Arbovirus and seizures

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Abstract

The high prevalence and spread of arthropod-borne viruses (arboviruses) make them an important cause of viral encephalitis in humans. Most epidemic viral encephalitides have an etiology associated with arboviruses. Among various arboviruses, the Japanese encephalitis virus, West Nile virus, Zika virus, Dengue virus and Chikungunya virus can induce seizures. Arboviruses of the genus *Flavivirus* are usually transmitted by mosquitoes and other host animals. These vector-borne pathogens can cause epidemic viral encephalitis. Seizures may not be the major manifestation in these viral encephalitides, but may predict a poor prognosis. In this article, we discuss the relationships between these viruses and seizures from perspectives of clinical characteristics, pathogenesis, prognosis and treatments of each.

Keywords: Seizures, Japanese encephalitis, West Nile virus, Zika virus, Dengue virus, Chikungunya virus

Japanese encephalitis virus (JEV)
Clinical characteristics

Japanese encephalitis (JE) is the most common form of arbovirus encephalitis and is related to acute symptomatic seizures, especially in children. JEV is usually transmitted by *Culex* mosquitoes and has a bird-pig life cycle. Human beings are the dead-end host of the virus. Most infected cases are in developing countries located at Southeast Asia, Western Pacific and Eastern Mediterranean regions.

Seizure is one of the major clinical manifestations of JEV infection, but has varied frequencies of occurrence among different reports. According to a case report in Central Sarawak, Malaysia [1], seizures occurred in 50–80% of infected patients, more frequently in children than in adults. The epidemiological reports of early seizures often underestimated the incidence, probably due to the poor access to appropriate caregivers and facilities for diagnosis. Early seizures are often detectable only by continuous electroencephalographic monitoring (EEG) [2], which is limited in developing countries compared to developed countries. This results in variable

conclusions for seizure occurrence rate in JEV encephalitis. MRI has revealed thalamic, basal ganglia and brainstem involvement in JE [3]. The clinical manifestations of subtle seizures may appear as eye, mouth or extremity twitching/myoclonus, nystagmus, excessive salivation, or irregular respiration [4]. The EEG patterns of JEV brain infection include isolated discharges, periodic lateralized epileptiform discharges, multiple seizures, continuous seizures, and status epilepticus [5]. In a study conducted in India, seizures occurred in 40% of JE patients, and generalized tonic-clonic seizures were the most common type in this case series [3].

Neuroimaging findings

The MRI characteristics of JE patients are bilateral thalamic lesions. These lesions show high signal intensities in T2 and fluid attenuation inversion recovery (FLAIR) sequences [6] (Fig. 1).

In JE, real-time monitoring of EEG is important for appropriate treatment and enables detection of early seizures. The general EEG findings in JE are a constant pattern of diffuse delta activity, which is likely due to bilateral thalamic involvement [8]. These characteristic EEG findings are very common and do not predict a poor outcome. When seizures occur, patients typically manifest abnormalities including theta and delta coma,

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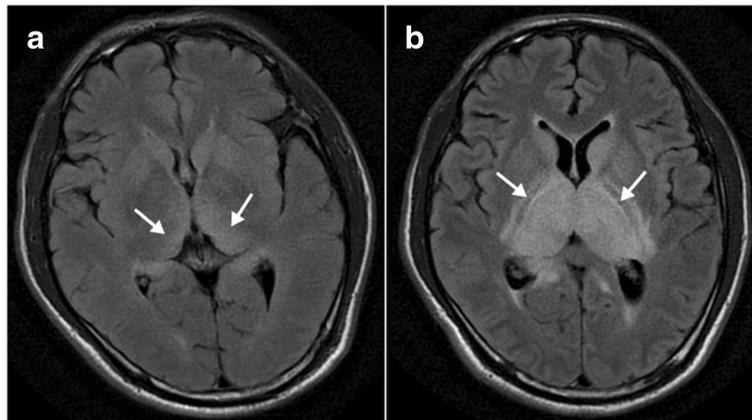Full list of author information is available at the end of the article

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Fig. 1 Characteristic changes on MRI with FLAIR sequence on day 1 (**a**) and day 5 (**b**) of JEV patients [7]

burst suppression, an isoelectric pattern, or occasionally alpha coma [4].

Pathogenesis
Tropism with the brain
JEV's neurotropism is a relevant factor of its pathogenesis. Neurotropism is not synonymous with neurovirulence, but they can be associated with each other in some cases. The JEV typically replicates in the skin before it spreads to local lymph nodes. Then it travels to the liver, heart, kidney and other organs before crossing the blood-brain barrier (Fig. 2). To cross the blood-brain barrier, JEV replicates in endothelial cells or inflammatory cells that carry the virus (Fig. 3).

Activated glia
In mice with central nervous system (CNS) infection with JEV, researchers have observed activation of astrocytes [9]. The activated astrocytes can inhibit the intake of glutamic acid and the synthesis of γ-aminobutyric acid (GABA), resulting in neuronal hyperexcitability. In addition, inwardly rectifying potassium channels are down-regulated in epilepsy and inflammation. This may make astrocyte unable to balance extracellular K+ concentration [10, 11]. Further detailed mechanisms remain to be elucidated by more experiments.

Activated microglia are also observed in the CNS. JEV-infected microglia can up-regulate miR-146a, facilitating the expression of miR-146a and the replication of the virus [12]. On the other hand, the levels of IL-1β, IL-6, TNF-α and other proinflammatory mediators are significantly elevated during JEV infection. These proinflammatory mediators released by activated microglia can induce neuronal loss [13]. The auto-toxic loop led by microglial activation possibly results in proliferation and formation of microglial nodules, contributing to the pathogenesis of refractory epilepsy. Moreover, microglia also participate in the formation of blood-brain barrier.

In addition, JEV has tropism for neuroblast-derived cells [14], which may be related to the formation of abnormal synapses. The formation of abnormal synaptic connections will result in abnormal discharges [15].

Further information
Research by Yao et al. showed that the expression of miR-16-1 and heat shock protein 70 was upregulated in astrocytes during the occurrence of epilepsy after JEV infection [16]. Another case report led by Ma et al. showed that JEV infection can trigger anti-N-methyl-*D*-aspartate receptor encephalitis [17]. This implies an autoimmunity-related mechanism underlying neuronal damage by JEV. However, studies on the specific mechanisms of JEV-induced epilepsy are limited because of its rare occurrence.

Treatments
Currently, no clinically-approved therapy is available for the treatment of any flavivirus infection [18], but hospitalization for supportive care is generally required [19]. Therefore, complications such as seizures should be diagnosed at an early time for appropriate treatment, and AED treatment is indicated for neonatal seizures, which may be subclinical.

Prognosis
The prognosis of epilepsy is determined by etiology, severity, site of infection, and certain host factors [20]. Timely and effective control of seizures is an important measure to improve prognosis. Antiepileptic drugs are commonly used to treat epilepsy after infection. Yet, due to the lack of effective treatment of CNS infection, it is difficult to prevent post-encephalitic epilepsy.

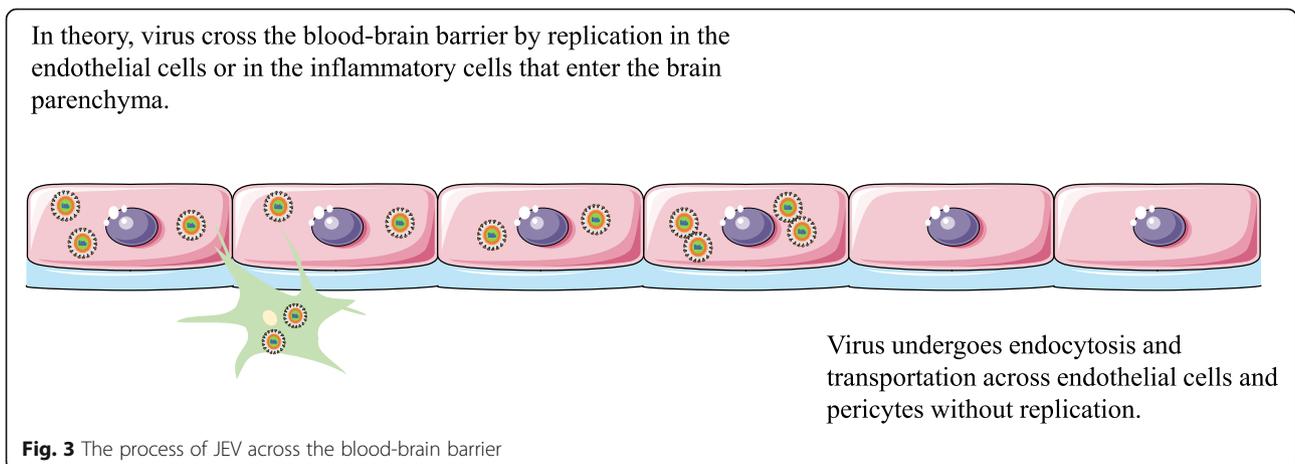**Fig. 2** The process of JEV infection in the human body
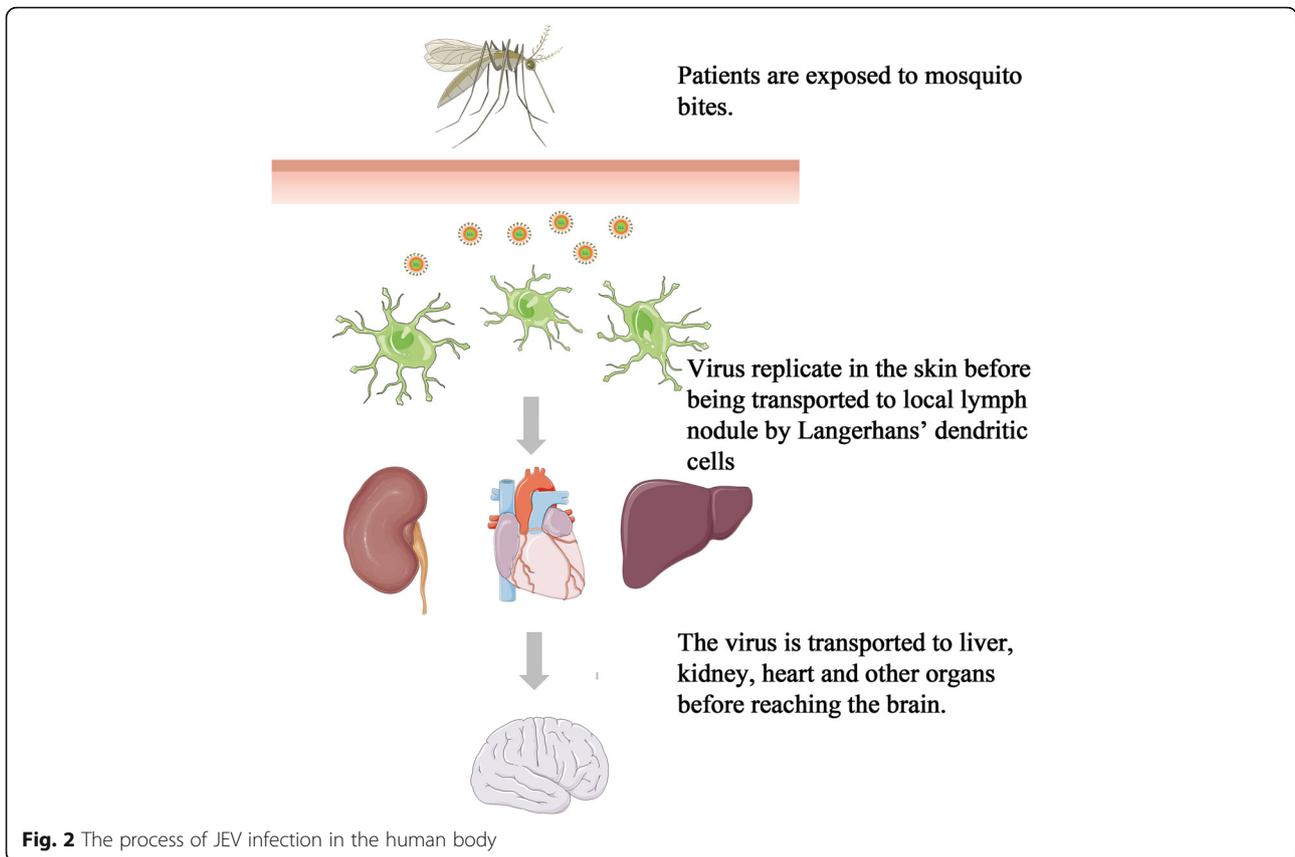
It is important to note that seizures in JEV infection often indicate a poor prognosis. Around 20% of patients who survive the acute JEV infection develop long-term seizures. More detailed studies assessing long-term consequences are lacking in epidemic regions. Timely diagnosis and treatment of seizures may reduce the associated damage to the brain and improve the prognosis by preventing increased intracranial pressure, brain herniation and death. As long-term seizures may occur as a result of epileptogenesis due to cortical dysfunction, timely medical treatment is the best choice to find and control early seizures in arbovirus-infected patients.

West Nile virus (WNV)

WNV is related antigenically to the JE antigenic complex of the *Flaviviradae* family, so the pathogenesis of WNV infection is very similar to that of JEV. Humans and horses are the dead-end hosts of WNV. Horses are commonly recognized to develop symptomatic infections. Seizures are not a common symptom for WNV

In theory, virus cross the blood-brain barrier by replication in the endothelial cells or in the inflammatory cells that enter the brain parenchyma.

Virus undergoes endocytosis and transportation across endothelial cells and pericytes without replication.

Fig. 3 The process of JEV across the blood-brain barrier

infection, and their occurrences are also lower than those in JEV. WNV-associated epilepsy is rarely reported. In a report of WNV disease outbreak in Pakistan [21], 15% of patient with confirmed WNV had seizures. In addition, there are no definitive reports of prognosis of WNV-associated seizures.

Clinical characteristics
In recent studies, most WNV infections are asymptomatic. Only 20% of patients manifest some mild symptoms such as flu-like illnesses. Virus entry into the CNS occurs in < 1% of the symptomatic individuals. However, in horses, the percentage of neurologic symptoms is 10%. Older patients tend to have a higher frequency of severe neurological symptoms and higher mortality. While the incidence varies between series, seizures appear uncommon in West Nile encephalitis and are estimated to occur in 3 to 6% of patients [22].

MRI
The most characteristic MRI findings in West Nile encephalitis patients are bilateral signal abnormalities in the basal ganglia and thalami on T2, FLAIR and diffusion-weighted image sequences, indicating possible viral neurotropism for these deep gray structures [23]. However, these findings are not specific, which means that they can also appear in other *Flavivirus* encephalitides. In fact, MRI is not a sensitive diagnostic tool for West Nile encephalitis because sometimes MRI findings can be normal even in severe cases [24–26].

Pathogenesis
The frequency of seizures in WNV-infected cases is low, as previously discussed. As mentioned above, WNV entry to the CNS is uncommon and therefore poorly documented, but several possible routes for entry have been proposed: (1) entry through the blood-brain barrier disrupted by TNF-α, IL-1β and certain macrophage migration inhibitory factors [27, 28]; (2) entry through choroid plexus epithelial cells [29]; (3) infecting olfactory neurons and spreading via the olfactory bulb [30] (also seen in other flaviviruses); and (4) entry through infected immune cell infiltration into the CNS [30].

Treatments
Treatment for WNV infection is also mostly supportive. Seizures, although rare, should be appropriately treated to reduce possible complications such as increased intracranial pressure.

Zika virus (ZIKV)
ZIKV is another member of the flavivirus family. About 80% of ZIKV infections are asymptomatic. The association with seizures has only been described recently.

Analysis of clinical data shows that ZIKV infection in pregnant women is related to infant congenital microcephaly [31], an extreme consequence with spontaneous epileptic activity developing in 50–60% of microcephalic babies congenitally infected with ZIKV [32, 33]. Therefore, we discuss in the following the possible relationship between seizures and ZIKV-induced microcephaly.

Clinical characteristics
ZIKV infection is asymptomatic in three of every four infected patients [34]. Most symptoms are mild and self-limited, and often disappear within a week. The only two exceptions are Guillain-Barré syndrome and microcephaly. Microcephaly is a neurological condition generally associated with severe brain malformations. The increased incidence of microcephaly among children in Brazil has been accounted for by several reasons, including the rise of ZIKV infections, and seizures appear to be a common symptom in ZIKV-induced microcephalic infants.

Although microcephaly does not manifest in all neonates infected by ZIKV in utero, seizures are also observed in neonates without microcephaly [35]. Congenital Zika syndrome (CZS) is a common manifestation in neonatal infection cases. CZS manifests as a consequence of direct neurological insult and severe intracranial volume loss [36]. The inhibited neurogenesis and increased neuronal apoptosis over progenitor cells in CZS result in microcephaly, facial disproportionality, hypertonia, hyper-reflexia and irritability [37, 38]. Hearing and visual loss are also seen in CZS infants [36]. Seizures are the major complication among CZS infants in the first 4 months of life [39].

CT and MRI
In microcephaly-induced by ZIKV infection, the most common neuroimaging features are calcifications in the junction between cortical and subcortical white matter, which are associated with malformations of cortical development. Additional findings are an enlarged cisterna magna, corpus callosum abnormalities, ventriculomegaly, delayed myelination, and cerebellum and brainstem hypoplasia [40].

Pathogenesis
Microcephaly is usually divided into two types--primary or congenital microcephaly and secondary or post-natal microcephaly [41, 42]. The primary microcephaly is usually due to the reduced amount of neurons, while the secondary microcephaly is often due to the decreased dendritic processes and synaptic connections. Both types of microcephaly can develop with seizures.

In cases that do not manifest microcephaly, the pathogenesis is similar to JEV–brain inflammation. In research

by Nem de Oliveira Souza et al. [43], ZIKV induced spontaneous seizures in young mice, and there was an increased level of proinflammatory cytokines in the placental tissue and neonatal brain, accompanying viral replication.

Treatments

Neonatal seizures have low response to conventional anticonvulsant drugs [44] and may require multiple anti-seizure medications. In murine models, researchers found that early inhibition of TNF-α-mediated neuroinflammation may be an effective therapeutic strategy to prevent the development of chronic neurological abnormalities [43]. More importantly, tests for ZIKV infection should be run in early pregnancy or before pregnancy to prevent neonatal CNS malformations and other abnormalities.

Prognosis

Since most ZIKV infections are asymptomatic, most patients go untreated and have a good prognosis. Severe cases such as neonatal ZIKV infection should receive seizure assessment and appropriate treatment from health care professionals. However, the overall prognosis of severe cases is typically poor.

Dengue virus (DENV)

DENVs are transmitted by *A.aegypti* mosquitoes. 75% of DENV infections are asymptomatic. The major clinical manifestations are systematic signs and symptoms without associated epileptic seizures, with rare exceptions.

Clinical characteristics

Although seizures and epilepsy are not a common manifestation in a dengue infection, they are more likely to occur if patients develop neurological symptoms. An investigation in Thailand [45] shows that among 1 493 children diagnosed with dengue infection, 5.4% of them developed neurological manifestations, including seizures in 67%. In some individual case reports, the patients with severe, fatal dengue fever could have concomitant seizures [46, 47].

Pathogenesis

Similar to JEV, DENV is able to cross the blood-brain barrier and have tropism to the brain. However, it replicates in the CNS, while JEV replicates in the skin where mosquitoes inject JEV. In some neurophathological autopsy studies, DENV and its antigen are found in brain tissues without histological inflammatory features [48–52]. This is probably why DENV causes a lower rate of seizure occurrence.

The occurrence rate of DENV neuroinfection remains unknown. It has been shown to occur preferentially in immune- or neurological-immature murine models, yet there are cases of adult patients without any sign of immune system impairment [53].

Chikungunya virus (CHIKV)

CHIKV was newly discovered in Puerto Rico in May 2014, and is mainly transmitted by mosquitoes of the *Aedes* genus (*A.ageypti* and *A.albospictus*) [54].

Clinical characteristics

Unlike ZIKV and DENV, most individuals with CHIKV infection are symptomatic. The major symptoms of CHIKV infection are similar to dengue fever. Other manifestations include arthralgias and myalgias, and neurological complications in severe cases. Seizures are a common neurological manifestation in CHIKV-infected children [55–58].

Pathogenesis

CHIKV has tropism for fibroblasts in the dermis, joint capsules and muscles. Human epithelial and endothelial cells can also be infected by CHIKV [59]. However, CHIKV cannot invade neural tissue or replicate in neurons [60]. There are no related autopsy and histopathological studies, so the target cells of CHIKV in the human brain remain unknown [60]. In experimentally infected mice, the virus preferentially infects astrocytes [61].

Prognosis

Early seizures can be subtle, so EEG is needed for diagnosis. As a result, hospital care is necessary for patients. However, there are also counterexamples. A report of an outbreak of Chikungunya Virus in 2014 [62] suggested that seizures occurred more frequently in hospitalized patients than non-hospitalized patients.

Treatments

There is no specific treatment for CHIKV infection.

Discussion

To treat epilepsy after arbovirus infection effectively, more information on specific mechanisms is needed. Most seizures triggered by arbovirus infection are induced by viral encephalitis. Only neurotropic viruses have abilities to invade, infect and subsequently replicate within the human nervous system. Epilepsy in viral encephalitis is mainly caused by direct cell damage by the virus and secondary inflammatory responses, during which glia and cytokines are active players. The associated damage to the blood-brain barrier also contributes to seizure occurrence.

Flavivirus nonstructural protein 1 (NS1), which is secreted by related flaviviruses and circulates in the host blood stream [63], triggers tissue-specific vascular

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endothelial dysfunction. In a study led by Puerta-Guardo and colleagues [64], the pathophysiology of each flavivirus is highly related to NS1. NS1 from different flaviviruses alter the human endothelial cell permeability in certain tissues at different degrees. For DENV, NS1 can enhance the endothelial permeability in all tissues so DENV usually causes systemic manifestations. NS1 from JEV and WNV can increase the endothelial permeability in brain tissues, promoting induction of encephalitis. Due to the high relevance between neuroinflammation and seizures as previously discussed, this factor explains why JEV induces seizures in a higher frequency as compared to other flaviviruses. However, why WNV is antigenically similar to JEV while having a much lower rate of neurological symptoms remains unclarified. NS1 from ZIKV has a high concentration in the human placental tissue and developing brain, inducing hyperpermeability of the umbilical vein and brain endothelial cells. This may explain the occurrence of neonatal congenital microcephaly after ZIKV infection during pregnancy.

Further directions

Given the limited treatment options for flavivirus CNS infections and associated seizures, there is a great need for further research to determine the underlying associated pathophysiological causes. Barriers to research include a lack of suitable animal models for testing CNS arbovirus infections [65]. The relationship between neuroinflammation caused by these viruses and seizures requires further research. Animal models for seizures induced by infection can be established in rabbits, rats and mice. However, these animals often develop acute encephalitis before seizures occur. The unpredictable rate of seizures in animal models is another important barrier for further research. There is still a great need of appropriate animal models for viral infection-induced seizures.

Conclusions

Flavivirus infections are associated with neurological diseases, including seizures and epilepsy. The type of flavivirus plays an important role in the probability of CNS involvement and associated seizures after viral infection. Appropriate clinical care requires cautions of possible flavivirus infection, as well as involvement of seizures. Specifically, some patients will require appropriate EEG recording to detect seizures. Effective treatment of associated epileptic seizures enables good supportive care and optimal control of CNS-related comorbidities.

Abbreviations
JEV: Japanese encephalitis virus; EEG: Electroencephalography; CNS: Central nervous system; AEDs: Antiepileptic drugs; WNV: West Nile virus; ZIKV: Zika virus; CZS: Congenital Zika syndrome; DENV: Dengue virus; CHIVK: Chikungunya virus; NS1: Nonstructural protein 1

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