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Current Review
In Clinical Science

Epilepsy and Viral Infections

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Viral infections may cause seizures via several pathogenetic mechanisms. Systemic infections, such as influenza, can lead to metabolic compromise, as well as occasional direct central nervous system (CNS) invasion—even though not usually neurotrophic. Although viral infection confined to the meninges rarely causes seizures and does not increase risk for later epilepsy, encephalitis is a major cause of seizures and subsequent epilepsy (1). In addition to the acute pathogens, syndromes caused by "unconventional" agents, such as Creutzfelt–Jacob disease or progressive multifocal leukoencephalopathy, often are associated with seizures or myoclonus at some time in their course. Seizures are caused by direct CNS infection by human immune deficiency virus (HIV), as well as with the secondary infections associated with acquired immune deficiency syndrome (AIDS). In addition, recent data suggest that persistent infection with a latent agent, human herpesvirus 6, may be associated with development of mesial temporal sclerosis.

Systemic Viral Infections and Seizures

Several systemic infections may involve the CNS. Neurologic complications of influenza—although rare in comparison to the overall incidence of the disease—include seizures provoked by fever and systemic illness, encephalitis, extrapyramidal syndromes, Guillain-Barré syndrome, transverse myelitis, myositis, and myocarditis (2). Although neurologic complications are reported most often in children, this may be related to higher overall attack rates; adults over 60 were relatively spared, perhaps due to prior exposure to antigenically similar agents. Influenza may be associated with as many as 20% of uncomplicated febrile seizures (3).

Some viral strains may be more likely to cause neurologic disease. H1N1 patients had more severe neurological disease, including encephalopathy and focal findings, but the incidence of seizures was the same as in previous influenza epidemics. Children with neurological complications during the 2009 H1N1 epidemic were more likely to have had underlying neurological disease—such as seizures or developmental delay—than those with neurologic involvement during previous seasonal influenza (4). In patients with influenza and altered mental status, evidence for direct CNS infection is limited but may include edema and increased thalamic signal on MRI (5). Seizures occur in about 50% of patients.

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Most patients recover without sequelae, and there are no data to suggest that antiviral treatment affects the neurologic course (2). A rarer influenza-associated acute encephalopathy/encephalitis (> 80% occurring in children) can present with a fulminant neurological illness in association with any influenza viral serotype and may be associated with an underlying genetic disorder in proinflammatory cytokine release and hypercytokinemia (6).

Dengue is one of the most common systemic viral infections; more than 100 million people are infected yearly (7). It may be associated with neurologic disease, probably due to direct CNS invasion, in 0.5 to 6 percent of patients (8). In Jamaica, 13.5% of patients with suspected CNS viral illness had dengue (9). About half the patients with CNS illness have seizures, including status epilepticus (10–12).

Seizures occurred in 8 of 103 patients with yellow fever, a disease less common now but historically very important; patients with neurologic involvement had a worse prognosis than others (13).

Viral Encephalitis

A wide range of viruses is associated with encephalitis and seizures. Some occur sporadically in a worldwide distribution, while others have restricted geographic ranges, often related to specific viral vectors and hosts (Table 1, Figure 1). The overall incidence ranges from 1.5 to 10 per 100,000 (14). Since the incubation period for arbovirus encephalitis—such as Japanese B, for example—may be 5 to 15 days, it is important to remember that travelers to endemic regions may not become symptomatic until they return home.

Herpes Simplex Encephalitis

Herpes simplex is perhaps the most common cause of sporadic encephalitis (14, 15 Baranger 2008). About 90% of infections are due to HSV-1 and 10% to HSV-2; the latter is more common in neonates. Seizures occur in 40 percent to 70 percent of patients during acute infection (16 Misra et al 2008). The propensity to cause seizures probably is related to spread via olfactory pathways to limbic structures including temporal lobe, insula, and cingulate cortex (17 Baranger et al 2008).

Patients who survived in the past had a high frequency of epilepsy (40–60%), but this may be lower after acyclovir treatment, which reduced mortality from 70 percent to 20 to 30 percent (15). Initial therapy may not eradicate VNS virus. Relapses were reported several months after acute illness in 3 of 26 acyclovir-treated patients, with a good response to retreatment (18). One patient with a chronic seizure disorder

TABLE 1. *Common Forms of Viral Encephalitis*

Sporadic
Herpes viruses: HSV 1 & 2, VZV, EB, CMV, HHV 6 & 7
Enteroviruses: Coxsackie, echoviruses, enteroviruses 70 & 71, parechovirus, poliovirus
Paramyxoviruses: Measles, mumps
Others (rarer causes)
Influenza, adenovirus, parvovirus, LCM, rubella
Geographically restricted: mostly arthropod-borne
The Americas
West Nile, La Cross, St Louis, Rocio, Powassan, Venezuelan, eastern & western equine, Colorado tick fever, dengue, rabies
Europe/Middle East
Tick-borne encephalitis, West Nile, Tosana, rabies, dengue, louping ill
Africa
WNV, Rift Valley fever, Crimean–Congo hemorrhagic fever, dengue, chikungunya, rabies
Asia
Japanese, West Nile, dengue, Murray Valley, rabies, chikungunya virus, Nipah
Australasia
Murray Valley encephalitis, Japanese encephalitis, kunjin, dengue

Source: (14, 20).

developed a progressive illness 2 years after initial infection and died during status epilepticus 3 years later; autopsy showed persistent HSV infection (19).

Arbovirus Encephalitis

Given its geographic distribution, Japanese B probably is the most common arbovirus encephalitis (Figure 2). As much as 50% of the world's population may live in endemic regions (20). Only about 1% of infections are symptomatic, but at least 50,000 cases of clinical Japanese encephalitis (JE) occur annually in China, Southeast Asia, New Guinea, Pakistan and northern Australia. Seizures may occur in 50 to 80 percent, the fatality rate is 10 to 30 percent; up to 80% of survivors suffer from seizures or other neuropsychiatric sequelae (20, 21). Birds and pigs serve as a reservoir for infection and possible source of spread. There is no effective treatment, but several vaccines for Japanese B encephalitis are available (22).

Other common forms of arbovirus encephalitis include Eastern Equine (EEE), Western Equine (WEE), St Louis, LaCrosse, Venezuelan Equine, and Murray Valley Encephalitis (Figure 1). Seizure incidence during acute infection varies from about 5 percent for West Nile to 50 percent in some of the more severe syndromes such as EEE (23). Seizures were the presenting symptom in 46% of children with LaCrosse encephalitis; 11% had status epilepticus (24).

Seizures as sequelae after recovery vary as well, but generally are less common than after HSV encephalitis. About 20% of patients had seizures after WEE, usually in association with cognitive and motor impairment and, often, psychiatric symptoms (25 Earnest et al 1971). Children may be more likely to have severe sequelae of EEE (26). Nipah virus, an emerging cause of encephalitis in Southeast Asia, has an interesting pattern of causing seizures in 20 percent to 25 percent of patients with acute infection but as many as 50% who experience a relapse (without evidence of new infection) weeks to months after apparent recovery (27, 28).

In general, a remote symptomatic cause—such as viral encephalitis itself—increases risk of unprovoked seizure recurrence by 2.5 times (29). Status epilepticus, seizures during the acute illness, and focal weakness affect recurrence. Among patients with a history of viral encephalitis, the overall 20-year risk of developing unprovoked seizures was 22% for patients who had had seizures during acute infection, and 10% for patients with viral encephalitis without acute seizures (1). The relative risk is greater than for any other remote symptomatic etiology except traumatic brain injury or the ill-defined entity of cerebral palsy (1).

Tick-Borne Encephalitis

Tick-borne encephalitis (TBE) is due to a family of related *Flaviviridae*. The endemic area stretches from eastern France to northeastern China and northern Japan,, and Scandinavia to Greece (30). One form, Powassan virus, is found in the United States. Epidemiological studies based on serology suggest that clinical illness occurs in 2 to 30 percent of infected patients. Genetic factors may play a role in disease severity. Patients with symptomatic illness were more likely than controls to have the wild-type functional toll-like receptor 3 (31). TBE causes long-term neurological sequelae in up to 60% of symptomatic patients, although the fatality rate is reported to be 0.5 percent to 20 percent. Seizures occur during the acute illness but are less common as sequelae (30).

Mechanisms of Seizures in Viral Encephalitis

Some viruses may be more epileptogenic due to their anatomic distribution, as in the case of HSV, with a propensity to affect temporal lobes. HSV causes widespread inflammation, edema and parenchymal necrosis (15). Interestingly, experimental corneal inoculation of HSV in mice led to increased CA3 pyramidal cell excitability, mossy fiber sprouting, and clinical seizures (32). JE may be more likely to cause seizures than West Nile virus due to involvement of wider cortical regions as opposed to basal ganglia and subcortical structures; seizures and epileptiform discharges occur earlier in the course of JE than WNV (33). Children and patients with increased intracranial pressure may be more likely to have seizures (1, 16, 24).

Seizures and HIV Infection

In developed countries, 5 to 10 percent of HIV positive patients will present with seizures; a higher proportion has seizures at some time during their course (34). Potential etiologies include opportunistic infection, intracranial mass, and metabolic

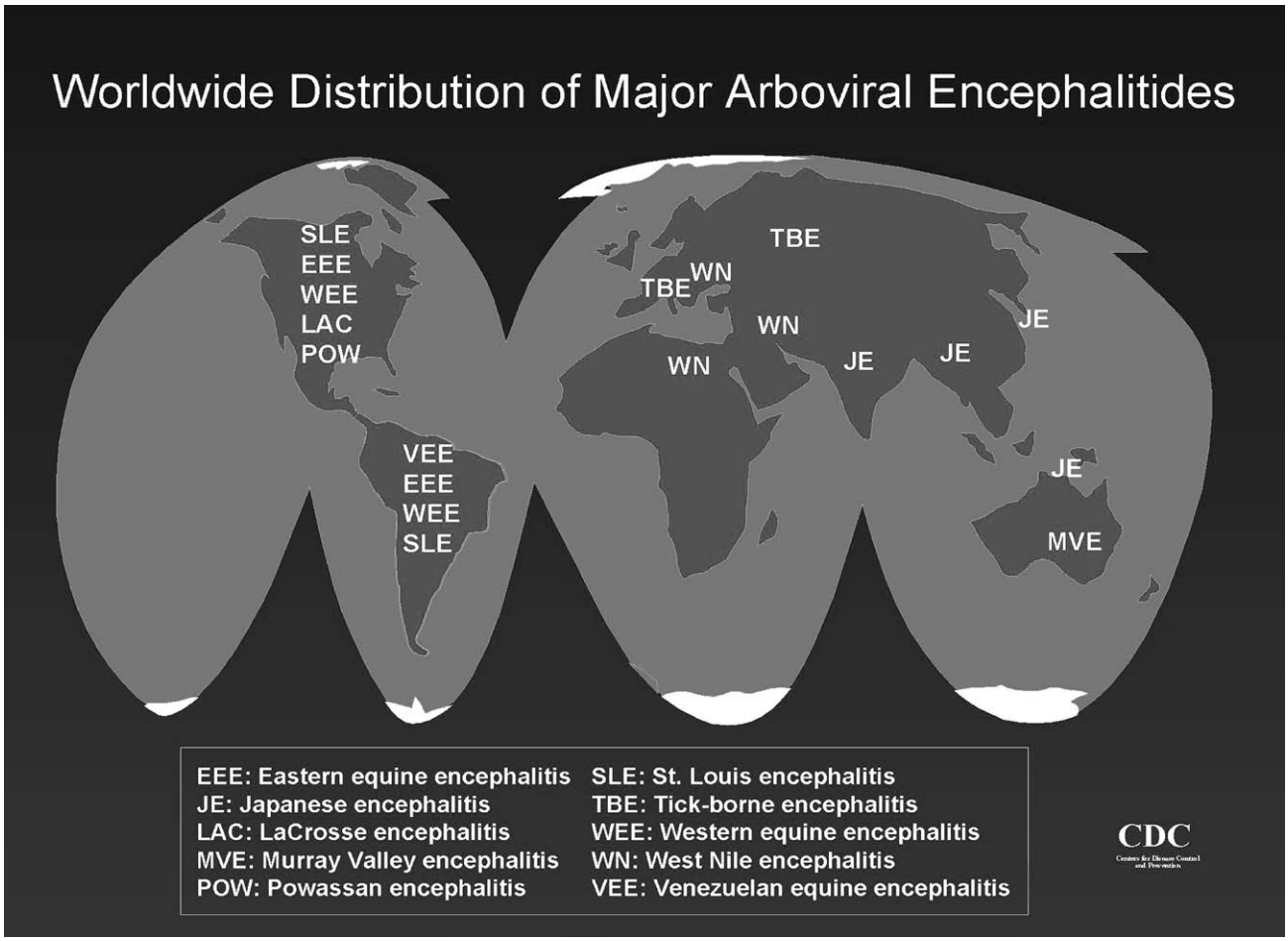

Figure 1. Worldwide distribution of arbovirus encephalitis. *Source*: http://www.cdc.gov/ncidod/dvbid/arbor/worldist.pdf

derangements, but about 1/3 have no clear etiology, suggesting possible direct brain involvement as part of the AIDS–dementia complex. One study from South Africa found that of 37 HIV positive patients with new-onset seizures, 21 had focal brain lesions (14 tuberculomas, 3 neurocysticercosis, 2 cerebral infarcts, 1 toxoplasmosis, 1 progressive multifocal leukoencephalopathy), 6 meningitis (3 tuberculous, 1 cryptococcal, 1 syphilitic, 1 viral), and 10 with no identifiable cause (35). CD4 counts did not differ among the three groups. In Burkina Faso, suspected cerebral toxoplasmosis (65%), tuberculous meningitis (7%) and cryptococcal meningitis (16%) were found in 43 patients with seizures (36). CD4 count was under 250 in 74% of the cases. As could be expected, a recent review found that patients with HIV presenting to emergency rooms with a first seizure in the United States were much more likely to have abnormalities on CT than other patients (37). Some studies suggest that new-onset seizures in HIV positive patients are more likely to recur, even in the absence of opportunistic infection or other CNS lesions, and that they may be more difficult to control (38, 39).

Enzyme-inducing AED use presents a problem in patients with HIV/AIDS. In developing countries, their use is widespread due to cost. Another advantage of drugs such as phenytoin and phenobarbital is their long half-life. Pharmacokinetic interactions due to protein binding and hepatic enzyme induction with protease and non-nucleoside reverse transcriptase inhibitors include increased or decreased AED levels, associated with drug toxicity or recurrent seizures, and reduced antiretroviral levels, with rebounds in viral load (40, 41). Other potential problems are increased hypersensitivity reactions and valproic acid effects on viral replication (of uncertain clinical relevance).

Emerging Viruses

In recent years, a number of viruses have spread into new regions (20). Potential factors include international travel, increased population pressure on the environment (leading to greater human–animal interaction), and environmental changes. Global warming, for example, can lead to greater ranges of vectors such as mosquitoes. The WNV epidemic in the United States may have been initiated by migratory birds (20).

Chikungunya virus has spread from its first recognition in Tanzania to other regions in Africa, India, Southeast Asia, Italy, and the United States (20). Moreover, the virus added a new mosquito species, *Aedes albopictus*, to its original vector *Aedes aegypti*. The wider range of this species accounts for the spread of the virus. In children, seizures are reported in up to 33% of patients (42).

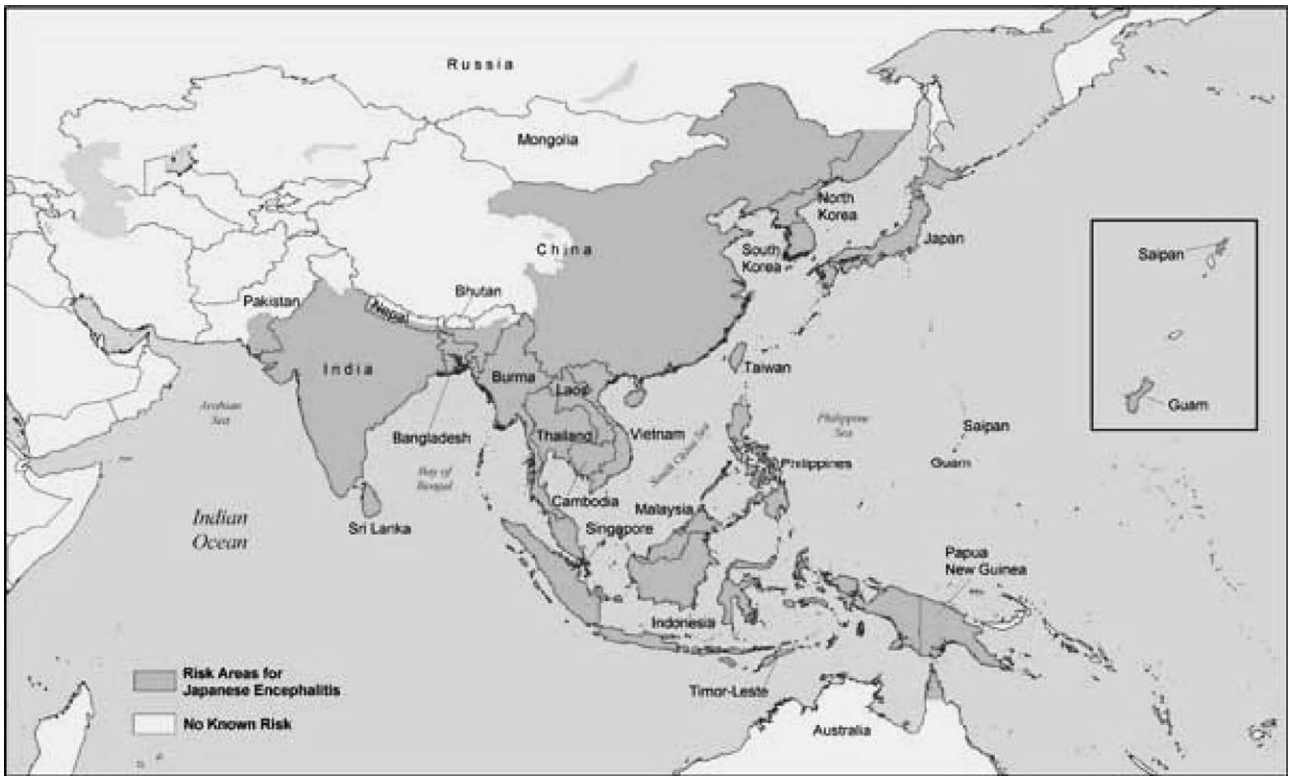

Figure 2. Geographical range of Japanese encephalitis. *Source:* http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx

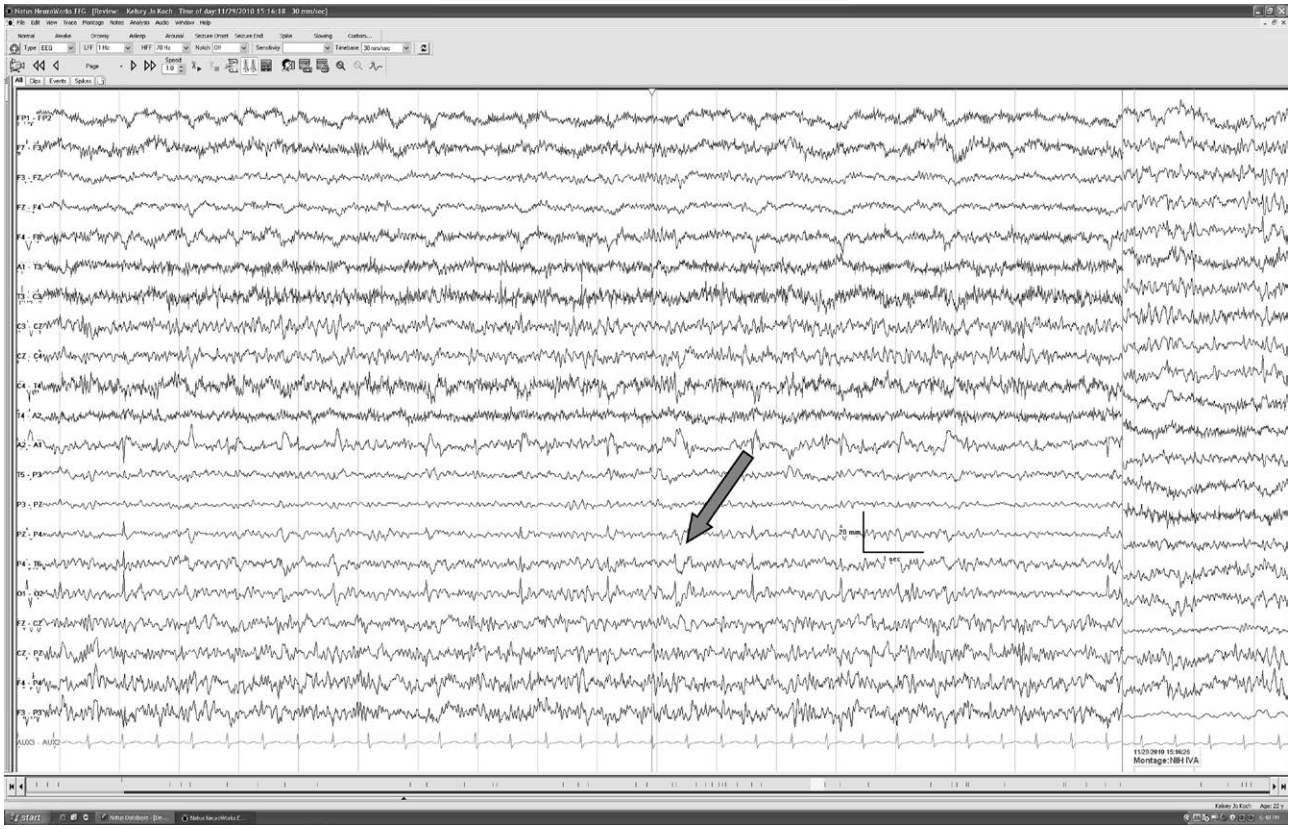

Figure 3. Epileptiform discharges in an immunosuppressed patient with HHV6 encephalitis. Note distinction from ECG (arrow). Courtesy Dr. Susumu Sato and Shumel Appel.

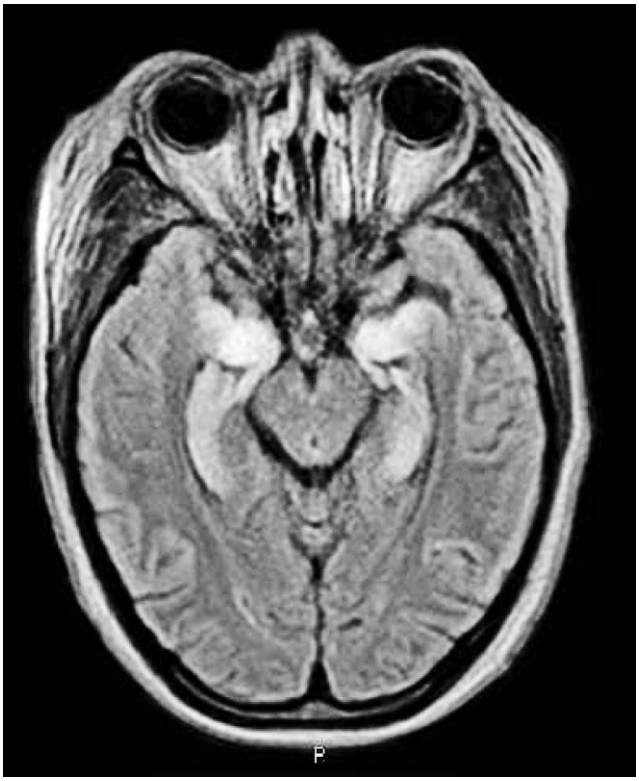

Figure 4. FLAIR sequence MRI in the same patient showing increased signal in limbic structures. Courtesy Dr. Alexandra Freeman.

In some cases, new infections appear without a clear explanation. Enterovirus 71 has caused several recent epidemics in the Pacific Rim; seizures are rare, however (**43).**

Human Herpes Virus 6B

Nearly 90% of children have evidence of exposure to human herpesvirus 6 (HHV6) by age 3 (44 Theodore et al 2008). CNS invasion appears occur at the time of primary infection, but rarely leads to clinical disease, although long-term latent infection may be established.

Acute limbic encephalitis can occur, probably due to viral reactivation, in immunosuppressed patients and particularly after allogeneic hematopoietic stem cell transplantation (45). Mortality and degree of recovery vary. Patients can have seizures or status epilepticus accompanied by epileptiform discharges and increased MRI signal intensity on T2 or FLAIR sequences in limbic structures, such as hippocampus and amygdala, followed in some cases by focal atrophy (45) (Figures 3 and 4).

Roseola infantum or exanthem subitum, a common childhood disorder, has long been associated with HHV6, and a relationship to febrile seizures has been suggested as well (44). Febstat, a prospective multicenter study, is investigating the relationships between HHV6 and 7, febrile status epilepticus, MRI changes, and later epilepsy (46).

Several PCR studies of tissue removed during temporal lobectomy from patients with mesial temporal lobe epilepsy have examined the potential etiologic role of HHV6 (47–52). Results have been variable (Table 2).

HHV6B, but not HHV6A, was detected in 15 of 24 patients with mesial temporal sclerosis/MTLE, in contrast to none of 14 with other localization-related epilepsy syndromes and pathological substrates, including tumors and malformations (48, 50). HHV6B was co-localized to astrocytes, identified by GFAP immunofluorescence and morphology (Figure 5). A recent study found HHV6 only in patients with temporal lobe epilepsy and mesial temporal sclerosis (MTS) who had a history of encephalitis—but not complex or prolonged febrile seizures alone (52).

Although the studies have varied in the frequency of finding HHV6 in epilepsy, it is encouraging that no controls—either autopsy or other surgical specimens—have been positive. It is possible that the chance of detecting persistent HHV6 in mesial temporal lobe foci depends on the severity of the initial infection.

Diagnosis and Treatment

Patients presenting with seizures and suspected encephalitis have to be investigated for a wide range of etiologies (Table 1). Initially, it is very difficult to distinguish encephalitis from meningitis; either diagnosis may be missed by ignoring subtle cognitive impairment or need for lumbar puncture (21). For encephalitis, travel and medical history may be very important, and syndromes such as rhomboencephalitis may point toward specific viral etiologies (21). Climate and host range may be important clues. In the United States, most arbovirus

TABLE 2. ***Results of Investigations of HHV 6 in Temporal Lobe Epilepsy***

Study	Patients	HHV 6 Present	Comments
Uesugi et al. 2000	17	6	3/6 had history of encephalitis
Eeg-Olofsson et al. 2004	23	4	0/13 with pathology other than "gliosis"
Donati et al. 2003; Fotheringham et al. 2007	24	15	0/14 with other epilepsy etiologies (tumor, AVM) positive
Karatas et al. 2007	33	3	0/7 autopsy controls positive
Niehusmann et al. 2010	35	9	All HHV6 positive had history of encephalitis. 0/10 autopsy controls positive

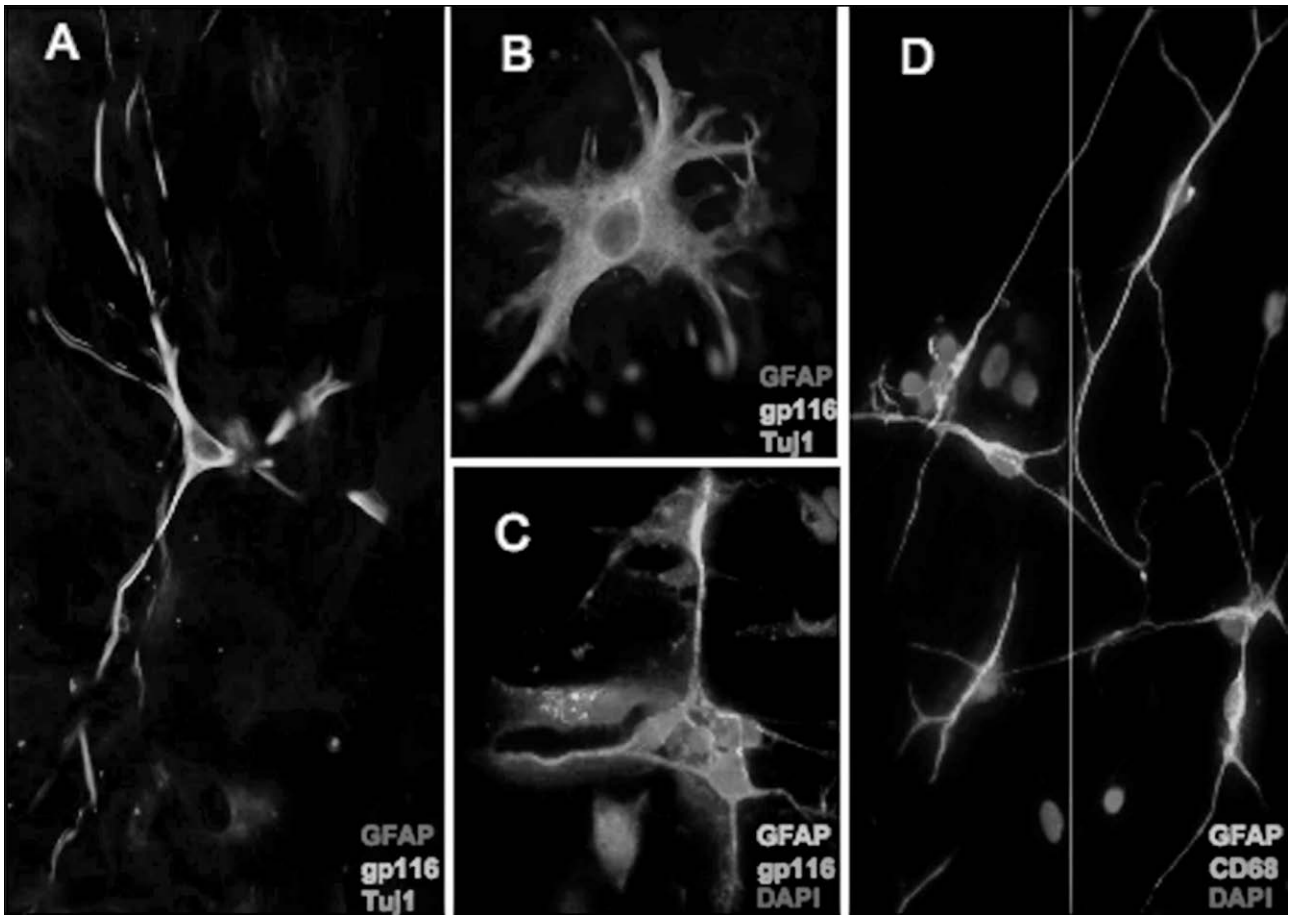

Figure 5. Primary astrocytes isolated and cultured from HHV-6B–Positive MTLE brain resections express viral antigen (50).
Primary astrocytes were isolated from fresh brain material obtained during epilepsy brain resection. Cells were cultured for 3–4 wk and costained for the nonvariant specific HHV-6 gp116 surface glycoprotein and GFAP as a marker for astrocytes (A–C), the neuronal marker Tuj1 (A–B), or the microglial marker CD68 (D).
(A) Epilepsy patient 2a: GFAP = blue; HHV-6 = green; Tuj1 = red, 20×.
(B) Epilepsy patient 2a: GFAP = blue; HHV-6 = green; Tuj1 = red, 32×.
(C) Epilepsy patient 15; GFAP = green, HHV-6 = red; DAPI = blue, 40×.
(D) Epilepsy patient 15; GFAP = green; CD68 = red; DAPI = blue, 40×.

encephalitis occurs in June through September, while Japanese B encephalitis occurs throughout the year in many parts of Asia, due in part to chronic pig infection (53).

Imaging should be performed in any patient suspected of having CNS infection. Fever, history of systemic disease, and abnormal neurologic exam increase the chance of positive findings (37). However, negative imaging findings are common, at least in children; only 3 of 13 children with new onset status epilepticus and infection diagnosed on clinical and CSF criteria had abnormal CT and MRI (54). MRI performed a mean of 10 days after onset was more likely to be revealing in HSE, Japanese B, or Epstein-Barr virus than dengue or unspecified infection (55). T2-weighted and FLAIR sequences provided the highest yield, especially when performed in the first week of illness.

Acyclovir is effective for HSV encephalitis (15). If suspected, treatment should be initiated while studied are pending. Gangcyclovir and foscarnet have been used to treat HHV6 encephalitis, with variable results (45). Considerations for antiepileptic drug use in patients with viral encephalitis include the need to avoid drug interactions and overlapping toxicity in patients who may have severe systemic illness and immunologic compromise.

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