HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Encephalitis

Chapter 142 | Part 5: Infectious Diseases | Part 5 – Infectious Diseases: Bacterial | DETAILED EDITION

KEY CLINICAL POINTS

1. HSV encephalitis is the most common cause of sporadic acute encephalitis in immunocompetent adults.
2. MRI findings in HSV encephalitis typically show asymmetric hyperintensity in the frontotemporal, cingulate, or insular regions.
3. CSF HSV PCR sensitivity is ~96% and specificity ~99% in the first week of illness.
4. Acyclovir is the treatment of choice for HSV encephalitis (10 mg/kg IV q8h for adults).
5. WNV is the most common cause of epidemic encephalitis in the US since 2002.
6. Naegleria fowleri causes primary amebic meningoencephalitis with near 100% mortality.
7. Rabies presents with hydrophobia, aerophobia, and autonomic hyperactivity.
8. Autoimmune encephalitis mimics viral encephalitis and is associated with specific antibodies (NMDA, LGI-1).
9. Supportive care includes ICP monitoring, seizure management, and fever suppression.
10. Brain biopsy is reserved for cases with progressive deterioration despite acyclovir and negative CSF PCR.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

• Harrison's defines encephalitis as: *Encephalitis is defined as an inflammation of the brain caused either by infection, usually with a virus, or from a primary autoimmune process.*

• This chapter focuses on infectious causes of encephalitis.

• Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis).

• In some cases, involvement of the spinal cord or nerve roots occurs (encephalomyelitis, encephalomyeloradiculitis).

• Encephalitis is typically an acute febrile illness.

• The patient with encephalitis commonly has an altered state of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma.

• Evidence of either focal or diffuse neurologic signs and symptoms is present.

• Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state.

• Focal or generalized seizures occur in many patients with encephalitis.

• Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis.

• The signs and symptoms reflect the sites of involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

• Even though neurotropic viruses typically cause injury in distinct regions of the central nervous system (CNS), variations in clinical presentations make it impossible to reliably establish the etiology of a specific case of encephalitis on clinical grounds alone.

2. EPIDEMIOLOGY

• In the United States, there are an estimated ~20,000 cases of encephalitis per year.

• The actual number of cases is likely to be significantly higher.

• Despite comprehensive diagnostic efforts, most cases of acute encephalitis with a suspected viral etiology remain of unknown cause.

• Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified.

• Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including Alphaviruses (e.g., eastern equine encephalitis [EEE] virus and chikungunya virus), Flaviviruses (e.g., West Nile virus [WNV], St. Louis encephalitis virus, Japanese encephalitis virus), and Bunyaviruses (e.g., California encephalitis virus serogroup, La Crosse virus, Jamestown Canyon virus).

• Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup.

• Since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States.

• WNV caused 28,684 confirmed cases of neuroinvasive disease (encephalitis, meningitis, or myelitis) in the years 1999–2022 with 2641 deaths.

• In 2023, there were 1599 reported cases of neuroinvasive disease (encephalitis, meningitis, acute flaccid paralysis).

• The majority of cases occur in August and September.

• It is important to recognize that WNV epidemics are unpredictable and that cases have occurred in every state in the continental United States.

• Since 2006, there have been increasing numbers of cases of the tick-borne Powassan virus primarily in the northeastern United States and Minnesota and Wisconsin.

• New causes of viral CNS infections are constantly appearing, as evidenced by multiple outbreaks of cases of encephalitis in Southeast Asia caused by Nipah virus, meningitis in Europe caused by Toscana virus, neurologic disorders associated with Zika virus, and neurologic disorders associated with major epidemics of chikungunya virus in Africa, India, and Southeast Asia.

• Dengue virus is common in >100 countries worldwide with cases on the rise in the Caribbean and Puerto Rico and rare cases reported in the United States in Florida and in southern Texas.

• Parechoviruses including human parechovirus 3 (HPeV3) have been reported as causes of fever, sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

3. ETIOLOGY & PATHOPHYSIOLOGY

• In the United States, there are an estimated ~20,000 cases of encephalitis per year, although the actual number of cases is likely to be significantly higher.

• Despite comprehensive diagnostic efforts, most cases of acute encephalitis with a suspected viral etiology remain of unknown cause.

• Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified.

• The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], and Epstein-Barr virus [EBV]).

• Epidemics of encephalitis are caused by arboviruses (Chap. 215), which belong to several different viral taxonomic groups including Alphaviruses (e.g., eastern equine encephalitis [EEE] virus and chikungunya virus), Flaviviruses (e.g., West Nile virus [WNV], St. Louis encephalitis virus, Japanese encephalitis virus), and Bunyaviruses (e.g., California encephalitis virus serogroup, La Crosse virus, Jamestown Canyon virus).

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• Parechoviruses including human parechovirus 3 (HPeV3) have been reported as causes of fever, sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

• Infection caused by the ameba Naegleria fowleri can also cause acute meningoencephalitis (primary amebic meningoencephalitis).

• That caused by Acanthamoeba and Balamuthia more typically produces subacute or chronic granulomatous amebic meningoencephalitis.

• Naegleria thrive in warm, iron-rich pools of water, including those found in drains, canals, and both natural and human-made outdoor pools.

• Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water.

• There have been an increasing number of cases of Balamuthia mandrillaris amebic encephalitis in children and immunocompetent adults, mimicking acute viral encephalitis.

• This organism has also been associated with encephalitis in recipients of transplanted organs from a donor with unrecognized infection.

• No effective treatment has been approved, and mortality approaches 100%.

• Encephalitis can be caused by the raccoon pinworm Baylisascaris procyonis.

• Clues to the diagnosis include a history of raccoon exposure, especially of playing in or eating dirt potentially contaminated with raccoon feces.

• Most patients are children, and many have an associated eosinophilia.

• Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis.

• This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection.

• Infection by a variety of other organisms can mimic viral encephalitis.

• In studies of biopsy-proven HSV encephalitis, common infectious or mimics of focal viral encephalitis included mycobacteria, fungi, rickettsiae, Listeria, Mycoplasma, and other bacteria (including Bartonella sp.) as well as neurosyphilis.

• There are an increasing number of antibodies reported that cause autoimmune encephalitis and mimic those caused by viral infection, including those associated with antibodies against N-methyl-d-aspartate (NMDA) receptor, two components of the voltage-gated potassium channels/leucine-rich glioma inactivated protein-1 (LGI-1) and contracting-associated protein-like 2 (CASPR2), and antibodies against thyroglobulin and thyroperoxidase (Hashimoto's encephalopathy) and with prion diseases.

• Subacute or chronic forms of encephalitis may occur in association with autoantibodies against thyroglobulin and thyroperoxidase (Hashimoto's encephalopathy) and with prion diseases.

• Infection caused by the ameba Naegleria fowleri can also cause acute meningoencephalitis (primary amebic meningoencephalitis), whereas that caused by Acanthamoeba and Balamuthia more typically produces subacute or chronic granulomatous amebic meningoencephalitis.

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3.1 Viral Etiology

• The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], and Epstein-Barr virus [EBV]).

• Epidemics of encephalitis are caused by arboviruses (Chap. 215), which belong to several different viral taxonomic groups including Alphaviruses (e.g., eastern equine encephalitis [EEE] virus and chikungunya virus), Flaviviruses (e.g., West Nile virus [WNV], St. Louis encephalitis virus, Japanese encephalitis virus), and Bunyaviruses (e.g., California encephalitis virus serogroup, La Crosse virus, Jamestown Canyon virus).

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• Dengue virus is common in >100 countries worldwide with cases on the rise in the Caribbean and Puerto Rico and rare cases reported in the United States in Florida and in southern Texas.

• Parechoviruses including human parechovirus 3 (HPeV3) have been reported as causes of fever, sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

Table 1 TABLE 142-1 Viruses Causing Acute Encephalitis in North America

COMMON	LESS COMMON
Herpesviruses	Rabies
Cytomegalovirus	Eastern equine encephalitis virus
Herpes simplex virus 1	Powassan virus
Herpes simplex virus 2	Cytomegalovirus
Human herpesvirus 6	Colorado tick fever virus
Varicella-zoster virus	Mumps
Epstein-Barr virus	Jamestown Canyon virus
Arthropod-borne viruses	La Crosse virus
West Nile virus	
St. Louis encephalitis virus	
Zika	
Enteroviruses	

3.2 Non-Viral Etiology

• Infection caused by the ameba Naegleria fowleri can also cause acute meningoencephalitis (primary amebic meningoencephalitis).

• That caused by Acanthamoeba and Balamuthia more typically produces subacute or chronic granulomatous amebic meningoencephalitis.

• Naegleria thrive in warm, iron-rich pools of water, including those found in drains, canals, and both natural and human-made outdoor pools.

• Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water.

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• Clues to the diagnosis include a history of raccoon exposure, especially of playing in or eating dirt potentially contaminated with raccoon feces.

• Most patients are children, and many have an associated eosinophilia.

4. CLINICAL FEATURES

• Encephalitis is typically an acute febrile illness.

• The patient with encephalitis commonly has an altered state of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma.

• Evidence of either focal or diffuse neurologic signs and symptoms is present.

• Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state.

• Focal or generalized seizures occur in many patients with encephalitis.

• Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis.

• The signs and symptoms reflect the sites of involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

• Even though neurotropic viruses typically cause injury in distinct regions of the central nervous system (CNS), variations in clinical presentations make it impossible to reliably establish the etiology of a specific case of encephalitis on clinical grounds alone.

• Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms, or neuroimaging abnormalities may be infected by flaviviruses (WNV, St. Louis encephalitis virus, Japanese encephalitis virus), HSV, enterovirus A71 (EV-A71), rabies, Listeria monocytogenes.

• Significant involvement of deep gray matter structures, including the basal ganglia and thalamus, should also suggest possible flavivirus infection.

• These patients may present clinically with prominent movement disorders (tremor, myoclonus) or other parkinsonian features.

• Patients with WNV infection can also present with a poliomyelitis-like acute flaccid myelitis (AFM), as can patients infected with EV-A71, EV-D68, and less commonly, other enteroviruses.

• Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation.

• Patients often have multisegmental increased FLAIR and T2 signal in the anterior horns of the spinal cord and a CSF lymphocytic pleocytosis.

5. DIFFERENTIAL DIAGNOSIS

• Infection by a variety of other organisms can mimic viral encephalitis.

• In studies of biopsy-proven HSV encephalitis, common infectious or mimics of focal viral encephalitis included mycobacteria, fungi, rickettsiae, Listeria, Mycoplasma, and other bacteria (including Bartonella sp.) as well as neurosyphilis.

• There are an increasing number of antibodies reported that cause autoimmune encephalitis and mimic those caused by viral infection, including those associated with antibodies against N-methyl-d-aspartate (NMDA) receptor, two components of the voltage-gated potassium channels/leucine-rich glioma inactivated protein-1 (LGI-1) and contracting-associated protein-like 2 (CASPR2), and antibodies against thyroglobulin and thyroperoxidase (Hashimoto's encephalopathy) and with prion diseases.

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• Encephalitis can be caused by the raccoon pinworm Baylisascaris procyonis.

• Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis.

• This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection.

6. INVESTIGATIONS & DIAGNOSIS

• Patients with suspected encephalitis almost always undergo neuroimaging studies and often electroencephalogram (EEG).

• These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal and a diffuse encephalitic process.

• Specific focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis.

• Examples of focal findings found in HSV encephalitis include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, fluid-attenuated inversion recovery (FLAIR), or diffusion-weighted magnetic resonance imaging (MRI); (2) focal areas of low absorption, mass effect, and contrast enhancement in frontotemporal areas on computed tomography (CT); or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude (flattened) activity on EEG.

• Approximately 10% of patients with PCR-documented HSV encephalitis may have a normal MRI, although nearly 80% will have asymmetric abnormalities in the temporal lobe, and an additional 10% in extratemporal regions.

• The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity.

• Children with HSV encephalitis may have atypical patterns of MRI lesions and often show involvement of brain regions outside the frontotemporal areas.

• CT is less sensitive than MRI and is normal in up to 20–35% of patients.

• EEG abnormalities occur in >75% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific.

• Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped, sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2–3 s.

• The periodic complexes are typically noted between days 2 and 15 of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

• Significant MRI abnormalities are found in only approximately two-thirds of patients with WNV encephalitis, a frequency less than that found with HSV encephalitis.

• When present, abnormalities often involve deep brain structures, including the thalamus, basal ganglia, and brainstem, rather than the cortex, and may only be apparent on T2/FLAIR images.

• Similar MRI patterns can be observed in patients infected with other arboviruses, including other flaviviruses such as Japanese encephalitis virus and St. Louis encephalitis virus, as well the Alphavirus EEE virus.

• EEGs in patients with WNV encephalitis typically show generalized slowing that may be more anteriorly prominent rather than the temporally predominant pattern of sharp or periodic discharges more characteristic of HSV encephalitis.

• Patients with VZV encephalitis may show multifocal areas of hemorrhagic and ischemic infarction, reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis.

• Immunocompromised patients with CMV often have enlarged ventricles with areas of increased T2 signal on MRI outlining the ventricles and subependymal enhancement on T1-weighted postcontrast images.

• Prominent cerebellar T2/FLAIR abnormalities have been observed with Powassan virus encephalitis and in children with herpesviruses like EBV and VZV.

• CSF Examination: Cerebrospinal fluid (CSF) examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased intracranial pressure (ICP).

• Ideally, at least 20 mL of the initial CSF sample should be collected, with 5–10 mL stored frozen for later studies, including additional direct detection tests like virus-specific polymerase chain reaction (PCR) or metagenomic next-generation sequencing, since many neuroinvasive viruses are only transiently present in the CSF.

• The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration.

• A CSF pleocytosis (>5 cells/µL) occurs in >95% of immunocompetent patients with documented viral encephalitis.

• In rare cases, a pleocytosis may be absent on the initial lumbar puncture (LP) but present on subsequent LPs.

• Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response.

• CSF cell counts exceed 500/µL in only about 10% of patients with encephalitis.

• Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and lymphocytic choriomeningitis virus (LCMV) may occasionally result in cell counts >1000/µL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes.

• Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including cytomegalovirus (CMV), HSV, and enteroviruses.

• Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis.

• Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients.

• Large numbers of CSF polymorphonuclear leukocytes may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses.

• However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis.

• About 20% of patients with encephalitis will have a significant number of red blood cells (>500/µL) in the CSF in a nontraumatic tap.

• The pathologic correlate of this finding may be punctate microhemorrhages of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides.

• A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis.

• Rare patients with mumps, LCMV, VZV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

• CSF Polymerase Chain Reaction: CSF PCR has become the primary diagnostic test for CNS infections caused by HSV, CMV, EBV, HHV-6, and enteroviruses.

• In the case of VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis.

• The sensitivity (~96%) and specificity (~99%) of HSV CSF PCR are equivalent to or exceed those of brain biopsy.

• It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy.

• A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory abnormalities significantly reduces the likelihood of HSV encephalitis but does not exclude it.

• For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%.

• In both situations, a positive test makes the diagnosis almost certain (98–99%).

• There have been reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset and that became positive when repeated 1–3 days later.

• The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining positive after ≥14 days.

• PCR results are generally not affected by ≤1 week of antiviral therapy.

• In one study, 98% of CSF specimens remained PCR positive during the first week of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

• The sensitivity and specificity of CSF PCR tests for viruses other than HSV have not been definitively characterized.

• Enteroviral (EV) CSF RT-PCR appears to have a sensitivity and specificity of >95%.

• EV RT-PCR sensitivity for EV-A71 may be considerably lower (~30% in some reports).

• Patients with EV-D68-associated acute flaccid myelitis (AFM) only rarely have a positive CSF RT-PCR (<3%) but may have a positive test on nasopharyngeal swab specimens.

• Parechoviruses are also not detected by standard EV RT-PCRs.

• The specificity of EBV CSF PCR for diagnosis of CNS infection is unknown.

• Positive tests may occur in patients with a CSF pleocytosis due to other causes.

• Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis.

• Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

• In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary because patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs.

• In the case of WNV infection, CSF PCR appears to be less sensitive than detection of WNV-specific CSF IgM, although PCR of testing remains useful in immunocompromised patients who may not mount an effective anti-WNV antibody response.

• The recent pandemic due to SARS-CoV-2 (COVID-19) has been associated with cases of encephalopathy due to the indirect effects on the nervous system of multiorgan system failure and/or to a hyperinflammatory syndrome and disseminated intravascular coagulation, but also with rare cases of true encephalitis caused by viral CNS invasion.

• In both sets of patients, nasopharyngeal reverse transcriptase (RT)-PCR tests for SARS-CoV-2 are positive, but only cases with encephalitis have a positive CSF RT-PCR for SARS-CoV-2.

• Rare cases of neuroinvasion by SARS-CoV-2 has also been detected by RT-PCR of brain tissue.

• Unbiased metagenomic sequencing technologies capable of identifying infectious genomes in CSF, brain, and other tissues have recently shown great promise for rapid diagnosis of obscure cases of encephalitis and other brain infections, especially in immunocompromised patients.

• CSF Culture: CSF culture is generally of limited utility in the diagnosis of acute viral encephalitis.

• Culture may be insensitive (e.g., >95% of patients with HSV encephalitis have negative CSF cultures, as do virtually all patients with EBV-associated CNS disease) and often takes too long to significantly affect immediate therapy.

• Serologic Studies and Antigen Detection: For many arboviruses including WNV, serologic studies remain important diagnostic tools.

• Serum antibody determination is less useful for viruses with high seroprevalence rates in the general population such as HSV, VZV, CMV, and EBV.

• For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies.

• For viruses with high seroprevalence such as VZV and HSV, demonstration of synthesis of virus-specific antibodies in CSF, as shown by an increased IgG index or the presence of CSF IgM antibodies, may be useful and can provide presumptive evidence of CNS infection.

• Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a diagnosis, rather than in aiding acute diagnosis or management.

• In patients with HSV encephalitis, antibodies to HSV-1 glycoproteins and HSV glycoprotein antigens have been detected in the CSF.

• Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis.

• Nonetheless, HSV CSF antibody testing is of value in selected patients whose illness is >1 week in duration and who are CSF PCR negative for HSV.

• In the case of VZV infection, CSF IgM antibody tests may be positive when PCR fails to detect viral DNA, and both tests should be considered complementary rather than mutually exclusive.

• Demonstration of CSF WNV IgM antibodies is diagnostic of WNV encephalitis because the high molecular weight of IgM antibodies restricts their passage from serum to CSF through the blood-brain barrier and their presence in CSF is therefore indicative of intrathecal synthesis.

• Timing of antibody testing may be important because the rate of CSF WNV IgM seropositivity increases during the first week after illness onset, reaching 80% or higher on day 7 after symptom onset.

• Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule, and WNV serum IgM has been shown to persist in some patients for >1 year following acute infection.

• Detection of intrathecal synthesis (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of HSV-specific antibody may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative.

• Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.

• Negative CSF viral cultures are of no value in excluding the diagnosis of HSV or EBV encephalitis.

• VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.

• The specificity of EBV CSF PCR for diagnosis of CNS infection is unknown.

• Positive tests may occur in patients with a CSF pleocytosis due to other causes.

• Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis.

• Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

• In addition to broad-based PCR assays for bacterial and fungal infections, metagenomic next-generation sequencing (mNGS) allows for unbiased detection of nucleic acids from the whole range of infectious agents (except prions), which can then be confirmed by independent pathogen-specific techniques.

• Due to the sensitivity of this technology, there is a risk of false-positive results.

• As this technology becomes refined and the turnaround time faster, mNGS is likely to become a routine test on CSF for the diagnosis of encephalitis.

• Brain Biopsy: Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis and who have focal abnormalities on MRI, no serologic evidence of autoimmune disease, and continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy.

• A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis.

6.1 Diagnostic Test Utility

• The best test for WNV encephalitis is the CSF IgM antibody test.

• The prevalence of positive CSF IgM tests increases by about 10% per day after illness onset and reaches 70–80% by the end of the first week.

• Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).

• Approximately 80% of patients with proven HSV encephalitis have MRI abnormalities involving the temporal lobes.

• This percentage likely increases to >90% when FLAIR and diffusion-weighted MRI sequences are also used.

• The absence of temporal lobe lesions on MRI reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.

• The CSF HSV PCR test may be negative in the first 72 h of symptoms of HSV encephalitis.

• A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.

• Detection of intrathecal synthesis (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of HSV-specific antibody may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative.

• Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.

• Negative CSF viral cultures are of no value in excluding the diagnosis of HSV or EBV encephalitis.

• VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.

• The specificity of EBV CSF PCR for diagnosis of CNS infection is unknown.

• Positive tests may occur in patients with a CSF pleocytosis due to other causes.

• Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis.

• Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

• In addition to broad-based PCR assays for bacterial and fungal infections, metagenomic next-generation sequencing (mNGS) allows for unbiased detection of nucleic acids from the whole range of infectious agents (except prions), which can then be confirmed by independent pathogen-specific techniques.

• Due to the sensitivity of this technology, there is a risk of false-positive results.

• As this technology becomes refined and the turnaround time faster, mNGS is likely to become a routine test on CSF for the diagnosis of encephalitis.

Table 2 TABLE 142-2 Use of Diagnostic Tests in Encephalitis

Diagnostic Test/Feature	Clinical Utility/Key Finding
WNV CSF IgM antibody test	Best test for WNV encephalitis. Prevalence of positive tests increases by ~10% per day after illness onset, reaching 70–80% by end of first week.
Serum WNV IgM	Provides evidence for recent WNV infection, but in absence of other findings does not establish diagnosis of neuroinvasive disease.
MRI abnormalities (Temporal lobes)	Approximately 80% of patients with proven HSV encephalitis have MRI abnormalities involving temporal lobes. Increases to >90% when FLAIR and diffusion-weighted sequences used.
Absence of temporal lobe lesions on MRI	Reduces likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.
CSF HSV PCR	May be negative in first 72 h of symptoms. Repeat study should be considered in patients with initial early negative PCR in whom diagnostic suspicion remains high.
Intrathecal synthesis of HSV antibody	Useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative.
Serum serology for HSV	Of no value in diagnosis of HSV encephalitis due to high seroprevalence rate in general population.
CSF viral cultures	Negative CSF viral cultures are of no value in excluding the diagnosis of HSV or EBV encephalitis.
VZV CSF IgM antibodies	May be present in patients with negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.
EBV CSF PCR	Specificity for diagnosis of CNS infection is unknown. Positive tests may occur in patients with CSF pleocytosis due to other causes.
EBV CSF IgM or intrathecal synthesis of antibody to VCA	Supports the diagnosis of EBV encephalitis.
Serologic studies for EBV	IgM VCA, presence of antibodies against EA but not against EBNA can help support the diagnosis.
Metagenomic next-generation sequencing (mNGS)	Allows for unbiased detection of nucleic acids from whole range of infectious agents (except prions). Risk of false-positive results. Likely to become routine test on CSF.

6.2 Diagnostic Algorithm

• Step 1: Suspected Encephalitis → Perform CSF examination (cell count, protein, glucose) and Neuroimaging (MRI preferred).

• Step 2: If MRI shows focal temporal lobe abnormalities → Perform CSF HSV PCR.

• Step 3: If CSF HSV PCR is positive → Diagnosis of HSV Encephalitis established. Initiate Acyclovir.

• Step 4: If CSF HSV PCR is negative → Consider repeat PCR if suspicion remains high (e.g., early in illness).

• Step 5: If repeat PCR negative → Consider WNV IgM, other arbovirus serology, or mNGS.

• Step 6: If WNV IgM positive → Diagnosis of WNV Encephalitis established.

• Step 7: If all viral tests negative and clinical deterioration continues → Consider Brain Biopsy or Autoimmune Encephalitis workup.

7. MANAGEMENT & TREATMENT

• Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required.

• In the initial stages of encephalitis, many patients will require care in an intensive care unit.

• Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction, avoidance of hypotonic intravenous solutions, and suppression of fever.

• Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis.

• As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures, deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

• Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies.

• Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV.

• HSV, VZV, and EBV all show a decline in CSF pleocytosis and a reduction in CSF viral DNA copy number on quantitative PCR testing (where available).

• Acyclovir: Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for 21 days.

• Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

• Prior to intravenous administration, acyclovir should be diluted to a concentration ≤7 mg/mL.

• A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.

• Each dose should be infused slowly over 1 h, rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction.

• Care should be taken to avoid extravasation or intramuscular or subcutaneous administration.

• The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%).

• Dose adjustment is required in patients with impaired renal glomerular filtration.

• Complications of therapy include elevations in blood urea nitrogen and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%).

• Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase.

• To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals.

• It is now appreciated that some patients with worsening symptoms in the weeks following recovery from HSV encephalitis have developed NMDA receptor encephalitis requiring immunosuppression rather than having developed an acyclovir-resistant isolate.

• However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

• Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis as primary therapy.

• Additional oral valaciclovir following a 14- to 21-day course of intravenous acyclovir does not improve outcomes in adult patients with HSV encephalitis.

• The role of adjunctive intravenous glucocorticoids in treatment of HSV and VZV infection remains unclear.

• Experimental models and case reports of HSV encephalitis suggest that glucocorticoids may be efficacious, although no data from randomized controlled human trials are available.

• Ganciclovir and foscarnet, as combination therapy, are used in the treatment of CMV-related CNS infections.

• Cidofovir (see below) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

• Ganciclovir is a synthetic nucleoside analogue of 2′-deoxyguanosine.

• The drug is preferentially phosphorylated by virus-induced cellular kinases.

• Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination.

• Following intravenous administration, CSF concentrations of ganciclovir are 25–70% of coincident plasma levels.

• The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h.

• Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period.

• Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available).

• Doses should be adjusted in patients with renal insufficiency.

• Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy.

8. PROGNOSIS & COMPLICATIONS

• WNV caused 28,684 confirmed cases of neuroinvasive disease (encephalitis, meningitis, or myelitis) in the years 1999–2022 with 2641 deaths.

• In 2023, there were 1599 reported cases of neuroinvasive disease (encephalitis, meningitis, acute flaccid paralysis).

• No effective treatment has been approved for Naegleria fowleri infection, and mortality approaches 100%.

• Some patients with worsening symptoms in the weeks following recovery from HSV encephalitis have developed NMDA receptor encephalitis requiring immunosuppression rather than having developed an acyclovir-resistant isolate.

• However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

• Patients with WNV infection can also present with a poliomyelitis-like acute flaccid myelitis (AFM), as can patients infected with EV-A71, EV-D68, and less commonly, other enteroviruses.

• Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation.

• Patients often have multisegmental increased FLAIR and T2 signal in the anterior horns of the spinal cord and a CSF lymphocytic pleocytosis.

9. SPECIAL CONSIDERATIONS

• Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response.

• CSF cell counts exceed 500/µL in only about 10% of patients with encephalitis.

• Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and lymphocytic choriomeningitis virus (LCMV) may occasionally result in cell counts >1000/µL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes.

• Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including cytomegalovirus (CMV), HSV, and enteroviruses.

• Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis.

• Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients.

• Large numbers of CSF polymorphonuclear leukocytes may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses.

• However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis.

• About 20% of patients with encephalitis will have a significant number of red blood cells (>500/µL) in the CSF in a nontraumatic tap.

• The pathologic correlate of this finding may be punctate microhemorrhages of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides.

• A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis.

• Rare patients with mumps, LCMV, VZV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

• Dose adjustment is required in patients with impaired renal glomerular filtration.

• Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy.

9.1 Immunocompromised Hosts

• Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response.

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• Rare patients with mumps, LCMV, VZV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

• There have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

9.2 Renal Impairment

• Dose adjustment is required in patients with impaired renal glomerular filtration.

• Care should be taken to avoid extravasation or intramuscular or subcutaneous administration.

• The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%).

10. KEY PEARLS & CLINICAL TRAPS

• HSV encephalitis should be considered when clinical features suggest involvement of the inferomedial frontotemporal regions of the brain, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance.

• HSV encephalitis should always be suspected in patients with signs and symptoms consistent with acute encephalitis who have focal findings on clinical examination, neuroimaging studies, or EEG.

• The absence of temporal lobe lesions on MRI reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.

• The CSF HSV PCR test may be negative in the first 72 h of symptoms of HSV encephalitis.

• A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.

• Detection of intrathecal synthesis (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of HSV-specific antibody may be useful in diagnosis of HSV encephalitis in patients

in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative.

• Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.

• Negative CSF viral cultures are of no value in excluding the diagnosis of HSV or EBV encephalitis.

• VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.

• The specificity of EBV CSF PCR for diagnosis of CNS infection is unknown.

• Positive tests may occur in patients with a CSF pleocytosis due to other causes.

• Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis.

• Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

• In addition to broad-based PCR assays for bacterial and fungal infections, metagenomic next-generation sequencing (mNGS) allows for unbiased detection of nucleic acids from the whole range of infectious agents (except prions), which can then be confirmed by independent pathogen-specific techniques.

• Due to the sensitivity of this technology, there is a risk of false-positive results.

• As this technology becomes refined and the turnaround time faster, mNGS is likely to become a routine test on CSF for the diagnosis of encephalitis.

• The best test for WNV encephalitis is the CSF IgM antibody test.

• The prevalence of positive CSF IgM tests increases by about 10% per day after illness onset and reaches 70–80% by the end of the first week.

• Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).

• Approximately 80% of patients with proven HSV encephalitis have MRI abnormalities involving the temporal lobes.

• This percentage likely increases to >90% when FLAIR and diffusion-weighted MRI sequences are also used.

• The absence of temporal lobe lesions on MRI reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.

• The CSF HSV PCR test may be negative in the first 72 h of symptoms of HSV encephalitis.

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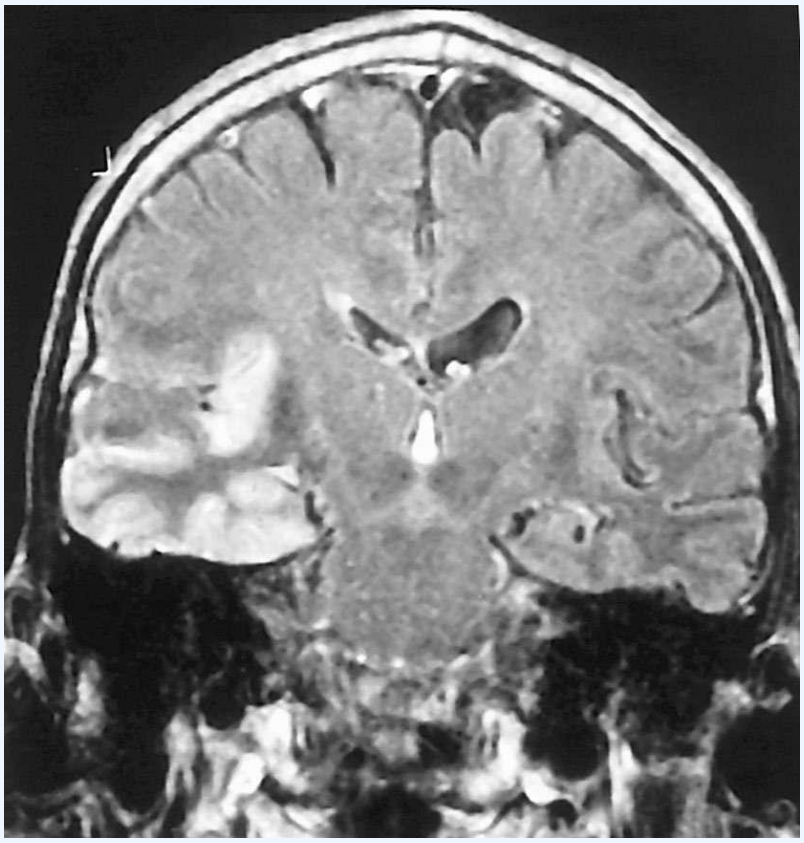
FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 142-1 Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity. — Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.