

Encephalitis

Summary

Encephalitis is an inflammation of the brain parenchyma, caused by viral (most common), bacterial, parasitic, or fungal infection (infectious encephalitis) or an antibody-mediated autoimmune response (autoimmune encephalitis).

Prodromal symptoms include fever, headache, and nausea, with progression to neurological and psychiatric symptoms within hours to weeks, including altered mental status, seizures, focal neurological deficits, hallucinations, and psychosis. Diagnosis is based on laboratory studies (serology, CSF analysis), MRI of the head, and EEG.

Epidemiologic clues (e.g., season of the year, geographic location, travel, and exposure history) and clinical features may guide the diagnostic process. Additional testing with antibody detection of specific pathogen antibodies or autoantibodies is not necessary for all patients and should be performed as directed by clinical suspicion. Brain biopsy is limited to idiopathic cases that do not respond to empiric treatment. Paraneoplastic encephalitis, mediated by autoantibodies targeted against intracellular antigens, may be the first manifestation of malignancy, which is why malignancy screening may be part of the diagnostic workup. Treatment is based on the etiology and may include antiinflammatory or immunomodulatory treatment. Acyclovir or empirical antibiotic treatment should be started immediately if viral or bacterial encephalitis is suspected, respectively.

Definition

Anatomical classification

- **Encephalitis:** inflammation of the brain parenchyma
 - **Limbic encephalitis:** inflammation of brain tissue that primarily affects the limbic system in the medial temporal lobes
 - **Cerebellitis:** inflammation of the cerebellum
 - **Brainstem encephalitis:** inflammation of the brain tissue that primarily affects the brainstem and adjacent regions
 - **Meningoencephalitis:** concurrent inflammation of meninges (meningitis) and brain parenchyma (encephalitis)
- **Encephalomyelitis:** concurrent inflammation of the brain (encephalitis) and spinal cord (myelitis)

Etiological classification

- **Infectious encephalitis:** inflammation of the brain parenchyma caused by pathogens
 - **Viral encephalitis:** inflammation of the brain parenchyma caused by viruses (most common type of infectious encephalitis)^[1]

Viruses that commonly cause encephalitis include arboviruses (St. Louis, Western equine, Eastern equine, and West Nile virus), influenza, and the herpes viruses
 - **Bacterial encephalitis:** inflammation of the brain parenchyma caused by bacteria
 - **Other:** fungal (e.g., *Cryptococcus neoformans*), parasitic (e.g., *Naegleria fowleri*)
- **Autoimmune encephalitis:** inflammation of brain tissue mediated by autoimmune antibodies^[2]
 - According to its association with neoplasms
 - **Paraneoplastic encephalitis:** mediated by antibodies targeted against intracellular and extracellular neuronal proteins
 - **Non-paraneoplastic:** idiopathic, postinfectious (e.g., acute disseminated encephalomyelitis, anti-NMDAR encephalitis post herpes simplex encephalitis infection)
 - According to the targeted neuronal antigens
 - **Intracellular antigens** (commonly tumor-associated)^[3]
 - **Surface antigens**

Etiology:

be diffuse or localized. Organisms cause encephalitis by one of two mechanisms: (1) **direct infection of the brain parenchyma** via an extension of meningitis, secondary to viremia, or retrograde spread via peripheral nerves or (2) **a postinfectious, immune-mediated response** in the CNS that usually begins several days to weeks after clinical manifestations of the infection.

Viruses are the principal infectious causes of acute infectious encephalitis (Table 101.1). The most common viral causes of encephalitis in the United States are enteroviruses, arboviruses, and herpesviruses. Human immunodeficiency virus (HIV) is also an important cause of subacute encephalitis in children and adolescents and may present as an acute febrile illness

but, more commonly, is insidious in onset (see Chapter 125). Other less common viral causes of encephalitis include measles, JC virus, lymphocytic choriomeningitis virus (LCMV), rabies, influenza, and Japanese encephalitis. Numerous other infectious etiologies for encephalitis are possible in the appropriate setting, including prion-diseases (e.g., Creutzfeldt-Jakob disease) and parasites such as amoeba, *Bartonella henselae*, *Mycobacterium tuberculosis*, *Plasmodium falciparum*, and *Mycoplasma pneumoniae*. Encephalitis also may result from metabolic, toxic, and neoplastic disorders. In many cases, the cause remains unknown.

Acute disseminated encephalomyelitis (ADEM) is the abrupt development of multiple neurological signs related to an inflammatory, demyelinating disorder of the brain and spinal cord. ADEM can follow childhood viral infections (such as **measles** and **chickenpox**) or vaccinations, and can clinically resemble multiple sclerosis.

Autoimmune encephalitis is a relatively common cause of encephalitis and is associated with specific autoantibodies directed to brain antigens, such as anti-N-methyl-D-aspartate receptor antibodies. The presentation is often subacute with psychological manifestations, cortical dysfunction, movement disorders, autonomic dysfunction, and seizures.

TABLE 101.1 Causes of Acute Encephalitis

VIRUSES	BACTERIA
Enteroviruses	<i>Borrelia burgdorferi</i> (Lyme disease)
Parechoviruses	
Herpes simplex viruses (types 1 and 2)	<i>Bartonella henselae</i> (cat-scratch disease)
EBV	<i>Mycoplasma pneumoniae</i>
Arboviruses (West Nile virus, St. Louis, Japanese, LaCrosse, Powassan and equine encephalitis viruses)	<i>Rickettsia rickettsii</i> (Rocky mountain spotted fever)
Cytomegalovirus	PARASITES
Human immunodeficiency virus	<i>Plasmodium falciparum</i>
Rabies virus	<i>Naegleria fowleri</i>
LCMV	<i>Acanthamoeba</i> spp
VZV	FUNGI
Influenza virus	<i>Cryptococcus neoformans</i>
Mumps virus	<i>Coccidioides</i> species
Measles virus	<i>Histoplasma capsulatum</i>

EBV, Epstein-Barr virus; LCMV, lymphocytic choriomeningitis virus; VZV, varicella-zoster virus.

Clinical features

- **Progression:** acute (hours to days) or subacute (weeks to 3 months)
- **Nonspecific prodromal symptoms** (hours to weeks prior)
 - Fever
 - Headache
 - Nausea
- **Neurological**
 - **Altered mental status**
 - **Memory loss**
 - Seizures (focal or generalized)
 - **Focal neurological deficit** 
 - Hemiparesis
 - Hyperreflexia
 - Cranial nerve palsies
 - Language dysfunction (e.g., aphasia, dysarthria)
 - Extrapyrimal symptoms
 - Dysautonomia
- **Psychiatric**
 - Behavioral changes (e.g., hypersexuality, hypomania, agitation)
 - Hallucinations
 - Anxiety
 - Psychosis



Subacute onset of psychiatric symptoms in combination with **seizures** and/or **focal neurological deficits** should raise clinical suspicion for encephalitis.

Diagnosis:

- **Diagnosis:**
- **Best initial test:**
 - **CT scan of the head may show abnormalities of the temporal lobe in 20% to 50% of patients (HSV has a predilection for involvement of the temporal lobes).**
 - **MRI is abnormal in 90%.**
- **Most accurate test:**
 - **PCR of the CSF for herpes simplex (detecting viral DNA) is 95% to 99% sensitive and specific.**
 - **The PCR is more accurate than a brain biopsy.**
- Lumbar puncture usually shows cerebrospinal fluid (CSF) findings of elevated white blood cell count with lymphocytic predominance, normal glucose, and elevated protein concentration.

Neuroimaging

- **Brain MRI with contrast:** most sensitive and specific imaging modality 
 - Indicated in all patients with suspected encephalitis
 - **Limbic encephalitis:** hyperintensity in the **medial temporal lobes** in T2/FLAIR sequence ^[5]
 - **Herpes simplex encephalitis:** hyperintense temporal lobe lesions and signal abnormalities in T2/FLAIR sequence (see “Neuroimaging” in “Herpes simplex encephalitis”)
 - **Postinfectious encephalitis:** multifocal white matter lesions in T2WI/FLAIR sequence ^[6]
- **Brain CT (with or without contrast):** indicated if **MRI** is not available or contraindicated
- **Electroencephalography**
 - Indicated in all patients with suspected encephalitis
 - Usually nonspecific findings
 - Used in cases of suspected viral encephalitis (see “Herpes simplex encephalitis EEG findings”) and inconclusive diagnosis of seizures (e.g., non-convulsive, subtle motor seizures)
- **Brain FDG PET scan**
 - Indicated in patients with negative **neuroimaging** and laboratory findings, but with high clinical suspicion for autoimmune encephalitis
 - Abnormal **brain metabolism** findings in autoimmune encephalitis ^[7]

! A normal brain **MRI** does not exclude the diagnosis of encephalitis.

! Always consider HSE when imaging suggests potential **meningoencephalitis** and **temporal lobe involvement**; bilateral temporal lobe abnormality is pathognomonic of HSE.

Laboratory studies

- **Blood studies**
 - **CBC, CRP, ESR, and blood cultures**
 - **Renal function tests and liver function tests**
 - **Coagulation panel**
 - **HIV testing**
- **CSF analysis**
 - Perform **PCR, Gram stain, and cultures**
 - **Viral and autoimmune encephalitis CSF findings**
 - May be normal in **immunocompromised patients**
 - ↑ **Lymphocytes (lymphocytic pleocytosis)**
 - **Inflammatory markers:** ↑ **IgG index** and/or **oligoclonal bands**

Other studies

- **Serologic studies:** autoantibodies in **CSF and serum** (e.g., anti-Hu antibodies, anti-NMDAR antibodies)
- **Brain biopsy:** last resort; consider in patients with encephalitis of unknown cause who continue to deteriorate despite empiric and supportive treatment
- **Malignancy evaluation** ^[2]
 - Consider if an **autoantibody** against an intracellular **antigen** has been detected and refine screening based on **antibody results**
 - E.g., CT or **MRI** scan of the chest, abdomen, and **pelvis**, **mammography**, serum **prostate-specific antigen** testing, **ultrasound**

Differential diagnoses

- Encephalopathies (e.g., toxins, electrolyte disturbances, uremia)
- Meningitis
- Epilepsy
- Vascular (e.g., stroke, thrombosis)
- Degenerative disorders (e.g., Alzheimer disease, frontotemporal dementia)

Treatment

General

- Initial stabilization for acute seizures.
- Seizure management: antiepileptic drugs [3]
- Empiric treatment should not be delayed. Once the responsible pathogen or autoantibody is identified, therapy should be tailored accordingly.
- Monitor intracranial pressure (see “ICP management”).

Infectious encephalitis

• Viral encephalitis

- Start immediate antiviral therapy with **acyclovir** for all patients with suspected **viral** encephalitis (see “Antimicrobial treatment for herpes simplex encephalitis”).
- CMV encephalitis: IV ganciclovir AND IV foscarnet

• Bacterial encephalitis [8]

- Start immediate **empiric** antibiotic therapy for all patients with suspected **bacterial** encephalitis or meningitis (see also “Empiric antibiotic therapy for bacterial meningitis”).
- Initiate definitive antibiotic treatment as soon as microbiological results become available
 - Neuroborreliosis: ceftriaxone, cefotaxime, or penicillin G
 - Neurosyphilis: penicillin G
 - Listeria encephalitis: ampicillin plus gentamycin
 - Rocky Mountain spotted fever: doxycycline
 - Ehrlichiosis: doxycycline

Intravenous acyclovir is the treatment of choice for HSV and VZV infections. CMV disease is treated with ganciclovir. HHV-6 encephalitis in patients who are post-bone marrow transplant can also be treated with ganciclovir or foscarnet. HIV infections may be treated with a combination of antiretroviral agents. *M. pneumoniae* infections may be treated with doxycycline, fluoroquinolones, or macrolides, although the clinical value of treating encephalitis associated with *Mycoplasma* disease is uncertain.

ADEM has been treated with high-dose intravenous corticosteroids, but it is unclear whether the improved outcome with corticosteroids reflects milder cases recognized by MRI, fewer cases caused by measles (which can cause severe ADEM), or improved supportive care. Autoimmune encephalitis has been treated with steroids, intravenous immunoglobulin (IVIG), and rituximab.

Immune-mediated encephalitis

- **Paraneoplastic encephalitis**: treatment of primary tumor and immunotherapy [9]
- **Autoimmune encephalitis** [2]
 - First-line: high-dose corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis
 - Second-line: rituximab, cyclophosphamide

FEEDBACK

COMPLICATIONS AND PROGNOSIS

Among survivors, symptoms usually resolve over several days to 2-3 weeks. Although most patients with epidemic forms of infectious encephalitis (St. Louis, California, West Nile, and enterovirus infections) in the United States recover without sequelae, severe cases leading to death or substantial neurological sequelae can occur with virtually any of these neurotropic viruses. Sequelae can include paresis or spasticity, cognitive impairment, weakness, ataxia, and recurrent seizures. Most patients gradually recover some or all of their function. The overall mortality for infectious encephalitis is low, depending on the etiology.

Disease caused by HSV, Eastern equine encephalitis, or *M. pneumoniae* is associated with a worse prognosis, especially in children younger than 1 year of age or with coma. Rabies, with very rare exceptions, is fatal.

Relapses of ADEM occur in 14%, usually within 1 year with the same or new clinical signs. Recurrences of ADEM may represent the onset of multiple sclerosis in childhood.

PREVENTION

The best prevention for arboviral encephalitis is to avoid mosquito-borne or tick-borne exposures and to remove ticks carefully (see [Chapter 122](#)). There are no vaccines in use in the United States for the prevention of arboviral infection or for enteroviruses except for poliomyelitis. There are no specific preventive measures for HSV encephalitis except for cesarean section for mothers with active genital lesions (see [Chapter 65](#)). Rabies can be prevented by preexposure or postexposure vaccination. Influenza encephalitis can be prevented by use of influenza vaccination. Reye syndrome can be prevented by avoiding use of aspirin or aspirin-containing compounds for children with fever as well as use of varicella and influenza vaccines.