

Viral Encephalitis in India: Management Update

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Viral infections of the central nervous system (CNS) result in the clinical syndromes of aseptic meningitis or encephalitis. The presence or absence of normal brain function is the important distinguishing feature between encephalitis and meningitis. In patients with meningitis their cerebral function remains normal, though they may be uncomfortable, lethargic, or distracted by headache. But in encephalitis, however, abnormalities in brain function are common which include altered mental status, motor or sensory deficits, altered behavior/personality changes, and speech or movement disorders. Seizures and postictal states can be seen with meningitis alone and are uncommon with encephalitis. Rare neurologic manifestations of encephalitis may include hemiparesis, flaccid paralysis, and paresthesias. However, the distinction between the two entities is frequently blurred since some patients may have both a parenchymal and meningeal process with clinical features of both. The patient is usually labeled as having meningitis or encephalitis based upon which features predominate in the illness although meningoencephalitis is also a common term that recognizes the overlap.

Viral encephalitis can be either primary or post infectious. Etiology of post infectious viral encephalitis in the tropical countries of Asia and the Indian subcontinent is different from those of the Western and developed world. St. Louis encephalitis in North America and West Nile fever are common viral encephalitis found in the Americas while Japanese encephalitis is common in Asia/India. A common cause of sporadic encephalitis in the both these areas is herpes simplex virus type 1

Although Japanese encephalitis virus (JEV) is a key etiological agent for AES in India, many recent studies suggest that enteroviruses and rhabdoviruses also account for outbreaks viral encephalitis. (1)

Beig et al in their study among eighty-seven children from Uttar Pradesh observed that the most common etiology of viral encephalitis was enterovirus 71 (42.1%), followed by measles (21.1%), varicella zoster virus (15.8%), herpes simplex virus (10.5%), and mumps (10.5%). Japanese encephalitis virus was not found in any of these eight cases. (2)

Clinical Manifestations

Patients with encephalitis have an altered mental status ranging from subtle deficits to complete unresponsiveness. Photophobia/Nuchal rigidity which are symptoms / signs of meningeal irritation are usually absent with a pure encephalitis but often accompany a meningoencephalitis. Seizures are common and focal neurologic abnormalities can occur, including hemiparesis, cranial nerve palsies, and exaggerated deep tendon and/or pathologic reflexes can occur with encephalitis. Patients may appear confused, agitated, or obtunded.

Although there are usually no pathognomonic findings on the initial patient encounter, certain physical examination features may suggest a particular diagnosis:

- I. Parotitis strongly suggests mumps encephalitis in an unvaccinated patient with mental status changes
- II. Encephalitic rabies usually presents with hydrophobia, aerophobia, pharyngeal spasms, and hyperactivity. Atypical presentations of rabies include seizures, cranial nerve palsies, and myoclonus.
- III. Grouped vesicles in a dermatomal pattern suggest varicella-zoster virus, which can occasionally cause encephalitis

Diagnosis

1. Imaging

Imaging in patients with encephalitis may or may not be diagnostic. CT scanning is useful to rule space-occupying lesions or brain abscess. MRI is sensitive for detecting demyelination, which may be seen in other clinical states presenting with mental status changes (e.g. progressive multifocal leukoencephalopathy). However, the location of abnormal signal can sometimes be suggestive of specific etiologies:

- I. Temporal lobe involvement is strongly suggestive of HSV encephalitis, although other herpes viruses (e.g., VZV, EBV, human herpesvirus 6) can also produce this clinical picture. (3)
 - II. Involvement of the thalamus or basal ganglia may be observed in the setting of encephalitis due to respiratory viral infection, Creutzfeld-Jacob disease & arbovirus,
 - III. The presence of hydrocephalus may suggest nonviral etiologies, such as bacteria, fungal, or parasitic agents
2. **Electroencephalography** is often abnormal in acute encephalitis. Focality in the temporal lobe region is suggestive of HSV encephalitis. (4).

3. Cerebrospinal fluid findings

Examination of the cerebrospinal fluid (CSF), although not diagnostic, will usually confirm the presence of inflammatory disease of the CNS. Increased white blood cell (WBC) count (usually less than 250/mm³), the differential showing a predominance of lymphocytes (early infection may reveal a predominance of neutrophils), elevated protein concentration (usually less than 150 mg/dL) and normal glucose concentration are common CSF abnormalities which may be observed in patients with viral encephalitis. Red cells are usually absent (in a nontraumatic tap); their presence in the appropriate clinical setting suggests HSV-1 infection or other necrotizing encephalitis.

An important initial diagnostic step in the patient with suspected viral encephalitis is analysis of the CSF. The opening CSF pressure should be measured and CSF should be tested for cell count, glucose, and protein. Specific diagnostic tests to consider include: polymerase chain

reaction (PCR) tests for viruses, culture for bacteria, fungi and mycobacteria and serology for the arboviruses. However, even with use of polymerase chain reaction testing, the etiology in most cases remains undefined. (6)

The most important viral etiology to rule out in a patient with encephalitis is HSV, since this clinical entity is usually fatal if untreated. HSV should be considered particularly if there is temporal lobe focality suggested by symptoms, signs or imaging studies. Diagnosis is most readily made by detecting HSV DNA by polymerase chain reaction on CSF. Identification of HSV-1 in the CSF is a rapid, sensitive, and specific diagnostic test for HSV-1 encephalitis. (7)

Enteroviruses are more commonly associated with viral meningitis, but infrequently they may cause encephalitis as well. PCR testing on the CSF sample is the diagnostic test of choice. The pathogen can also be cultured from the stool and throat; however, a positive stool or throat culture is not necessarily diagnostic of disease, especially in summer months.

4. **Serologic testing** is most important for patients who are not improving and who do not have a diagnosis based upon CSF analysis, culture, and PCR. Most viral etiologies require paired sera for diagnosis; thus it is prudent to save serum in the setting of acute illness that can later be used if necessary. Convalescent serology should be obtained no sooner than three weeks after the onset of the clinical illness.
5. **Brain biopsy** — As a last resort, brain biopsy can be considered in the patient if the etiology of encephalitis is still unknown.

Differential Diagnosis

A number of noninfectious etiologies can mimic CNS infections. These include primary intracranial or metastatic tumors, adverse effects of medications, and autoimmune or paraneoplastic diseases. Other non-viral infectious etiologies to consider in the patient with suspected CNS infection include brain abscess, syphilis, tuberculous meningitis, and fungal meningitis (e.g., coccidioides), which can affect the sensorium.

Treatment

There are no specific therapies for most CNS viral infections.

- a) Empiric treatment for HSV-1 infection with acyclovir (10 mg/kg IV Q8h) should always be initiated as soon as possible if the patient has encephalitis without apparent explanation. Early therapy is vital because it is associated with a significant decrease in mortality and morbidity.(8)
- b) Acyclovir should also be considered if VZV encephalitis is likely.

Increased Intracranial Pressure — Symptoms and signs of increased intracranial pressure include headache, vomiting, and a decreased level of consciousness. Steroids/mannitol have been used to decrease the Increased Intracranial Pressure, but none have been shown to be of any well-established benefit. However, serial intracranial pressure (ICP) monitoring should

be part of the management of a patient with encephalitis with documented elevated ICP since this parameter has been associated with a negative prognosis. Relieving elevated ICP may decrease secondary brain injury while the patient is responding to anti-infective therapy. (9)

Japanese encephalitis

Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most important cause of viral encephalitis in Asia based on its frequency and severity. Bandopadhyaya et al in their study from various districts of West Bengal, observed that 22.76% and 5% of the Acute Encephalitic Syndrome cases were positive for JE IgM in 2011 and 2012, respectively. (10)

Japanese encephalitis virus (JEV) is transmitted in an enzootic cycle involving mosquitoes (*Culex vishnui* subgroup, particularly *Cx. Tritaeniorhynchus*), and vertebrate amplifying hosts, primarily pigs and wading birds. Humans are incidental and dead end hosts in the JEV transmission cycle as they do not develop sufficiently high viremia to infect feeding mosquitoes. Therefore, mosquitoes do not transmit the virus directly from one person to another person. Pigs are a key host as they develop high levels of viremia.

The most commonly clinical presentation of Japanese encephalitis (JE) is acute encephalitis. After an incubation period of 5 to 15 days, initial symptoms are usually nonspecific and may include fever, diarrhea, and rigors followed by headache, vomiting, and generalized weakness. Over the next few days, mental status changes, focal neurologic deficits (including paresis, hemiplegia, tetraplegia, or cranial nerve palsies), and/or movement disorders develop. Many patients lapse into coma and some require ventilatory assistance.

Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) scanning for detecting JEV-associated abnormalities such as changes in the thalamus, basal ganglia, midbrain, pons, and medulla. Thalamic lesions are the most commonly described abnormality; although these can be highly specific for JE in the appropriate clinical context, they are not a very sensitive marker of JE. (11) EEG abnormalities may include theta and delta coma, burst suppression, epileptiform activity, and occasionally alpha coma

JE is diagnosed serologically by detection of JEV-specific immunoglobulin M (IgM) antibodies in CSF or serum by an enzyme-linked immunosorbent assay (ELISA). The presence of JEV-specific IgM antibodies in CSF confirms recent central nervous system infection. IgM antibody in serum is suggestive of JE but could indicate asymptomatic infection or recent JEV vaccination. On admission to hospital, CSF antibodies are detectable in 70 to 90 percent of JE patients; JEV IgM is detectable in most CSF samples collected five to eight days after symptom onset. On admission to hospital, serum antibodies are detectable in about 60 to 70 percent of patients; serum antibodies are detectable in nearly all serum samples collected at least nine days after symptom onset. If JE is suspected and acute samples are negative, a convalescent serum sample should be collected.

Treatment

Treatment of Japanese encephalitis (JE) consists of supportive care with emphasis on control of intracranial pressure, maintenance of adequate cerebral perfusion pressure, seizure control, and prevention of secondary complications. A randomized, placebo-controlled trial of oral ribavirin in 153 Indian children did not show any difference in outcome between the treatment and control groups. (13) Work is ongoing to investigate other potential antiviral agents.

Prevention

Personal protective measures to prevent mosquito bites are important to reduce the risk of Japanese encephalitis (JE) among travelers to endemic regions. In addition, JE vaccine provides substantial additional protection for travelers to high-risk settings. There are several groups of vaccines which are currently in use: purified, formalin-inactivated mouse-brain derived, cell-culture derived inactivated, and cell-culture derived live attenuated.

Formalin-inactivated vaccines have been safe and effective against JEV for at least 30 years of these, the most widely produced and internationally distributed is the mouse-brain derived inactivated vaccine. Mouse-brain derived inactivated vaccines are based on the Nakayama and Beijing-1 strains (seroconversion rate 80% to 90%). This is the only vaccine against JE approved by the World Health Organization. The Central Research Institute in Kasauli is the manufacturer in India. It is available in lyophilized form, in which gelatin and sodium glutamate are used as stabilizers, and thimerosal is used as a preservative.

The primary vaccination is done between the ages of 1 and 3 at doses of 0.5 mL to 1 mL (0.25 to 0.5 with children under age 3) subcutaneously. The dose regimen consists of one injection on days zero, seven, and 30 with a booster after one year and thereafter every three years until age 10. The protective efficacy is above 90%. Due to its high production cost, lack of long-term immunity, and adverse allergic reactions, this vaccine is not practical to be administered in poor rural areas, where it is urgently needed.

Several vaccines are still in various stages of development. These include: recombinant protein based vaccines, recombinant virus based/chimeric vaccine, and DNA vaccines. Second generation recombinant vaccines are in development with the aim of improving immunogenicity and decreasing adverse reactions.

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