

REVIEW

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Seizures and epilepsy secondary to viral infection in the central nervous system



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Abstract

Viral infection in the central nervous system (CNS) is a common cause of seizures and epilepsy. Acute symptomatic seizures can occur in the context of almost all types of acute CNS viral infection. However, late unprovoked seizures and epilepsy may not be frequent after viral infection of the CNS. The incidence of seizures and epilepsy after CNS viral infection is mainly dependent on the brain region of infection. It remains to be determined whether treatment of CNS viral infection using antiepileptic drugs (AEDs) can prevent seizures and subsequent epilepsy in patients, particularly with regard to the timing, drug choice and dosage, and duration of AEDs. The postoperative outcome of seizures in patients with intractable epilepsy caused by viral encephalitis primarily depends on the epileptogenic zone. In addition, neuroinflammation is known to be widely involved in the generation of seizures during CNS viral infection, and the effects of anti-inflammatory therapies in preventing seizures and epilepsy secondary to CNS viral infection require further studies. In this review, we discuss the incidence, mechanisms, clinical management and prognosis of seizures and epilepsy secondary to CNS viral infection, and summarize common CNS viral infections that cause seizures and epilepsy.

Keywords: Seizures, Epilepsy, Viral infection, Central nervous system

Background

Viral infections can cause a broad range of diseases in the central nervous system (CNS). Many types of CNS viral infections have characteristic geographic distribution patterns, and they can be transmitted across regions or countries through travel [1]. Understanding the epidemic regions of viruses is helpful for diagnosing viral infection in the CNS. In addition, with the development of molecular biological and neuroimaging techniques, the diagnosis of CNS viral infection is becoming more and more rapid and accurate.

Seizures are a common presenting symptom of CNS viral infection, and can occur during the acute phase of infection or late after recovery [2]. Acute symptomatic seizures can manifest in almost all types of acute CNS viral infection, while late unprovoked seizures and epilepsy may not be frequent after recovery from the acute

stage of infection [2]. Previous study has suggested that concurrent seizures with viral encephalitis are predictive of death and severe sequela on follow-up [3]. Theoretically, early management of seizures and epilepsy after CNS viral infection may improve prognosis. However, there are limited data on the timing, drug choice and dosage, and duration of antiepileptic drugs (AEDs) treatment. Neurosurgery is not always effective in producing an ideal seizure outcome, however, in certain subgroups of patients with postencephalitic epilepsy, the postoperative seizure outcome has been reported to be generally satisfactory [4].

In this paper, we provide a comprehensive overview on seizures and epilepsy secondary to viral infection in the CNS, primarily focusing on the clinical management and prognosis of seizures and epilepsy following CNS viral infection.

Seizures and epilepsy in CNS viral infection

Viral infection in the CNS can present with either acute symptomatic or late unprovoked seizures [1, 2]. A large

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variety of CNS viral infections are associated with seizures [1, 2, 4]. The incidence of early seizures varies among CNS viral infections and is underestimated probably due to the underdiagnosis of nonconvulsive seizures [2]. Acute symptomatic seizures do not recur in general, but they may increase the risk of subsequent unprovoked seizures and epilepsy [1]. For example, a population-based study found that the 20-year-risk of late unprovoked seizures is 22% in viral encephalitis complicated by early seizures, and 10% in patients who have not experienced early seizures during viral encephalitis [5].

Common CNS viral infections associated with seizures and epilepsy

CNS viral infection is a prevalent etiology of seizures and acquired epilepsy. More than 100 types of viruses may cause encephalitis [1]. According to the epidemiological behavior, viral encephalitis can be classified into sporadic encephalitis and epidemic encephalitis [1, 2]. Most types of epidemic viral encephalitis are caused by arboviruses which are transmitted to humans by arthropods such as mosquitoes and ticks [2], and they have different characteristic geographical distributions [1]. Adequate knowledge on the epidemic regions of each type of virus is beneficial for clinical diagnosis of CNS viral infection. A list of common viruses associated with seizures and epilepsy is provided in Table 1.

Japanese encephalitis (JE), caused by Japanese encephalitis virus (JEV), is the most common acute epidemic encephalitis worldwide [1]. The associated factors for the occurrence of early seizures in patients with JE include young age, focal weakness, electroencephalogram (EEG) slowing, a low score on the Glasgow Coma Scale, increased intracranial pressure, as well as cortical and thalamic involvement on computed tomography or magnetic resonance imaging [2, 20]. Previous studies have shown that 50–80% of JE cases have seizures [21]; more specifically, 61% of children versus 37% of adult patients manifest with seizures [2]. Notably, repeated status epilepticus (SE) is associated with poor prognosis [20]. Clinical investigative findings have suggested that JE should be highly suspected in patients who develop symptoms of CNS viral infection in the epidemic regions of JE, for which virological and serological tests should be performed to verify the suspicion.

Dengue is largely endemic in tropical and sub-tropical countries. Dengue encephalitis is an infrequent but critical complication of Dengue virus infection. Seizures are common in dengue encephalitis cases with an incidence of 47% and are typically generalized [22–24].

Herpes simplex encephalitis (HSE) is the most common type of sporadic encephalitis and most of the cases are caused by Herpes simplex virus type 1 (HSV-1) [19, 25]. The most common clinical symptoms of HSE include

fever, seizures, headache, and focal neurological deficits [26]. HSE inflammation is characterized by hemorrhagic-necrotizing inflammation, a predisposition to occur in epileptogenic areas within the fronto-temporal regions, and the involvement of cerebral cortex [19, 27, 28], which can partly explain the high incidence of seizures during HSE. Previous studies indicated that 75% of HSE cases have seizures in the acute stage of infection [29], 40–65% of adult patients present with late unprovoked seizures after resolution of HSE symptoms [30, 31], and 29% of HSE patients have SE [32], which is more intractable than other causes [33, 34]. The main seizure types associated with HSE are focal seizures followed by generalized seizures [35]. Notably, HSV can remain in the CNS tissue for a long time after primary infection [36], forming a source of HSV reactivation, which can be induced under conditions of stress, ultraviolet light, immunosuppressed state, intercurrent infection, hormonal changes, epilepsy surgery and trigeminal ganglia operation [37–40], thus resulting in HSE recurrence.

Other types of herpes viruses only contribute to a small proportion of encephalitis cases. Cytomegalovirus (CMV) is a frequent cause of intrauterine infection [41–43] and is closely related to postnatal seizures [44, 45]. However, approximately 90% of cases with congenital CMV infection are asymptomatic [46], while only 10–15% of infant cases have clinical symptoms or signs at birth [47]. The incidence of postnatal seizures in symptomatic infected children ranges from 10 to 56%, whereas the rate is 0.9% in asymptomatic patients [48–50].

Human immunodeficiency virus (HIV) infection has become a common etiology for new-onset seizures especially in developing countries [1]. Seizures have been reported in 2–20% of cases with HIV infection [51], and most of them manifest generalized seizures; in contrast, partial seizures are rarely observed [52–55]. Causes for the seizures in patients with acquired immune deficiency syndrome include cerebral HIV infection, and more commonly, secondary opportunistic CNS infection [1]. Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic viral infection caused by a common John Cunningham virus (JCV) in immunocompromised individuals, especially those with advanced HIV infection. In a previous study of Miskin et al., 44% of PML survivors had seizures, and 25% had seizures immediately at the onset of PML symptoms [56]. Hyperintense cortical signal on T1-weighted precontrast magnetic resonance images and immune reconstitution inflammatory syndrome are both related to seizures in patients with PML [57, 58].

Mumps virus and Measles virus are members of the *Paramyxoviridae* family and are implicated in encephalitis. Subacute sclerosing panencephalitis (SSPE) is a progressive fatal disease caused by Measles virus [59]. In an

Table 1 Common viruses associated with seizures and epilepsy

Genus or family [6]	Virus and type of nucleic acid [6]	Route of transmission	Geographical distribution	Peak seasonal incidence	Laboratory testing
<i>Flaviviridae</i>	Japanese encephalitis virus (RNA virus)	Transmitted by genus <i>Culex</i>	India, China, Japan, South East Asia, Eastern Mediterranean region, Papua New Guinea, Australia [1]	Summer and early fall	CSF PCR; serum and CSF IgM (elevated in CSF in the first few days, sensitivity and specificity > 90%) and IgG [7]
	Dengue virus (RNA virus)	Transmitted by genus <i>Aedes</i>	India, China, Japan, South East Asia, Eastern Mediterranean region, Papua New Guinea, Australia [8]	Summer and early fall	PCR or antigen testing of respiratory secretions [8]
	Zika virus (RNA virus)	Transmitted by genus <i>Aedes</i> ; mother-to-child transmission through placenta; sexual transmission [9]	Africa, South America, Southeast Asia (Pacific region)	More frequent in summer and early fall (in the temperate zone); no seasonality (in the tropics)	Serum or urine PCR; serum or CSF IgM [9]
<i>Herpesviridae</i>	Herpes simplex virus (DNA virus)	Sexual; contact transmission	Worldwide	No seasonality	CSF PCR [8]; CSF IgG (if neurological manifestations last more than a week) [10, 11]
	Cytomegalovirus (DNA virus)	Mother-to-child transmission through placenta, labour, breast milk; sexual transmission; blood transfusion	Worldwide	No seasonality	Serum and CSF PCR; serum and CSF IgM or IgG [8]
	Varicella zoster virus (DNA virus)	Close contact and droplet transmission [12]	Worldwide	All seasons, more frequently in late winter and spring [12]	CSF PCR
	Epstein Barr virus (DNA virus)	Saliva or droplets transmission [13]	Worldwide	No seasonality	CSF PCR; serum viral capsid antigen, IgM [14]
<i>Retroviridae</i>	Human immunodeficiency virus (RNA virus)	Sexual transmission; direct contact; blood or blood products	Sub-Saharan Africa, Central Asia, Latin America, Eastern Europe [1]	No seasonality	PCR or serum IgG
<i>Paramyxoviridae</i>	Measles virus (RNA virus)	Droplet transmission; direct contact with nasal or throat secretions [15]	Worldwide [8]	All seasons, more frequently in late spring	Serum IgM; CSF PCR; nasopharyngeal, throat or urine PCR [8]
	Mumps virus (RNA virus)	Droplet transmission	Worldwide [8]	Winter and spring (in the temperate zone); no seasonality (in the tropics) [16]	Serum IgM; CSF PCR (high sensitivity); viral isolation from CSF, saliva, urine [8]
	Nipah virus (RNA virus)	Droplet transmission; direct contact transmission (bats-to-human, pigs-to-human, human-to-human occasionally) [17]	Bangladesh, India, South-East Asia, Australia [8]	More frequent from January to May [18]	Serum and CSF IgM/IgG; CSF, serum and urine PCR [8]
<i>Orthomyxoviridae</i>	Influenza (RNA virus)	Droplet transmission; contact transmission	Worldwide distribution but encephalopathy most frequently reported in Japan and Australia [8]	Winter and spring	Nasopharyngeal swab, respiratory secretions PCR [19]

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; IgM: immunoglobulin M; IgG: immunoglobulin G

earlier study, 43% of patients with SSPE develop epilepsy, and the epileptogenic activities are mainly localized in the frontal lobe (58%) [59].

Emerging viral infectious diseases include old infections that have recently spread to new geographic locations, infected new host species, or changed their pathology and

morbidity, and new infections by previously unknown pathogens [1, 60]. Examples of emerging viral infections include Nipah virus infection that spread from Malaysia to Bangladesh and India [1, 2, 61], and Zika virus (ZIKV), which is the latest member of arboviruses and causes sporadic illness at first and then large outbreaks in the Pacific [62].

A previous study showed that in cases of acute Nipah encephalitis, 23–27% of them had seizures and 30–54% of them had continuous segmental myoclonus [61]. Comparatively, seizures commonly occur in patients with relapsing Nipah encephalitis [1, 61]. ZIKV infection during pregnancy can cause congenital Zika syndrome (CZS), a distinct pattern of birth defects and disabilities, as ZIKV tends to attack the embryo matrix of fetal brain [63]. ZIKV infection can cause a broad range of underlying neurological abnormalities and frequent epileptic seizures [9]. Epilepsy has been observed in infants with CZS during their first year of life [64]. The incidence of epilepsy according to previous studies ranges from 9 to 71.4% [64–69], with the main seizure types being epileptic spasms (72%) followed by focal motor seizures (21%), and tonic seizures (4%) [69].

Mechanisms of seizures and epilepsy in CNS viral infection

The incidence of seizures and epilepsy varies among different types of CNS viral infections, which is thought to be largely dependent on the anatomic location of the lesion [2]. HSV predominantly involves the mesial temporal lobe which is known to be a highly epileptogenic brain region, while other viruses such as JEV and West Nile virus generally affect subcortical structures and spare cerebral cortex [1, 2].

Neurotropic viruses can invade the CNS via blood or axonal transport, and induce neuronal injury, abnormal modification of neural circuits linked to seizure cascade, and production of proinflammatory cytokines during infection [1, 6, 70]. The proinflammatory cytokines can activate the innate immune system as well as the adaptive immune system [70]. The activated macrophages and microglia, effector cells of the innate immunity, can produce interleukin (IL)-6 and tumor necrosis factor (TNF)- α during viral infection [71–73]. A previous study has found that the number of infiltrating macrophages, which are inflammatory cells, reaches a peak coincidentally with the peak of post-infectious seizures during CNS viral infection [74]. The inflammatory macrophages play a role in the clearance of virus from the brain, but at the same time may trigger seizures via promoting the production of IL-6 [71]. The proinflammatory cytokines such as IL-6 and TNF- α have been demonstrated to disrupt the neuronal excitation/inhibition balance and increase neuronal hyperexcitability [71, 75, 76]. In a murine model of Theiler's encephalomyelitis virus-induced seizures, researchers found significantly decreased inhibitory currents and markedly increased excitatory currents in CA3 pyramidal neurons during the acute phase of viral infection [77, 78]. In addition, previous studies have revealed that inflammatory cytokines may break down the blood-brain barrier, leading to cerebral edema and

ultimately triggering seizures [1, 79, 80]. The acute symptomatic seizures secondary to CNS viral infection may induce functional and structural alterations of the brain such as neuronal loss, neurogenesis, activation of microglia and astrocytes, gliosis, and neural circuit alteration, which in turn promote epileptogenesis and subsequent epilepsy [70, 81].

Clinical management and prognosis

Rapid diagnosis and timely initiation of antiviral treatment are essential for an optimal outcome in patients with CNS viral infection [19]. Evidence for the effectiveness of routine use of corticosteroids in treating CNS viral infection is insufficient [19]. Empirical interventions should be implemented in patients suspected clinically to have CNS viral infection despite the fact that virological tests remains uncompleted [82, 83].

The occurrence of seizures during the course of CNS viral infection is closely related to severe sequelae and indicates a high risk of subsequent epilepsy [26, 84]. Theoretically, prophylactic use of AEDs for primary or secondary prevention may potentially improve prognosis. In a previous systematic review, Pandey et al. intended to determine the primary and secondary preventive effects of prophylactic AEDs use on the occurrence of seizures in patients with viral encephalitis, but failed to obtain any relatively high-quality publications [85]. In addition, the timing, specific agent and dosage, and duration of AEDs have not been well-established due to the lack of evidence-based information [85]. Further studies on these topics are required. In clinical practice, AEDs are commonly used for preventing additional seizure after the first acute symptomatic seizure has occurred during the acute stage of infection [86]. The duration of prophylactic use of AEDs can range from 1 to 6 months in patients with complicated acute brain insults [86, 87], and the choice of AEDs mainly depends on the seizure type [88]. Narrow-spectrum AEDs (e.g., carbamazepine, oxcarbazepine, phenytoin, and lacosamide) are considered for decreasing seizure frequency in patients with focal seizures [88–90]. Broad-spectrum AEDs (e.g., lamotrigine, levetiracetam, topiramate, valproate, and zonisamide) are typically used in patients with focal seizures or most generalized seizures [88–90]. Long-term antiepileptic medication is recommended when the diagnosis of epilepsy following CNS viral infection is established. If the first AED titrated to a therapeutic dose fails to control seizures, adding a second AED may increase the probability of achieving the goal of seizure-free [91]. The duration of antiepileptic therapy in post-infectious epilepsy should be customized. It is reasonable to consider AEDs withdrawal in those who has been seizure-free for at least 2 years [88, 92–94]. In addition, it is commonly accepted that

antiepileptic therapy be initiated once the diagnosis of SE is established. Rapid initiation of AEDs treatment, start of critical care and simultaneous monitoring are strongly recommended until clinical and electrographic seizures are halted [95].

Adrenocorticotrophic hormone is considered an effective treatment for infantile spasms, but it may cause severe side effects in patients presenting infantile spasm after CMV infection due to its suppression of immune response [96–98]. Notably, previous study has reported that 56% of patients with infantile spasm and CMV infection achieve cessation of seizures after ganciclovir and AEDs treatment [99]. This indicates that a combined antiviral and antiepileptic regimen is preferred in order to avoid potential side effects induced by steroid therapy.

Several antiviral agents are principally metabolized by CYP3A4, but most old-generation AEDs can induce or inhibit such enzymatic function, which lead to the alterations of plasma concentrations of antiviral drugs [100]. Therefore, the efficacy of antiviral drugs should be reassessed when antiviral and antiepileptic agents are administered together. Valproic acid, a strong inhibitor of hepatic enzymes, can inhibit the metabolism of zidovudine [101]. On the contrary, carbamazepine, an enzyme-induced antiepileptic drug, significantly reduces the plasma concentration of indinavir, and the dose of which may need to be increased [102]. Notably, second- or third-generation AEDs such as levetiracetam, lamotrigine, gabapentin and brivaracetam may be favorable options as they have less effect on enzymatic function of CYP3A4 [103].

Epilepsy secondary to CNS viral infection is usually intractable, even with the use of multiple AEDs [26, 104, 105]. Patients with intractable epilepsy due to CNS viral infection should be considered as candidates for epilepsy surgery [106]. However, previous studies have found that the seizure outcomes after neurosurgery are not ideal as the lesions of CNS viral infection are generally widely distributed [4, 107, 108]. Notably, there is evidence that certain patients may have a favorable prognosis after epilepsy surgery. A recent study has indicated that in patients with postencephalitic epilepsy who were completely seizure-free or had significant improvement after operation, the seizure onset area was located either in the anteromesial temporal structures or focal gyrus; while in patients who had a relatively poor postoperative seizure outcome, the seizure started from multiple lobes [107]. Therefore, rigorous presurgical evaluation should be performed to determine which patients with intractable epilepsy secondary to CNS viral infection are suitable for surgical treatment. Stereoelectroencephalography or electrocorticography should be performed to elucidate the epileptogenic zone since scalp EEG is generally inadequate for presurgical evaluation [106, 107].

Remarkably, after initial infection, HSV can establish persistent latent infections in the CNS, acting as a source of HSE recurrence [109, 110]. HSV reactivation after HSE rarely occurs to our knowledge, but there have been reports of HSE recurrence after neurosurgery for postencephalitic epilepsy [110, 111]. Therefore, antiviral agents should be considered for prophylactic preoperative treatment in postencephalitic epilepsy patients with known histories of HSE [109, 110].

Immune inflammatory response after CNS viral infection is a common pathophysiological mechanism that leads to seizures and epilepsy [1]. Animal experiments showed that anti-inflammatory therapy may be beneficial in improving the seizure threshold [112]. Further clinical trials are required to assess the effects of anti-inflammatory drugs in seizures and epilepsy secondary to CNS viral infection.

Notably, recent studies have indicated a possible association of CNS viral infection with subsequent autoimmune encephalitis (AE) [113–117]. AE is also one of the causes of seizures and epilepsy [118]. Neuronal injury and neuroinflammation induced by CNS viral infection can lead to the exposure of neuronal surface proteins, which triggers subsequent generation of antibodies against these antigens [113, 119]. In addition, molecular mimicry has been involved in the pathogenesis of AE after viral infection of the CNS [113, 114]. In a recent prospective study in a cohort of patients with HSE, 27% of the cases developed AE associated with autoimmune responses against N-methyl-D-aspartate receptor and other neuronal surface proteins within 3 months after antiviral therapy [113]. In addition, there were no differences in the use of AEDs or immunotherapy during HSE between AE and non-AE groups [113]. However, as the number of cases in this study is relatively small, whether prophylactic use of AEDs or immunotherapy during CNS viral infection is effective in preventing the development of AE requires further investigations.

Conclusion

Both acute symptomatic and late unprovoked seizures are associated with CNS viral infection. The incidence of seizures and epilepsy differs among various CNS viral infections, which may be attributed to the different brain regions involved by different types of viruses. Routine prophylactic use of AEDs in patients with CNS viral infection remains controversial, and the postoperative seizure outcome primarily depends on the epileptogenic zone. The immune inflammatory response during CNS viral infection is a frequent pathophysiological mechanism that leads to seizures and epilepsy, and anti-inflammatory therapy may be advantageous for a better seizure outcome. Currently, there are limited data on the incidence, clinical management and prognosis of seizures and epilepsy secondary to CNS viral infection, so further investigations are needed to advance understanding in these facets.

Abbreviations

AE: Autoimmune encephalitis; AED: Antiepileptic drug; CMV: Cytomegalovirus; CNS: Central nervous system; CSF: Cerebrospinal fluid; CZS: Congenital Zika syndrome; EBV: Epstein Barr virus; EEG: Electroencephalogram; HIV: Human immunodeficiency virus; HSE: Herpes simplex encephalitis; HSV: Herpes simplex virus; HSV-1: Herpes simplex virus type 1; IL: Interleukin; JCV: John Cunningham virus; JE: Japanese encephalitis; JEV: Japanese encephalitis virus; PML: Progressive multifocal leukoencephalopathy; SE: Status epilepticus; SSPE: Subacute sclerosing panencephalitis; TNF: Tumor necrosis factor; VZV: Varicella zoster virus; ZIKV: Zika virus

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Authors' contributions

PZ made substantial contributions to the content of the study, drafted and revised the manuscript, and read and approved the final manuscript. YY, JZ, XY and QL drafted and revised the manuscript, and read and approved the final manuscript. YC made substantial contributions to the content of the study, revised the manuscript, and read and approved the final manuscript.

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