Viral Encephalitis

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INTRODUCTION

Viral infection of the central nervous system (CNS) can present as several different clinical syndromes, including encephalitis, meningitis, myelitis, and neuritis, depending on the neurologic regions that are affected. Encephalitis is defined as the presence of inflammation in the brain parenchyma accompanied by clinical evidence of neurologic dysfunction. Viruses are the most common cause of infectious encephalitis, but certain bacteria, fungi, helminthes, and amebae have also been implicated. Noninfectious etiologies such as autoimmune, paraneoplastic, or collagen vascular diseases can also cause illness indistinguishable from infectious encephalitis. Because of the wide range of differential diagnoses, it is often challenging in clinical practice to secure the diagnosis of viral encephalitis and to determine its exact cause. Moreover, treatment options are often limited even when a diagnosis is confirmed.

EPIDEMIOLOGY

Encephalitis in general accounts for a substantial burden of disease in the United States. Patients may have prolonged hospitalizations and require expensive diagnostic tests. One study in the United States conducted from 1988 to 1997 showed that encephalitis accounted for 19,000 hospitalizations and 1400 deaths annually. Based on National Hospital Discharge Survey data, the most common etiology of encephalitis was viral infection, which accounted for 38.2% of cases with an identified cause. Cases tended to occur in elderly patients older than 65 years and in children, particularly in children less than 1 year old.

PATHOGENESIS

In order for viruses to cause encephalitis, they must first reach the CNS through either a hematogenous or a neuronal route. An example of hematogenous spread is transmission of an arbovirus to the bloodstream from an insect bite. The host immune response is important in suppressing replication of the virus in the skin, lymph nodes, and bloodstream before the virus can enter the CNS. A resulting viremia can then spread to the mononuclear phagocyte system, formerly known as the reticuloendothelial system, as well as to the muscle tissue. Continued replication in these...
sites can then cause a secondary viremia, which may seed the CNS. Active replication in the capillary endothelial cells of vessels in the gray matter or gray-white matter junction or passive transfer of virus across the endothelium may lead to perivascular lymphocytic infiltration. Viruses can also travel via peripheral intraneuronal routes, as exemplified by herpes simplex virus (HSV) and rabies virus. After the virus reaches the brain, the infection progresses and astrocytosis and gliosis may occur in the brain tissue.

**CLINICAL MANIFESTATIONS**

The clinical features of encephalitis are fever, headache, and an altered level of consciousness. Although mental status changes are more commonly associated with encephalitis, they can also occur in viral or bacterial meningitis and other infections of the CNS. Encephalitis can also occur concomitantly with meningeval inflammation, and this condition is termed meningoencephalitis. Systemic manifestations may also occur and may point to specific organisms. For example, non-polio enteroviruses may cause an exanthem. Rashes are also associated with varicella-zoster virus (VZV), West Nile virus (WNV), HIV, measles, and rubella.

Neurologic symptoms may correlate loosely with the regions of the brain that are affected by the virus. The most common focal neurologic signs associated with encephalitis are hemiparesis, aphasia, ataxia, cranial nerve palsies, myoclonus, and seizures. Seizures are more common with encephalitides that affect the cortex, such as HSV. Signs of parkinsonism, such as bradykinesia, rigidity, and resting tremor, are associated with flavivirus infections. These viruses, which include WNV and Japanese encephalitis virus, mostly affect deep matter structures, such as the basal ganglia and thalamus. Personality changes can be a result of limbic encephalitis, which can be caused by HSV and human herpesvirus 6 (HHV-6). Infection by HSV, along with enterovirus 71 and flaviviruses, can also involve the brainstem. Flaviviruses, enterovirus 71, and poliovirus can cause acute flaccid paralysis by infecting the anterior horn of the spinal cord. Other neurologic findings that may result from viral encephalitis include cognitive dysfunction, cerebellitis, autonomic dysfunction, and even diabetes insipidus or syndrome of inappropriate antidiuretic hormone from hypothalamic dysfunction.

**DIFFERENTIAL DIAGNOSIS**

In the interest of patient prognosis and public health measures, effort should be made to obtain a diagnosis. Viral encephalitis must first be differentiated from a bacterial CNS infection, which would require immediate treatment with antibiotics. Other syndromes that can mimic encephalitis include brain abscess, cerebritis, subdural or epidural empyema, and septic cerebral venous or sinus thrombosis. The clinical picture of viral encephalitis can also be confused with encephalopathy, which is characterized by diffuse cerebral dysfunction in the absence of inflammation. Encephalopathy is less likely to cause fever, headache, focal neurologic signs, and seizures. Causes of encephalopathy include metabolic disturbances, hypoxia, ischemia, drugs, intoxication, and organ dysfunction. Systemic infections, including viral infections, can also cause encephalopathy. For example, HIV can commonly cause encephalopathy and dementia.

Acute viral encephalitis should also be differentiated from postinfectious or postimmunization encephalitis due to an immunologic response to a prior antigenic stimulus. This can be seen after
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vaccine administration or after a CNS-sparing infection. This phenomenon is now commonly called acute disseminated encephalomyelitis (ADEM), and it is a clinical and radiologic diagnosis. Unlike acute viral encephalitis, ADEM causes a perivenular inflammatory demyelinating pattern in the absence of an acute infectious process. Patients exhibit a rapid onset of encephalopathy associated with neurologic deficits, usually over an average period of 4 to 5 days. Most patients with ADEM report an infection or vaccination in the prior few weeks. ADEM has been associated with measles, mumps, rubella, VZV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), HSV, hepatitis A, influenza, and enteroviruses. Postvaccination cases have been reported with vaccines for measles, Japanese encephalitis virus, poliovirus, tetanus toxoid, influenza, and hepatitis B. ADEM more commonly affects children, but it can occur at any age.

The findings of viral encephalitis can also be mimicked by the presence of paraneoplastic antibodies, such as anti-Hu and anti-Ma. Of note is a recently described new form of autoimmune encephalitis called anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, which was first noted in the setting of young women with ovarian teratomas. In the California Encephalitis Project, an attempt to characterize encephalitis cases in California since 2007, patients were selectively tested for anti-NMDAR encephalitis in addition to viral etiologies. A 2012 update of the project reported that 41% of 79 individuals under the age of 31 years with an identified cause of encephalitis tested positive for anti-NMDAR encephalitis. In comparison, the next most common etiology was enterovirus, which comprised 38% of cases. Although there is inherent referral bias in the design of the project, this data suggests that autoimmune encephalitis may be a significant cause of encephalitis in young individuals. Cases of anti-NMDAR encephalitis were characterized by psychiatric symptoms, movement abnormalities, and autonomic instability.

ETIOLOGY

In the California Encephalitis Project, extensive testing was done in 1570 cases of encephalitis identified over a 7-year period. As of 2005, a confirmed or probable etiology was identified in only 16% of cases, of which 69% were viral, 20% were bacterial, 7% were prion-related, 3% were parasitic, and 1% were fungal. An additional 13% of cases had a possible etiologic agent identified, and 8% of cases were due to a noninfectious etiology; however, 63% of cases were left without an explanation. There may have been referral bias in this study toward more diagnostically challenging cases, but the proportion of undiagnosed cases is still significantly high. Another similar study completed in Finland from 1999 to 2003 left 64% of cases unexplained despite extensive testing.

The causes of viral encephalitis have shifted over the recent decades due to the introduction of routine vaccination for measles, mumps, rubella, and VZV. The most common pathogens in the United States currently are HSV-1, WNV, enteroviruses, and other herpes viruses, but there is no single predominant cause; in most cases an etiology is not identified, even with extensive testing. HSV is the most common cause of sporadic encephalitis in the United States, accounting for approximately 1250 to 2000 cases of encephalitis per year. In immunocompetent adults, HSV-1 causes 90% of cases of HSV encephalitis while HSV-2 causes only 10% of cases. Despite its prevalence, HSV accounts for only 10% of all cases of viral encephalitis. Immunocompromised individuals...
are more susceptible to VZV and CMV. Patients with HIV infection are susceptible to JC virus–induced progressive multifocal leukoencephalopathy (PML) as well as encephalitis due to HIV itself.6

**DIAGNOSIS**

**EPIDEMIOLOGIC CLUES**

Obtaining a detailed history from the patient or family members can be helpful in directing the search for the etiology of suspected viral encephalitis and may also reveal possible nonviral causes. Age and immune status affect the patient’s susceptibility to different viral agents. Epidemiologic clues such as season, location, travel, vocation, and avocation are useful in determining a patient’s potential exposure to insects, animals, or humans, which may serve as vectors or hosts of viral agents.4 Table 1 lists the most common viral causes of encephalitis with their associated epidemiologic characteristics.2,8,26–45

**PHYSICAL EXAMINATION FINDINGS**

A thorough physical examination should be done on all patients with encephalitis, as certain findings, such as lymphadenopathy, rash, or respiratory tract abnormalities, may suggest certain viruses. Specific neurologic findings may also be helpful, given the predilection of some viruses to infect particular parts of the brain. The viral etiologies with specific physical findings are presented in Table 2.4

**DIAGNOSTIC TESTS**

All patients with suspected encephalitis should receive magnetic resonance imaging (MRI) imaging of the brain and cerebrospinal fluid (CSF) analysis, if not contraindicated.4 Serum and CSF testing should be guided by epidemiologic clues. Other basic tests that should be done include complete blood cell count, comprehensive metabolic panel, coagulation studies, and chest radiography. Blood cultures may be helpful for uncovering a systemic infection causing encephalopathy and may steer the diagnosis away from infectious encephalitis.4 Serologic testing for the presence of antibodies is available for most of the viral causes of encephalitis. In some cases, a four-fold rise in titers from the acute to convalescent phase is required to make the diagnosis.4

Viral cultures and polymerase chain reaction (PCR) assay of specimens of skin lesions, serum, or respiratory samples may also be helpful. For example, PCR of respiratory specimens can be done for adenovirus and influenza.4,31,46 Finding an infectious agent outside of the CNS, however, does not necessarily mean it is the cause of a CNS process.4 Biopsies and cultures of skin lesions can also be helpful. If herpes B virus is suspected, a sample from a vesicular lesion at the bite site can be sent for culture of PCR testing.47 In rabies virus infection, a nuchal skin biopsy with appropriate staining has a sensitivity of 50% to 94% and a specificity approaching 100%.4

**NEUROIMAGING**

Neuroimaging in patients with suspected encephalitis is helpful for excluding nonviral diagnoses, as well as for detecting abnormalities that may be associated with specific viral infections. MRI of the brain is the most sensitive and specific test,48 but if it is contraindicated, computed tomography (CT) with and without contrast should be done, if possible.4 One example of a classic MRI finding in viral encephalitis is temporal lobe inflammation in HSV encephalitis. Patients typically have edema and hemorrhage in the temporal lobes and high-signal-intensity lesions on T2-weighted and fluid-attenuated
inversion recovery (FLAIR) images. Involvement of bilateral temporal lobes is almost pathognomonic for HSV-1 encephalitis, but it is a late development. Over 90% of patients with HSV-1 encephalitis will display some abnormality on their MRI. Other viruses may show a predilection for other areas of the brain. Flaviviruses and Eastern equine encephalitis virus may show a characteristic pattern of mixed intensity or hypodense lesions on T1-weighted images in the thalamus, basal ganglia,
Enterovirus 71 may cause hyperintense T2 and FLAIR lesions in the midbrain, pons, and medulla. VZV can cause large-vessel arteritis, multifocal hemorrhagic infarctions, and demyelinating lesions.50

**CSF ANALYSIS**

Unless contraindicated, lumbar puncture and CSF analysis should be completed. Viral encephalitis typically causes a mild mononuclear pleocytosis, but early in the course of illness, polymorphonuclear cell predominance can be seen. In WNV, tick-borne encephalitis virus, and sometimes in Eastern equine encephalitis virus, a neutrophilic pleocytosis may persist.51 Although biopsy-proven HSV encephalitis often shows hemorrhagic necrosis on pathologic examination, CSF red blood cell counts are not significantly higher in HSV encephalitis patients than non-HSV encephalitis patients.52,53 CSF protein level in viral encephalitis is usually mildly to moderately elevated. CSF glucose measurement is usually normal. Up to 10% of pa-

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**Table 1. Epidemiology of Selected Viral Causes of Encephalitis (Continued)**

<table>
<thead>
<tr>
<th>Epidemiologic Factor</th>
<th>Viral Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geographic Locales</strong></td>
<td></td>
</tr>
<tr>
<td>International</td>
<td></td>
</tr>
<tr>
<td>Southeast Asia, China, Pacific Rim</td>
<td>JEV, tick-borne encephalitis virus, Nipah virus, Powassan virus</td>
</tr>
<tr>
<td>New Guinea</td>
<td>Murray Valley encephalitis virus</td>
</tr>
<tr>
<td>Australia</td>
<td>Murray Valley encephalitis virus, JEV, Hendra virus</td>
</tr>
<tr>
<td>India, Nepal</td>
<td>Rabies virus, JEV, Nipah virus</td>
</tr>
<tr>
<td>Middle East</td>
<td>WNV</td>
</tr>
<tr>
<td>Russia</td>
<td>Tick-borne encephalitis virus</td>
</tr>
<tr>
<td>Europe</td>
<td>WNV, tick-borne encephalitis virus</td>
</tr>
<tr>
<td>Africa</td>
<td>Rabies virus, WNV</td>
</tr>
<tr>
<td>South America</td>
<td>Rabies virus, EEEV, WEEV, VEEV, SLEV</td>
</tr>
<tr>
<td>Central America</td>
<td>Rabies virus, EEEV, WEEV, VEEV, SLEV, WNV</td>
</tr>
<tr>
<td>Canada</td>
<td>Powassan virus, WNV</td>
</tr>
<tr>
<td>United States</td>
<td></td>
</tr>
<tr>
<td>New England states</td>
<td>Powassan virus</td>
</tr>
<tr>
<td>Florida</td>
<td>VEEV</td>
</tr>
<tr>
<td>Midwestern and Eastern states</td>
<td>La Crosse Virus, SLEV (periodic outbreaks), WNV</td>
</tr>
<tr>
<td>Southwestern states</td>
<td>VEEV</td>
</tr>
<tr>
<td>Western states</td>
<td>SLEV, WNV, WEEV</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; EEEV = eastern equine encephalitis virus; HSV = herpes simplex virus; JEV = Japanese encephalitis virus; LCMV = lymphocytic choriomeningitis virus; SLEV = St. Louis encephalitis virus; VEEV = Venezuelan equine encephalitis virus; VZV = varicella-zoster virus; WEEV = western equine encephalitis virus; WNV = West Nile virus.

* These animals are reservoirs or incidental hosts that do not directly transmit the virus to humans.
† Virus may be directly transmitted by animal contact.

Patients with viral encephalitis can have a completely normal CSF analysis.\textsuperscript{4} The viral PCR test for HSV should be done in all patients with suspected encephalitis,\textsuperscript{4} and it has a sensitivity of 96% to 98% and a specificity of 95% to 99% in adults.\textsuperscript{5,4} The PCR becomes positive early in the disease course and should remain positive during the first week of therapy. A false-negative HSV PCR can occur if hemoglobin or other inhibitors are present in the CSF.\textsuperscript{5,5} PCR studies for VZV and enteroviruses should also be considered, as these are also common causes of viral encephalitis.\textsuperscript{4} In immunocompromised patients, CSF PCR for CMV, HHV-6, and JC virus may be included in the initial evaluation as well.\textsuperscript{4} CSF PCR tests are also available for adenovirus, WNV, herpes B virus, EBV, HIV, measles, mumps, polio, rabies, and Venezuelan equine encephalitis virus.\textsuperscript{4}

In addition to qualitative PCR tests, quantitative PCR tests may be available for some viruses. In JC virus infection, a higher viral load in immunocompromised patients is associated with a worse outcome.\textsuperscript{56} In HIV patients with PML, CSF JC virus DNA levels have been shown to decrease over time in patients treated with highly active antiretroviral therapy (HAART). Thus, the quantitative PCR for JC virus may be useful as a marker of disease activity in HIV patients on HAART.\textsuperscript{56}

For WNV, the PCR test is less sensitive compared to CSF IgM measurement.\textsuperscript{57} Approximately 80% of patients with WNV neuroinvasive disease are positive for CSF IgM within a week of symptom onset.\textsuperscript{58}

### Table 2. Possible Etiologic Agents of Encephalitis Based on Clinical Findings

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Viral Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General findings</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>HIV, Epstein-Barr virus, cytomegalovirus, measles virus, rubella virus, West Nile virus</td>
</tr>
<tr>
<td>Parotitis</td>
<td>Mumps virus</td>
</tr>
<tr>
<td>Rash</td>
<td>Varicella zoster virus, B virus, human herpesvirus 6, West Nile virus, rubella virus, some enteroviruses, HIV</td>
</tr>
<tr>
<td><strong>Respiratory tract findings</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venezuelan equine encephalitis virus, Nipah virus, Hendra virus, influenza virus, adenovirus</td>
</tr>
<tr>
<td><strong>Retinitis</strong></td>
<td>Cytomegalovirus, West Nile virus</td>
</tr>
<tr>
<td><strong>Urinary symptoms</strong></td>
<td>St. Louis encephalitis virus (early)</td>
</tr>
<tr>
<td><strong>Neurologic findings</strong></td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>Varicella zoster virus (children), Epstein-Barr virus, mumps virus, St. Louis encephalitis virus</td>
</tr>
<tr>
<td>Cranial nerve abnormalities</td>
<td>Herpes simplex virus, Epstein-Barr virus</td>
</tr>
<tr>
<td>Dementia</td>
<td>HIV, measles virus (subacute sclerosing panencephalitis)</td>
</tr>
<tr>
<td>Parkinsonism (bradykinesia, masked facies, cogwheel rigidity, postural instability)</td>
<td>Japanese encephalitis virus, St. Louis encephalitis virus, West Nile virus, Nipah virus</td>
</tr>
<tr>
<td>Poliomyelitis-like flaccid paralysis</td>
<td>Japanese encephalitis virus, West Nile virus, tick-borne encephalitis virus, enteroviruses (enterovirus-71, coxsackieviruses), poliovirus</td>
</tr>
<tr>
<td>Rhombencephalitis</td>
<td>Herpes simplex virus, West Nile virus, enterovirus 71</td>
</tr>
</tbody>
</table>

NOTE: These findings may or may not be present at the time the patient presents with encephalitis.

Finding WNV IgM in the CSF usually indicates active CNS disease because IgM antibodies do not readily cross the blood-brain barrier. CSF IgM testing is also available for the La Crosse virus, Japanese encephalitis virus, Powassan virus, St. Louis encephalitis virus, tickborne encephalitis virus, VZV, rubella, Venezuelan equine encephalitis virus, and Western equine encephalitis virus.

Viral cultures of CSF generally are not recommended due to low yield. In one study of 22,394 samples, virus was recovered in only 5.7% of CSF cultures. However, bacterial and fungal cultures of the CSF should be done to evaluate for nonviral causes.

OTHER DIAGNOSTIC TESTS

Electroencephalogram (EEG) should also be performed on patients with encephalitis to evaluate for nonconvulsive seizures. EEG findings are nonspecific and cannot definitively identify encephalitis of viral etiology; nevertheless, the EEG is a sensitive test for cerebral dysfunction. The most common EEG finding in viral encephalitis is generalized slowing. In HSV-1 encephalitis, more than 80% of patients display a temporal focus with periodic lateralizing epileptiform discharges on EEG testing. Sharp and slow-wave complexes occurring at 2- to 3-second intervals are usually seen 2 days to 2 weeks after symptom onset. These findings can be seen in other types of viral encephalitis such as La Crosse and California encephalitis viruses; thus, these EEG results are not definitively diagnostic for HSV-1 encephalitis.

Although it is rarely done now, brain biopsy may be useful for patients with suspected encephalitis who continue to deteriorate despite treatment with empiric acyclovir. Tissue samples should be sent for viral PCR testing, immunofluorescence, electron microscopy, pathogen isolation, and histopathologic examination and staining. In encephalitis, damage to the parenchyma, reactive gliosis, and inflammatory cellular infiltration is seen on histopathology. In rabies encephalitis, some infected neural cells may have characteristic round or oval cytoplasmic inclusions called Negri bodies. They are usually eosinophilic, and they contain viral nucleocapsids. HSV encephalitis is associated with the presence of Cowdry type A inclusion bodies.

TREATMENT

All patients with suspected encephalitis should be hospitalized for monitoring. Empiric intravenous acyclovir at a dose of 10 mg/kg intravenously every 8 hours (in patients with normal renal function) in adults should be started while awaiting test results because of the relatively high prevalence of HSV-1 encephalitis, as well as the risk of morbidity and mortality if HSV-1 encephalitis is not treated promptly. Empiric treatment for acute bacterial meningitis and/or rickettsial or ehrlichial infection may also be necessary until diagnostic studies are performed. If ADEM is suspected, patients should be started on corticosteroids.

Most viral encephalitides have no specific treatment, and care is supportive. The clearest indication for treatment is for HSV-1 encephalitis. Patients should be given 14 to 21 days of acyclovir therapy for confirmed or highly suspected HSV-1 encephalitis. Mortality from HSV-1 encephalitis is high even with treatment, with a rate of 28% 18 months after treatment. Predictors of poor outcome include age greater than 30 years, Glasgow coma scale score less than 6, and duration of symptoms more than 4 days prior to starting therapy. Mortality can be decreased to 8% if acyclovir is started less than 4 days after onset of symptoms. Thus, all patients with suspected encephalitis should be started on acyclovir immediately while awaiting CSF HSV.
PCR results. For patients who do not respond as expected by the end of the treatment course, a repeat HSV PCR of the CSF may be sent. If the repeat test is still positive, treatment should be continued.\(^{54}\) Even after treatment, HSV encephalitis can relapse.\(^{68}\)

The evidence for antiviral treatment of other viral causes of encephalitis is not as strong.\(^{4}\) In some cases, attention is directed toward reducing the level of immunosuppression in the patient. For example, in patients with JC virus with HIV, HAART should be initiated.\(^{4}\)

There are 2 cases in which viral encephalitis may be prevented by post-exposure prophylaxis. First, any patient bitten or scratched by a macaque or other Old World primate known to carry B virus, a type of herpes virus endemic to certain primates, should have his or her wound decontaminated. The patient should then be given prophylactic antiviral therapy with valacyclovir.\(^{69}\) Second, any patient with suspected exposure to rabies should have his or her wound cleansed with soap and water followed by povidone-iodine. The patient should then receive human rabies immunoglobulin and a series of rabies vaccinations.\(^{70}\)

Patients with encephalitis may develop increased intracranial pressure. The role of corticosteroids in managing increased intracranial pressure is currently unclear.\(^{60,71,72}\) In severe cases of encephalitis that are refractory to medical management, surgical decompression may be indicated to relieve intracranial pressure and prevent impending uncal herniation.\(^{73}\)

**CONCLUSION**

The approach to the patient with suspected viral encephalitis is challenging. Diagnosis requires a detailed evaluation and the synthesis of epidemiologic and clinical clues with laboratory and radiographic data. Many times a definitive viral etiology will not be obtained. Nonetheless, thorough evaluation can help direct future public health measures, and prompt administration of empiric treatment can improve patient outcome in some cases.

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