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Encephalitis

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Encephalitis is inflammation of the parenchyma of the brain, resulting from direct viral invasion. **Acute disseminated encephalomyelitis** is brain and spinal cord inflammation caused by a hypersensitivity reaction to a virus or another foreign protein. Both disorders are usually triggered by viruses. Symptoms include fever, headache, and altered mental status, often accompanied by seizures or focal neurologic deficits. Diagnosis requires CSF analysis and neuroimaging. Treatment is supportive and, for certain causes, includes antiviral drugs.

(See also Introduction to Brain Infections.)

Etiology

Encephalitis is usually a primary manifestation or a secondary (postinfectious) immunologic complication of viral infection.

Primary viral infection

Viruses causing primary encephalitis directly invade the brain. These infections may be

- Epidemic (eg, due to arbovirus, echovirus, coxsackievirus, or poliovirus [in some underdeveloped countries])
- Sporadic (eg, due to cytomegalovirus or to herpes simplex, varicella-zoster, lymphocytic choriomeningitis, rabies, or mumps virus)

Mosquito-borne arboviral encephalitides infect people during the spring, summer, and early fall when the weather is warm (see table Some Arboviral Encephalitides). Incidence in the US varies from 150 to > 4000 cases yearly, mostly in children. Most cases occur during epidemics.

Some Arboviral Encephalitides

Virus	Distribution	Mortality Rate	Comments
Chikungunya virus	Florida, Puerto Rico, the US Virgin Islands Common in Africa, India, Guam, Southeast Asia, New Guinea, China, Mexico, Central America Reunion Islands, limited areas of Europe	—	Should be considered in US travelers who develop encephalitis after visiting endemic areas Can lead to severe encephalitis and even death, especially in infants and people > 65
Colorado tick fever virus	Western US and Canada in areas that are 4,000 to 10,000 ft above sea level	Rarely causes death	Causes a nonspecific febrile illness, rarely complicated by meningitis or encephalitis
Japanese encephalitis virus	Asia and the western Pacific; uncommon in the US (mainly in travelers returning from endemic areas)	< 1%="" overall,="" but="" up="" to="" 30%="" of="" severe="">	Affects mainly children Usually mild and self-limiting, but severe in about 1 in 250 cases Vaccine used in endemic areas and recommended for travelers to these areas

La Crosse virus (California virus)	Primarily in the north central US but geographically widespread	Probably <>	Is probably underrecognized Accounts for most cases of arbovirus encephalitis in children
St. Louis encephalitis virus	Mostly in urban areas of the central and southeastern US but also in western states	—	Occurs in periodic urban epidemics; otherwise sporadic and rare
Powassan virus	Primarily in the northeastern states and the Great Lakes region of the US Southeastern Canada and Russia (southeastern Siberia, northeast of Vladivostok)	About 10%	Although rare, appears to be increasing since 2007; occurs in the late spring to mid-fall, when ticks are most active Should be considered in patients with encephalitis, especially those with a history of tick bite, a lot of time spent outdoors, and/or residence in or recent travel to an endemic area
Tick-borne encephalitis virus	Northern Asia, Russia, and many parts of Europe	Usually 1–2% but varies based on subtype (0.5–35%)	Occurs from early spring to late summer when ticks are most active Highest incidence and most severe symptoms in people ≥ 50 yr Should be suspected in travelers who have a nonspecific febrile illness that progresses to neuroinvasive disease within 4 wk after arriving from an endemic area and who may have been exposed to ticks
Venezuelan equine encephalitis	Mainly in parts in South and Central America; only rarely in the US (mainly in travelers returning from endemic areas)	0–1%, primarily in children	Vaccine available for equines; investigational vaccine used in laboratory workers at risk
West Nile virus	Throughout the US	About 9% of patients with CNS involvement	As of 2017, spread from the East Coast, where it first appeared in 1999, to all of the western states
Eastern equine encephalitis virus	Eastern US; a few cases in the Great Lakes states	About 50–70%	Occurs as small epidemics every 10–20 yr, mainly among young children and people > 55
Western equine encephalitis virus	—	—	For unknown reasons, has largely disappeared from the US since 1988
Zika virus	Florida South America, Central America, Caribbean Islands, Pacific Islands, Cape Verde (a nation of islands off the northwest coast of Africa), Southeast Asia	—	May cause a dengue-like illness and has been implicated in causing Guillain-Barré syndrome, severe brain damage, and microcephaly in infants of infected mothers

In the US, the most common sporadic encephalitis is caused by herpes simplex virus (HSV); hundreds to several thousand cases occur yearly. Most are due to HSV-1, but HSV-2 may be more common among immunocompromised patients. HSV encephalitis occurs at any time of the year, tends to affect patients < 20 or > 40 yr, and is often fatal if untreated.

Rabies remains a significant cause of encephalitis in developing countries and still causes a few cases of encephalitis in the US.

Primary encephalitis can also occur as a late reactivation of latent or subclinical viral infection. The best known types are

- HIV-associated encephalopathy and dementia
- Subacute sclerosing panencephalitis (which occurs years after a measles infection and is thought to

represent reactivation of the original infection; it is now rare in Western countries)

- Progressive multifocal leukoencephalopathy (which is caused by reactivation of JC virus; particularly in AIDS or immunosuppressed patients)

Immunologic reaction

Encephalitis can occur as a secondary immunologic complication of certain viral infections or vaccinations. Inflammatory demyelination of the brain and spinal cord can occur 1 to 3 wk later (as acute disseminated encephalomyelitis); the immune system attacks one or more CNS antigens that resemble proteins of the infectious agent. The most common causes of this complication used to be measles, rubella, chickenpox, and mumps (all now uncommon because childhood vaccination is widespread); smallpox vaccine; and live-virus vaccines (eg, the older rabies vaccines prepared from sheep or goat brain). In the US, most cases now result from influenza A or B virus, enteroviruses, Epstein-Barr virus, hepatitis A or hepatitis B virus, or HIV. Immunologically mediated encephalitis also occurs in patients with cancer and other autoimmune disorders.
Encephalopathies caused by autoantibodies to neuronal membrane proteins (eg, *N*-methyl-d-aspartate [NMDA] receptors) may mimic viral encephalitis. Some evidence suggests that anti-NMDA receptor encephalitis is a more common type of encephalitis than was previously thought. It occasionally develops after encephalitis due to herpes simplex virus, even when the encephalitis was successfully treated.

Pathophysiology

In acute encephalitis, inflammation and edema occur in infected areas throughout the cerebral hemispheres, brain stem, cerebellum, and, occasionally, spinal cord. Petechial hemorrhages may be present in severe infections. Direct viral invasion of the brain usually damages neurons, sometimes producing microscopically visible inclusion bodies. Severe infection, particularly untreated HSV encephalitis, can cause brain hemorrhagic necrosis.
Acute disseminated encephalomyelitis is characterized by multifocal areas of perivenous demyelination and absence of virus in the brain.

Symptoms and Signs

Symptoms of encephalitis include fever, headache, and altered mental status, often accompanied by seizures and focal neurologic deficits. A GI or respiratory prodrome may precede these symptoms. Meningeal signs are typically mild and less prominent than other manifestations.
Status epilepticus, particularly convulsive status epilepticus, or coma suggests severe brain inflammation and a poor prognosis.
Olfactory seizures, manifested as an aura of foul smells (rotten eggs, burnt meat), indicate temporal lobe involvement and suggest HSV encephalitis.

Diagnosis

- MRI
- CSF testing

Encephalitis is suspected in patients with unexplained alterations in mental status. Clinical presentation and differential diagnoses may suggest certain diagnostic tests, but MRI and CSF analysis (including PCR for HSV and other viruses) are usually done, typically with other tests (eg, serologic tests) to identify the causative virus. Despite extensive testing, the cause of many cases of encephalitis remains unknown.

MRI

Contrast-enhanced MRI is sensitive for early HSV encephalitis, showing edema in the orbitofrontal and temporal areas, which HSV typically infects. MRI shows demyelination in progressive multifocal leukoencephalopathy and may show basal ganglia and thalamic abnormalities in West Nile and eastern equine encephalitis. MRI can also exclude lesions that mimic viral encephalitis (eg, brain abscess, sagittal sinus thrombosis).
CT is much less sensitive than MRI for HSV encephalitis but can help because it is rapidly available and can exclude disorders that make lumbar puncture risky (eg, mass lesions, hydrocephalus, cerebral edema).

CSF testing

Lumbar puncture (spinal tap) is done. If encephalitis is present, CSF is characterized by lymphocytic pleocytosis, normal glucose, mildly elevated protein, and an absence of pathogens after Gram staining and culture (similar to CSF in aseptic meningitis). Pleocytosis may be polymorphonuclear in severe infections. CSF abnormalities may not develop until 8 to 24 h after onset of symptoms. Hemorrhagic necrosis can introduce RBCs into CSF and elevate protein. CSF glucose levels may be low when the cause is varicella-zoster virus or lymphocytic choriomeningitis virus.

PCR testing of CSF is the diagnostic test of choice for HSV-1, HSV-2, varicella-zoster virus, cytomegalovirus, enteroviruses, and JC virus. PCR for HSV in CSF is particularly sensitive and specific. However, results may not be available rapidly, and despite advances in technology, false-negative and false-positive results may still occur because of a variety of conditions; not all are technical failures (eg, the blood in a mildly traumatic CSF tap may inhibit the PCR amplification step). False-negative results can occur early in HSV-1 encephalitis; in such cases, testing should be repeated in 48 to 72 h. A new technique, next-generation sequencing is becoming more widely available and may identify nucleic acids of agents that otherwise escape detection.

CSF viral cultures grow enteroviruses but not most other viruses. For this reason, CSF viral cultures are rarely used in diagnosis.

CSF viral IgM titers are often useful for diagnosing acute infection, especially West Nile encephalitis, for which they are more reliable than PCR. CSF IgG and IgM titers may be more sensitive than PCR for varicella-zoster virus encephalitis. Paired acute and convalescent serologic tests of CSF and blood must be drawn several weeks apart; they can detect an increase in viral titers specific for certain viral infections.

Brain biopsy

Brain biopsy may be indicated for patients who

- Are worsening
- Are responding poorly to treatment with acyclovir or another antimicrobial
- Have a lesion that is still undiagnosed

However, brain biopsy has a low yield unless it targets an abnormality seen on MRI or CT.

Prognosis

Recovery from viral encephalitis may take a very long time. Mortality rate varies with cause, but severity of epidemics due to the same virus varies during different years. Permanent neurologic deficits are common among patients who survive severe infection.

Treatment

- Supportive care
- Acyclovir for HSV or varicella-zoster virus encephalitis

Supportive therapy for encephalitis includes treatment of fever, dehydration, electrolyte disorders, and seizures. Euvolemia should be maintained.

Because prompt identification of HSV or varicella-zoster virus by PCR is difficult, treatment should not be withheld pending confirmation by testing. Until HSV encephalitis and varicella-zoster virus encephalitis are excluded, acyclovir 10 mg/kg IV q 8 h should be started promptly and continued usually for 14 days or until infection with these viruses is excluded. Acyclovir is relatively nontoxic but can cause liver function abnormalities, bone marrow suppression, and transient renal failure. Giving acyclovir IV slowly over 1 h with adequate hydration helps prevent nephrotoxicity. Cytomegalovirus encephalitis can be treated with ganciclovir and/or other antiviral drugs.

Because a bacterial CNS infection is often difficult to exclude when patients who appear seriously ill present, empiric antibiotics are often given until bacterial meningitis is excluded.

If encephalitis is due to an immunologic reaction (eg, acute disseminated encephalomyelitis [postinfectious encephalomyelitis]), treatment should be begun immediately; it may include corticosteroids (prednisone or methylprednisolone) and plasma exchange or IV immune globulin.

Key Points

- Viruses that cause epidemic or sporadic infections can invade and infect brain parenchyma (causing encephalitis) and/or trigger postinfectious inflammatory demyelination (acute disseminated encephalomyelitis).
- Encephalitis causes fever, headache, and altered mental status, often accompanied by seizures and focal neurologic deficits.
- Do contrast-enhanced MRI and CSF testing.
- Until HSV encephalitis and varicella-zoster virus encephalitis are excluded, promptly treat with acyclovir and continue, usually for 14 days or until infection with these viruses is excluded.
- Treat encephalitis due to an immunologic reaction with corticosteroids and plasma exchange or IV immune globulin.

Drugs Mentioned In This Article

Drug Name	Select Trade
methylprednisolone	MEDROL
immune globulin	Gammagard S/D
ganciclovir	CYTOVENE
prednisone	RAYOS
acyclovir	ZOVIRAX

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