Viral Encephalitis in the ICU

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KEYWORDS

• Encephalitis • Herpes simplex virus • Varicella zoster virus • Arbovirus
• West Nile virus • Acute disseminated encephalomyelitis (ADEM)
• Anti-NMDA receptor antibodies • Coma

KEY POINTS

- Optimal critical care of patients with viral encephalitis requires a high index of suspicion, appropriate diagnostic testing, and timely initiation of antiviral therapy.
- Intensivists should also consider postinfectious, autoimmune, and paraneoplastic encephalitis, because the treatment of these entities is very different.
- To maximize the chance of a favorable neurologic recovery, efforts should be directed at identification and treatment of neurologic (eg, cerebral edema, high intracranial pressure, and seizures) and systemic (eg, hypoxemia, low cerebral perfusion pressure, and fever) complications, which could potentially exacerbate brain damage.

BACKGROUND

Several viruses may infect the central nervous system (CNS) and cause inflammation of the meninges and brain parenchyma. The term "aseptic meningitis" is used when there is clinical evidence of meningeal irritation, including a characteristic headache or nuchal rigidity, in combination with an elevated cerebrospinal fluid (CSF) white blood cell (WBC) count, occurring in the absence of bacterial growth. The term "encephalitis" is used when there are features of cerebral dysfunction, which may include an altered level of consciousness or focal neurologic deficits, such as hemiparesis, aphasia, hemispatial neglect, or movement disorders. Seizures can occur with both meningitis and encephalitis, but are far more common and difficult to treat with encephalitis. Coma occurs in a subgroup of patients and is the main reason patients may require mechanical ventilation and admission to an intensive care unit (ICU). In recognition of the fact that meningitis and encephalitis frequently coexist in individual patients, the term "meningoencephalitis" is sometimes used.[1,2]

Because isolated aseptic meningitis is rarely life-threatening, this review focuses primarily on encephalitis. In recent years, there has been increasing recognition of various

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noninfectious, usually autoimmune, forms of encephalitis. In addition, systemic viral infections may precede the development of postinfectious encephalitis, which is largely due to the effects of the host immune response rather than the virus itself.

A clinical case definition for encephalitis was recently proposed by a group in the United Kingdom. To be diagnosed, a patient should have evidence of "encephalopathy" (altered level of consciousness persisting for more than 24 hours) and at least 2 of the following criteria: fever or history of fever; seizures and/or focal neurologic deficits; CSF pleocytosis; electroencephalogram characteristics consistent with encephalitis; or neuroimaging abnormalities consistent with encephalitis.[3]

EPIDEMIOLOGY

The reported incidence of encephalitis varies widely across studies and geographic regions. In the absence of an outbreak, the annual incidence is estimated to be in the range of 3.5 to 7.5 cases per 100,000 persons. Although viral encephalitis affects all age groups, the overall incidence is significantly higher in children.[4–7]

In many patients thought to have encephalitis, no specific pathogen or cause can be detected. With advances in molecular techniques, especially the use of polymerase chain reaction (PCR), the relative proportion of idiopathic cases may be decreasing. Still, even with systematic testing for known infectious and noninfectious causes, a specific cause is found in less than half of the cases. It is likely that emerging infections and still unrecognized immune-mediated encephalitis are responsible for many of these cases.[8]

There are dozens of viruses and bacteria that may cause encephalitis (**Table 1**), including some pathogens that occur worldwide and others that are clustered in certain regions.[4]

Herpes Simplex Virus

In recent multicenter studies performed in Europe, North America, Australia, and New Zealand, the most common pathogen to be implicated continues to be herpes simplex virus (HSV), consistently accounting for more than 40% to 50% of cases where a cause is determined, and 10% to 20% overall.[9–14] HSV-1 accounts for most cases; HSV-2 is a frequent cause of aseptic meningitis, but not encephalitis. A large proportion of the population has previously been exposed to HSV, as reflected by an 80% to 90% rate of seropositivity.[15] A nationwide study from Sweden revealed an annual incidence of HSV encephalitis of 2.2 cases per million persons.[16] HSV occurs across all age categories and the incidence does not differ based on gender.[15–17]

Varicella-Zoster Virus and Other Herpes Viruses

Varicella zoster virus (VZV) is now recognized as the most common cause of encephalitis among immunocompromised patients, occurring as a complication of human immunodeficiency virus (HIV)/AIDS, hematopoietic stem cell transplantation, and the use of corticosteroids or other immunosuppressive drugs.[18–21] However, it also develops in the immunocompetent and is the second most common viral cause of sporadic encephalitis not occurring during an outbreak.[7–15] Encephalitis may develop with acute varicella (chickenpox; primarily in children) or during herpes zoster infections (shingles). It is one of numerous neurologic conditions that may complicate VZV infections; others include myelitis, polyradiculo-neuropathy, and postherpetic neuralgia.

Other herpes viruses account for only a small proportion of cases. CMV encephalitis is almost exclusively a disease of immunosuppressed patients.[22] In contrast, Epstein-Barr virus (EBV) and human herpesvirus (HHV)-6 may cause encephalitis in both immunocompetent and immunosuppressed patients and can sometimes also trigger