with refractory epilepsy, PLEX or IVIG can be combined with corticosteroid therapy [27]. Seizures can be effectively controlled after several weeks of immunotherapy. Second-line therapy is based on the effect of the acute immunotherapy regimen and the specific autoantibodies identified. Broad-spectrum immunosuppressive agents such as cyclophosphamide and mycophenolate mofetil are preferred for PLE with intracellular antigens (e.g., anti-Hu IgG) [27]. Anti-Hu IgG is mainly considered to be related to a T cell-mediated immune response. Antibodies against neural cell surface antigens (e.g., anti-VGKC IgG) are directly pathogenic. In this case, therapies that inhibit the antibodies produced by B cell are preferred. Rituximab depletes B cells through cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis [27]. Bortezomib and tocilizumab are novel second-line immunotherapeutics. Bortezomib reduces circulating antibodies by inhibiting plasma cell secretion and has been used in the treatment of refractory NMDA-R encephalitis, but the effect is not significant [71]. Tocilizumab, an interleukin-6 inhibitor, has also been used in the treatment of NMDA-R encephalitis and controlled neurological symptoms [72]. In addition, the side effects should be considered when choosing the treatment methods, especially the risk of seizures.

The most appropriate AED for autoimmune-mediated LE-related seizure is uncertain. There have been no reports of non-AEDs that can control seizures in LE patients when used alone. Therefore, AEDs may be needed to control LE-related seizures. Some antiepileptic drugs such as valproic acid and oxcarbazepine also have antiepileptic, antitumor, and immunomodulatory effects, and valproic acid has been approved as an antitumor drug [73].

Most patients with LE present with refractory epilepsy. However, whether AEDs control epileptic seizures by directly suppressing epileptic seizures or by indirectly regulating the immune system is unclear, and more clinical studies are still needed. For example, valproic acid can inhibit histone deacetylation, thereby exerting immunomodulatory and antitumor effects [73]. Valproic acid may be effective in autoimmune-mediated LE patients with seizures and malignant tumors. The ketogenic diet (KD) is known to be a valuable therapeutic approach for patients with intractable epilepsy. The KD diet is effective for LE patients with refractory epilepsy. Moriyama et al. [74] reported a child with LE whose convulsive seizures were difficult to control, even with the use of intravenous antiepileptic drugs (midazolam and phenobarbital). After applying the KD, the frequency of seizures decreased by 50%. Notably, the KD can also cause a variety of complex complications. In Moriyama's report, this child had to stop KD therapy because of severe protein-losing enteropathy. Therefore, the use of KD therapy for LE patients requires careful monitoring for complications

SLEE (NPSLE)

SLE is an autoimmune disease with multiple organ involvement. The disease is often associated with CNS damage, of which cerebral injury is the most common; when that occurs clinically, it is referred to as SLEE. Patients with SLE can have seizures, the incidence of seizures in SLEE is 7–84% [45].

Clinical features of seizures

Seizures are one of the 19 neuropsychiatric symptoms of SLE [4]. Most of these manifestations are generalized tonic–clonic seizure, focal aware seizures, and focal impaired awareness seizures [47]. Seizures that reoccur after the first epileptic seizure is adequately controlled are defined as "recurrent seizures". A systematic review by González-Duarte et al. investigated 75 cases of SLEE with seizures and found that 40 (53%) of the patients experienced recurrent seizures, of which 54% occurred in the first year after the first seizure and 13 (17%) of which occurred in the first month after the first seizure. The main factor affecting recurrent seizures is the adjustment of AEDs [46].

Treatment

The main treatment for SLE is glucocorticoids and immunosuppressants [75]. When manifestations are related to antiphospholipid antibodies, especially for thrombotic cerebrovascular disease, anticoagulant or antithrombotic drugs

should be considered. In recent years, biologic agents (e.g., belimumab) and monoclonal antibodies (e.g., rituximab) have also shown therapeutic effects on SLE [49]. Whether these drugs have a therapeutic effect on seizures is still unclear. For patients with seizures, glucocorticoids alone or in combination with immunosuppressive therapy may be given. Methylprednisolone combined with cyclophosphamide has a good therapeutic effect on refractory seizures [52]. AED therapy is necessary in patients with recurrent epilepsy, and some patients also require a second AED to control seizures [52]. Due to the complexity of the etiology of SLE, AEDs are selected according to special antibodies. Reinaldo et al. described a patient who received a combination of prednisone and azathioprine for a long time. Multiple AEDs (valproic acid, levetiracetam, lamotrigine, etc.) could not effectively control the patient's seizures. Considering that the patient's anti-P antibody was persistently positive, doctors used topiramate to treat the seizures and achieved good results [76].

ANCA-associated systemic vasculitis encephalopathy

ANCA-associated systemic vasculitis (AASV) is a rare autoimmune disease involving the kidneys, respiratory system, and nervous system. Currently, few reports of AASV and seizures or status epilepticus are available. Most epileptic seizures in AASV encephalopathy (AASVE) manifest as generalized seizures, focal seizures, and status epilepticus. Moore et al. described a female patient misdiagnosed with acute disseminated encephalomyelitis who showed focal to bilateral tonic–clonic seizures and was then diagnosed with Wegener's granulomatosis (one type of AASV) by lung biopsy 1 month later [54]. Ferlazzo et al. reported a case of Wegener's granulomatosis complicated with epileptic seizures and headaches, with repeated episodes of focal seizures [53]. At the same time, they also reported one 44-year-old male patient with AASV who presented with refractory status epilepticus in the left part of the body [53].

In AASV patients with seizures, the efficacy of AEDs alone may be poor. The treatment of AASV includes inducing remission with high-dose steroids or cyclophosphamide and maintaining remission with immunosuppressants. Additionally, new treatments such as rituximab can be applied. Ferlazzo et al. [53] described a 44-year-old man who was positive for P-ANCA and presented with refractory status epilepticus with left hemibody clonic jerks. He was successively treated with lorazepam, phenytoin, levetiracetam, and topiramate, none of which were effective. The patient was then treated with methylprednisolone and rituximab without recurrence during a 5-year follow-up and with levetiracetam 2 g/day to achieve a seizure-free status. The authors also reported that seizures in another patient with AASV were described by the patient as continuous, short-lasting episodes of a sensation that the "eyes move like a windshield wipers". After treatment with topiramate and carbamazepine, the seizures were still recurrent. Hematological examination of this patient suggested ANA1:320 and positivity for p-ANCA. Considering that both p-ANCA and ANA were positive, in addition to carbamazepine, prednisone and azathioprine were given, and seizures did not occur in the next 30 months of follow-up.

VE

VE is a common infectious disease of the CNS. The mechanisms of different types of VE with seizures are different. Currently, viral infections and adaptive immune responses are proposed to play important roles in VE with seizures [56]. VE caused by herpes simplex virus 1 (HSV-1) is one of the most serious human CNS infectious diseases and the most common cause of secondary epilepsy in humans [8]. Recurrent seizures in VE often indicate a poor prognosis [8]. Seizures occur in most patients with VE. It is reported that the incidence of seizures in patients with VE was 10–35% [8, 56]. The types of seizures that develop in patients with VE include generalized seizures, focal seizures, focal to bilateral tonic–clonic seizures and status epilepticus, and even refractory epilepsy. Generalized seizures are the most common [8].

The timing of the administration of antiepileptic drugs has long been controversial. A randomized controlled trial found no significant difference in the recurrence rate of epilepsy between patients with VE who received antiepileptic drugs for 1 year and patients who received antiepileptic drugs for 2 years [77]. Meanwhile, they found that epilepsy recurrence is related to disease persistence, lesion calcification, and abnormal EEG [77]. Therefore, 1 year of treatment with antiepileptic drugs is sufficient for patients with no symptoms. Seizures in patients with HIV encephalitis tend to have a high recurrence rate, so it is recommended to use antiepileptic drugs for a longer period [78]. However, attention should be paid to the interaction between antiepileptic drugs and antiviral drugs. This is important for HIV patients because antiretroviral drugs are thought to interact with antiepileptic drugs. Some new antiepileptic drugs (such as levetiracetam and topiramate) demonstrate little interaction with antiretroviral drugs and may, therefore, be preferable [78]. Therefore, the specific length of administration of antiepileptic drugs depends on many individual factors. The question of whether antiepileptic drugs can be used to prevent seizures in VE is still being explored, and no studies or published guidelines are available. The study by Pandey et al. showed that no randomized controlled trial had been performed to compare the effect of antiepileptics and a placebo (or no medication) on seizure prevention in VE [60].

For VE patients with refractory epilepsy, the KD is another possible effective treatment, especially in cases where multiple anti-epileptic drugs are ineffective. Nam et al. [61]

reported five cases of VE. After treatment with benzodiazepine, diphenylhydantoin, and phenobarbital, seizures still could not be reduced, but after treatment with the KD for 1 month, two patients no longer had seizures, the general seizures of the other patients almost disappeared, and the intensity of partial seizures was substantially reduced.

PCNSL

PCNSL is a rapidly progressing neurological malignancy that is a type of non-Hodgkin's lymphoma (NHL). PCNSL is characterized by impaired neurological function and intracranial hypertension, and seizures are uncommon. Bataille et al. reported 248 patients with CNS lymphoma without immunodeficiency and found that the incidence of seizures was 14% [62].

The types of seizures caused by PCNSL include generalized tonic–clonic seizures, clonic seizures, myoclonic seizures, and status epilepticus as well as febrile seizures. Jordaan et al. reported a patient with PCNSL without immunodeficiency who had myoclonic seizures and focal to bilateral tonic–clonic seizures [64]. Other scholars reported a case of a 2.5-year-old patient with PCNSL combined with immune hemolytic anemia, and febrile seizures was the main manifestation [65].

PCNSL is sensitive to corticosteroids, chemotherapy, and radiation therapy [65]. The use of corticosteroids before histologically confirming PCNSL is controversial. Lymphoid tumors respond rapidly to corticosteroids, and at least 40% of patients may have partial improvement on imaging [79], which may affect the diagnosis. For patients with suspected lymphoma, using only dehydrating drugs is best to reduce intracranial pressure before diagnosis. For most patients, the improvement in tumors due to corticosteroid use is only temporary; therefore, other chemotherapy drugs must be used further or simultaneously. After biopsy, central nervous system lymphoma should be treated with systemic chemotherapy combined with intrathecal chemotherapy [65]. High-dose methotrexate (HDMTX) is the main chemotherapy drug [65]. If a patient is not sensitive to chemotherapy, HDMTX combined with rituximab treatment can also effectively control the condition. HDMTX and rituximab can be used as a basic combination of chemotherapy, and PCNSL in adolescents or children can be effectively treated with this combination treatment, followed by whole-brain radiation therapy [67].

Summary

Steroid-responsive encephalopathy is a brain disease caused by immune dysfunction. Understanding the rules and characteristics of seizures is beneficial for clinicians to understand and address the prominent symptoms of steroid-responsive encephalopathy and to determine the prognosis of the disease. The comprehensive treatment of epileptic seizures in hormone-sensitive encephalopathy requires multiple methods. Etiological treatment, especially hormonal therapy, should be considered first. At the same time, according to clinical experience, seizures do not spontaneously remit. Therefore, antiepileptic treatment is necessary. Levetiracetam has been suggested as an effective alternative treatment for patients with steroid-responsive encephalopathy who are insensitive to glucocorticoids or unable to receive steroid therapy because levetiracetam has both anti-inflammatory and antiepileptic properties. In addition, valproic acid and oxcarbazepine have antiepileptic, antitumor, and immunomodulatory effects, and valproic acid has been approved as an antitumor drug. For patients with steroid-responsive encephalopathy with seizures and malignant tumors, valeric acid may be effective. Most patients with steroid-responsive encephalopathy are sensitive to steroids and immunotherapy; however, they are prone to relapses. The possibility of recurrence of steroid-responsive encephalopathy is related to whether a patient receives standard and timely treatment and other related factors. The specific timing of antiepileptic drug administration depends on many individual factors, and further research is needed.

Furthermore, in recent years, autoantibodies against the synapses of the central nervous system have gradually been recognized to be present in some patients with autoimmune encephalopathy. Autoantibodies against synaptic surface antigens or intracellular autoantigens produce a variety of neurological insult manifestations. Autoantibodies that change the function of neuronal circuits by targeting synaptic antigens increase the excitability of neurons and lead to epileptic seizures [20]. Patients in this category usually do not respond to antipsychotic or AEDs but respond well to immunosuppressants [80]. Cellular or humoral immunity will be activated during the onset of the disease. At this time, changes in the patient's blood antibodies should be closely monitored. Patients with different pathologies require different therapies. For example, autoimmune tissue damage mediated by the intracellular antigen-antibody response is more amenable to IVIG, steroids, or anti-T cell therapy rather than PLEX or anti-B cell therapy. In the presence of antibodies against synaptic antigens, PLEX or anti-B cell agents targeting autoantibodies are more promising [20]. In the treatment of patients with steroid-responsive encephalopathy with epileptic seizures, the etiology should be carefully discerned, and appropriate treatment should be selected according to the antibody. At present, large-scale clinical studies evaluating the therapeutic effect of seizure in steroid-responsive encephalopathy are still lacking. In the future, the therapeutic effect of immunosuppressive therapies on seizures must be further evaluated to guide clinicians.

Authors' contributions XX and AL conceived the article and wrote the manuscript.

XW reviewed and edited the manuscript.

All authors read and approved the manuscript.

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Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

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