Management of Acute Encephalitis

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Multiple causes of encephalitis exist, including infectious and autoimmune agents. Christina M. Marra, MD, University of Washington, Seattle, Washington, USA, discussed the pathophysiology of acute encephalitis related to several more common forms of the disease.

Infectious encephalitis is typically caused by a virus, although there are more than 100 etiologies of encephalitis currently identified (Table 1). In other cases of encephalitis, the etiology can be antibody mediated, such as when antibodies target the N-methyl-D-aspartate receptor (NMDAR) or a voltage-gated potassium channel (VGKC) complex protein, leucine-rich, glioma inactivated 1 (LGI1). Encephalitis causes altered mental status, which can be mild or subtle in nature, and may mimic psychiatric disease. The cerebrospinal fluid (CSF) in encephalitis typically demonstrates a mildly elevated opening pressure, mild to moderate pleocytosis, protein levels of 50 to 100 mg/dL, and normal glucose levels.

Table 1. Common Etiologies of Encephalitis

Virus	**Comments**
HSV 1 and 2	Type 1 most common cause of sporadic viral encephalitis
VZV	Elderly and immunocompromised Rash may be absent
Enteroviruses, Parechoviruses	Myelitis, brainstem encephalitis
WNV, JEV, SLEV	Parkinsonian movement disorder Flaccid paralysis
Bacteria	**Comments**
Mycoplasma pneumoniae	Likely parainfectious
Mycobacerium tuberculosis	Immigrants Immunocompromised
Bartonella henselae	Seizures, neuroetinitis
Treponema pallidum	Imaging may mimic HSVE
Rickettsia spp	Geographic distribution
Erlichiosis, Anaplasmosis	Geographic distribution
Infectious endocarditis	Infarcts in multiple vascular distributions
Antibody Mediated	**Comments**
NMDA receptor	Young women Movement disorder Autonomic instability Ovarian teratoma
Leucine-rich, glioma inactivated 1 (LGI1; VGKC)	Older men Faciobrachial seizures Hyponatremia

HSV=herpes simplex virus; HSVE=herpes simplex virus encephalitis; JEV=Japanese encephalitis virus; NMDA=N-methyl-D-aspartate; SLEV=Saint Louis encephalitis virus; spp=multiple species; VGKC=voltage-gated potassium channel; VZV=varicella zoster virus; WNV=West Nile virus.

Given that there are multiple potential etiologies for encephalitis, it is important to look for clues that may indicate the correct etiology. For example, cases that develop in the late summer or early fall may be a result of a tickborne or mosquitoborne agent, whereas travel to particular geographic regions may provide a clue, such as infection with the Japanese encephalitis virus after travel to Asia. Other clues include underlying comorbidities, such as HIV, organ transplant, or immunosuppression therapy, all of which can increase susceptibility to infection and encephalitis by particular infectious agents.

A common noninfectious type of encephalitis is anti-NMDAR encephalitis, which may be the most common cause of encephalitis in patients younger than 30 years of age [Gable MS et al. *Clin Infect Dis* 2012]. Common characteristics of patients with anti-NMDAR encephalitis include female sex and early and prominent psychiatric symptoms [Titulaer MJ et al. *Lancet Neurol* 2013]. Serum and

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CSF antibodies to the *N*-terminus of the NR1 subunit of the NMDAR and CSF characteristics can diagnose anti-NMDAR encephalitis [Gresa-Arribas N et al. *Lancet Neurol* 2014]. In addition, nonspecific abnormalities on magnetic resonance imaging, slowing and electrographic seizures on electroencephalography, and identification of a teratoma by pelvic or transvaginal ultrasound may be present. Initial treatment includes the administration of corticosteroids or IV ig with or without cyclophosphamide, as well as removal of the teratoma if present. For patients who do not respond to initial therapy, treatment with rituximab may lead to improvement. Although the majority of patients recover or have mild sequelae following anti-NMDAR encephalitis, 4% die from the disease, 20% remain severely disabled, and up to 25% will experience relapse.

The most common sporadic cause of encephalitis is herpes simplex virus (HSV), primarily HSV-1, which can occur at any time of the year. It affects a bimodal age distribution, with the greatest number of patients being older than 40 years of age and younger than 20 years of age. Common symptoms include fever, headache, change in consciousness, dysphasia, personality changes, and seizures. Patients with HSV-associated encephalitis are typically treated with acyclovir for up to 21 days, or until polymerase chain reaction tests of CSF are negative for HSV. Treatment is important, as untreated patients have a mortality rate of 70% whereas treatment reduces the rate to 28%. In addition, as many as 50% of patients will experience neurologic or neuropsychiatric sequelae following HSV encephalitis.

Another type of encephalitis is caused by the intracellular parasite *Toxoplasmosis gondii*, which is contracted by ingestion of oocysts that are present in cat feces or cysts present in undercooked meat. It is estimated that 12% to 50% of the US population is seropositive for *T gondii*. Encephalitis can develop in patients who experience reactivation of a latent infection, and presents as one or more brain abscesses. Common symptoms include headache, confusion, fever, altered mental status, seizures, hemiparesis, slowness, and cranial nerve palsies [Porter SB, Sande MA. *N Engl J Med* 1992]. Other characteristics that may help lead to the diagnosis of *Toxoplasma* encephalitis is more than one enhancing lesion on MRI, detectable serum anti-*Toxoplasma* IgG, exclusion of other diagnoses, and improvement of symptoms and neuroimaging abnormalities with a 10-day trial of therapy. Typical treatment includes primary therapy with pyrimethamine plus sulfadiazine or clindamycin plus folinic acid followed by maintenance therapy with the same agents at reduced doses.

Although rare, encephalitis can result in high morbidity and mortality, even after treatment. There are multiple potential etiologies associated with encephalitis, which pose a challenge when determining a differential diagnosis.

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