Encephalitis is an inflammation and swelling of the brain, which is often caused by a viral infection; it is an important cause of acute symptomatic seizures as well as subsequent epilepsy. Herein we describe the definition, epidemiology, and etiology of encephalitis as a cause of seizures. We then focus on encephalitis due to herpes simplex virus (the most common sporadic viral cause of encephalitis) and Japanese encephalitis virus (the most common epidemic viral cause). We also discuss the evidence for seizures occurring in the context of antibody-associated encephalitis, an increasingly important condition. Finally, we describe the acute and longer-term management of encephalitis-related seizures and their potential pathophysiologic mechanisms, concluding with the emerging etiologic role of human herpesvirus 6.

KEY WORDS: Encephalitis, Seizures, Epilepsy, Herpes simplex virus, Japanese encephalitis virus, Human herpesvirus 6, Antibody-associated encephalitis, Voltage-gated potassium channel complex, N-Methyl-D-aspartate receptor.
7 days after acute CNS infection (Berg et al., 2010). Studies from Western industrialized countries show that patients with encephalitis overall are about 16 times more likely than the general population to develop later unprovoked seizures (Misra et al., 2008). Those with seizures during the acute illness are up to 22 times more likely to develop later unprovoked seizures than the general population; even those with no acute seizures have a 10 times greater risk. Encephalitis accounts for similar numbers of new causes of epilepsy per year in the United States, as does head injury, even though there are 1.4 million CNS trauma cases per year, compared to fewer than 50,000 cases of CNS infection (Misra et al., 2008). If seizures develop, it is usually within the first 5 years following the encephalitic illness, but can occur up to 20 years later. The pathogen causing the encephalitis appears important in predicting the likelihood of later developing epilepsy. For example, in those with La Crosse virus encephalitis, the cumulative incidence may be 10–12%, whereas in encephalitis caused by Nipah virus, this may be as low as 2.2% (Misra et al., 2008). Nevertheless, in countries where there is limited access to antiepileptic drugs (AEDs) and where seizures may have significant socioeconomic consequences, postencephalitis epilepsy may present a considerable lifelong burden.

**Definition**

“Encephalitis” encompasses a broad range of pathophysiologic processes that result in inflammation of the brain parenchyma (Solomon et al., 2001; Michael et al., 2010; Kneen et al., 2012; Solomon et al., 2012). Strictly, therefore, the diagnosis is established only by histopathologic examination of brain tissue. However, tissue is available only for those patients who have a postmortem or in the minority where biopsy is clinically justified antemortem. Therefore, proxy markers of brain inflammation are routinely used (Kneen et al., 2012; Solomon et al., 2012). Most important of these is an elevated cerebrospinal fluid (CSF) leukocyte count, although neuroimaging may also be supportive.

Encephalitis typically presents with an encephalopathy syndrome, that is, altered consciousness. However, encephalopathy has a broad differential diagnosis, including systemic metabolic disturbance and infection outside the CNS (Michael et al., 2010). The absence of evidence of inflammation on imaging or in the CSF helps to distinguish these from encephalitis (Solomon et al., 2012).

**Epidemiology**

**Incidence**

The incidence of encephalitis is reported variably as between 0.7 and 13.8 per 100,000 per year (Michael et al., 2010; Solomon et al., 2012). This equates to approximately 700 cases per year in the United Kingdom; in the United States, it corresponds to approximately 19,000 hospitalizations and 1,400 deaths per year (Misra et al., 2008). Encephalitis is relatively rare but is important for two reasons; first, encephalitis is often suspected even though many cases are not confirmed, and second, delays in diagnosis and in starting treatment can cause significant morbidity and mortality. In encephalitis due to herpes simplex virus (HSV) type 1, those untreated or treated late have a mortality as high as 90%; this falls to 20–30% if treatment is started early. If treatment starts before there is significant clouding of consciousness, the mortality may be zero (Solomon et al., 2007, 2012). There are no detailed epidemiologic data on encephalitis in many lower-income countries, where paradoxically, the global burden of disease is most heavy (Misra et al., 2008).

**Etiology of Encephalitis**

Infection is by far the most common cause of encephalitis, either by direct CNS infection or through parainfectious or postinfectious immune-mediated processes (Kneen et al., 2012; Solomon et al., 2012). An immune-mediated encephalitis can also occur as part of a paraneoplastic disease, with specific antibodies directed against CNS antigens. Some forms of antibody-associated
encephalitis can also develop as part of a primary autoimmune process, without neoplasia (Vincent et al., 2004). However, this is relatively uncommon compared to infective encephalitis, and the exact underlying pathogenic processes are unknown (Granerod et al., 2010). Acute infections causing encephalitis group broadly into those occurring sporadically or epidemically.

**Sporadic**

The most commonly identified sporadic cause of viral encephalitis is herpes simplex virus; this is usually type 1, although 10% of cases are type 2; it is particularly important in neonates where encephalitis may be as part of a disseminated infection (Michael et al., 2010; Solomon et al., 2012). Other important causes of sporadic viral encephalitis include the varicella zoster virus and enteroviruses. Immunocompromised people risk infection from a wider range of pathogens, including viruses such as cytomegalovirus, and small intracellular bacteria and parasites such as *Toxoplasma gondii* (Solomon et al., 2012; Kneen et al., 2012). Moreover, immunocompromised patients who develop CNS infections from common CNS pathogens may present subacutely or chronically (Solomon et al., 2007; Solomon et al., 2012).

**Epidemic** encephalitis is usually due to arthropod-borne viruses (arboviruses), which vary greatly by geographic distribution. Globally, the most important epidemic cause is Japanese encephalitis virus (Solomon et al., 2001); many others are of local importance, such as West Nile virus, tick-borne encephalitis virus and Nipah virus (Solomon et al., 2007). Table 1 summarizes the global distribution of causes of epidemic viral encephalitis (Table 1).

**HSV encephalitis**

HSV encephalitis has an annual incidence of 1 in 250,000–500,000 (Solomon et al., 2007; Michael et al., 2010). HSV is an alpha herpes DNA virus; most people are exposed to HSV type 1 during childhood, and almost everybody has been infected by adulthood (Whitley, 2006). The virus is transmitted by droplet spread and it then crosses the mucous membrane of the nasal and oral cavity. From there, it travels by retrograde axonal transport, using the cellular cytoskeleton, along the trigeminal nerve to the trigeminal ganglion, where it establishes latency. Periodically, the virus reactivates and travels by anterograde axonal transport to be shed; this is usually asymptomatic, but can manifest as herpes labialis (a cold sore) in a small proportion (Whitley, 2006). The pathophysiologic processes underlying latency and reactivation are not fully understood, but toll-like receptors and the resultant interferon response are probably important. Rarely, the virus replicates in the brain, causing encephalitis; it is not clear if this follows directly on from further retrograde axonal transport after reactivation in the trigeminal ganglion, or whether this is due to reactivation of virus already latent within the brain. Indeed, a proportion of people who die without any previous neurologic disease have HSV nucleic acid within the brain parenchyma. HSV type 1 encephalitis has a bimodal age distribution, with peaks in incidence in young adults and the elderly (Whitley, 2006; Solomon et al., 2007).

Seizures occur in approximately 40% of patients with encephalitis due to HSV type 1 and may be the presenting

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**Figure 2.** Immunohistochemical staining of brain sections in a patient who died of herpes simplex encephalitis showing (A) evidence of herpes simplex infection, (B) diffuse microglial activation, and (C) perivascular inflammatory infiltrates. (Courtesy of Dr. Daniel Crooks, Walton Centre NHS Foundation Trust, United Kingdom.)

*Epilepsia* © ILAE
symptom (Whitley, 2006; Solomon et al., 2007). The traditional view was that herpes simplex virus encephalitis (HSE) might present with simple partial olfactory seizures, reflecting orbitofrontal cortex infection, or simple and complex partial seizures, reflecting temporal lobe infection; we now recognize that these occur only in the minority and often later in the disease (Solomon et al., 2007). Instead the focus has shifted to the early clinical features, typically preceding any seizures (Michael et al., 2010; Solomon et al., 2012). These include alterations in cognition, consciousness, personality, or behavior, in the context of concurrent or recent febrile illness. The fever may be low-grade, and approximately 11% of HSE cases are afebrile on admission (Solomon et al., 2001; Granerod et al., 2010; Michael et al., 2010). Associated clinical features include headache, which may be severe, nausea, and vomiting, or features suggesting either meningeal (neck stiffness,) or raised intracranial pressure (e.g., papilledema).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Viruses</th>
<th>Comments</th>
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<tr>
<td>Sporadic causes (not geographically restricted) listed by group</td>
<td></td>
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<tr>
<td>Herpes viruses (family Herpesviridae)</td>
<td>Herpes simplex virus type 1</td>
<td>Most commonly diagnosed sporadic encephalitis</td>
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<tr>
<td></td>
<td>Herpes simplex virus type 2</td>
<td>Causes meningitis in adults (esp. recurrent); meningoencephalitis occurs typically in the immunocompromised. Also causes a radiculitis</td>
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<td></td>
<td>Varicella zoster virus</td>
<td>Postinfective cerebellitis, or acute infective encephalitis or vasculopathy</td>
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<td></td>
<td>Epstein–Barr virus</td>
<td>Encephalitis in the immunocompromised</td>
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<td></td>
<td>Cytomegalovirus</td>
<td>Encephalitis in the immunocompromised; also retinitis or radiculitis; often neutrophilic CSF with low glucose</td>
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<td></td>
<td>Human herpesviruses 6 and 7</td>
<td>Febrile convulsions in children (after roseola); encephalitis in immunocompromised</td>
</tr>
<tr>
<td>Enteroviruses (family Picornaviridae)</td>
<td>Enterovirus 70</td>
<td>Epidemic hemorrhagic conjunctivitis, with CNS involvement</td>
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<td></td>
<td>Enterovirus 71</td>
<td>Epidemic hand foot and mouth disease, with aseptic meningitis, brainstem encephalitis, myelitis</td>
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<td></td>
<td>Poliovirus</td>
<td>Myelitis</td>
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<td></td>
<td>Coxsackie viruses, echoviruses, parechovirus</td>
<td>Mostly aseptic meningitis</td>
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<tr>
<td>Paramyxoviruses (family Paramyxoviridae)</td>
<td>Measles virus</td>
<td>Causes acute postinfectious encephalitis, subacute encephalitis and subacute sclerosing panencephalitis</td>
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<td></td>
<td>Mumps virus</td>
<td>Parotitis, orchitis or pancreatitis may occur before, during or after meningoencephalitis</td>
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<tr>
<td>Others (rarer causes)</td>
<td>Influenza viruses, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, rubella virus</td>
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<td>Arthropod-borne and zoonotic viruses*</td>
<td>West Nile virus</td>
<td>North America, Southern Europe, Africa, Middle East, West and Central Asia associated with flaccid paralysis and parkinsonian movement disorders</td>
</tr>
<tr>
<td></td>
<td>Japanese encephalitis virus</td>
<td>Asia, associated with flaccid paralysis and parkinsonian movement disorders</td>
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<td></td>
<td>Tick-borne encephalitis virus</td>
<td>Travel in Eastern Europe, Former USSR; tick bite; upper limb flaccid paralysis</td>
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<td></td>
<td>Dengue viruses (types 1–4)</td>
<td>Causes fever, arthralgia, rash and hemorrhagic disease, occasional CNS disease</td>
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<td></td>
<td>Western, Eastern and Venezuelan equine encephalitis viruses</td>
<td>Found in the Americas; encephalitis of horses and humans</td>
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<td>Chikungunya virus</td>
<td>Asia Pacific, Africa</td>
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<td>Chikungunya virus</td>
<td>Encephalitis in America</td>
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<td>Colorado tick fever virus</td>
<td>North America</td>
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<td></td>
<td>Rabies, virus other lyssaviruses</td>
<td>Non–arthropod-borne zoonotic viruses transmitted by dogs, cats, bats, depending on location</td>
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<td></td>
<td>Chandipura virus</td>
<td>Transmitted by sandflies, causing outbreaks in India</td>
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<td></td>
<td>Nipah virus</td>
<td>Transmitted in faeces of fruit bats in Malaysia, Bangladesh</td>
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Most are zoonotic, that is, animals rather than humans are the main natural hosts, the exceptions being dengue and chikungunya viruses. Note viral causes of chronic encephalitis such as JC viruses are not included.
Seizures and Encephalitis

Japanese encephalitis

Japanese encephalitis virus (JEV) is thought to infect 7 million people per year, with nearly 70,000 cases of encephalitis and at least 14,000 deaths, although these may be underestimates (Solomon et al., 2008; Campbell et al., 2011). Most cases are in South East Asia, but some occur in the Western Pacific and Eastern Mediterranean regions. JEV is an enzoonotic flavivirus transmitted by Culex mosquitoes; the main cycle of transmission is between wading birds and pigs, with the pigs acting as amplifying hosts. Humans are dead-end hosts, becoming infected when bitten by a virus-carrying mosquito while living in or traveling to endemic areas (Solomon et al., 2008). A mosquito bite results in an acute viremic illness, and in some people leads to the virus spreading across the blood–brain barrier. Once in the brain parenchyma, there is rapid viral replication in neurons. Leukocytes cross the blood–brain barrier into the brain, leading histologically to perivascular cuffing. It is unclear how much of the neuronal injury results from direct viral cytopathy and how much is secondary to the inflammatory response. There is currently no specific treatment for JEV encephalitis and so the management of its complications, such as seizures and raised intracranial pressure, is paramount. Vaccination against JEV has advanced considerably in recent years, but delivering wider vaccination programs is difficult in resource-poor settings; therefore, JEV encephalitis will likely remain an important disease for the foreseeable future (Solomon et al., 2008).

Seizures occur in 7–67% of JEV encephalitis cases (Misra et al., 2008; Solomon et al., 2008); however, many studies have been limited by poor access to diagnostic investigations. Furthermore, the seizure semiology in JEV encephalitis is often subtle and therefore easily missed if there is limited access to EEG. Acute symptomatic seizures are more likely in younger patients with JEV encephalitis, those with reduced level of consciousness on admission, and those with cortical inflammatory changes on neuroimaging (Solomon et al., 2001; Misra et al., 2008).

The development of seizures in JEV encephalitis correlates with there being clinical signs of cerebral herniation, high CSF opening pressure, and mortality (Solomon et al., 2001; Misra et al., 2008). In a prospective 3-year study of 144 adults and children with JEV encephalitis in Southern Vietnam, 59 (41%) had acute symptomatic seizures; those with a witnessed seizure while an inpatient were at least four times more likely to have a poor outcome (odds ratio [OR] 4.50, 95% confidence interval [95% CI] 1.94–10.52, p < 0.0001). In addition, those patients who developed status epilepticus were more likely to die than those with self-limiting seizures (11/25 [44%] vs. 0/15 [0%] p = 0.003). In this cohort, seizures were more common in children. Of interest, an isolated seizure before admission was common and did not predict increased mortality. The

(Solomon et al., 2001; Granerod et al., 2010; Michael et al., 2010).

The relatively higher rate of acute symptomatic seizures in patients with encephalitis due to HSV type 1 may be result from the predilection of HSV to areas of high epileptogenic potential: the mesial temporal lobes, particularly the hippocampus, and, to a lesser extent, the orbitofrontal cortices (Misra et al., 2008). This concurs with the findings that ex vivo rat brain tissue infected with HSV type 1 shows acute electrographic evidence of seizure activity and longer term hippocampal changes with neuronal loss, predominantly in the cornu ammonis area 3 (Chen et al., 2004). Both these findings suggest that the hippocampus is uniquely susceptible. In addition the necrotizing nature of HSV encephalitis, the extent of leukocyte infiltration, and the degree of cortical involvement may all be important in promoting seizures (Misra et al., 2008). Acute symptomatic seizures predict a worse outcome, as do a lower Glasgow coma scale score, delays in commencing acyclovir treatment, and older age (Misra et al., 2008; Whitley, 2006).

Following HSV encephalitis, 40–65% of patients develop later unprovoked seizures (Misra et al., 2008; Whitley, 2006). Treatment of seizures is similar to that in patients with other focal epilepsies. However, epilepsy following HSV encephalitis is typically refractory to AEDs, often requiring combination treatment (Misra et al., 2008). Early refractory epilepsy, particularly with progressive neurocognitive or neuropsychiatric impairment, may indicate encephalitis relapse or chronic infection, especially in those with immune compromise or suboptimal antiviral treatment. Although most relapses occur immediately following the acute encephalitic illness, some patients show progressive deterioration due to chronic infection (De Tiege et al., 2003). Relapse of encephalitis develops in 5–26% of patients, particularly when the duration of acyclovir treatment is insufficient (Whitley, 2006; Solomon et al., 2007). The recently published United Kingdom guidelines recommend that all immunocompetent adults should receive 14 days of intravenous acyclovir; they should then undergo repeat lumbar puncture. If this CSF remains positive for HSV by polymerase chain reaction (PCR), acyclovir should continue for further 7 days cycles and the lumbar puncture repeated at the end of each to demonstrate viral clearance before stopping the treatment (Solomon et al., 2012). Patients with immune compromise, or those aged between 3 months and 12 years, should receive 21 days of intravenous acyclovir before the lumbar puncture is repeated, but otherwise the approach for stopping acyclovir in children is the same (Kneen et al., 2012; Solomon et al., 2012). Further work is needed to delineate the complex mechanisms by which HSV establishes neurotropism, evades the host immune system, and results in acute symptomatic seizures and later unprovoked epileptic seizures.
combination of symptoms for at least 7 days, seizures, a reduced Glasgow Coma Scale score, and signs of brainstem herniation had a composite positive predictive value of 77% for poor outcome and a negative predictive value of 91% (OR 35.88, 95% CI 12.46–108.15, p < 0.001) (Solomon et al., 2001). Others have reported that seizures during encephalitis correlate with morbidity, but there is no association with mortality overall; however, these are unpublished observations and the lack of statistical significance may reflect smaller patient numbers (Misra et al., 2008).

The literature on the neurologic sequelae of JEV encephalitis has focused on neurocognitive impairments and movement disorders, particularly those reflecting subcortical involvement, for example, of basal ganglia and thalamus. Another focus has been the “polio-like” flaccid paralysis (Misra & Kalita, 1997; Solomon et al., 1998). We clearly need more detailed cohort studies of the long-term sequelae of this important cause of viral encephalitis, with a particular focus on late unprovoked seizures.

Antibody-associated encephalitis

In patients with an acute—or, more commonly, subacute—onset of encephalitis, immune-mediated encephalitis should be considered, particularly as the treatment is very different and early intervention may significantly improve outcome (Buckley & Vincent, 2005; Irani et al., 2010a,b).

The two most frequently identified causes of antibody-associated encephalitis are those due to antibodies to the N-methyl-D-aspartate (NMDA) receptor and (voltage-gated potassium channel) VGKC-complex. There are important clinical differences between these conditions. For VGKC-complex antibody-associated disease, the median age at presentation is 65 years and the male-to-female ratio is 2:1 (Buckley & Vincent, 2005), although children are now beginning to be identified. In NMDA receptor-associated disease, the median age at presentation is 25 years and the male-to-female ratio is 1:2. Patients with VGKC-complex disease do not usually have a fever or headache, whereas both of these are common in those with NMDA receptor antibodies; indeed many have a febrile flu-like prodrome. Both can present with seizures, often refractory to treatment, as well as confusion, amnesia, and psychosis. However, NMDA receptor disease often has a second phase of presentation, days to weeks later, in which there are involuntary movements, including orofacial dyskinesias and choreoathetosis. Faciobrachial dystonic seizures were recently described in patients with VGKC-complex disease and are associated with leucine-rich glioma inactivated 1 (LGI1) antibodies (Irani et al., 2010a,b). Indeed, faciobrachial dystonic seizures appear pathognomonic for this condition, sometimes preceding the other clinical features by several weeks.

About 60% of patients with VGKC-complex disease have low serum sodium levels, and about 60% have hippocampal high signal on MR scans; however, this may be well localized and subtle (Irani et al., 2010a,b). CSF abnormalities are common with NMDA receptor antibody encephalitis, including a lymphocytosis and detectable antibodies; in those with VGKC-complex antibodies, there are usually no significant CSF abnormalities and no detectable CSF antibodies. Indeed, it is a moot point as to whether, by the strictest definition, these are truly examples of encephalitis, or rather an encephalopathy. All patients need appropriate imaging to identify an associated tumor. In women with NMDA receptor disease, 20–50% have a tumor, almost always an ovarian teratoma; in men the rates of neoplasia are lower (Buckley & Vincent, 2005; Dalmau et al., 2011). In those with VGKC-complex disease, up to 10% have a tumor, usually a thymoma or small cell lung cancer (Buckley & Vincent, 2005; Irani et al., 2010a,b).

The optimum treatment regimens are still uncertain for these recently identified conditions. In the acute phase, immunomodulatory therapy with corticosteroids and either intravenous immunoglobulin or plasma exchange is advised (Kneen et al., 2012; Solomon et al., 2012). Seizures (which can lead to status epilepticus) should be managed as described below.

The important point is that a recurrence or worsening in seizures may reflect relapse or progression of the disease; in such cases, antibody titers should be reassessed and, in consultation with an appropriate specialist, more aggressive immunomodulatory therapy considered. Although relapse is uncommon in those with VGKC antibodies, up to one third of patients with NMDA receptor antibodies may relapse, even those without a tumor. Such patients may need long-term immunosuppression and annual tumor screening (Kneen et al., 2012; Solomon et al., 2012).

Management of Seizures

Acute symptomatic seizures

With such a wide range in incidence of acute symptomatic seizures in encephalitis, there is currently no evidence to support routine prophylactic AEDs in all patients with encephalitis (Misra et al., 2008; Kneen et al., 2012; Solomon et al., 2012). This is particularly the case in settings with limited resources to manage the sedative consequences of some AEDs. However, if a high-risk group for acute symptomatic seizures were identifiable, then prophylactic AEDs might be justified. Furthermore, if there is an excitotoxic component responsible for the increased incidence of morbidity and mortality in this group, then this gives a stronger argument for using AEDs prophylactically. However, there have been only a few and poor quality studies to provide data by which clinicians can
reliably identify such a high-risk group. Until we have data from large multicenter stratified randomized controlled trials, we cannot recommend routine prophylactic AEDs (Misra et al., 2008; Kneen et al., 2012; Solomon et al., 2012). Nevertheless, all patients should be managed in a clinical setting where neurologic observations can be performed so that, should seizures develop, they can be treated promptly (Kneen et al., 2012; Solomon et al., 2012). Convulsiv status epilepticus is treated in the same way as when due to other causes, with stabilization of the patient’s airway, oxygenation, and administration of intravenous lorazepam, or rectal diazepam if intravenous access is not available. There is little evidence to guide the AED choice as second-line therapy. Patients who do not respond to these treatments should be sedated and intubated as for other causes of status epilepticus.

The paradox of managing seizures associated with encephalitis is that the developing world, where there is the greatest global burden of disease, has the least sufficient services to manage these patients (Misra et al., 2008).

**Differential diagnoses not to miss**

When managing a patient with encephalitis who develops seizures, it is important not to miss parainfectious processes, which could potentially cause the seizure. These include hyponatremia and cerebral venous sinus thrombosis (Solomon et al., 2007). In patients with acute encephalitis with reduced level of consciousness, particularly if there are fluctuations or subtle repetitive motor features, clinicians need a low threshold for arranging EEG to exclude complex partial status epilepticus or subtle motor status epilepticus, as these require specific treatment (Kneen et al., 2012; Solomon et al., 2012).

**Management of epilepsy following encephalitis**

The treatment of postencephalitic epilepsy depends on the natural history of the disease. For example the seizure frequency and rates of relapse may vary greatly, and there are no clear predictors of postencephalitic epilepsy (Solomon et al., 2007; Misra et al., 2008). Two randomized controlled trials showed that acyclovir reduces the short-term mortality from encephalitis. However, there are few data to clarify the role and timing of administering acyclovir, or other antivirals, in preventing long-term sequelae such as postencephalitic epilepsy (Skoldenberg et al., 1984; Whitley et al., 1986). It is clear that we urgently require further investigation into the association between CNS infections and epilepsy to assess who is at risk, what are the structural correlates, what is the clinical course/prognosis, and what is the effect of antimicrobial and antiepileptic treatment.

As for other causes of epilepsy, AED treatment should be directed toward the seizure semiology. However, patients with epilepsy following encephalitis are frequently refractory to AEDs and therefore many will require combination therapy or neurosurgery to attempt to control seizures. Patients and their relatives should be made aware of support groups, such as the Encephalitis Society (http://www.encephalitis.info), which can provide great support to cope with the sequelae of encephalitis (Kneen et al., 2012; Solomon et al., 2012).

**Potential Pathogenic Mechanisms of Seizures in Encephalitis**

There are several potential mechanisms for the development of seizures in viral encephalitis. In particular, there is growing support for the role of the extensive parainfectious inflammatory response (Winter et al., 2004; Kamei et al., 2009). The pathophysiologic mechanisms driving the inflammatory response have yet to be fully elucidated, but there is growing evidence that the innate cytokine/chemokine responses are important. Moreover, these inflammatory peptides, which are produced by neurons, astrocytes, and microglia, are increasingly recognized to promote excitatory neurotransmitter release and consequent depolarization. In addition, depolarization itself can result in the release of certain proinflammatory cytokines, in the context of costimulation (Tsakiri et al., 2008). Therefore, a dynamic interplay between cytokines, chemokines, neurotransmitters, and other factors is likely to be important.

**Potential novel roles for encephalitis in epilepsy pathogenesis: Human herpesvirus 6 and febrile seizures**

Human herpesvirus 6 (HHV-6) is a relatively recently isolated ubiquitous, lymphotropic beta herpes DNA virus. It is the most common cause of roseola infantum, a febrile rash syndrome, in children younger than 2 years of age (Campadelli-Fiume et al., 1999). HHV6 achieves 90–100% seroprevalence following transmission from the mother and possibly siblings, predominantly during the first 2 years of life (Yamanishi, 1992; Hall et al., 1994; Campadelli-Fiume et al., 1999; Zerr et al., 2005). It is now known to account for 20% of emergency department admissions for febrile illnesses in those aged 6–12 months, of whom approximately 13% develop seizures (Hall et al., 1994). HHV6 infection accounts for one third of febrile seizures in patients younger than 2 years; there is serologic persistence in approximately 66% and reactivation in 6–16% as soon as 1–2 years later (Studahl et al., 2000). HHV6 is present in the CSF in approximately 10% of cases of suspected viral CNS disease, regardless of age (Studahl et al., 2000). Moreover, following primary infection, approximately 60% of individuals have viral DNA detectable in CSF as the sole source of latency,
suggesting that this is a highly neurotrophic virus (Chen & Hudnall, 2006).

PCR detects HHV6 viral DNA in 50–69% of surgical resection specimens for mesial temporal lobe epilepsy, predominantly the variant HHV6B subtype (Donati et al., 2003; Fotheringham et al., 2007). In these studies, there was no HHV6 DNA in control specimens of neocortical temporal lobe epilepsy and autopsy. However, these studies recruited only 8–16 patients. In the largest and most recent study, including 33 cases of mesial temporal lobe epilepsy and 7 nonepileptic controls, HHV6 viral DNA was identified by PCR in 3 of the 33 mesial temporal lobe cases (Karatas et al., 2008). Two of the National Institute for Neurology and Stoke Key Benchmarks for research into epilepsy are to identify infectious etiologic risk factors for epilepsy and the pathologic development of epileptogenic foci. In this effort, HHV6 is clearly a pathogen that justifies further research.

**Conclusions**

Seizures are important in encephalitis, both in the acute presentation and the long-term neurologic sequelae. The exact risks of developing seizures are poorly understood, but appear to relate to the pathogen, the degree of cortical involvement, and the cytokine-mediated inflammatory response. This is clearly an area of great clinical importance requiring further investigation. However, there are barriers to undertaking this work, particularly in resource-poor settings, which must be addressed if we are to improve our understanding of the pathophysiologic processes underlying this and ultimately to translate this into meaningful benefits for our patients.

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**Disclosures**

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