Epidemiology and Etiology

Encephalitis causes significant morbidity and mortality, and it is a significant burden on the health care system. The hospital admission rate in one study was 7.3 per 100,000 people. The case-fatality rate among patients with encephalitis varies from 3.8% to 7.4% and is significantly higher among patients also infected with HIV. There is significant morbidity among survivors of encephalitis, with resultant loss of productivity and the need for prolonged rehabilitation or skilled nursing care.

Infectious causes of encephalitis are diverse and include viruses (most common), bacteria, fungi, and parasites. Clues in the patient's history that aid identification include seasonal variation, geographic location, prevalence of disease in the local community, travel history, recreational activities, occupational exposures, insect contact, animal contact, vaccination history, and immune status of the patient.

The most commonly identified viral causes in the United States are herpes simplex virus type 1 (HSV-1), West Nile virus, and the enteroviruses, followed by other herpesviruses (e.g., varicella-zoster virus). Other agents may be highly endemic regionally (e.g., La Crosse virus in the Midwest) or internationally (e.g., rabies virus, Japanese encephalitis virus). Bacterial agents, including *Ehrlichia* species and *Rickettsia rickettsii*, are potentially treatable causes of encephalitis, and prompt administration of appropriate antimicrobial therapy may be lifesaving.

Perhaps the most challenging aspect of encephalitis is that no pathogen is identified in 50% to 70% of cases. Up to 10% of patients have a noninfectious cause.

Clinical Presentation

Because encephalitis is infrequently confirmed by pathologic means, the signs and symptoms of neurologic dysfunction are used as surrogate markers, and they are often nonspecific. The clinical signs and symptoms of encephalitis are determined by the specific area of the brain involved and by the severity of the infection. Some organisms show neurotropism for particular anatomic sites. HSV-1 infection almost universally involves the temporal lobe, and the clinical presentation typically includes temporal lobe seizures. With this comes an associated change in personality, decreasing consciousness, focal neurologic findings (including dysphagia), paresthesias and weakness, and focal seizures. Sudden onset of fever and headache can also accompany these mental status changes.

Diffuse brain involvement is frequently seen with arboviral infections, and it is associated with global impairment in neurologic function and coma. Fever and headache frequently precede the onset of altered mental status, which can range from mild confusion to obtundation. Other neurologic manifestations may include behavioral changes (e.g., psychosis), focal paresis or paralysis, cranial nerve palsies, and movement disorders (e.g., chorea). About 80% of patients infected with West Nile virus are asymptomatic, and about 20% have only fever. Symptomatic patients may have fever, headache, myalgia, and flaccid paralysis. A maculopapular rash is seen in 50% of patients.

Evidence of inflammation or infection at sites distant from the CNS may be useful in making a microbiologic diagnosis for patients with encephalitis and myelitis. For instance, rickettsial diseases, varicella-zoster virus, and West Nile virus often have associated skin manifestations. Stomatitis and ulcerative lesions in the mouth or an exanthem in a peripheral distribution can suggest enterovirus infection. Patients with tuberculous and fungal meningoencephalitis may have suggestive pulmonary findings.

A syndrome frequently misclassified as encephalomyelitis based on the similar clinical presentation is postinflammatory encephalomyelitis. The most widely cited example is acute disseminated encephalomyelitis (ADEM), which is seen primarily in children and adolescents. ADEM is characterized by poorly defined white matter lesions on magnetic resonance imaging (MRI) that enhance after gadolinium administration. Postinflammatory encephalomyelitis is likely mediated by an immunologic response to an antecedent antigenic stimulus such as infection or immunization. Viral infections associated with ADEM include measles, mumps, rubella, varicella-zoster, Epstein-Barr, cytomegalovirus, herpes simplex, hepatitis A, and coxsackievirus. Immunizations temporally associated with ADEM include vaccines for Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax, and rabies, but a direct causal association with these vaccines is difficult to establish. ADEM usually begins between 2 days and 4 weeks after the antigenic stimulus, and patients develop rapid onset of encephalopathy, with or without meningeal signs. The neurologic features depend on the location of the lesions.

Another important disorder to consider is anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, which is the most common cause of autoimmune encephalitis after ADEM. The disorder is seen in patients of all ages but occurs mostly in young adults and children with or without teratomas. Patients usually have an acute behavioral change, psychosis, and catatonia that evolves to include seizures, memory deficit, dyskinesias, speech problems, and autonomic and breathing dysregulation. Symptoms are more often neurologic in children and psychiatric in adults, but in most cases, symptoms progress to a similar syndrome.

Diagnosis

The initial laboratory testing of an individual should include a complete blood count, tests of renal and hepatic function, and coagulation studies. A low white blood cell count, low platelet count, and elevated liver transaminase levels may suggest *Ehrlichia* or *Anaplasma* infection. A baseline chest radiograph should be obtained because a focal infiltrate can suggest particular pathogens (e.g., fungal or mycobacterial infections).

Neuroimaging studies are important to perform for all patients with encephalitis; MRI is more sensitive at detecting abnormalities than CT, and it is the preferred study. Diffusion-weighted MRI is superior to conventional MRI for the detection of early signal abnormalities in viral encephalitis caused by HSV, enterovirus 71, and West Nile virus. In patients with HSV encephalitis, there may be significant edema and hemorrhage in the temporal lobes. Patients with flavivirus (e.g., West Nile virus, Japanese encephalitis virus) encephalitis may display characteristic patterns of mixed-intensity or hypodense lesions on T1-weighted images of the thalamus, basal ganglia, and midbrain. In patients with ADEM, MRI usually reveals multiple