Viral Encephalitis — Causes and Symptoms

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Viral encephalitis is defined as the inflammation of the central nervous system due to viral agents. Several viruses can cause encephalitis, but herpes viruses are the most commonly implicated. Patients present with confusion, altered level of consciousness, seizures and focal neurologic signs. Polymerase chain reaction testing can help identify the causative organism in a few cases, but antiviral therapy should be initiated immediately in any suspected case regardless of the diagnosis confirmation.

Definition of Viral Encephalitis

Acute viral encephalitis indicates an acute inflammatory process of the brain that is restricted to the central nervous system without involving the meninges. The leading cause is the enteroviruses group of viruses. In reality, most cases of viral encephalitis have some form of meningitis as well; hence, the term meningoencephalitis. It makes meningoencephalitis more common compared to pure encephalitis. Patients with viral meningoencephalitis usually have aseptic meningitis because cerebrospinal fluid examination does not reveal any bacterial growth. Viral encephalitis’ involvement is dependent on the viral agent, the environment, genetics, as well as the immune status of the patient.
Epidemiology of Viral Encephalitis

Viral encephalitis is an uncommon occurrence with an estimated incidence of 3.5 to 7.4 per 100,000 per year. According to the Centers for Disease and Control, it estimates, 20,000 new cases of viral encephalitis are expected per year.

Different viruses have been implicated in the pathology of viral encephalitis. The viruses enter into the bloodstream and migrate to the brain where they multiply and, in responding to the invasion, the actions of the immune system leads to cerebral edema, the point at which symptoms occur. Herpes simplex virus and rabies virus encephalitis is the most common. It usually attacks the temporal lobes. Herpes simplex virus encephalitis has an incidence of 4 cases per 1 million per year.

Other causes of viral encephalitis include arboviral encephalitis, which is responsible for up to 3,000 cases per year and West Nile encephalitis which is identified as the etiology in 370 cases per year.

Viral encephalitis is more common in children and young adults. Infants and the elderly are more likely to develop more severe encephalitis. Mumps meningoencephalitis is more common in men.

Geographic clues

- Entire U.S.
  - West Nile virus (especially southwest)
  - St. Louis encephalitis virus
- Eastern Seaboard
  - Eastern equine encephalitis virus (and great lake states)
- East of Mississippi River
  - California encephalitis virus group

Etiology of Viral Encephalitis

The most common etiology of viral encephalitis is herpes virus encephalitis. Mortality is very high in untreated cases. Herpes simplex virus type 1 encephalitis more commonly involves the brainstem, while type 2 is usually associated with myelitis.

Varicella-Zoster virus, another member of the herpes virus family, is characterized by encephalitis accompanied by a skin rash. Children might develop cerebellar ataxia due to cerebellitis as a complication of chickenpox.

Influenza virus has also been associated with rare forms of reversible frontal lobe
Encephalitis in children in addition to Guillain-Barre syndrome. Enteroviruses are responsible for a minority of the cases and usually present with hand, foot, and mouth disease.

All patients infected with the rhabdovirus responsible for rabies are going to develop encephalitis. Patients develop confusion, paresthesia and signs of brainstem involvement.

Mumps and measles viruses can also cause encephalitis. Patients with measles encephalitis usually have characteristic EEG changes and mortality is reported to be about 10%.

Rubella, adenovirus, cytomegalovirus, Epstein-Barr virus, as well as Murray Valley encephalitis virus, HIV-1 and the JC virus, have also been identified as cellular receptors of viruses that lead to encephalitis.

**Pathophysiology of Viral Encephalitis**

In order for the different etiological viruses to cause encephalitis, they need to interact with specific receptors on cell membranes. Herpes simplex viruses usually interact with receptors known as Hve A, B, C and tumor necrosis factor receptor superfamily 14. Measles interacts with the CD46 receptor, while rabies virus interacts with AchR and NCAM receptors.

In order for the viruses to get into contact with the neuronal cells, they can spread through the blood or by retrograde neuronal dissemination. Arboviruses usually spread via the blood, while rabies virus gets access to the central nervous system via the retrograde neural dissemination process. Rabies virus first resides in peripheral nerves before being transferred to the central nervous system.

Most viruses cause non-distinctive patterns of central nervous system involvement and necrosis; hence, cannot be differentiated by imaging. Eastern equine encephalitis and Japanese encephalitis are associated with severe and widespread neural necrosis, making them more distinctive.

Encephalopathy is the consequence of encephalitis and can be identified as the impairment of normal brain function due to viral replication.

In some cases, however, direct viral infection of neuronal cells is not the main cause of encephalopathy. In these cases, certain inflammatory markers, such as interleukin 6 and the monocyte chemotactic protein 1, are over-expressed without direct viral invasion of the central nervous system. In these cases, it is hypothesized that the cause of the encephalopathy is the hyperactivated cytokine response.

Transmission mode:

- When an infected person coughs or sneezes and the virus they have is airborne.
- Some viruses can be transferred by insects through bites.
- Dominant viral infections may increase one’s chances of contracting this disease.
- Contaminated foods and drinks, as well as being in contact with an infected person.
Presentation of Viral Encephalitis

Patients develop an **acute onset fever** in addition to **headache** and **neck stiffness**. The neck stiffness and **photosensitivity** are signs of meningism. **Seizures**, **confusion**, and **altered level of consciousness** are also common symptoms of viral encephalitis. Fever, anosmia, personality changes, gustatory hallucinations, developing photophobia, malaise, Korsakoff’s amnesia, paralysis, and vomiting may also occur. **Focal neurological signs** can be evident in patients with encephalitis.

**Frontal lobe involvement**, which is usually reversible and characterized by **behavioral changes**, is suggestive of influenza-related encephalitis, especially if the patient is a child. Patients presenting with psychiatric symptoms might have the herpes virus encephalitis.

Patients affected with **Japanese encephalitis** often develop **recurrent seizures** during their illness. **Dengue fever** is associated with severe influenza-like illness in addition to encephalitis and transverse myelitis. Patients can also develop **hepatic failure**.

Japanese encephalitis is also associated with **Parkinsonism**. **Enterovirus 71** can cause **myoclonus**, **tremors**, **ataxia**, and **coma**. Mothers affected by the **Zika virus** during pregnancy put the newborns at risk of developing **microcephaly**.

**Diagnostic Workup for Viral Encephalitis**

**Laboratory investigations** are not helpful in confirming the diagnosis or differentiating between the different viral agents but can give some clues. **Complete blood count** shows **leukocytosis** mainly with a lymphocytic predominance. As some of the causes of encephalitis can be associated with hepatic failure, **liver and renal function tests** are indicated.
The most important diagnostic modality is perhaps the analysis of cerebrospinal fluid with the application of polymerase chain reaction techniques to identify the causative virus.

**Blood cultures** are indicated to exclude bacterial meningoencephalitis. Serologic tests might be used to detect the Japanese encephalitis virus or West Nile virus but cross-reactivity is common. Polymerase chain reaction testing for the detection of the West Nile virus is available and reliable. Unfortunately, most other etiologies remain undetected in up to 60% of the cases.

**Brain imaging** is useful but usually at later stages of the disease. Three to four days after the onset of herpes virus encephalitis, computed tomography can reveal low-density lesions, especially in the temporal lobes. Edema and hemorrhage are common consequences of encephalitis but, again, are usually seen late.

**Magnetic resonance imaging** can also be useful in the diagnostic workup of the encephalitis patient. It can show hyperintense signals in the brain stem of enterovirus 71 encephalitis. Patients with Japanese encephalitis have evidence for gray matter involvement, while Nipah virus lesions tend to be restricted to the white matter. Herpes viruses can cause temporal lobe lesions on MRI, but the picture might be more widespread in infants and young children.

**Electroencephalography** (EEG) is useful in the evaluation of the encephalopathy patient. Focal temporal lobe discharges and diffuse slowing are common findings in herpes virus encephalitis. Patients with Japanese encephalitis have diffuse and continuous delta wave activity, spikes and can develop an alpha rhythm if in coma.

### Treatment of Viral Encephalitis

Medication should be administered intravenously to reduce cerebral edema. The current treatment of viral encephalitis is largely symptomatic. Airway, bladder and nutrition maintenance are essential. Patients can become dehydrated and might develop electrolyte imbalances which can complicate their neurological exam; therefore, proper electrolyte and fluid replacement therapy is indicated. Hydration should be moderate to prevent worsening edema. Anticonvulsants, as well as pain killers, may be used.

Patients who are suspected to have herpes virus encephalitis should always receive
treatment. **Antiviral therapy** with *acyclovir* and *vidarabine* is usually effective, but acyclovir is recommended as first-line therapy. Patients with varicella-zoster virus encephalitis should also receive acyclovir.

*Ribavirin* might be useful in arbovirus encephalitis and Nipah virus encephalitis. Specific treatment for most of the other etiologies is not available, but acyclovir should be always used as initial therapy in any patient with encephalitis, even if the diagnosis of herpes virus encephalitis is not confirmed.

Patients with viral encephalitis might develop **increased intracranial pressure**. In this case, the elevation of the bed-head, diuresis with mannitol and hyperventilation should be used. In refractory cases of increased intracranial pressure, **surgical decompression** might be indicated.

Patients who develop **seizures** should receive **phenytoin** or **Valproic acid**, both of which should be given intravenously. **Benzodiazepines** are indicated for the abortion of status epilepticus. Patients who have persistent seizures after the acute stage of viral encephalitis might need **long-term antiepileptics**. Once the immune system stops reacting with viral encephalitis, the inflammation subsides leaving lesions that had resulted from the replication and packaging of viral cells. The lesions heal, but the neurons that were lost during the infection do not regenerate; thus, even after a full recovery, patients have neurological deficits.

Complications of viral encephalitis include permanent brain damage, intracerebral hemorrhage, hypoxemia, hypotension, as well as death.

**References**


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