89 Encephalitis

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SHORT VIEW SUMMARY

Definition
- Encephalitis is an inflammatory process involving the brain parenchyma associated with clinical or laboratory evidence of neurologic dysfunction.

Epidemiology
- It occurs most frequently in infants younger than 1 year and in elderly patients older than 65, with intermediate incidence in individuals between these age extremes.

Etiology
- Up to 60% of encephalitis cases result from an unidentified etiologic agent.
- Viruses, bacteria, and autoimmune inflammation cause the majority of known encephalitis cases.

Diagnosis
- A compatible febrile syndrome with evidence of central nervous system impairment exists (see Table 89.1).
- Standard cerebral spinal fluid (CSF) analysis and neuroimaging with magnetic resonance imaging are preferred.
- Specific CSF and/or serum studies for defined etiologies of encephalitis are warranted (see Table 89.3).

Therapy
- Early empirical use of high-dose acyclovir is warranted to treat possible herpes simplex encephalitis pending diagnostic studies.
- Antiviral therapy is indicated for the treatment of other herpesviruses that cause encephalitis.
- Empirical antiviral therapy is recommended for suspected encephalitis associated with influenza.
- There is currently no therapy of known benefit for patients with encephalitis due to arthropod-borne viruses.

Prevention
- Routine vaccination for common pathogens and vaccination for Japanese encephalitis virus in selected travelers may prevent some cases of encephalitis.
- Procedures to decrease exposure to mosquito bites may decrease the risk for arthropod-borne virus–related cases of encephalitis.

Viral invasion of the central nervous system (CNS) can result in various clinical syndromes, including encephalitis, meningitis, myelitis, and neuritis.[1] *Encephalitis* is defined as an inflammatory process of the brain parenchyma associated with clinical or laboratory evidence of neurologic dysfunction. The infectious causes of encephalitis, predominantly viruses, are the focus of this chapter. Noninfectious forms of encephalitis may result from inflammatory processes associated with autoimmune, paraneoplastic, neoplastic, or collagen vascular diseases and are discussed only as they affect the differential diagnosis. Focal suppurative infections of the CNS including cerebritis, brain abscess, and empyema are discussed in Chapters 90 and 91.

Patients with suspected encephalitis often have prolonged hospitalizations, may require a multitude of expensive diagnostic tests, and frequently have poor outcomes including disability and death.[2] There were an estimated 263,352 encephalitis-associated hospitalizations in the United States from 1998 to 2010, with an overall mortality rate of approximately 6%.[3] Total medically related charges for encephalitis-associated hospitalizations were an estimated $2 billion per year in 2008–2010.[4] A diagnosis of encephalitis was most frequent in infants younger than 1 year (11.1 per 100,000) and elderly patients older than 65 years (13.2 per 100,000), with an intermediate incidence of 4.0 to 8.4 per 100,000 individuals between these age extremes.[4]

In patients with encephalitis, the success in finding a specific defined pathogen varies widely and is influenced by factors such as season of the year, geographic location, vector exposure, patient age, patient immune status, and case definition. In general, approximately half of the patients diagnosed with encephalitis have no defined etiology identified despite an extensive diagnostic workup.[1,2,4] Using the Nationwide Inpatient Sample for 1998 through 2010, one study found that 50% of hospitalizations due to encephalitis had no specified etiology.[3]

In a retrospective series reviewing etiologies of "neuroinfectious diseases" in hospitalized patients from an academic tertiary referral center, a specific pathogen was identified in 62.5% of patients who tested negative for human immunodeficiency virus (HIV) and 89% of HIV-positive patients.[2] The most common identified pathogens and conditions in HIV-negative patients were viruses (38%), bacteria (33%), Lyme disease (7%), fungi (7%), syphilis (5%), mycobacteria (5%), prions (3%), and *Pneumocystis jirovecii* (2%). Among HIV-positive patients, the common pathogens included viruses (46%), fungi (32%), and *Toxoplasma* (11%), with bacteria, tuberculosis, and syphilis accounting for the remaining infections (11%).[2] Among the 22 cases of viral encephalitis, the most commonly identified viruses in HIV-negative patients were varicella-zoster virus (VZV; 36%), herpes simplex virus (HSV; 32%), cytomegalovirus (CMV; 9%), West Nile virus (WNV; 9%), enteroviruses (9%), and hepatitis C virus (5%).[2] In HIV-positive patients, the viral etiologies included HIV encephalopathy (54%), JC virus–induced progressive multifocal leukoencephalopathy (PML; 31%), VZV (7.5%), and CMV (7.5%).

The California Encephalitis Project (CEP) searched for etiologies of encephalitis in immunocompetent hospitalized patients who met defined criteria for encephalitis, including altered consciousness for 24 hours or more and at least one of the following characteristics: fever, seizures, focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, or consistent electroencephalogram (EEG) or neuroimaging findings.[1,5] A confirmed or probable cause was found in only 16% of cases; these causes included viruses (69%), bacteria (20%), prions (7%), parasites (3%), and fungi (1%). The most commonly identified viruses included enteroviruses (25%), HSV-1 (24%), VZV (14%), WNV (11%), and Epstein-Barr virus (EBV) (10%), with other agents accounting for 16%.[5] In a prospective study in England, 42% of patients had encephalitis due to an infection; HSV(19%) and VZV(5%) were the most commonly identified infectious agents.[6] Acute immune-mediated encephalitis (21%) was a major cause of encephalitis, and unknown causes (37%) of encephalitis were still common.

CLINICAL SYNDROMES

Clinicians frequently encounter patients with fever and signs or symptoms of CNS disease in whom infectious encephalitis is part of a larger differential diagnosis. This clinical presentation is nonspecific with a broad differential diagnosis including diseases as diverse as viral

encephalitis; viral meningitis; bacterial meningitis; focal suppurative infections (brain abscess, subdural or epidural empyema, and cerebral venous sinus thrombophlebitis); acute disseminated encephalomyelitis (ADEM); autoimmune encephalitis; and encephalopathy. The challenge to the clinician is to differentiate among these clinical entities quickly and efficiently, because appropriate diagnosis and therapy can have an important effect on neurologic outcomes and mortality.

When evaluating a patient with possible encephalitis, it is important to distinguish among (1) infectious processes; (2) encephalopathy; and (3) autoimmune processes such as autoimmune encephalitis (Fig. 89.1).[7] *Encephalopathy* refers to diffuse cerebral dysfunction without associated inflammation of brain tissue.[8] Although there are multiple causes of encephalopathy, the most commonly encountered causes include toxins (e.g., alcohol, licit or illicit drugs) and metabolic dysfunction (e.g., hypoxia, hypoglycemia or hyperglycemia, electrolyte disorders, renal or hepatic failure).[8] Table 89.1 lists common factors that can be used to differentiate encephalitis from encephalopathy. Fever, headache, peripheral leukocytosis, and CSF pleocytosis all favor encephalitis. Although some encephalopathies may produce focal neurologic signs, these are more typical in encephalitis, as are focal seizures. Neuroimaging studies are generally normal in patients with encephalopathy, and EEG abnormalities are generally limited to diffuse slowing and the occasional appearance of triphasic waves. Conversely, patients with encephalitis frequently have neuroimaging abnormalities and may show focal EEG

TABLE 89.1 Comparison of Encephalitis and Encephalopathy

	ENCEPHALITIS	ENCEPHALOPATHY
Clinical Features		
Fever	Common	Uncommon
Headache	Common	Uncommon
Depressed mental status	May fluctuate	Steady decline in mental status
Focal neurologic signs	Common	Uncommon
Seizures	Common	Uncommon
Types of seizures	Generalized or focal	Generalized
Laboratory Results		
Complete blood count	Leukocytosis common	Leukocytosis uncommon
Cerebrospinal fluid	Pleocytosis common	Pleocytosis uncommon
Electroencephalogram	Diffuse slowing and occasional focal abnormalities or periodic patterns	Diffuse slowing
Magnetic resonance imaging	May have focal abnormalities	No focal abnormalities

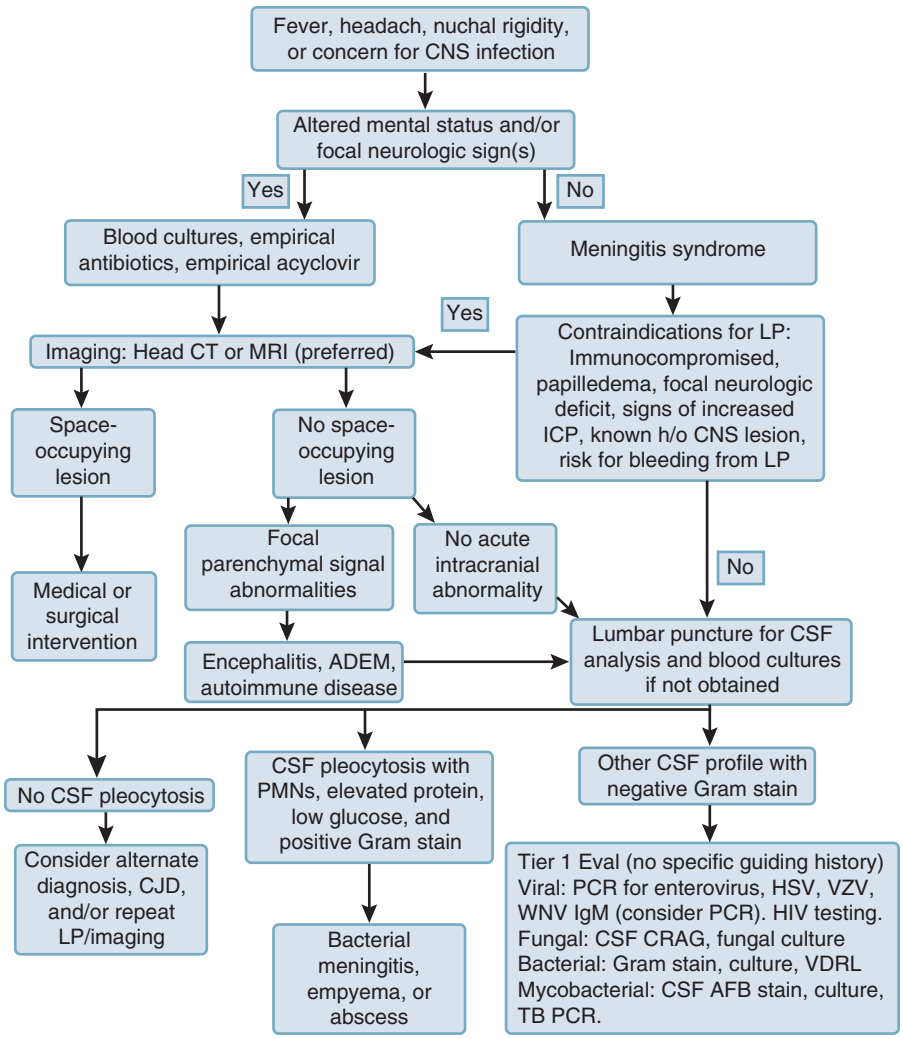

FIG. 89.1 Approach to the patient with possible central nervous system *(CNS)* infection. *ADEM,* Acute disseminated encephalomyelitis; *AFB,* acid-fast bacilli; *CJD,* Creutzfeldt-Jakob disease; *CSF,* cerebrospinal fluid; *CRAG,* cryptococcal antigen; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *ICP,* intracranial pressure; *IgM,* immunoglobulin M; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PMN,* polymorphonuclear leukocyte; *TB,* tuberculosis; *VDRL,* Venereal Disease Research Laboratory; *VZV,* varicella zoster virus; *WNV,* West Nile virus. Tier 1 evaluation described. See text for subsequent evaluation based on exposures.

abnormalities or specific patterns of dysfunction that are rarely seen in encephalopathy (see later).

AUTOIMMUNE ENCEPHALITIS

Antibody-mediated autoimmune encephalitis is an important cause of encephalitis and should be considered in the differential diagnosis of patients with encephalitis. In addition to traditional paraneoplastic autoimmune etiologies of encephalitis (e.g., anti-Ma, anti-Yo, anti-Hu), neuronal antigen targeting by antibodies in the CNS is increasingly identified as an important cause of encephalitis and was recently reviewed.[9] About 70% of patients develop prodromal symptoms including headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms. Within a few days to 2 weeks, patients can develop psychological symptoms including anxiety, insomnia, delusions, mania, or paranoia. Short-term memory loss is common but may be underrecognized owing to rapid disintegration of language and reduction in verbal output, which can progress to frank mutism. In more advanced stages of disease, patients develop decreased responsiveness, autonomic instability, dyskinesias, dystonia, rigidity, and opisthotonic postures.

In an analysis of patients younger than 30 years and enrolled in the CEP, anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis and viral encephalitis were noted to be equally important etiologies of encephalitis.[10] CSF in patients with anti–NMDA receptor encephalitis was characterized by a mild pleocytosis (median white blood cell count, 23 cells/mL) in the CSF with normal protein and glucose levels. The findings of neuroimaging with magnetic resonance imaging (MRI) were often abnormal but nonspecific, with no characteristic pattern or defining imaging results. When brain MRI findings were abnormal (50%), changes included T2 and fluid-attenuated inversion recovery (FLAIR) signal hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and rarely the spinal cord. EEGs in patients with anti-NMDA receptor encephalitis were often abnormal, most commonly due to diffuse or focal slowing patterns with occasional superimposed epileptic activity.

Autoimmune encephalitis is diagnosed by demonstrating the presence of specific antineuronal antibodies in the serum and/or the CSF in a patient with characteristic features of autoimmune encephalitis and negative findings on evaluation for infectious etiologies. Guidelines have been established to facilitate diagnosis of autoimmune limbic encephalitis in the absence of detectable autoantibodies.[9] Studies have also shown that viral causes of encephalitis such as HSV may be associated with production of autoreactive antibodies.[11] It is important to remember that the diagnoses of autoimmune encephalitis and viral encephalitis are not mutually exclusive; patients with HSV and other viral encephalitides may also have or develop autoantibodies and patients in whom autoantibodies are detected may also have an associated viral encephalitis. The list of autoantibodies associated with autoimmune encephalitis is rapidly expanding; the most commonly identified antibodies are those against the NMDA receptor; leucine-rich, glioma-inactivated 1 (LGI-1) protein; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR); and γ-aminobutyric acid B receptor ($GABA_BR1$). Although patients with autoimmune encephalitis generally have antibodies present in serum, in the case of anti-NMDA receptor encephalitis, CSF autoantibodies may be present in the absence of serum antibodies.

Treatment of autoimmune encephalitis is largely based on immunosuppressive regimens. Response to treatment for autoimmune encephalitis is variable, and relapse can occur in up to 24% of patients.[12] In female patients with NMDA receptor encephalitis, evaluation for an underlying ovarian teratoma and removal, if a tumor is found, is indicated. First-line immunotherapy consists of corticosteroids, intravenous immunoglobulins (IVIGs), or plasma exchange. In patients without a tumor, delayed diagnosis, or poor response to first-line therapy, second-line immunotherapy with rituximab, cyclophosphamide, or both is indicated. Despite the difficulty in treating these patients, the mortality rate is low, yet long-term neurologic outcomes are variable with potential for severe, fixed neurologic impairment.

It is also important to consider postinfectious encephalomyelitis or ADEM when evaluating patients with possible encephalitis. ADEM is an inflammatory demyelinating disease of the CNS that follows an infection or vaccination, typically after a delay of 1 to 4 weeks.[13] Most cases are monophasic and associated with MRI findings of diffuse or multifocal subcortical and central white matter lesions with increased signal on T2-weighted and FLAIR sequences.[14,15] A preceding infection or vaccination is found in about two-thirds of pediatric cases and half of adult cases.[14,16] Studies have stressed the importance of antecedent infections caused by influenza A and B, hepatitis viruses, nonspecific flu-like upper respiratory tract infections, and nonviral infectious agents including *Mycoplasma*.[16] Postvaccination cases of ADEM are rare with the vaccines in general use now.

GENERAL CLINICAL APPROACH

When an infection of the CNS is considered in the differential diagnosis, the evaluation should progress efficiently to rule out important reversible causes of disease (see Fig. 89.1). Diagnostic algorithms have been developed to help standardize the clinical approach to these complex patients.[8] In cases of bacterial meningitis and herpes simplex encephalitis (HSE), studies have shown that delay in therapy increases morbidity and mortality.[17–19] When evaluating a patient with possible encephalitis, the initial diagnostic goals are to obtain CSF for appropriate studies and to perform neuroimaging, preferably MRI, unless contraindicated. In patients who are older than 60; are immunocompromised; have a history of known CNS disease; or have recent seizures, altered consciousness, focal neurologic deficits, or other signs suggestive of increased intracranial pressure (ICP), neuroimaging should be completed before lumbar puncture.[18,20] In patients with suspected bacterial meningitis, empirical antibiotic therapy should be initiated after blood cultures are performed if lumbar puncture is delayed for neuroimaging (see Chapter 87).[18] Empirical acyclovir therapy should be initiated in patients with suspected encephalitis, pending results of diagnostic studies.[7]

MRI is more sensitive and provides more detailed diagnostic information than computed tomography (CT) in patients with suspected CNS infections, including encephalitis, and is the procedure of choice.[21,22] Neuroimaging studies can provide valuable clues that can assist in specific diagnosis of encephalitis. The most common abnormalities include areas of increased signal on T2 and FLAIR sequences. Diffusion-weighted imaging sequences may show abnormalities before, or that are more extensive than those seen in, T2 and FLAIR sequences.[21–26]

CSF examination is part of basic testing in all patients with suspected encephalitis or meningitis.[7,18] The most common CSF profile in patients with viral encephalitis is a lymphocytic pleocytosis with a normal glucose concentration and an elevated protein concentration. This pattern is similar to that seen in most cases of autoimmune encephalitis, ADEM, and several other causes of noninfectious encephalitis. The presence of neutrophils rather than lymphocytes as the predominant cell type occurs frequently in patients with WNV neuroinvasive disease or tick-borne encephalitis virus and can occur with eastern equine encephalitis and some enteroviruses (see specific virus sections for details).

Suggested CSF diagnostic studies in immunocompetent adults in the United States with suspected encephalitis include a CSF opening pressure, cell count and differential, protein and glucose concentrations, Gram stain, and bacterial cultures (see Fig. 89.1, tier 1 studies). Initial viral studies of the CSF should include polymerase chain reaction (PCR) studies for HSV, VZV, and enteroviruses, and WNV immunoglobulin M (IgM) serology (in the appropriate season). Routine testing should also include HIV testing, CSF Venereal Disease Research Laboratory (VDRL) test with serum treponemal assessment, and cryptococcal antigen testing. Additional diagnostic tests, or tier 2 tests, are guided by and prioritized according to the clinical and epidemiologic clues obtained during evaluation of the patient (Table 89.2). Diagnostic algorithms for patients with encephalitis have been proposed.[8]

In immunocompromised patients, CSF PCR for CMV, human herpesvirus type 6 (HHV-6), and in specific settings JC virus can be included in the initial evaluation depending on the underlying risk factors. A second tier of CSF diagnostic studies in immunocompetent patients might include PCR studies of the CSF for HIV, *Mycoplasma pneumoniae,* and *Mycobacterium tuberculosis*; IgM serologies for specific viruses such as WNV, Powassan virus, La Crosse virus (California encephalitis), St. Louis encephalitis virus, and eastern equine encephalitis virus, and Lyme disease (as geographically appropriate); acid-fast bacillus smear and culture; tuberculosis PCR; fungal cultures; *Coccidioides*

TABLE 89.2 Possible Etiologic Agents of Encephalitis Based on Epidemiology and Risk Factors

EPIDEMIOLOGY OR RISK FACTOR	POSSIBLE INFECTIOUS AGENTS
Travel	
Caribbean islands, Central America, South America	Rabies virus; eastern equine encephalitis virus; western equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Rocio virus; Zika virus; chikungunya virus; Dengue virus
Australia	Murray Valley encephalitis virus; Japanese encephalitis virus; Hendra virus
Southeast Asia, China	Japanese encephalitis virus; tick-borne encephalitis; Nipah virus; Me Tri virus; Semliki Forest virus
India, Nepal	Rabies virus; Japanese encephalitis virus; chikungunya virus
Africa	Rabies virus; WNV; Rift Valley fever virus
Middle East	WNV
Europe	WNV; tick-borne encephalitis; louping ill virus; Toscana virus
Russia	Tick-borne encephalitis; Powassan virus
Insect Contact	
Mosquitoes	WNV; Zika virus; Eastern equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Murray Valley encephalitis virus; Japanese encephalitis virus; California encephalitis group; chikungunya virus
Ticks	Tick-borne encephalitis; Powassan virus; louping ill virus
Animal Contact	
Old World monkeys	Herpesvirus B
Birds	WNV; eastern equine encephalitis virus; Venezuelan equine encephalitis virus; St. Louis encephalitis virus; Murray Valley encephalitis virus; Japanese encephalitis virus
Rodents	Eastern equine encephalitis virus (South America); Venezuelan equine encephalitis virus; tick-borne encephalitis; Powassan virus; La Crosse virus (chipmunks and squirrels); LCMV; monkeypox
Horses	Eastern equine encephalitis virus; western equine encephalitis virus; Venezuelan equine encephalitis virus; Hendra virus
Swine	Japanese encephalitis virus; Nipah virus
Dogs	Rabies virus
Bats	Rabies virus; Nipah virus
Raccoons	Rabies virus
Skunks	Rabies virus
Sheep and goats	Louping ill virus
Human Contact	
Person-to-person transmission	HSV (neonatal); VZV; Venezuelan equine encephalitis virus (rare); poliovirus; enteroviruses; measles virus; mumps virus; rubella virus; EBV; HHV-6; herpesvirus B; WNV (transfusion, transplantation, breast-feeding); HIV; rabies virus (transplantation); influenza virus
Season	
Late summer, early fall	All agents transmitted by mosquitoes and ticks (see above); enteroviruses
Winter	Influenza virus; LCMV
Recreational Activities	
Sexual contact	HIV; Zika virus
Swimming	Enteroviruses
Camping, hunting	All agents transmitted by mosquitoes and ticks (see above)
Spelunking	Rabies virus
Occupation	
Physicians and health care workers	VZV; HIV; influenza virus
Veterinarians	Rabies virus
Laboratory workers	WNV; HIV
Workers exposed to Old World primates	Herpesvirus B
Workers exposed to horses	Hendra virus
Ingestions	
Unpasteurized milk	Tick-borne encephalitis
Age	
Neonates	HSV-2; CMV; rubella virus; Zika virus
Infants and children	Eastern equine encephalitis virus; Murray Valley encephalitis virus (rapid in infants); influenza virus; La Crosse virus
Elderly	Eastern equine encephalitis virus; St. Louis encephalitis virus; WNV

Continued

TABLE 89.2 Possible Etiologic Agents of Encephalitis Based on Epidemiology and Risk Factors—cont'd

EPIDEMIOLOGY OR RISK FACTOR	POSSIBLE INFECTIOUS AGENTS
Other	
Unvaccinated	VZV; Japanese encephalitis virus; poliovirus; measles virus; mumps virus; rubella virus
Recent vaccination	ADEM
Transfusion and transplantation	CMV; EBV; WNV; HIV; tick-borne encephalitis virus; rabies virus; LCMV
Immunocompromised	VZV; CMV; HHV-6; WNV; HIV; JC virus
Agammaglobulinemia	Enteroviruses

ADEM, Acute disseminated encephalomyelitis; *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *LCMV,* lymphocytic choriomeningitis virus; *VZV,* varicella-zoster virus; *WNV,* West Nile virus.
Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

complement fixation titer; and antibody titer. Other studies to consider based on epidemiologic risk profiles include PCR studies of the CSF for *Rickettsia, Ehrlichia,* and *Anaplasma*; CSF *Histoplasma* antigen; and CSF enzyme-linked immunosorbent assay (ELISA) and Western blot for *Borrelia burgdorferi.* Such tests are appropriate in areas where these agents are endemic or with potential exposure history.

CSF studies should be supplemented with serum diagnostic studies. Common tests include HIV serology and plasma HIV RNA viral load; EBV serologies (IgG and IgM antibodies against viral capsid antigen and IgG antibodies against early and nuclear antigens); *Mycoplasma* serologies; syphilis serology; *Borrelia* serologies[a]; *Rickettsia, Ehrlichia,*[a] and *Anaplasma* serologies[a]; serum cryptococcal antigen[a]; serum antibodies against *Coccidioides*[a]; and urine *Histoplasma* antigen.[a]

An EEG can be helpful in evaluating the type and frequency of seizures and the presence of nonconvulsive status epilepticus. The degree and severity of slowing is a sensitive indicator of the presence and severity of metabolic encephalopathies. Specific EEG patterns may suggest an increased likelihood of specific diagnoses (see "Diagnostic Tests").

Clinical Manifestations

The clinical presentation of patients with viral encephalitis can be heterogeneous, necessitating a high index of suspicion in any patient with signs of infection and CNS dysfunction. The syndrome of acute viral encephalitis is characterized by fever, headache, and altered mental status.[7] These may be combined with focal neurologic deficits corresponding to areas of the CNS that are infected and injured, which vary with specific pathogens. This constellation of signs and symptoms is not unique for encephalitis and can occur in various other diseases, including viral and bacterial meningitis, brain abscess, cerebritis, subdural and epidural empyema, and septic cerebral venous or sinus thrombosis. The frequency of specific signs and symptoms varies among different types of encephalitis and is discussed more completely in the sections on individual viral pathogens.

The presence of specific sets of neurologic signs and symptoms by themselves does not allow unequivocal diagnosis of a specific cause of encephalitis. Findings of neurologic examination can increase the likelihood of some etiologic agents and reduce the likelihood of other pathogens, facilitating and guiding confirmatory diagnostic testing. The most common focal neurologic signs associated with encephalitis include hemiparesis, aphasia, ataxia, cranial nerve (CN) palsies, myoclonus, and seizures. Other important neurologic findings include loss of temperature and vasomotor control because of autonomic dysfunction and either diabetes insipidus or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) resulting from hypothalamic dysfunction.

Signs of parkinsonism (bradykinesia, rigidity, rest tremor) may suggest infection with a flavivirus (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus [JEV]), and frontotemporal signs such as aphasia, memory impairment, and personality changes may suggest limbic encephalitis from HSV, HHV-6 infection, a paraneoplastic etiology, or autoimmune limbic encephalitis. Seizures occur most frequently in encephalitides that involve the cortex (e.g., HSV encephalitis) and less commonly with flavivirus infections (e.g., WNV, St. Louis encephalitis virus, JEV) that involve predominantly deep gray matter structures such as the basal ganglia and thalamus. Brainstem involvement can occur with HSV, enterovirus 71 infections, and flaviviruses (e.g., WNV), whereas cerebellitis is associated with EBV, VZV, mumps, and flavivirus (e.g., WNV, St. Louis encephalitis virus) infections. Flaviviruses (e.g., WNV, JEV), enteroviruses D-68 and 71, and poliovirus can cause disease in the anterior horn of the spinal cord, resulting in a poliomyelitis and the clinical syndrome of acute flaccid paralysis.

The frequency of CN palsies varies greatly in patients with encephalitis. CN palsies are common in several nonviral infections that can mimic viral encephalitis (e.g., Lyme disease, syphilis, tuberculosis, fungal infections) and most commonly produce peripheral facial palsy (CN VII), vestibular or cochlear dysfunction (CN VIII), or paralysis of extraocular movements (CN III, IV, or VI). CN palsies are generally infrequent in viral encephalitis, unless there is concomitant brainstem involvement. However, WNV infection and VZV vasculopathy have been associated with palsies of various CNs (see specific sections).

The epidemiologic features of different neurotropic viruses vary widely and often help guide diagnostic testing (see Table 89.2). Immunocompromised patients are at increased risk for neuroinvasive viral infections resulting from VZV, CMV, HHV-6, JC virus (PML), and WNV. Similarly, older individuals have an increased risk of neuroinvasive disease after infection with many arboviruses (*ar*thropod-*b*orne *viruses*), including WNV, St. Louis encephalitis virus, and eastern equine encephalitis virus, and have an increased incidence of HSV encephalitis. Prenatal infection with subsequent pregnancy loss or devastating postnatal complications including microcephaly, intracranial calcifications, ventriculomegaly, and developmental abnormalities frequently occurs after infection with CMV and Zika virus (ZIKV).

Seasonal incidence is characteristic of all arbovirus infections in the United States. Most arboviruses are transmitted by a mosquito vector during summer and early fall months in patients living in areas of epizootic transmission of virus. By contrast, infection with some viruses, including lymphocytic choriomeningitis virus (LCMV) and influenza, are more frequent during late fall and winter months. Many arboviruses are geographically restricted, and residence or a recent travel history can provide important clues to potential exposures. WNV is now endemic throughout the United States and causes sporadic seasonal epidemics (www.cdc.gov/ncidod/dvbid/westnile/). Other arboviruses are also geographically restricted in the United States, and Powassan virus has emerged as an increasingly common cause of encephalitis (Fig. 89.2). A history of travel to specific foreign countries where other arboviruses are endemic should be specifically sought, and diagnostic studies should be adjusted appropriately.

The general physical examination also provides important clues that assist in the diagnosis of encephalitis. Skin rashes are common and characteristic for VZV, WNV, ZIKV, some enteroviruses, measles, and rubella and may occur with various nonviral infections, including Lyme

[a]Based on geographic setting and exposure history.

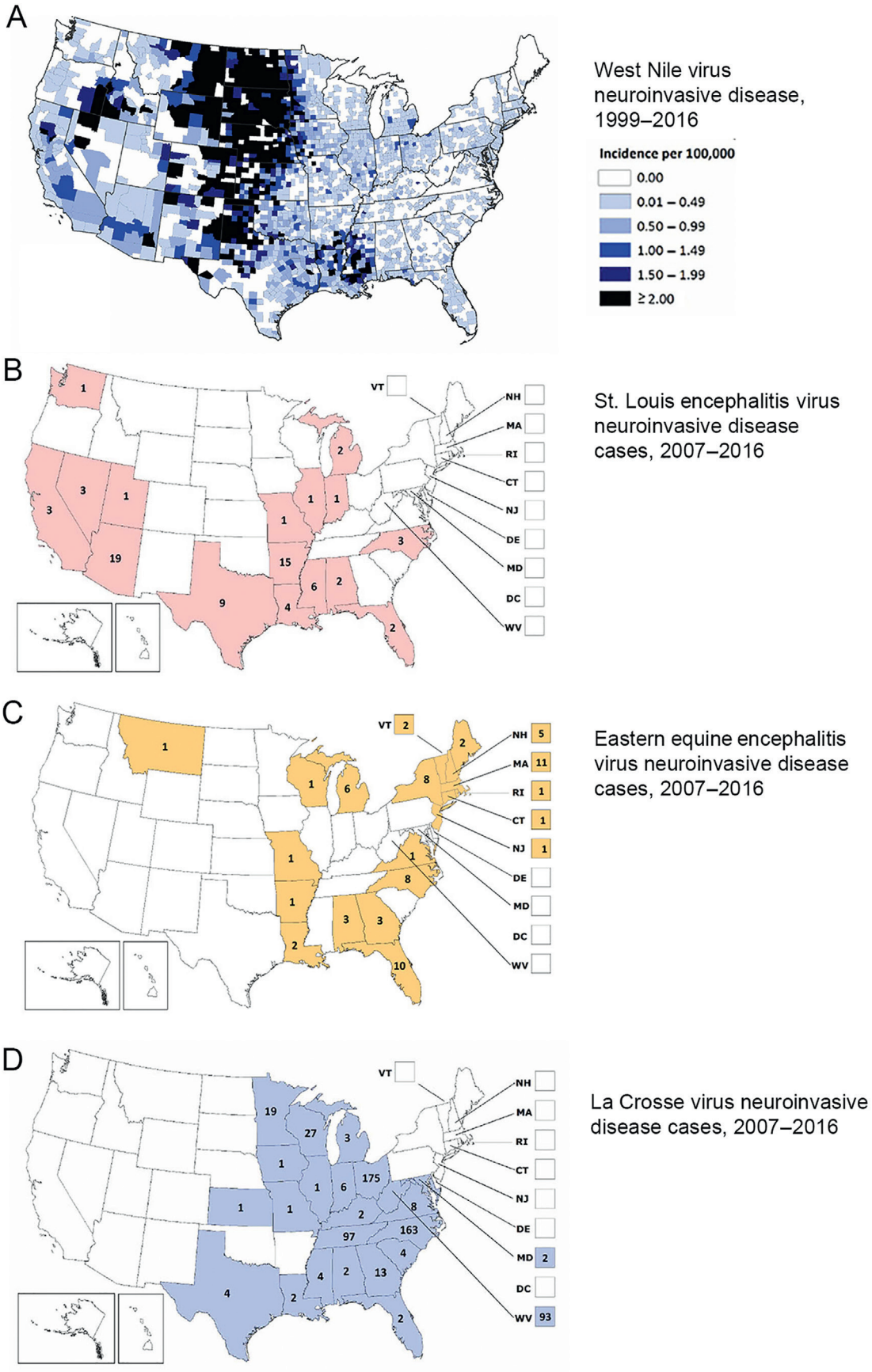

FIG. 89.2 **Incidence of select arboviruses in the United States.** (A) Annual incidence of West Nile virus neuroinvasive cases by county from 1999 to 2016. Number of neuroinvasive cases of (B) St. Louis encephalitis virus, (C) eastern equine encephalitis virus, and (D) La Cross virus reported to the Centers for Disease Control and Prevention from 2007 to 2016. *(Modified from Centers for Disease Control and Prevention.* www.cdc.gov/westnile, www.cdc.gov/sle, www.cdc.gov/easternequineencephalitis, www.cdc.gov/lac.*)*

disease, syphilis, mycoplasmosis, rickettsiosis, anaplasmosis, and ehrlichiosis. Oral mucosal ulcerations may suggest herpangina and an enterovirus. Ocular findings including chorioretinitis occur with WNV, CMV, and *Bartonella* infection (cat-scratch disease). Parotitis, orchitis, and oophoritis can occur with mumps and LCMV infections.

Diagnostic Tests

When a patient develops encephalitis, specific diagnosis is usually based on CSF studies. Diagnostic studies obtained from samples outside the CNS, including serum serologies, serum nucleic acid amplification tests, serum or urine antigen tests, and cultures of body fluids (blood, nasopharyngeal swab, sputum, and urine), may be useful in establishing the presence of a particular infectious process. Despite the presence of a systemic infection, additional testing may be required to establish a definitive cause of CNS disease. General diagnostic studies such as a complete blood count and markers of inflammation (e.g., erythrocyte sedimentation rate, C-reactive protein) may support the presence of an infectious or inflammatory process but do not help determine a specific etiology. Chest radiography may suggest an infectious cause, such as influenza, mycoplasmosis, tuberculosis, or coccidioidomycosis. It may also suggest the presence of cancer or other noninfectious causes of encephalitis.

Neuroimaging

Unless specifically contraindicated, all patients with suspected encephalitis should undergo MRI. The sensitivity and specificity of different patterns of neuroimaging abnormalities for the diagnosis of specific forms of encephalitis have not been formally defined. Different forms of encephalitis may produce distinctive MRI patterns that can provide clues suggestive of particular agents, which can guide more definitive confirmatory tests.

Temporal lobe and limbic abnormalities are seen in HSV, HHV-6, and autoimmune encephalitis, whereas subependymal enhancement occurs with CMV ventriculitis. MRI often reveals multifocal hemorrhagic infarctions and demyelinating lesions in cases of VZV vasculopathy.[27] Predominant demyelination on MRI studies suggests PML caused by JC virus infection, ADEM, or encephalitis mimics such as multiple sclerosis or other noninfectious CNS inflammatory diseases. PML lesions typically do not enhance or do so faintly at lesion margins, whereas MRI lesions associated with ADEM typically uniformly enhance acutely and become nonenhancing over time.

In HSV encephalitis, MRI is significantly more sensitive than CT, revealing temporal lobe abnormalities in 90% of PCR-proven HSV cases (Fig. 89.3).[28] In one study, 79% of patients with HSV encephalitis had abnormalities on their initial CT scan, but 100% of the 17 patients whose CT scan was initially normal and who had repeat scans had abnormalities an average of 5 days later.[28] MRI abnormalities of the temporal lobe were shown in 89% of patients with HSV; 36% also had frontal lobe involvement. Only 9% of adult patients with HSV encephalitis had MRI with abnormalities exclusively outside the frontotemporal area, although patterns in infants and children may be more variable. In 57% of HSV encephalitis patients, the abnormalities were predominantly unilateral.[17] Characteristic MRI changes occur early in the course of HSV encephalitis and include high–signal intensity lesions on T2-weighted and FLAIR images involving the medial and inferior temporal lobes with extension into the insula. MRI abnormalities can also include the orbitofrontal gyri and inferomedial frontal lobes.[29,30] Diffusion-weighted imaging abnormalities may antedate and be more extensive than abnormalities seen on T2 and FLAIR sequences.[21–26]

CT scans are almost invariably normal early in WNV infection. MRI abnormalities are less frequent in cases of WNV than in cases of HSV encephalitis. In two series involving 34 patients, initial MRI studies were normal in approximately one-third of patients. MRI abnormalities associated with WNV encephalitis included areas of increased T2 and FLAIR and low T1 signal that involved the basal ganglia, thalamus, and brainstem.[31,32] The MRI abnormalities in WNV infection are generally distinct from the abnormalities seen in HSV encephalitis, although in one series about 20% of patients with WNV encephalitis had abnormalities limited to the mesial temporal lobes.[32] Some patients with WNV infection have only meningeal enhancement or abnormalities seen only on diffusion-weighted images.

Patients with JEV and St. Louis encephalitis virus have MRI abnormalities similar to those reported for WNV. In one study, MRI was more sensitive than CT for JEV infections, showing abnormalities in more than 90% of adults and children.[33] The most commonly involved areas were the thalamus (88%), basal ganglia (41%–54%), and brainstem,[33,34] but some patients can have medial temporal lesions resembling those seen in HSV encephalitis.[35] Patients infected with enterovirus 71 may show increased T2 and FLAIR signal intensity in the midbrain, pons, and medulla. Congenital and neonatal ZIKV infection can result in a wide spectrum of abnormalities including microcephaly, intracranial calcifications, ventriculomegaly, and developmental abnormalities.

Cerebrospinal Fluid Analysis

Cerebrospinal Fluid Profile

CSF examination is an essential part of the diagnosis of encephalitis and should be performed in all patients unless absolutely contraindicated.[7] The most typical CSF profile in patients with viral encephalitis is a CSF pleocytosis with a predominance of lymphocytes, a normal glucose level, and an elevated protein level. In cases of flavivirus infection, particularly WNV, neutrophils may predominate,[36] a finding also associated with eastern equine encephalitis. In one large series, the median percentage of neutrophils in patients with WNV encephalitis was 45%, and 37% of cases had a neutrophil predominance.[36] By contrast, patients with HSV encephalitis typically have 5% to 24% neutrophils.[17,37]

The magnitude of CSF pleocytosis varies greatly in different forms of encephalitis. In the classic studies of biopsy-proven HSV encephalitis by the Collaborative Antiviral Study Group (CASG), patients had a median CSF white blood cell count of 130 cells/mm^3; 68% of patients had 50 to 500 cells/mm^3. Only 4% of patients had fewer than 5 cells/mm^3, and only 8% had more than 500 cells/mm^3.[38] Similar CSF profiles were noted in a study of HSV encephalitis confirmed with CSF PCR. In that study, no patient with HSV encephalitis had fewer than 5 cells/mm^3, and 69% of HSV encephalitis patients had 50 to 500 cells/mm^3.[28] Two later PCR-based studies reported that patients had a mean of 202 to 237 leukocytes/mm^3.[17,37] In a large series of cases with serologically proven WNV encephalitis, the mean CSF cell count was 227 cells/mm^3 (95% confidence interval [CI], 133–321).[36] Patients with mumps meningoencephalitis had higher mean cell counts compared with WNV patients, with a mean of 540 ± 460 cells/mm^3 and an average of 56% lymphocytes.[39]

Although pathologic evaluation of HSV encephalitis often shows the presence of hemorrhagic necrosis, CSF red blood cell counts do not differ significantly between patients with biopsy-proven HSV encephalitis and nonherpetic encephalitis.[38,40] Glucose concentrations are normal in more than 95% of patients with encephalitis caused by HSV and flaviviruses (WNV, St. Louis encephalitis virus) but may be low in some cases of CMV, mumps, and eastern equine encephalitis infection.[38,39,41,42]

Polymerase Chain Reaction and Antibody Studies

For some neuroinvasive viruses, PCR of the CSF has high sensitivity and specificity, making it the diagnostic study of choice for identifying a specific viral etiology.[43] HSV PCR of the CSF has a sensitivity of 98% and a specificity of 94%.[30,44] The sensitivity of PCR for detection of HSV encephalitis varies with the timing of the study. In the CEP, three patients with negative CSF HSV PCR test results performed within 72 hours of symptom onset had positive test results 4 to 7 days later.[45] By contrast, in a study using nested PCR to detect HSV DNA in CSF, 100% (18 of 18) of patients tested within 72 hours of onset of neurologic symptoms had amplifiable DNA.[46] CSF HSV PCR sensitivity declines as a function of duration of antiviral therapy; 98% of studies remain positive in patients treated for 7 days or less, followed by a decrease in sensitivity with ongoing treatment to 47% at 8 to 14 days and 21% after 15 days of antiviral treatment.[44] These results reflect the progressive decline in CSF viral load that occurs as a function of duration of acyclovir therapy. With use of quantitative PCR, acyclovir-treated patients had negative PCR results 19 ± 6 days (range, 9–28 days) after initiation of acyclovir

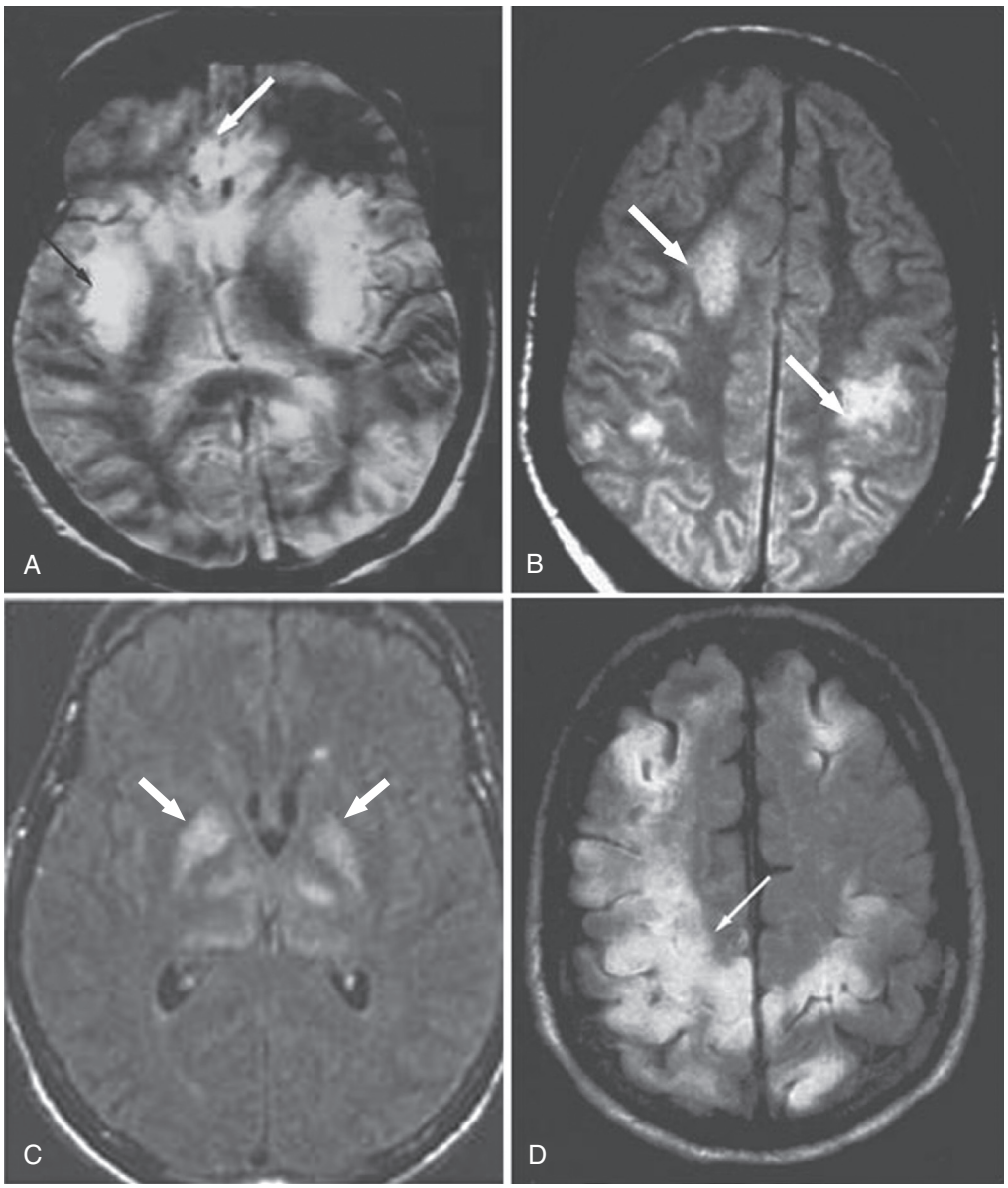

FIG. 89.3 Typical magnetic resonance imaging (MRI) changes associated with viral encephalitis. (A) Herpes simplex virus type 1 encephalitis with increased T2-weighted signal in bilateral temporal lobes. Increased signal does not extend beyond the insular cortex *(black arrow)* but does involve the cingulate gyrus *(white arrow).* (B), Varicella-zoster virus vasculopathy on proton-density MRI scan with multiple areas of infarction in both hemispheres *(arrows).* (C) West Nile virus encephalitis with increased signal on FLAIR MRI image of the basal ganglia *(arrows).* (D) Enterovirus encephalitis with increased signal intensity on FLAIR MRI image in both hemispheres, greater on the right, in the posterior cerebral hemisphere *(arrow). (Modified from Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system.* Nat Clin Pract Neurol. *2007;3:83; and Debiasi RL, Tyler KL. West Nile virus meningoencephalitis.* Nat Clin Pract Neurol. *2006;2:264.)*

therapy.[47] Neither the initial CSF HSV viral load nor its maximal level predicts outcome[47,48]; however, one study found that patients with extremely high copy number (>100,000 copies HSV DNA per milliliter) were more likely to have a reduced level of consciousness, CT scan lesions, and poor outcomes compared with patients with less than 100,000 DNA copies/mL.[49]

The results of HSV PCR should be interpreted in the context of the timing of the study and the pretest probability of disease. In patients with a high pretest probability of HSV encephalitis (e.g., 60%), a positive PCR result increases the posttest probability to 99%, and a negative study result reduces it to 6%. In patients with a moderate pretest probability of HSV (e.g., 35%), the posttest probability for a positive test result is 98%, and probability for a negative test result decreases to 2%. In patients with low pretest probability of HSV encephalitis (e.g., 5%), the posttest probabilities are 84% for a positive test result and 0.2% for a negative test result.[50]

HSV-specific CSF antibody testing to detect intrathecal synthesis of antibody can complement PCR testing when specimens are obtained later in the course of illness. After the first week of disease, the sensitivity of CSF HSV PCR declines (see earlier), whereas the sensitivity of CSF antibody testing increases. In one series of patients with HSV encephalitis, none of 36 CSF samples taken later than 30 days after onset of neurologic symptoms had amplifiable DNA, but all had detectable HSV antibody.[46]

PCR detection of VZV DNA in the CSF has a specificity of greater than 95%, but sensitivity can decrease after 2 to 3 weeks following presentation. In cases of VZV CNS vasculopathy, CSF should also be tested for intrathecal synthesis of VZV-specific antibody (CSF–to–serum IgG ratio) because these studies are complementary to PCR.[51]

PCR for EBV or HHV-6 DNA in the CSF can be a valuable addition to the evaluation of a patient with viral encephalitis.[52,53] However, the

results must be interpreted with caution and correlated with the clinical presentation, imaging, and serology results because latently infected, HHV-6– or EBV-positive mononuclear cells in the CSF can produce false-positive results.

CSF PCR is extremely specific (>95%) for diagnosis of PML in immunocompromised patients with appropriate clinical and radiographic findings. The sensitivity of CSF JC virus PCR is quite variable in different settings (50%–80%). For example, patients with PML associated with use of immunomodulatory drugs such as natalizumab frequently have a low JC virus CSF copy number and those with HIV-associated PML a higher copy number, with assay sensitivity paralleling copy number. Higher CSF JC viral loads correlate with worse outcomes in patients with HIV-associated PML.[54] A positive JC virus serum antibody finding is of limited diagnostic use because approximately 55% to 85% of individuals are seropositive in serum by adult life, although the absence of detectable anti–JC virus antibodies may decrease the likelihood of PML in the differential diagnosis unless a patient is severely immunocompromised and unable to mount an antibody response. In some studies, increasing titers of CSF or serum JC virus antibodies have immediately preceded the onset of PML.

In the case of flaviviruses including WNV, CSF PCR is less sensitive (57%–70%) compared with detection of CSF IgM antibodies for diagnosis of neuroinvasive disease.[55] An exception may occur in immunocompromised patients, such as bone marrow and solid organ transplant recipients, who have a prolonged, high-titer viremia, and can have positive serum or CSF PCR studies, or both, when antibody tests are negative or seroconversion is delayed.[56,57]

In a study of blood donors with asymptomatic WNV infection detected with positive results of serum nucleic acid amplification testing, peak serum RNA levels occurred at 5 to 6 days after an infected mosquito bite, IgM seroconversion occurred 3.9 days after RNA detection (95% CI, 3.4–4.4), and IgG seroconversion occurred at 7.7 days after RNA detection (95% CI, 6.9–8.5).[58] CSF IgM WNV antibodies are diagnostic of acute WNV infection and neuroinvasive disease; their presence is indicative of intrathecal synthesis because IgM molecules cross the blood-brain barrier poorly owing to their large size. CSF IgM antibodies are found in approximately 80% of patients with WNV neuroinvasive disease within 1 week of onset of symptoms, increasing at a rate of about 10% per day after symptom onset.[59] It is unclear how long CSF WNV IgM antibodies persist. In one small study, 60% of patients with WNV encephalitis had persisting CSF IgM antibody for as long as 500 days.[60]

Future diagnostic approaches. Recent advances in nested PCR testing using film-array technology now allow for multiplex testing of patient samples against a panel of pathogens. Clinical laboratories are increasingly using multiplex PCR testing for multiple clinical samples including respiratory samples, stool samples, and CSF samples. A multicenter study of a multiplex diagnostic CSF panel found that the assay exhibited high specificity for all tested pathogens but exhibited variable sensitivity for several that ranged from 0% to 100%.[61] Some variability in sensitivity was due to low numbers of pathogens in the study groups. Also, inclusion of targets such as HHV-6 that can produce positive test results in situations that are not likely due to HHV-associated disease may create problems with interpretation. The current commercially available CSF arrays are more applicable for pediatric populations, and further development of these arrays will likely provide new diagnostic approaches for cases of adult encephalitis. In addition to multiplexed assays, next-generation sequencing (NGS) assays of CSF samples are being evaluated and applied to clinical samples.[62] As the cost for sequencing technology continues to decrease and processes are simplified, future diagnostic approaches may include routine metagenomic NGS for unbiased detection of pathogens. To date this technology has proven to be most useful in immunocompromised patients rather than as a global diagnostic tool. It is important to recognize that the major advantage of this approach is its "unbiased" nature—meaning its ability to enable detection of a wide variety of pathogens. Conversely, NGS may be less sensitive than individually targeted PCR assays for specific pathogens and requires meticulous attention to technique to avoid contamination from reagents or other ambient sources.

Electroencephalography

EEGs in patients with viral encephalitis are frequently abnormal, but the results only rarely provide a clue to a specific etiologic diagnosis. The most common abnormality is the presence of generalized slowing.[63] Focal EEG abnormalities, most commonly involving the temporal lobes, are seen in 75% to 80% of patients with HSV encephalitis.[28,38] Common abnormalities include the presence of frontotemporal slowing, temporal sharp or spike activity, and periodic lateralizing epileptiform discharges at a rate of 2 to 3 Hz.[38] None of these patterns is diagnostic of HSV encephalitis. Periodic lateralizing epileptiform discharges, previously considered characteristic of HSV encephalitis, can also be seen in other types of encephalitis (e.g., La Crosse/California virus encephalitis).[64] Appearance and resolution of EEG abnormalities do not correlate well with clinical presentation or resolution of disease.[30,65]

EEG abnormalities have been reported in approximately 60% to 90% of patients with WNV encephalitis. The most common finding is the presence of diffuse irregular slow waves, although the presence of anteriorly predominant slowing may suggest the diagnosis.[66] Triphasic slow waves, generally considered more characteristic of metabolic encephalopathies, have also been reported in WNV encephalitis.[67]

Other Diagnostic Studies

In general, CSF culture is of limited value in cases of viral encephalitis and is not recommended for routine clinical application.[7] Occasionally, acute and convalescent serum studies suggest a viral etiology and may be required in rare cases when CSF evaluation is impossible. Additional studies, such as PCR assay of gastrointestinal samples for enteroviruses, have been used as supportive diagnostic tests for viral encephalitis.[63] Other supportive tests include PCR or antigen detection of respiratory secretions for adenoviruses, parainfluenza, or influenza viruses. Fluid from skin vesicles should be examined with PCR for evidence of enteroviruses, VZV, or HSV. Brain biopsy is rarely used today because of the availability and accuracy of PCR and antibody tests. Brain biopsy still serves a diagnostically useful function, however, in unexplained cases of encephalitis associated with progressive neurologic deterioration.[7]

Management

The clinical status of patients with encephalitis can deteriorate rapidly; patients should be closely monitored in an intensive care unit or equivalent setting. Viral encephalitis caused by arboviruses or herpesviruses does not require patient isolation for infection control. Respiratory or contact isolation should be considered in cases of encephalitis of unknown etiology or in patients with possible bacterial meningitis or a skin rash. Universal precautions should be applied to handling all body fluids, including CSF, blood, saliva, respiratory secretions, stool, and urine because their potential infectivity varies with the inciting pathogen.

Patients with encephalitis may develop increased ICP. Patients with potential signs of increased ICP, such as decreased level of consciousness, papilledema, or cerebral edema, often require continuous ICP monitoring. Clinical trials studying the role of corticosteroids in encephalitis patients have been inconclusive, and further studies are necessary; however, in cases of encephalitis with increased ICP, corticosteroids may be used to treat cerebral edema.[63,68,69] Additional measures to reduce increased ICP acutely include hyperventilation and administration of intravenous (IV) mannitol.

Patients with certain types of encephalitis are likely to be at increased risk of seizures, and seizures can contribute to transiently increased ICP. There is no proven clinical value for primary prophylactic anticonvulsant therapy in patients with encephalitis. Patients with seizures are generally treated urgently with lorazepam or diazepam followed by maintenance therapy with IV fosphenytoin. Patients may require continuous EEG monitoring because clinical observation in obtunded patients may not reliably detect seizures.

Patients with encephalitis can experience autonomic dysfunction resulting in hypotension or cardiac arrhythmias and should undergo close monitoring of blood pressure and electrocardiogram until clinically stable. If the airway is compromised because of alterations in

consciousness, intubation should be considered to protect the airway and prevent aspiration. If clinically indicated, empirical antimicrobial agents should be initiated in patients with suspected bacterial infection or bacterial meningitis.

Few randomized controlled trials have assessed the efficacy of antiviral treatments or immunomodulatory therapy in patients with viral encephalitis, other than acyclovir therapy in patients with HSV encephalitis. Current recommended treatments for viral encephalitis are largely based on case reports or small clinical case series. (See the Herpesviruses section later for more information on acyclovir therapy.)

VIRAL ETIOLOGY OF ENCEPHALITIS

General features of the basic biology, pathogenesis, clinical features, epidemiology, diagnosis, and treatment of particular agents are discussed in the individual chapters devoted to these agents and have been reviewed.[70] Brief summaries of relevant issues related to encephalitis are provided in the subsequent sections, and additional encephalitis viruses not discussed in the text are summarized in Table 89.3. Table 89.4 presents the Infectious Diseases Society of America (IDSA)–US Public Health Service (USPHS) grading system for ranking recommendations.

TABLE 89.3 Other Important and Emerging Causes of Viral Encephalitis

VIRAL ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
Adenovirus	Children and immunocompromised patients	Associated pneumonia	PCR or culture of brain biopsy specimen or CSF	Supportive
Chikungunya virus	Epidemic setting; India and Southeast Asia; mosquito vector	Febrile syndrome with rash and arthralgias	CSF and serum IgM and PCR	Supportive
Hendra virus	Australia; fruit bat reservoir; humans infected by secretions of bats	Fever, drowsiness, seizures, and coma associated with a flulike prodrome	Contact Special Pathogens Branch at CDC	Supportive
HIV	Worldwide epidemic; recent high-risk behavior	Fever, headache-associated acute retroviral syndrome; commonly associated with HIV dementia	HIV serology testing and HIV quantitative PCR of CSF; MRI may reveal T2 or FLAIR hyperintense lesions in periventricular regions and centrum semiovale	Combination antiretroviral therapy
Influenza	Fall and winter seasonal predilection; worldwide distribution; rare complication in children	Associated febrile syndrome, myalgias, respiratory prodrome; may be associated with bilateral thalamic necrosis	Viral culture, antigen detection, and PCR in respiratory secretions	Oseltamivir (III-C); poor outcomes
Japanese encephalitis	Mosquito vector, swine and bird reservoirs; most common cause of epidemic viral encephalitis throughout Southeast Asia and Australia	Seizures and parkinsonian features common; acute flaccid paralysis; case-fatality rate of 20%–30%	Serum IgM or acute/convalescent IgG; CSF IgM or antigen; MRI can show T2 and FLAIR hyperintense lesions at basal ganglia, thalami, and midbrain	Supportive; formalin-inactivated mouse brain–derived vaccine available for prevention
JC virus	Cell-mediated immunodeficiencies (AIDS) and immunomodulating therapy (e.g., natalizumab)	Cognitive dysfunction, limb weakness, gait disturbance, visual loss, focal neurologic findings	CSF PCR (sensitivity 50%–70% for PML); MRI shows ≥1 nonenhancing, confluent subcortical white matter hyperintensity on T2 and FLAIR sequences	Combination antiretroviral therapy in AIDS patients or reversal of immunosuppression
Louping ill virus	Tick-borne disease; found in Ireland, Scotland, and England; associated with livestock	Usually mild febrile illness with associated confusion and stupor in some; deaths are rare	Serum IgM ELISA or a fourfold increase in IgG antibody in paired acute and convalescent sera	Supportive
LCMV (see Chapter 167)	Rodent-borne virus infects humans with exposure to infected urine, feces, saliva, or blood; severe disease in immunocompromised patients	Fever, headache, leukopenia, and thrombocytopenia; encephalitis characterized by personality changes, increased ICP, paraplegia, and cranial nerve and sensory dysfunction	CSF and serum IgM ELISA	Supportive
Me Tri virus	Mosquito-borne; Southeast Asia; transmitted among livestock	Fever, rash, seizures, lethargy, and meningismus	CSF PCR and IgM ELISA, serology	Supportive
Monkeypox	Prairie dog exposure	Vesiculopustular rash on head, extremities, palms, and soles; adenopathy; encephalitis is rare, with confusion, somnolence, and diminished reflexes	Skin biopsy, CSF, and serum IgM, serology; MRI showing T2 and FLAIR hyperintense lesions of the pons, thalamus, and subparietal cortex	Supportive care; consider cidofovir or vaccinia immune globulin (III-C)
Mumps virus	Unvaccinated	Previous parotitis followed by headaches, vomiting, seizures, altered consciousness, and sensorineural hearing loss	Fourfold IgG increase in paired acute and convalescent sera, culture of saliva, CSF culture and PCR	Supportive
Murray Valley encephalitis virus	Mosquito vector; bird reservoir; Australia and New Guinea	Rapid onset in infants with case-fatality rate of 15%–30%	IgG antibody testing with fourfold increase in paired acute and convalescent sera	Supportive
Nipah virus	Exposure to infected pigs; pteropid bat reservoir; exposure to infected bats or bat roosting sites; close contact to infected humans; South Asia	Fever, headache, altered consciousness, dizziness, vomiting, myoclonus, dystonia, areflexia, hypotonia; pneumonitis	Fourfold IgG increase in paired acute and convalescent sera; CSF culture; MRI may show T2 focal hyperintensity of subcortical and deep white matter of cerebral hemispheres; contact Special Pathogens Branch at CDC	Supportive; ribavirin (III-C)

Continued

TABLE 89.3 Other Important and Emerging Causes of Viral Encephalitis—cont'd

VIRAL ETIOLOGY	EPIDEMIOLOGY	CLINICAL FEATURES	DIAGNOSIS	TREATMENT
Powassan virus	Tick vector; rodent reservoir; New England states, Canada, and Asia	Case-fatality rate of 10%–15% and focal neurologic findings in >50% of patients	Serum and CSF IgM; IgG antibody fourfold increase in acute and convalescent paired sera	Supportive
Rift Valley fever virus	Sub-Saharan Africa, Egypt, Saudi Arabia, Yemen; mosquito vector and livestock reservoir; humans infected via exposure to infected animal secretions	1% of infected humans develop encephalitis with headache, meningismus, and altered consciousness	ELISA antigen detection or culture from serum and PCR; contact Special Pathogens Branch at CDC	Supportive
Rocio virus	Cause of epidemic encephalitis in Brazil; mosquito vector	Fever, headache, confusion, motor impairment, and cerebellar syndrome; sequelae include ataxia, dysphagia, incontinence, and memory problems	Fourfold IgG increase in acute and convalescent sera	Supportive
Rubella virus	Unvaccinated adults	Rash followed by headache, dizziness, behavioral changes, and seizures	CSF IgM; fourfold IgG increase in paired acute and convalescent sera	Supportive
Snowshoe hare virus	Mosquito-borne; North America; children predominantly affected by encephalitis	Fever, headache, confusion, and lethargy; low mortality and rare long-term neurologic sequelae	CSF and serum IgM ELISA or fourfold increase in IgG acute and convalescent sera	Supportive
Tick-borne encephalitis virus	Tick vector; rodent reservoir; unpasteurized milk; Eastern Russia, central Europe, Far East	Acute encephalitis; acute flaccid paralysis	Serum IgM or fourfold increase in IgG antibody in paired acute and convalescent sera	Supportive
Toscana virus	Sandfly vector; infection during summer months in Mediterranean countries	Fever, headache, meningismus, and meningoencephalitis with coma, lethargy, hydrocephalus, and hepatosplenomegaly	CSF PCR; serum and CSF IgM; fourfold increase in IgG acute and convalescent sera	Supportive
Vaccinia	Most cases are postinfectious; rare event after vaccination	Abrupt encephalopathy with focal neurologic signs 2–30 days postvaccination	CSF PCR or IgM	Supportive; corticosteroids if postvaccination (III-C); consider cidofovir or vaccinia immune globulin
Zika virus	Mosquito-borne, epidemic febrile rash	Fever, rash, congenital infection	PCR of serum and ZIKV-specific IgM	Supportive

AIDS, Acquired immunodeficiency syndrome; *CDC,* Centers for Disease Control and Prevention; *CSF,* cerebrospinal fluid; *ELISA,* enzyme-linked immunosorbent assay; *FLAIR,* fluid-attenuated inversion recovery; *HIV,* human immunodeficiency virus; *ICP,* intracranial pressure; *LCMV,* lymphocytic choriomeningitis virus; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PML,* progressive multifocal leukoencephalopathy.
Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

TABLE 89.4 Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations

CATEGORY, GRADE	DEFINITION
Strength of Recommendation	
A	Good evidence to support recommendation for use
B	Moderate evidence to support recommendation for use
C	Poor evidence to support recommendation for use
Quality of Evidence	
I	Evidence from ≥1 randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-control analytical studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Modified from Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis. *2008;47:303–327.*

Herpesviruses

The Herpesviridae are ubiquitous viruses found in multiple animal species. Herpesviruses that cause neuroinvasive disease in humans include HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, and simian herpesvirus B.

Herpes Simplex Virus Types 1 and 2

Herpes Simplex Virus Pathogenesis

The exact mechanism by which HSV-1 and HSV-2 invade the CNS is unknown. Primary HSV-1 infection frequently causes gingivostomatitis, which is followed by axoplasmic transport of virus to the trigeminal sensory ganglion, where latency can be detected in virtually all seropositive individuals.[30,71] Trigeminal ganglion reactivation of HSV-1 usually results in retrograde axonal transport and the development of herpes labialis, but rarely reactivation may result in spread via the tentorial nerves to the anterior and medial cranial fossa.[72] It has been suggested, on the basis of animal inoculation studies, that the olfactory tract could also provide a potential route of neuroinvasion for HSV-1. In the case of primary infection, virus could invade the olfactory bulbs through the nose and spread via olfactory pathways to the orbitofrontal and medial temporal lobes.[30] At autopsy, approximately one-third of HSV-seropositive individuals with no known neurologic illness have PCR-amplifiable HSV DNA in the CNS, including the olfactory bulbs, hippocampus, and brainstem.[73] If this represents latent virus, which has not yet been convincingly established, reactivation from CNS sites could provide another mechanism for development of HSV encephalitis.

Cell death and tissue injury in HSV encephalitis likely result from direct viral killing of neurons and immune-mediated mechanisms of cell death. Several studies have shown that apoptosis plays a role in

neuronal cell death in human HSV encephalitis.[74,75] Studies in humans and mice have shown that the host's immune response may contribute to HSV-induced neuronal injury and death during encephalitis.[76–78] Genetic defects in TLR3-interferon and interferon responses have been shown to predispose to HSV encephalitis in several studies and may be particularly important in individuals with recurrent disease or in families with multiple cases of herpetic encephalitis.

HSV is the most common cause of sporadic encephalitis in the United States, with an incidence of hospitalization ranging from 1 to 1.2 per 100,000 population per year; it accounted for approximately 3300 hospitalizations per year from 1998 to 2010.[4] A recent multinational study in immunocompetent adults found that HSV-1 accounted for 92% of HSV encephalitis cases, with the remainder caused by HSV-2.[79] In patients with HSV in the CNS without evidence of encephalitis, largely meningitis cases, HSV-1 accounted for 45% of cases and HSV-2 accounted for the remainder. Although HSV encephalitis is the most commonly identified specific cause of viral encephalitis, it still accounts for only approximately 10% of all encephalitis cases.[30,80,81] HSV encephalitis has no seasonal or gender predilection. Cases occur in a bimodal age distribution with approximately one-third of individuals affected at younger than 20 years, and half of cases occur in individuals older than 50 years.[30]

Herpes Simplex Virus Encephalitis: Clinical Presentation

Patients with HSV encephalitis present with fever (90%–100%), altered consciousness (97%–100%), and headache (70%–81%).[17,38,82] Other common clinical features of HSV encephalitis include disorientation (70%–76%), seizures (40%–68%), behavior or personality change (41%–87%), memory disturbance (24%–45%), motor deficit (30%–40%), and speech disturbances (31%–59%).[17,28,38,40] A more recent multinational study of patients with HSV neuroinvasive disease found that fever (83%), change in consciousness (80.2%), headache (59.9%) and disorientation (58.3%) were the most common symptoms associated with encephalitis.[79] Mild or otherwise atypical presentations of HSV encephalitis have been reported in 14% to 17% of PCR-proven cases. These patients typically have mild alteration in level of consciousness and an absence of focal features at neurologic examination (although focal features may be present on EEG or neuroimaging studies).[28,83,84] A "normal" initial neurologic examination has been reported in less than 6% of patients.[17] In the original CASG trial comparing vidarabine and acyclovir, 29% of patients had a Glasgow Coma Scale (GCS) score of 6 or less, 41% had a GCS score of 7 to 10, and 30% had a GCS score of 10 or greater.[40] In later studies using CSF HSV PCR rather than brain biopsy for diagnosis, the level of consciousness of patients has been higher because of earlier detection. In the study by Domingues and associates,[28] 78% of patients had a GCS score of 12 or greater, including 28% with a GCS score of 15.

Herpes Simplex Virus Encephalitis: Diagnosis

PCR of HSV DNA in the CSF is the procedure of choice for diagnosis of HSV encephalitis[44,46] (see earlier for full discussion). Compared with brain biopsy, CSF HSV PCR has a sensitivity of 98% and a specificity of 94%, and more recent PCR tests for HSV exhibit sensitivity >95% and specificity >99%.[44,79] PCR results need to be evaluated in light of the timing of test performance. False-negative PCR results may also occur in bloody CSF specimens as a result of the presence of porphyrin compounds derived from degradation of heme in erythrocytes or during early stages of presentation, notably the first 48 hours after symptom onset.[46]

The results of diagnostic tests including CSF examination, neuroimaging, and EEG in HSV encephalitis were discussed in earlier sections. As noted, 96% to 100% of patients have a CSF pleocytosis (>5 white blood cells/mm^3) with a lymphocytic predominance. The protein is usually elevated (mean and median, 80–85 mg/dL), and the glucose level is normal in 95% of cases.[17,28,40] Initial CT scan can be abnormal in 40% to 79% of patients.[17] The most commonly observed abnormalities have been found to occur in the temporal (53%) or temporal and frontal lobes (36%).[17] MRI is more sensitive than CT and reveals abnormalities of the temporal lobes in 89% of cases confirmed with CSF HSV PCR (see Fig. 89.3A).[28] EEG patterns are not specific for HSV encephalitis, but as noted earlier, focal EEG abnormalities have been reported in 81% of biopsy-proven HSV encephalitis cases[38] and temporal lobe abnormalities occur in 75% of PCR-proven cases.[28] A more recent study found that MRI was abnormal in 84% of HSV encephalitis patients, and 91% of patients had an abnormal EEG.[79]

Herpes Simplex Virus Encephalitis: Treatment and Outcomes

The treatment and factors influencing prognosis for HSV encephalitis were discussed earlier. IV acyclovir (10 mg/kg every 8 hours) is the drug of choice for treatment of HSV encephalitis. The recommended duration of acyclovir therapy is 14 to 21 days according to the IDSA guidelines, and the mean duration of therapy in many studies is 21 days.[7] In the original CASG trial of adenine arabinoside for treatment of HSV encephalitis, the mortality in the 10 placebo-treated patients was 70%. Of the 3 survivors, 1 had minor, 1 had moderate, and 1 had severe sequelae.[85] A randomized placebo-controlled phase III clinical trial comparing long-term oral valacyclovir with placebo after completion of standard IV acyclovir treatment for HSE found no benefit to ongoing oral antiviral therapy for HSE.[86] Similarly, there is no proven benefit of adjunctive steroid therapy for treatment of HSV encephalitis, although uncontrolled studies and some experimental animal models suggest possible benefit.

Guidelines from IDSA advise that acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies (level III-A recommendation; see Table 89.4).[7] The goal of empirical treatment before diagnosis is to increase the likelihood of initiating treatment at an earlier stage in patients who ultimately prove to have HSV encephalitis. There is no proven benefit of acyclovir therapy in patients with non-HSV encephalitis (see discussion of specific herpesviruses for virus-specific details). The benefit of "empirical" use of acyclovir in patients with suspected encephalitis, rather than in patients with established HSV encephalitis, has not yet been established in a randomized controlled clinical trial.[40] Several studies have now shown that initiation of acyclovir within 2 days of hospitalization is associated with more favorable outcomes in patients with HSV encephalitis.[17,87,88] Multiple factors contribute to unfavorable outcomes, including advanced age, comorbid conditions, symptom duration before hospitalization, severely depressed consciousness, extent of brain involvement at MRI, and duration of hospitalization.[17,87–89]

A retrospective study found that only 29% of patients meeting specified criteria for suspected encephalitis (fever, neuropsychiatric abnormality, CSF pleocytosis, and negative Gram stain) received empirical acyclovir in the emergency department (median time to administration, 1.5 hours; 95% CI, 0–31.1 hours). The remaining 71% received acyclovir after inpatient admission (median time, 16 hours; 95% CI, 7.5–44 hours).[90] Five of 24 patients studied were eventually diagnosed with HSV encephalitis; only 2 of the 5 diagnosed with HSV encephalitis received acyclovir in the emergency department. In a large French study, a mean delay of 2 days ± 2.7 occurred between hospital admission and initiation of acyclovir therapy, and a mean of 5.5 days ± 2.9 lapsed between reported onset of symptoms and initiation of treatment.[17] These studies suggest that delays in administration of empirical antiviral therapy are common.

Several factors influence the prognosis of HSV encephalitis, including patient age, level of consciousness, immune suppression, and duration of clinical encephalitis before initiation of acyclovir therapy (measured by day of symptom onset or day of hospitalization). In the CASG trials of vidarabine versus acyclovir, age was stratified into patients younger than 30 years and patients 30 years of age or older.[40] Mortality was 6% (1 of 18) in acyclovir-treated patients younger than age 30 years but increased to 36% (5 of 14) in the older age group. It was subsequently reported that mortality in acyclovir-treated patients increased in a stepwise fashion from 11% (<2 years old) to 22% (22–59 years old) to 62% (≥60 years old).[91]

Similarly, level of consciousness at presentation, as evaluated according to GCS score, influenced mortality. In the original trial comparing vidarabine and acyclovir, mortality was 25% (2 of 8) in patients with a GCS score less than 6 compared with 17% (4 of 24) in patients with

a GCS score greater than 6.[40] It was subsequently noted that mortality was 0% in acyclovir-treated patients with a GCS score greater than 10 compared with 25% in patients with GCS score of 10 or less.[91] Patients with a GCS score of 7 to 10 and early institution of acyclovir therapy have improved outcomes compared with patients with lower GCS scores or late institution of acyclovir therapy.[91] In one large study, patients treated more than 2 days after hospital admission had a 3.1-fold (95% CI, 1.1–9.1) greater likelihood of a poor outcome compared with patients treated earlier.[17] In the vidarabine and acyclovir comparative study, the mortality rate in patients treated within 4 days of onset of fever, headache, and focal neurologic findings was 0% compared with a mortality of 35% in patients with symptoms of disease for more than 4 days.[40] Additional factors reported to influence prognosis include the Simplified Applied Physiology Score (SAPS II),[17] presence of lesions on an initial CT scan, and immunocompromised state.[92] Studies have indicated that the absolute value of the HSV PCR viral load in the CSF has no prognostic implications.[93,94] The role of management of increased ICP in HSV encephalitis has not been studied systematically, but use of aggressive medical and surgical therapy has been reported to be beneficial.[95]

HSV-2 Central Nervous System Disease

When evaluating patients with HSV neuroinvasive infections, the clinician must remember that HSV can also cause recurrent meningitis and myelitis. Although HSV-1 is the most common cause of sporadic, viral encephalitis, HSV-2 is the most common cause of recurrent, benign lymphocytic meningitis.[96] Patients with recurrent HSV-2 meningitis are more likely to be female (69%) and have a mean age of 38 years.[96,97] Patients present with acute onset of headache, fever, photophobia, and meningismus. Episodes last for a mean of 6 days, and patients have an average of four recurrences.[96,97] CSF is remarkable for lymphocytic pleocytosis (range, 86–1800), mildly elevated protein (range, 60–258), and normal glucose.[98] Diagnosis is made with HSV PCR of the CSF and is positive in 85% of patients with recurrent meningitis.[97] Neuroimaging is normal in the majority of patients (83%), although some patients develop nonspecific changes (14%) or meningeal changes (3%).[98] Of patients with CSF that was positive for HSV with PCR, 95% of cases are caused by HSV-2. Although recurrent HSV meningitis is a benign, self-limiting illness, acyclovir was used in the past for suppression of recurrences.[96] However, a double-blind, randomized trial demonstrated that suppressive therapy with valacyclovir was equivalent to placebo in suppressing HSV meningitis recurrences.[99] After 1 year of study drug exposure, patients were followed for an additional year off study drug, and patients exposed to valacyclovir had a significantly elevated risk (hazard ratio, 3.29) of recurrent HSV meningitis compared with the placebo group.

Herpes Simplex Virus Myelitis

HSV-1 and HSV-2 cause myelitis, but HSV-2 most commonly causes myelitis in adults. Most cases manifest as a monophasic illness (about 20% are recurrent) associated with acute onset of paralysis in the legs or less commonly the arms, reduced or absent reflexes, hyperreflexia with extensor-plantar responses, decreased sensation, and decreased anal tone or urinary incontinence with sacral dermatome involvement.[100–102] Severe forms of HSV myelitis include acute necrotizing myelopathy, which occurs in patients with underlying disease such as HIV, diabetes, or malignancy. CSF examination shows lymphocytic pleocytosis, elevated protein, and normal glucose concentration.[100,101] MRI typically exhibits intramedullary fusiform or spindle-shaped areas of increased T2-weighted signal.[100,101] Diagnosis is made with HSV PCR in the CSF, but measuring intrathecal synthesis of HSV-specific immunoglobulins may be helpful in the diagnosis of recurrent cases.[101] There are no controlled trials of antiviral therapy for HSV myelitis; however, there are anecdotal reports of success with IV acyclovir (10 mg/kg every 8 hours) for at least 14 days followed by oral antiviral drugs (valacyclovir, 1 g three times daily) until symptoms resolve. Despite therapy, the prognosis is extremely variable. In one small study of nine patients with HSV myelitis, one-third (three patients) made a complete recovery, whereas the remaining patients had residual sequelae including paraplegia and tetraplegia.[101]

Varicella-Zoster Virus

Varicella-Zoster Virus Pathogenesis and Central Nervous System Disease

Primary VZV infection (chickenpox) occurs mainly in children 1 to 9 years old, and seroprevalence by adult life is greater than 95%. After primary infection, the virus establishes latency in dorsal root ganglia. Reactivation results in herpes zoster (shingles). VZV CNS infection (encephalitis or vasculopathy) can occur during primary infection or after viral reactivation from latency.

During primary infection with VZV, acute cerebellar ataxia develops in 1 in 400 children younger than 15 years old.[103] It is unknown whether this clinical presentation is due to direct viral infection in the CNS[104] or represents a postinfectious immune-mediated state.[105] The clinical presentation is characterized by onset of gait ataxia, tremor, vomiting, and headache occurring 1 to 3 weeks after onset of chickenpox. CSF shows a lymphocytic pleocytosis with elevated protein. Imaging findings are often normal, and patients tend to have a full recovery. A study of VZV encephalitis cases found that a variety of VZV genotypes still cause neuroinvasive disease despite introduction of varicella vaccine, and vaccine genotypes are rarely associated with neuroinvasive infection in the CNS.[106]

VZV infection can cause myelitis associated with shingles or, more rarely, in the absence of rash ("zoster sine herpete"). In immunocompetent patients, myelitis is focal and typically manifests as weakness in myotomes corresponding to the dermatomes of the associated shingles outbreak (segmental zoster paresis). Immunocompetent and immunocompromised patients may develop more severe zoster myelitis.[107] In these cases, myelitis follows the rash by a median of 12 days, with maximal deficit being reached an additional 10.5 days later. The most common neurologic manifestations are weakness (75%), usually involving the leg ipsilateral to the rash, and less commonly paraparesis or paraplegia. Sensory abnormalities are common (approximately 50%) and can include dysesthesias, paresthesias, loss of pain-temperature or position-vibration sense or less commonly a sensory level to all modalities, or Brown-Séquard syndrome. Sphincter disturbances occur in approximately 25%. Some patients may have recurrent episodes of myelitis.[108] About 75% of patients have a lymphocytic CSF pleocytosis with elevated protein (approximately 70%) and normal glucose (approximately 95%) levels. MRI may show increased T2 signal lesions in the cord in association with cord swelling.[108] Diagnosis can be confirmed with demonstration of VZV DNA in CSF with PCR, or intrathecal anti-VZV antibody synthesis (increased CSF–to–serum IgG ratio).[108]

Varicella-Zoster Virus Vasculopathy

Modern studies suggest that most cases of VZV "encephalitis" are actually caused by VZV CNS vasculopathy, which most commonly involves large vessels (granulomatous arteritis) in immunocompetent patients and small vessels in immunocompromised patients.[108–113] However, a case series found that only 4 of 20 patients with VZV encephalitis developed a vasculopathy, and 14 of the 20 patients had nonvascular, nonspecific, or normal neuroimaging results.[114] In elderly immunocompetent patients, large vessel vasculopathy follows an episode of trigeminal herpes zoster by a few weeks to months with an average time to onset of 4 months, resulting in a mortality rate of 25%.[115] Most cases are monophasic, but relapses can occur. Patients develop myriad symptoms and acute focal deficits that vary with the location of the lesions. MRI findings are abnormal in 97%, with multifocal hyperintense lesions on T2-weighted FLAIR images (see Fig. 89.3B).[115] Lesions are typically located in the white matter or at the gray-white matter junction. Typical CSF findings include lymphocytic pleocytosis (67%), elevated protein level, and normal glucose level.

Small vessel VZV vasculopathy classically occurs in immunocompromised patients, resulting in a clinical syndrome of altered mental status changes, headache, focal deficits, and seizures.[115] The typical rash of herpes zoster is often absent. Neuroimaging shows evidence of multifocal infarcts, and CSF analysis reveals mild pleocytosis and a normal-to-mild elevation in CSF protein. In a retrospective study of VZV vasculopathy, 70% of patients had abnormalities at magnetic resonance angiography or traditional angiography.[115] Fifty percent had

evidence of small vessel and large vessel involvement. Angiography reveals focal narrowing or occlusion of involved vessels.

Diagnosis of VZV vasculopathy can be made by demonstration of intrathecal synthesis of VZV-specific antibody or by demonstration of VZV DNA in CSF with PCR.[115] Because VZV can cause a vasculopathy, some studies suggest that serum VZV PCR assay is sensitive and can help support a potential diagnosis of VZV CNS vasculopathy. At autopsy, involved vessels show focal inflammation with multinucleated giant cells, VZV antigen in endothelial cells, and Cowdry type A inclusion bodies in infiltrating histiocytes.[116]

Varicella-Zoster Virus Meningitis

VZV can produce an aseptic meningitis that can occur in the absence of rash. The frequency of VZV meningitis is uncertain; however, in one large series it accounted for 8% of cases. Patients typically have a lymphocytic pleocytosis in the CSF with elevated protein and normal glucose.[117] Neuroimaging findings are usually normal. Diagnosis can be made by showing VZV DNA in CSF with PCR. It has been reported that VZV viral loads are lower in patients with meningitis (mean, 4000 copies/mL) compared with patients with encephalitis (mean, 72,000 copies/mL).[118] It has been suggested that the severity of VZV CNS disease may correlate with CSF viral load. Patients with fewer than 10,000 VZV DNA copies/mL have a milder course compared with patients with higher viral loads.[118]

Varicella-Zoster Virus Central Nervous System Disease Treatment

No randomized controlled clinical trials are available to guide therapy for VZV CNS infection, but treatment with high-dose IV acyclovir (10–15 mg/kg every 8 hours for 10–14 days) has been recommended for severe disease.[7,111,112] Some experts also recommend a short course of adjunctive corticosteroid therapy (e.g., prednisone, 60–80 mg/day for 3–5 days).[109,111] In a noncontrolled retrospective review of VZV vasculopathies, 66% of patients who received acyclovir alone and 75% who received acyclovir and steroids improved or stabilized.[115] IDSA guidelines[7] indicate that acyclovir therapy is recommended (category III-B), that ganciclovir can be considered an alternative (category III-C), and that adjunctive corticosteroids can be considered (category III-B).

Cytomegalovirus

CMV is a ubiquitous human virus, with a 90% to 100% antibody seroprevalence in adults. It is transmitted through various routes, including body fluids such as saliva and genital secretions, blood transfusions, and organ transplants. CMV transmission typically occurs during childhood or early adulthood owing to common transmission via body fluid exposure. CMV causes acute infection and reactivation disease from latent virus. Primary infection with CMV is often clinically silent but may produce a mononucleosis-like syndrome. Neurologic complications from CMV infection in adults include retinitis, encephalitis, polyradiculomyelopathy, and neuropathy, all of which occur predominantly in immunocompromised hosts. CMV is also an important cause of congenital infections (see Chapter 137).

CMV encephalitis most commonly occurs in patients with a compromised immune system because of acquired immunodeficiency syndrome (AIDS) or organ transplantation; however, CMV neuroinvasive infections can infrequently occur in immunocompetent patients.[119] In patients with AIDS, CMV encephalitis occurs when the $CD4^+$ cell count is less than 50 cells/mm^3. Patients may develop a nonspecific febrile encephalopathy with or without focal signs. Some patients present with acutely altered mental status, and others present with a slowly progressive ventriculoencephalitis with CN palsies. Findings at MRI of the brain in AIDS patients with CMV encephalitis are variable, but hyperintense signal in the periventricular white matter is often seen on T2-weighted images and ependymal enhancement on contrast-enhanced T1-weighted images.[120] The CSF in patients with CMV encephalitis is nonspecific with mild lymphocytic pleocytosis and mild elevation in CSF protein level. In patients with CMV polyradiculopathy, the CSF profile is distinctive, with neutrophilic pleocytosis, low glucose, and elevated protein. Diagnosis is confirmed through amplification of CMV DNA from CSF by PCR. CMV PCR in the CSF of AIDS patients with CMV encephalitis has a reported sensitivity of 62% to 100% and specificity of 89% to 100%.[121]

Patients with HIV-associated CMV ventriculoencephalitis have a median survival of 42 days.[122] In a prospective study of 146 HIV patients with neurologic symptoms, the median survival was 50 days in patients with a positive CMV CSF PCR result compared with 205 days in patients with a negative CMV CSF PCR result ($P < .001$).[123]

Recommended initial treatment for CMV neuroinvasive disease includes the combination of ganciclovir (5 mg/kg IV every 12 hours) and foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours) (category III-B).[7] Initial therapy is generally maintained for 2 to 3 weeks and is often followed by lower-dose maintenance therapy. Efforts should be made to reduce the degree of host immunosuppression whenever possible.

Epstein-Barr Virus

Primary EBV infection can be asymptomatic or can result in a mononucleosis syndrome characterized by cervical lymphadenopathy, exudative pharyngitis, and splenomegaly. Significant CNS disease occurs in less than 1% of acute EBV infectious mononucleosis cases and can manifest with myriad CNS syndromes, including meningitis, encephalitis, transverse myelitis, and Guillain-Barré syndrome.[124] The frequency of EBV as a cause of encephalitis is unknown.

Patients with EBV encephalitis present with altered consciousness, seizures, and focal neurologic deficits. In a study of 21 children (<17 years old) with EBV CNS infection, only 1 patient had concomitant infectious mononucleosis.[124] Other patients had a nonspecific presentation with fever (81%), headache (66%), and seizures (48%). CSF shows a pleocytosis (mean, 58 cells/mm^3) with mildly elevated protein (mean, 48 mg/dL) and normal glucose levels. In one series, 60% of patients had a neutrophil predominance.[124] About 80% of patients have MRI abnormalities, which can take the form of increased signal on T2 and FLAIR sequences that most commonly involve the basal ganglia and thalamus, temporal lobes, and subcortical white matter. In some patients, lesions are consistent with the lesions seen in ADEM or acute hemorrhagic leukoencephalitis. EEG abnormalities occur in approximately 75% of patients, most commonly in the form of generalized slowing, although patients may also have focal slowing, frequent intermittent rhythmic delta-wave activity, or epileptiform discharges.

Diagnosis of EBV CNS disease includes serology testing including IgM and IgG antibodies to viral capsid antigens and antibodies against Epstein-Barr early antigen (EA) and Epstein-Barr nuclear antigen (EBNA), and CSF PCR testing. Diagnosis of neuroinvasive disease is typically made with EBV PCR of the CSF or demonstration of intrathecal antibody synthesis (CSF EBV viral capsid antigen IgM or elevated EBV viral capsid antigen IgG CSF-to-serum ratio). PCR testing in the CSF needs to be interpreted with caution because false-positive results due to presence of EBV DNA in CSF mononuclear cells resulting from other conditions may occur. A study of patients with EBV DNA in the CSF at PCR found evidence of EBV encephalitis in patients with stem cell transplantation, but positive EBV DNA in the CSF of other patients did not appear to be causally related and was often associated with another infection in the CNS.[125] EBV serology consistent with acute infection (e.g., EBV viral capsid antigen IgM in the absence of IgG, elevated IgG antibody titers against early antigen but not nuclear antigen) supports, but does not definitively establish, the presence of EBV CNS disease. A study of 28 patients with CNS EBV infection found that patients with encephalitis had a high EBV PCR copy number (4.2 $\log_{10}$ copies/mL) and high leukocyte counts (143 cells/mm^3) in the CSF.[52]

There are no controlled trials evaluating therapy in patients with EBV CNS infection; however, some case reports suggest that ganciclovir treatment improved outcomes in patients with EBV meningoencephalitis.[126] Steroids have shown benefit in uncontrolled trials in some patients, including patients with evidence of increased ICP (category III-C).[7] Mortality of EBV encephalitis is 10% or less. Prognosis for survivors is excellent; 90% return to normal function, and the remaining 10% have only mild residual deficits.[124]

Human Herpesvirus 6

HHV-6 is a ubiquitous viral infection of lymphocytes that causes a spectrum of disease on primary infection, including exanthem subitum (roseola) in infants, febrile seizures, and lymphadenopathy syndromes. Virus then becomes latent and can periodically reactivate to cause disease.

HHV-6 is increasingly recognized as a cause of encephalitis in immunocompromised adults,[127,128] particularly patients with allogeneic bone marrow transplants (hematopoietic stem cell transplants).[129,130] The predominant amount of data in hematopoietic stem cell transplant patients, which consists of small case series, case reports, and small cohort studies, supports a diagnosis of HHV-6 encephalitis in hematopoietic stem cell transplant patients with encephalitis, without other causes of neurologic disease, and CSF positive for HHV-6 with PCR assay.[131] In hematopoietic stem cell transplant patients, HHV-6 causes limbic encephalitis, characterized by short-term memory loss, insomnia, and seizures.[132] MRI exhibits characteristic increased hyperintense signal on T2 images of the medial temporal lobe.[133] Diagnosis is made through demonstration of HHV-6 DNA in the CSF. In a case-control study, HHV-6 PCR from the CSF of 22 bone-marrow transplant patients with neurologic symptoms was compared with 107 immunocompromised controls without neurologic symptoms.[134] Because HHV-6 is latent in lymphocytes, interpretation of PCR-positive samples in blood and in the CSF can be complicated by confounding detection of latent HHV-6 DNA in lymphocytes. Thus interpretation of PCR results should be placed in the context of the disease presentation and the degree of host immune suppression.

HHV-6 is most commonly associated with focal encephalitis in bone marrow transplant patients. Estimates of its frequency have ranged from 6.5% in specimens from the CASG HSV encephalitis treatment trials[135] to 0.4% (4 per 1000) in the CEP.[127] Patients typically have CSF lymphocytic pleocytosis, elevated protein level, and normal glucose level. MRI may be normal or may show temporal lobe abnormalities. Diagnosis is typically made with CSF PCR or serum serology. Sensitivity and specificity of these tests are unknown. It has been suggested that high CSF viral loads support the diagnosis.[127] The possibility that latent HHV-6 DNA in mononuclear cells may result in false-positive PCR test results may complicate diagnosis.

Treatment of HHV-6 encephalitis is similar to that of CMV CNS infections. In general, HHV-6 is not responsive to acyclovir therapy but is responsive to ganciclovir and foscarnet. Although HHV-6 is sensitive to cidofovir therapy, this drug is not recommended for treatment of HHV-6 CNS disease because of the high risk of adverse events and uncertainty about its degree of CNS penetration. There are no controlled clinical trials studying antiviral therapy for HHV-6 limbic encephalitis. Case studies have suggested that therapy with ganciclovir or foscarnet can be successful in bone marrow transplant recipients.[136,137] Other reports have found that antiviral treatments do not prevent death and do not reduce CSF HHV-6 DNA viral load.[138,139] IDSA guidelines recommend use of ganciclovir or foscarnet in immunocompromised patients (category III-B) and indicate that these agents can be considered in immunocompetent patients, although data on efficacy are lacking (category III-C).[7]

Herpesvirus B

Herpesvirus B infects Old World monkeys and is the only nonhuman herpesvirus that also infects humans, resulting in a high mortality.[140] Monkeys of the genus *Macaca* (macaques) are lifelong viral carriers and asymptomatically shed virus. Humans develop disease after a monkey bite or scratch or mucosal contact with infected body fluid. Vesicles develop at the site of exposure, followed by onset of a flulike syndrome characterized by fever, chills, myalgias, and headache.[140] When the virus invades the CNS, the patient develops diplopia, ataxia, hyperesthesias, agitation, and ascending paralysis.

Diagnosis is made through wound or contact site culture and demonstration of an antibody response with acute and convalescent sera.[140] Culture must occur in a Biosafety Level 4 facility, so local health authorities should be notified if herpesvirus B is suspected. Because mortality approaches 100% after CNS symptoms develop, treatment should be initiated at exposure rather than delayed until onset of symptomatic disease.

There are no controlled clinical trials studying regimens for post-exposure prophylaxis (PEP), treatment of symptomatic individuals who have not yet developed CNS symptoms, or treatment of patients with CNS disease. PEP refers to administration of antiviral drugs in individuals who have been potentially exposed to virus but who are not known to be infected. The regimen recommended for PEP in asymptomatic individuals is oral valacyclovir (1 g orally three times a day for 14 days).[141] In patients with symptomatic disease who do not have CNS signs or symptoms, either acyclovir (12.5–15 mg/kg every 8 hours) or IV ganciclovir (5 mg/kg every 12 hours) is recommended. In individuals with CNS symptoms, it has been suggested that ganciclovir treatment is preferable.[141] Therapy is generally continued for a minimum of 14 days and is extended if symptoms have not resolved or cultures remain positive. When IV therapy is discontinued, patients should be monitored for viral shedding (cultures of conjunctivae and oral mucosa) initially at weekly intervals and later less frequently (one to two times a year). Lifelong suppressive therapy with oral valacyclovir is usually recommended.[141]

Vector-Borne Viral Infections

Vector-borne viral infections are important causes of viral encephalitis in the United States as a result of the endemic establishment of WNV circulation. With the emergence of ZIKV in the Americas, close monitoring for continued emergence and spread of new neuroinvasive arthropod-borne viruses needs to be a priority. For example, the upper Midwest and Northeast of the United States have seen a significant increase in Powassan virus infections. Powassan virus is a member of the genus *Flavivirus* and related to WNV. This virus is spread by *Ixodes* ticks and causes disease similar to WNV (see later). The most common vectors that transmit encephalitic viruses in the United States are mosquito species[142] and tick species.[143] These arthropods and the viruses they transmit constitute a common group of viruses called *ar*thropod-*bo*rne viruses, or *arbo*viruses. Viruses included in this group belong to four families: Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae; each specific arbovirus within a family is commonly transmitted by a specific species of mosquito or tick.

Encephalitic Arbovirus Pathogenesis

Many encephalitic arboviruses maintain an enzootic (animal) cycle that does not involve human infection. However, some arboviruses, such as ZIKV, can establish an urban or epizootic cycle of transmission that involves humans as an amplifying host. After a bite from an infected mosquito, the virus replicates in dendritic cells and macrophages in local tissue and lymph nodes, resulting in a primary viremia that disseminates virus to end organs including the CNS. The ability of an arbovirus to invade the CNS (neuroinvasiveness) is determined by multiple viral and host factors.[144] Proposed routes of arboviral CNS entry include penetration of the cerebral microvasculature after infection of endothelial cells, diapedesis of infected leukocytes, penetration of fenestrated capillaries in structures such as the choroid plexus, and transneuronal spread of virus.

When the virus has penetrated the blood-brain barrier, arboviruses can directly infect and cause death of neurons. Several studies have shown that apoptosis is an important mechanism of WNV neuron cell death and CNS injury.[145–147] Immune responses also contribute to clearance of virus and immunopathologically mediated neuronal cell death.

West Nile Virus (Also See Chapter 153)

WNV is an arbovirus in the family Flaviviridae, genus *Flavivirus,* along with other important human viral pathogens including dengue virus, ZIKV, yellow fever virus, JEV, and many others. WNV infection is endemic in the United States and is the second most common cause of viral encephalitis in the United States after HSV (see Fig. 89.2A). Since its emergence in New York City in 1999 and through 2016, approximately 50,000 cases of WNV infection have been reported in the United States, including 18,810 cases (42%) of neuroinvasive disease and 1765 (4%) deaths (www.cdc.gov/ncidod/dvbid/westnile). The

epidemics of WNV in 2003 and 2012 were the largest outbreaks of neuroinvasive viral infections ever reported in the Western Hemisphere.[148]

West Nile Virus Pathogenesis

WNV is transmitted via a mosquito bite from an infected *Culex* mosquito. Transmission also can occur after organ transplantation of WNV-infected organs,[149] breastfeeding,[150,151] and blood transfusions.[152] Most (80%) infections are asymptomatic. Approximately 20% of infected individuals develop an acute febrile flulike illness (West Nile fever) characterized by fever, headache, fatigue, anorexia, nausea, myalgia, and lymphadenopathy. A maculopapular rash involving the trunk and limbs occurs in 25% to 50%.[153] Less than 1% of WNV-infected individuals develop neuroinvasive disease, including meningitis, encephalitis, and acute flaccid paralysis.[148,154–156] It has been estimated that 30% to 40% of patients with neuroinvasive WNV infection develop meningitis, 50% to 60% develop encephalitis, and 5% to 10% develop acute flaccid paralysis.[157,158] Other reported syndromes include rhabdomyolysis,[159] chorioretinitis,[160] myositis,[161] and autonomic nerve dysfunction.[162]

Neuroinvasive disease most commonly occurs in older individuals (>60 years old). In one study, the odds ratio of developing encephalitis was 2.2 (95% CI, 1.6–3.1) in individuals older than 64 years.[163] Additional identified risk factors for encephalitis include hypertension and diabetes.[154,163,164] Immunocompromised patients, including organ transplant recipients, are at high risk of developing severe WNV disease. Specific genetic factors in humans shown to enhance susceptibility to serious WNV disease include single nucleotide polymorphisms in the oligoadenylate synthetase gene, which encodes an interferon inducible enzyme involved in antiviral innate immunity,[165] and a genetic deficiency of the chemokine receptor CCR5, which may inhibit trafficking of WNV-specific $CD8^+$ T cells into the CNS.[166]

West Nile Virus: Infection Clinical Features

WNV meningitis is characterized by the abrupt onset of fever, headache, meningeal signs, photophobia, and phonophobia. Patients have lymphocytic CSF pleocytosis with an average of 226 cells/mm^3, mildly elevated protein, and normal glucose. Neutrophils, rather than lymphocytes, predominate in the CSF in approximately 50% of patients with WNV meningitis.[36] Neuroimaging studies are unremarkable, and the EEG is usually normal.

WNV encephalitis is distinguished from meningitis by the presence of signs and symptoms of brain parenchymal involvement or abnormalities at neuroimaging or on EEG indicative of brain parenchymal involvement. Patients with WNV encephalitis present with fever (70%–100%), headache (50%–100%), and altered mental status (45%–100%). Common signs unusual in other forms of viral encephalitis that may suggest the diagnosis of WNV or flavivirus infection include tremor, parkinsonism, and myoclonus (20%–40%).[156,157] Weakness is common and may be generalized or of a lower motor neuron type associated with hypotonia and areflexia with preserved sensation. Cranial neuropathies, most commonly involving unilateral or bilateral peripheral facial palsy, occur in approximately 20%.

The prevalence of tremors ranges from 12% to nearly 100% in different studies.[155] It is often coarse, typically involves the arms, and has postural and kinetic components.[167] Parkinsonian features also occur with variable frequency and include signs such as bradykinesia, hypomimia, and postural instability.[155,167] Myoclonus can resemble that seen in prion diseases and usually involves the upper extremities and face. Cerebellar abnormalities including incoordination and gait ataxia occur in a variable percentage of cases.[154,157,164,168]

Patients with WNV infection have a normal complete blood count or mild leukocytosis.[3] The CSF findings in patients with encephalitis are almost identical to the findings with meningitis, including pleocytosis (mean, 227 cells/mm^3), elevated protein level, and normal glucose level. There is a predominance of neutrophils rather than lymphocytes in 37% of cases.[36] MRI is abnormal in approximately 50% to 70% of WNV encephalitis cases, which is somewhat less frequent than in HSV encephalitis, and the frequency depends on the timing of the studies and the imaging sequences used. CT considerably less sensitive than MRI, and CT scans are usually normal. When present, MRI abnormalities typically involve the thalamus, basal ganglia, and brainstem. Less commonly, they involve the deep white matter (see Fig. 89.3C).

WNV can produce a poliomyelitis-like acute flaccid paralysis that results from viral injury to motor neurons in the anterior horns of the spinal cord. Patients typically develop acute onset of asymmetrical limb paralysis associated with decreased or absent reflexes and preserved sensation. Weakness may be associated with respiratory impairment from diaphragm or intercostal muscle paralysis. Electrophysiology studies obtained acutely show reduction in amplitude or absence of compound muscle action potentials with relatively preserved sensory nerve action potentials. Electromyographic studies obtained 2 to 3 weeks after onset show characteristic features of denervation, including increased insertional activity and fasciculations. In contrast to Guillain-Barré syndrome, there is no evidence of significant demyelination (slowed conduction velocities or conduction block). In most, but not all, cases of WNV, acute flaccid paralysis is associated with clinical signs and symptoms of systemic infection, and the syndrome may occur in association with meningitis or encephalitis. Patients typically have CSF features similar to the features seen in meningoencephalitis. MRI of the spinal cord may show increased signal in the anterior horns on T2 and FLAIR sequences.

West Nile Virus Infection: Diagnosis

WNV neuroinvasive disease is usually diagnosed through demonstration of WNV-specific IgM in CSF with ELISA.[169] In some patients, CSF WNV IgM may persist for 1 year or longer, and it may be necessary to perform serial studies of serum and CSF IgG and IgM to definitively distinguish acute from remote infection. CSF PCR for WNV is highly specific but less sensitive than serologic studies. CSF PCR may be particularly useful early in infection, however, before antibody responses have fully evolved, and in immunocompromised individuals who may have delayed or absent seroconversion.[169] Antibodies reacting with WNV antigens in ELISA tests may occur as a result of heterologous cross-reactions induced by infection with or vaccination against other flaviviruses, including St. Louis encephalitis virus, yellow fever virus, and JEV. In some cases, it may be necessary to confirm ELISA results with plaque reduction neutralization assays. Neutralization antibody titers are typically highest against the inciting virus compared with cross-reacting species.

West Nile Virus: Prevention and Treatment

There is no specific therapy of proven benefit for WNV infection. Thus prevention of mosquito bites remains the best strategy for WNV infection. This includes avoiding outdoor exposure during dawn and dusk time periods when *Culex* mosquito activity increases, wearing long sleeves and pants, and using *N,N*-diethyl-meta-toluamide (DEET)-containing insect repellent on exposed skin when outdoors. A study was able to show that a live-attenuated chimeric WNV vaccine (rWN/DEN4delta30) was immunogenic and well tolerated in a cohort of flavivirus-naïve adults aged 50 to 65 years.[170] Targeted development of a vaccine for older adults may be a cost-effective approach to deploy in regions of high endemic WNV circulation or during new epidemics. Isolated case reports and small series have revealed both benefit and lack of effect from treatment with IVIG-containing high-titer anti-WNV antibodies (Omr-IgG-am) and with interferon-α. A phase I/II trial to evaluate the safety and efficacy of a humanized monoclonal antibody (MGAWN1) directed against an epitope on the WNV envelope glycoprotein was closed owing to low enrollment (NCT00515385). Isolated reports of corticosteroid use in patients with WNV acute flaccid paralysis and brainstem disease do not permit any conclusions about efficacy.[171]

West Nile Virus: Infection Outcome

Mortality from WNV neuroinvasive disease is approximately 12% and occurs almost exclusively in the subsets of patients with severe encephalitis or severe acute flaccid paralysis. The frequency and severity of sequelae are still not well understood.[172] Six months after the acute infection, 40% of patients with movement disorders such as myoclonus, parkinsonism, or tremors have residual symptoms, and 20% have ongoing symptoms at 18 months of follow-up.[172] More recent studies have also suggested that 50% of WNV encephalitis survivors report cognitive

problems, decreased motor speed, and diminished dexterity 3 months after the initial infection.[172] Long-term follow-up of patients with WNV infection found that about 31% of participants experienced more than 6 months of fatigue symptoms after infection, with an average duration of 5 years.[173] However, it is not clear how different the infected cohort is from prospective, age-matched community control subjects.

St. Louis Encephalitis

St. Louis encephalitis virus has been an important cause of arbovirus encephalitis in the United States since the 1930s and was the most important neuroinvasive flavivirus in North America until the emergence of WNV.[3] St. Louis encephalitis virus is found in a broad range from Canada and the United States to Central and South America (see Fig. 89.2B). Transmission to humans in the western United States is primarily via *Culex tarsalis*; in the eastern United States, it is through *Culex pipiens, Culex quinquefasciatus,* and *Culex nigripalpus.* The incidence rates for St. Louis encephalitis virus in the United States range from 0.003 to 0.752 per 100,000, with a median of 35 cases per year.[174] In 1975 the largest outbreak recorded in the United States involved 2800 cases in 31 states. In 2015 and 2016, 19 and 7 respective cases of St. Louis encephalitis virus infection, mainly in Arizona and the Mississippi river basin, were reported to the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/ncidod/dvbid/sle/index.html). Thus St. Louis encephalitis continues to circulate in the continental United States.

St. Louis Encephalitis Virus Infection: Clinical Features

After the bite of an infected mosquito, an incubation period of 4 to 21 days precedes the onset of clinical symptoms. In adults, symptomatic infection occurs in 1 of 300 individuals exposed to virus.[3] These patients develop a flulike illness characterized by fever, myalgias, headaches, and other nonspecific symptoms including nausea, vomiting, cough, and sore throat. In patients younger than 20 years, 40% develop meningitis and 50% develop encephalitis.[175] In patients older than 60 years, more than 90% of patients develop encephalitis. Common manifestations of St. Louis encephalitis virus include reduced level of consciousness with lethargy, coma, tremors, myoclonic jerks, opsoclonus, nystagmus, and ataxia. Mortality of St. Louis encephalitis virus infections ranges from 4% to 27%,[175] seizures develop in 47% of patients, and acute flaccid paralysis has been associated with 6% of encephalitis cases.[176,177]

St. Louis Encephalitis Virus Infection: Diagnosis

MRI findings are often normal, but images may show high T2 signal intensity of the substantia nigra. In a case series of 11 patients, CSF studies revealed a lymphocytic pleocytosis in all patients (mean, 107 cells/mm^3; range, 5–446 cells/mm^3), elevated protein level (mean, 67 mg/dL) in 7 patients, and normal CSF glucose level.[177] EEG is almost invariably abnormal, with the most common finding being generalized slowing. Severely affected patients may have seizures or periodic lateralizing epileptiform discharges. General laboratory studies reveal a peripheral leukocytosis, hyponatremia, mild transaminitis, and sterile pyuria.[176] Diagnosis is based on demonstration of anti–St. Louis encephalitis virus IgM antibodies in the serum or CSF.[178] A fourfold increase in neutralizing antibody titers in the serum during the acute and convalescent phases of disease can also be used to establish a diagnosis. There is no therapy of proven efficacy for St. Louis encephalitis virus, although therapy with interferon-α2 may be considered (III-C).[7] An open-label, nonrandomized study of interferon-α2b suggested that therapy may improve outcome.[179]

Zika Virus (Also See Chapter 153)

ZIKV is an arbovirus in the flavivirus genus and shares many features with both dengue virus and WNV in terms of molecular structure and clinical features. Like dengue, ZIKV can be spread by *Aedes aegypti* mosquitos in an urban cycle that involves humans as an amplifying host. Like WNV, ZIKV is neuroinvasive, but ZIKV is the first flavivirus known to cause severe neurologic disease in human fetuses when a pregnant mother is acutely infected. ZIKV transmission in the Americas peaked in the summer and early fall of 2016. There have been 5590 reported symptomatic infections in the continental United States and 37,086 cases of symptomatic infection in US territories. This has resulted in possible ZIKV infections in 2311 and 4621 pregnant women in the US states and US territories, respectively (www.cdc.gov/zika/reporting).

Zika Virus Clinical Features

The pathogenesis in adults is likely similar to that of other flaviviruses described earlier and results in asymptomatic infection in up to 80% of adults exposed to infection.[180] In adult patients who develop disease, symptoms are characterized by fever, rash, myalgias, arthralgias, headache, and nonpurulent conjunctivitis that usually resolves in 7 days. Hospitalization and severe disease following acute ZIKV infection in adults are rare. During the ZIKV outbreak in Brazil, a prospective cohort of adult patients with neurologic complications was evaluated during a 3-month period of enrollment in the summer.[181] Of the 40 patients included in the study, 68% had Guillain-Barré syndrome, 13% had encephalitis, and 5% had transverse myelitis.

Despite relatively uncomplicated disease in adults, ZIKV complications can be clinically severe when pregnant women are acutely infected, resulting in infection in the fetus and congenital defects. Birth defects due to ZIKV are broadly categorized as congenital ZIKV syndrome and include chorioretinal atrophy and scarring, optic nerve abnormalities, microcephaly, developmental delay, arthrogryposis, hearing loss, and a variety of brain developmental abnormalities. Fetal abnormalities in the brain after ZIKV infection are directly related to virus infection of neuronal progenitor cells and astrocytes in the brain and other developing nervous system structures.

Zika Virus: Transmission

The major mode of ZIKV transmission remains mosquito-borne transmission from the bite of an infected *A. aegypti* mosquito. However, ZIKV is the first known arbovirus that can also be spread through sexual transmission. Because of the risk of sexual transmission, the CDC has published recommendations on prevention of ZIKV by sexual contact (www.cdc.gov/pregnancy/zika). ZIKV can also be spread through blood transfusion and organ transplantation, similar to WNV.

Zika Virus Infection: Diagnosis and Management

In suspected cases of ZIKV disease, diagnosis requires a compatible clinical syndrome and recent travel to an endemic area with ongoing ZIKV transmission.[180] Women who are pregnant and have traveled to endemic areas should be evaluated by health professionals with expertise in evaluation and monitoring of high-risk pregnancies associated with ZIKV. Suspected cases of ZIKV disease can be diagnosed through molecular detection of ZIKV RNA with reverse-transcriptase polymerase chain reaction (RT-PCR) testing in serum, CSF, and urine samples or serologic testing for ZIKV-specific IgM antibodies and ZIKV-specific neutralizing antibodies in serum or CSF. Serologic detection of ZIKV IgM and neutralizing antibodies is sensitive for infection after 1 week of symptoms but lacks specificity owing to antibody cross-reactivity among all related flaviviruses. However, ZIKV PCR testing is sensitive in the first week of symptoms and has a specificity of >95%.

There are no approved therapies for ZIKV infection. Prevention of infection is based on prevention of mosquito bites and avoidance of travel to an area of ongoing mosquito transmission of ZIKV. ZIKV may be shed for prolonged periods in semen, and sexual transmission of ZIKV has been described (see Chapter 153).

Multiple candidate ZIKV vaccines have shown efficacy in animal models, and have demonstrated immunogenicity in phase I clinical trials (see Chapter 153).

Eastern Equine Encephalitis Virus

Eastern equine encephalitis virus is an alphavirus that causes a sporadic, mosquito-borne viral infection endemic in the eastern United States and the Caribbean. There are four lineages of eastern equine encephalitis virus: group I causes most disease in humans, and groups IIA, IIB, and III cause primarily equine disease in Central and South America. Eastern equine encephalitis virus is maintained in an enzootic cycle with avian species after a bite from a mosquito vector, *Culiseta melanura*.[182] Birds serve as the primary reservoir host and amplifying hosts, and humans are incidentally infected by various mosquito bridging vectors, including

Culex and *Aedes* spp.[183] In the United States, most cases occur along the eastern seaboard. Cases are found sporadically along the Gulf Coast and upper Midwest, typically within 5 miles of swamplands or marshlands (see Fig. 89.2C). Approximately 1 in 30 individuals exposed to eastern equine encephalitis virus develops disease.[184] Eastern equine encephalitis virus causes sporadic infections in human populations during the summer months and occasional epidemic outbreaks.

Patients with eastern equine encephalitis virus develop nonspecific symptoms common to other causes of viral encephalitis, including fever, chills, malaise, and myalgias.[41] The prodrome is followed by either recovery without neurologic illness or the onset of encephalitis characterized by severe headache, confusion, nausea, and vomiting. Seizures, focal neurologic deficits such as CN palsies or focal weakness, and meningismus are common findings.[41] Brainstem involvement is common and is associated with gaze palsies, nystagmus, and pupillary abnormalities. Mortality is about 33% but increases to 50% in patients older than 60 years. Moderate-to-severe sequelae occur in one-third of survivors.[41]

In one study CT was reported to show findings suggestive of diffuse cerebral edema in 40% of cases.[185] Similar to the flaviviruses, in eastern equine encephalitis MRI abnormalities occur predominantly in the thalamus, basal ganglia, and brainstem.[41] EEG is typically diffusely slow, with some severely ill patients having burst suppression or diffuse high-voltage delta-wave slowing.[185] Laboratory studies may show a leukocytosis with a neutrophil predominance and hyponatremia in 60% of patients.[41] CSF typically shows a significant pleocytosis; two studies demonstrated a mean cell count of 370 leukocytes/mm^3 and 940 leukocytes/mm^3, respectively.[41,185] Two-thirds of eastern equine encephalitis virus cases display a neutrophil predominance, with a median neutrophil proportion of 70% of cells.[41,185] CSF protein is often elevated (median, 97 mg/dL), and 90% of patients have CSF glucose concentrations less than 60% of coincident serum values.[41,185] CSF red blood cells are common, reflecting the necrotic and hemorrhagic features of the encephalitis pathologically.

Diagnosis is typically made through demonstration of IgM antibodies in CSF with capture ELISA, demonstration of serum IgM antibodies, or a fourfold increase in IgG antibodies between acute and convalescent sera. No proven antiviral therapy exists for eastern equine encephalitis virus. Treatment is focused on supportive care and managing complications such as seizures and increased ICP. There is no commercial vaccine for eastern equine encephalitis virus, but standard precautions to prevent mosquito bites may help to prevent infection. In evaluating laboratory and imaging studies for prognostic value, one study found that CSF leukocytosis greater than 500 cells/mm^3 and hyponatremia less than 130 mEq/L were predictive of a poor outcome,[41] but a longer prodromal period was associated with a better prognosis. Overall mortality is approximately 30%, although higher mortality rates have been reported in older individuals. Sequelae are more common and generally more severe in children.[185]

Western Equine Encephalitis

Western equine encephalitis virus is an alphavirus that was originally isolated from the brains of horses in an epizootic outbreak in the San Joaquin Valley of California in 1930.[186] There have been 639 cases of western equine encephalitis virus in the United States since 1964 but none since 1994.[186a] A single case of probable western equine encephalitis was reported from Uruguay in 2009.[187]

Venezuelan Equine Encephalitis

Venezuelan equine encephalitis virus is an alphavirus that was originally isolated from the brains of dead horses.[188] Venezuelan equine encephalitis virus circulates between a mosquito vector, *Culex (Melanoconion),* and forest-dwelling small mammals and birds in Central and South America. It emerges during epizootic outbreaks to infect horses and humans via bridge vectors such as *Aedes taeniorhynchus.* Epidemics typically occur in northern South America but have extended as far north as Mexico and Texas.[189] In areas of sylvatic (forest) activity, seroprevalence can be 50%. During an outbreak of Venezuelan equine encephalitis virus in Venezuela and Colombia in 1995, approximately 3000 cases of neurologic disease were reported, resulting in 300 deaths.[190,191] In contrast to other arbovirus infections in humans, viremia in humans is sufficient to transmit virus to mosquitoes. Forty percent of patients with Venezuelan equine encephalitis virus have virus in the pharynx, suggesting that direct spread between humans may be possible, although this has never been shown.[190,192]

Symptomatic Venezuelan equine encephalitis virus results in neurologic disease in a few cases after a viral prodrome of fever, headache, photophobia, conjunctival injection, myalgia, arthralgia, nausea, and dizziness. Pharyngeal inflammation, painful cervical lymphadenopathy, somnolence, and tremulousness may occur.[193,194] CSF analysis reveals lymphocytic pleocytosis, elevated protein, and in some cases an elevated glucose ratio. There are few reports of neuroimaging studies. CT scans are usually normal. EEG typically shows diffuse slowing, although some cases have focal temporal slowing similar to that seen in HSV encephalitis. General laboratory abnormalities include leukopenia and elevated transaminase levels.[193]

Venezuelan equine encephalitis virus is diagnosed by detection of specific IgM antibody in the CSF or serum. Venezuelan equine encephalitis virus nucleic acid can also be amplified with PCR from the blood or pharynx on the eighth day of illness.[192] Fatality rates range from 0.2% to 1% of symptomatic Venezuelan equine encephalitis virus patients and 10% to 25% of patients with encephalitis. There is no antiviral therapy of proven benefit.

Chikungunya

Chikungunya virus (CHIKV) is an Old World alphavirus that reemerged as a cause of a major epidemic in Africa in 2004, then spread to the island of Réunion in the Indian Ocean in 2006 and to Southeast India itself. As of late July 2014, CHIKV had spread extensively into Caribbean islands and to multiple Central and South American countries (see Chapter 151). CHIKV generally causes an acute infection consisting of fever, rash, and polyarthritis that can be severe and prolonged (see Chapter 151). CNS involvement has been reported but appears to be uncommon.[226,227195–199]

The large outbreak of CHIKV infection in Réunion enabled a detailed study of CHIKV-associated encephalitis to be carried out.[200] CHIKV-associated encephalitis was defined by the presence of CHIKV RNA or anti-CHIKV IgM, along with clinical criteria of the International Encephalitis Consortium. Twenty-four cases of encephalitis were reported for a cumulative incidence rate of 8.6 per 100,000 persons. Incidence rates were highest in patients younger than 1 year and in those older than 65 years. The case-fatality rate of CHIKV-associated encephalitis was 16.6%, and the proportion of children diagnosed with persisting disabilities was between 30% and 45%. Poor prognoses (death or sequelae) were more frequent in adults (53.6%) than in children (18.2%).[200]

California Encephalitis Group

California encephalitis virus, La Crosse virus, Jamestown Canyon virus, and Tahyna virus are the major causes of encephalitis in the California encephalitis group within the family of Bunyaviridae and genus *Bunyavirus.* Of these viruses, La Crosse virus, California encephalitis virus, and Jamestown Canyon virus are causes of disease in the United States, and Tahyna virus is predominantly a cause of encephalitis in Russia. La Crosse virus is the most common cause of disease in the California encephalitis group. It was originally described in 1965 after a postmortem examination of a child who died of encephalitis in La Crosse, Wisconsin.[201] La Crosse virus is transmitted in an enzootic pattern between squirrels and chipmunks by the mosquito *Aedes triseriatus* in areas of the Mississippi and Ohio river basins (see Fig. 89.2D).[202,203] Recent outbreaks of La Crosse virus have demonstrated a shift in incidence to the Appalachian region and West Virginia.[204] Human exposure is often associated with camping or other recreational activities in wooded areas in endemic regions.

California encephalitis virus was originally isolated in 1941,[205] but it is rare. Most human cases occur in the western United States and Canada. The ratio of asymptomatic to symptomatic infections is 1000 : 1.[206]

Although La Crosse and California encephalitis viruses cause most disease in children, Jamestown Canyon virus affects predominantly elderly individuals in regions of the northern United States, with

seroprevalence in some areas reaching 10%.[207] A report of a Jamestown Canyon virus infection in Montana underscores continued low-level transmission in the northern continental United States.[208] La Crosse virus causes infection predominantly in children (mean age, 7.5 years). Symptoms of encephalitis include fever, headache, vomiting in 70%, seizures in 46%, and altered mental status in 42%.[206] Focal neurologic signs include hemiparesis, aphasia, dysarthria, and chorea. About 10% of patients develop increased ICP, and rarely cerebral herniation can occur.[206] Jamestown Canyon virus has similar clinical features.

CSF analysis reveals a lymphocytic pleocytosis of 600 cells/mm^3, normal glucose level, and an increased protein level in 30% of patients.[206] Peripheral leukocytosis and hyponatremia secondary to SIADH are common. IgM detection in the CSF or a fourfold increase in paired sera for IgG is considered diagnostic for infection.

No antiviral therapy currently exists for the California encephalitis group of viruses, and no vaccine is available. Mortality from La Crosse encephalitis is approximately 1% to 3%, and most survivors return to normal function.[204,206] Ribavirin treatment for La Crosse encephalitis in children is not recommended owing to problems with pharmacokinetics, toxicity at higher doses, and penetration into the CNS.[209] Predictors of a poor outcome include hyponatremia, persistently elevated body temperature, and a GCS score less than 13.[205,210]

Japanese Encephalitis

JEV was initially isolated in Japan in 1935. JEV causes infections across all of Asia, the western Pacific region, and parts of Australia. JEV is the most important cause of viral encephalitis in the world, causing 68,000 cases and 13,000 to 20,000 deaths annually.[211] The virus is transmitted naturally in an enzootic cycle among birds, pigs, and other vertebrate hosts by the *Culex tritaeniorhynchus* mosquito and other *Culex* spp. Similar to other flaviviruses, humans are incidental hosts that become infected when encountering the enzootic cycle. In rural areas where JEV is endemic, it is predominantly a disease of children, in whom seroprevalence approaches 100%, but only 1 in 300 exposures results in clinical disease.[211] Several reports also highlight the importance of JEV in returning travelers from endemic regions.[212,213]

After a 1- to 2-week incubation period, symptomatic patients develop a nonspecific febrile illness followed by neurologic symptoms of altered consciousness and seizures in 85% of children and 10% of adults.[214,215] Subtle focal seizures, such as twitching of an eyebrow or finger, can be important clinical findings in JEV infection.[211] Similar to other flaviviruses, in patients with JEV, movement disorders occur in 25% and are characterized by parkinsonism, dystonia, jaw dystonias, opisthotonus, choreoathetosis, orofacial dyskinesia, myoclonic movements, and opsoclonus-myoclonus.[211,215,216] Other focal neurologic findings include CN palsies, upper motor neuron weakness, and a lower motor neuron syndrome of acute flaccid paralysis.

CSF shows an elevated opening pressure in 50% of patients. The characteristic CSF profile is lymphocytic pleocytosis, normal glucose level, and mildly elevated protein level. MRI is often normal but may reveal high T2-weighted signal intensity in the thalami, basal ganglia, midbrain, brainstem, and occasionally spinal cord.[217,218] Diagnosis is confirmed with IgM capture ELISA in the CSF or with amplification of viral nucleic acid from CSF or brain tissue by PCR.[219–222] The sensitivity of commercial IgM ELISAs in CSF ranges from 65% to 69%, with specificities of 89% to 100%.[223]

The mortality rate in hospitalized patients ranges from 20% to 30%, and 50% of survivors have severe neurologic sequelae. Poor prognostic signs include altered level of consciousness, multiple seizures, increased ICP, isolation of virus in the CSF, and low titer of JEV–specific immunoglobulins in the CSF.[211–215,224] In a study of 118 cases of JEV in Malaysia from 1997 to 2005, the mortality rate was 8%, and 57% of survivors experienced moderate-to-severe long-term neurologic sequelae.[225] Predictors of long-term poor outcome included a GCS score of 8 or lower or two or more witnessed seizures.

No therapy for JEV has been proven efficacious in randomized controlled clinical trials. Prevention is the primary strategy to control JEV infection. Personal protection with insect repellents, mosquito avoidance, and mosquito population control programs are important approaches. The most effective prevention to date is vaccination. Two JEV vaccines are licensed in the United States. A mouse brain–derived, formalin-inactivated vaccine (JE-MB) showed efficacy in a randomized double-blind trial in Thailand and is approved in the United States for use in individuals older than 1 year. Production of JE-MB was discontinued in 2006, and remaining vaccine is reserved for use in children 1 to 16 years of age[227] (see Chapter 153). An inactivated Vero cell culture–derived vaccine (JE-VC) was approved for use in the United States in 2009 for individuals 17 years of age and older.[227] A live-attenuated vaccine developed in hamster kidney cells (SA14-14-2) is used in China, and several other vaccines are either currently in use (chimeric JEV–yellow fever 17D vaccine) or in development.[174,228]

Influenza

Influenza A is known to be associated with immune-mediated neurologic complications such as Guillain-Barré syndrome or transverse myelitis. The overall role of influenza as a cause of CNS disease has been difficult to ascertain. Less commonly, influenza has been associated with encephalitis in children and young adults. During the influenza A (H1N1) pandemic in 2009, influenza was associated with encephalitis and neurologic complications. In a study of 506 children hospitalized with H1N1, 1.4% ($n = 7$) of patients presented with encephalitis, and 5 of the patients with encephalitis had a preexisting medical condition.[229] When seizures are included, the incidence of neurologic complications associated with H1N1 influenza increases to 9.7%. Severe influenza in children and young adults with underlying neurologic or neurodevelopmental conditions has occurred in smaller outbreaks.[230]

Patients often present with typical influenza symptoms during the winter and spring months. Symptoms include fever; respiratory abnormalities (cough, coryza, wheezing, labored breathing); nausea; and diarrhea. Patients with severe influenza develop increased work of breathing, and neurologic involvement can be characterized by altered mental status, seizures, or focal neurologic signs. The diagnosis is commonly made on the basis of the association of the rapid influenza diagnostic test (RIDT) or positive RT-PCR studies on respiratory samples. CSF may show evidence of a pleocytosis with normal glucose and protein levels, but PCR studies for influenza are often negative.[231] It is unclear whether CNS complications associated with influenza are a result of direct neuroinvasion or secondary to immune-mediated mechanisms.[231]

Although the efficacy of antiviral therapy in neurologic complications associated with influenza has not been established in clinical trials, it would be prudent to administer antiviral therapy as early as possible, and ideally within 48 hours of symptom onset.[230] Antiviral therapy for influenza should be started regardless of vaccination status and is often initiated with other empirical antibiotic therapy (such as acyclovir), pending results of the clinical investigation. As therapy for influenza, oseltamivir (75 mg by mouth twice daily for patients > 40 kg) has been recommended for at least 10 days (https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm) (also see Chapter 165).

Colorado Tick Fever Virus (See Chapter 149)

Colorado tick fever virus belongs to the family Reoviridae. It is transmitted by the wood tick *Dermacentor andersoni* mainly in the western mountain regions of the United States and Canada above 4000 feet in elevation.[232] An enzootic infection cycle exists between small mammals, such as ground squirrels, marmots, or chipmunks, and *D. andersoni*. When infected, the tick is infected for life (transstadially) throughout the three main stages of development—larval, nymphal, and adult. Humans are exposed to the habitat of *D. andersoni* during summer months and are dead-end hosts.

A history of tick bite is obtained in approximately 90% of patients, and the incubation period is 0 to 14 days (mean, 3 days).[232] Patients develop abrupt onset of fever, chills, generalized myalgias, severe headache, hyperesthetic skin, and severe malaise. Gastrointestinal symptoms such as nausea, vomiting, or diarrhea may be present. About 15% of patients develop a maculopapular or petechial rash. Other physical findings include pharyngitis, mild lymphadenopathy, or mild splenomegaly. In 50% of patients, fever resolves after 2 days and then recurs in the biphasic or "saddleback" pattern.[232] After convalescence, patients older than age 30 may have persistent fatigue for 3 weeks.

Complications such as encephalitis or meningitis predominantly occur in children in about 5% to 10% of the cases. Colorado tick fever virus is rarely fatal.[233] In these patients, neurologic signs and symptoms include nuchal rigidity, photophobia, and mild altered mental status.

The diagnosis of Colorado tick fever virus infection is usually made through IgM capture ELISA, neutralization, or complement fixation.[234] There is no established treatment for Colorado tick fever virus. Most patients recover, although rare deaths have been reported as a result of intravascular coagulopathy after Colorado tick fever virus infection.[233]

Enteroviruses

Enteroviruses comprise more than 70 different viruses in the Picornaviridae family. They can be grouped into polioviruses, coxsackieviruses A and B, echoviruses, and numbered enteroviruses. Enteroviruses cause more than 80% of meningitis cases and also cause more severe neurologic diseases such as encephalitis. Enterovirus infections in the CNS have been reviewed[235] (see Chapters 170–172).

Poliovirus

In 1988 the World Health Assembly started the Global Polio Eradication Initiative, resulting in a decrease from more than 350,000 cases of poliovirus in 1988 to 223 cases in 2012. In 2017 there were only 20 cases of wild-type polio (all type 1) reported worldwide (12 in Afghanistan and 8 in Pakistan); 86 cases of polio associated with circulating vaccine-derived poliovirus strains occurred in 2017 (74 in Syria and 12 in Congo). Poliovirus is transmitted by fecal-to-oral contact and by pharyngeal spread during epidemics. Symptomatic poliovirus infection results in meningitis in 8% of cases and paralytic disease in 1% of all cases. After an incubation period of 1 to 2 weeks, patients develop fever, headache, meningismus, altered mental status, and seizures (in children and infants). Asymmetrical flaccid paralysis, diaphragm paralysis, and CN palsies may follow.

CSF evaluation reveals polymorphonuclear cells early followed by a shift to lymphocytes after several days, elevated protein level (100–300 mg/dL), and normal glucose level. Diagnosis is made with CSF RT-PCR. Treatment for poliovirus infection is supportive. The last large outbreak of poliovirus in the Western Hemisphere occurred in 2000, when 19 cases in the Dominican Republic were reported; the cases were due to a circulating recombinant poliovirus derived from the polio type 1 strain in the oral polio vaccine, rather than wild-type virus. As of 2000, the Advisory Committee on Immunization Practices has recommended the use of inactivated polio vaccine in the United States for the entire primary immunization series (see Chapter 171). Trivalent, live-attenuated (Sabin) vaccine is still used in endemic areas of poliovirus infection.

Nonpoliovirus Enteroviruses

Nonpolio enteroviruses cause a wide spectrum of disease in the CNS, including aseptic meningitis, encephalitis, acute poliomyelitis, acute cerebellar ataxia, optic neuritis, and cranial neuritis (see Chapter 172). In neonates, encephalitis is a complication of an overwhelming sepsis-like syndrome with 10% mortality. Enteroviruses may cause encephalitis, particularly in patients with hypogammaglobulinemia and neonates. In an analysis of the CEP, enteroviruses were responsible for 4.6% of encephalitis cases.[236] This is likely an underestimate, however, based on the referral bias inherent in the design of the study. Of the 73 patients diagnosed with confirmed enterovirus encephalitis, 23% were adults who often presented with mild symptoms and altered consciousness (46%), including rare cases of coma (5%) or personality changes (5%).[236] In 2014, enterovirus D-68 emerged as a major cause of acute upper respiratory infections in children. This outbreak was also associated with a dramatic upsurge in cases of polio-like acute flaccid myelitis (AFM) in children[237] resulting in 120 CDC-confirmed cases in children from 34 states. AFM appears to be following an alternating-year pattern; in 2015, cases returned to baseline levels (21 cases, 16 states), only to rise again in 2016 when 144 cases were reported from 37 states and then fall in 2017 (17 cases). Although the role of enterovirus D-68 in the upsurge in AFM cases has not been definitively proven, accumulating epidemiologic and virologic evidence increasingly suggests a potential causal role.

Enterovirus encephalitis occurs during the summer months from June to October. MRI has a variable sensitivity for enteroviral encephalitis; some studies can show increased T2-weighted signal intensity of both cerebral hemispheres with associated edema (see Fig. 89.3D). In the CEP, cases of enterovirus encephalitis were diagnosed with RT-PCR of the CSF, and serotyping was available for 20 cases, with echovirus 30 being the most common strain isolated, followed by enterovirus 71, echovirus 18, and coxsackieviruses.[236] Enterovirus 71 can produce more severe disease, with cases of focal and generalized encephalitis reported.[238,239] Cases of enterovirus 71 encephalitis have been associated with a syndrome of shock, pulmonary edema, and extensive brainstem injury (rhombencephalitis) linked to neurogenic pulmonary edema in some cases. In the CEP, two of the four deaths from enteroviruses were due to enterovirus 71, and the other two enteroviruses were not serotyped.[236]

Currently, no specific antiviral therapy is approved for the treatment of enterovirus infections. Various serotypes have been associated with variable sensitivity to pleconaril, an experimental drug.[240] However, clinical outcome data are insufficient to recommend its use in patients with enterovirus encephalitis, and its development has been halted.

Rabies Virus

Rabies virus belongs to a family of RNA viruses called Rhabdoviridae, genus *Lyssavirus*. It is most commonly transmitted to humans through the saliva of an infected animal after a bite (see Chapter 163). In 2012 there was no evidence of dog-to-dog transmission of rabies in the United States and Puerto Rico, and no human infections have been attributed to a dog bite in the United States.[241] Dogs that become infected in the United States are infected with rabies from wildlife. Approximately 93% of the rabies detected in the United States is found in animal wildlife, such as raccoons, bats, skunks, and foxes.[241] In contrast, canine rabies is enzootic in the dog population in many developing countries, and travelers to these countries can be at risk for exposure to rabies from domestic and feral dogs.[242,243] In Bali, 104 cases of human rabies were reviewed and 92% had a history of a dog bite.[243] In the United States, human cases of rabies are rare. Most human cases of rabies have followed bat exposure[244]; however, one patient who died of undiagnosed rabies in 2004 was subsequently found to have rabies only after organs were transplanted from this patient into four individuals, resulting in clinical rabies and death of all recipients.[245]

After a bite wound, rabies virus from infected saliva invades motor and sensory nerves. Neurologic disease is preceded by an incubation period that ranges from 7 days to more than 6 years, with a median incubation of 1 to 2 months.[246,247] The virus moves centripetally from the periphery to the dorsal root ganglia and the spinal cord using fast axoplasmic transport,[248–250] resulting in nerve dysfunction manifesting as a prodrome of neuropathic pain. When rabies has invaded the nerve cell body in the spinal cord, acute neurologic symptoms evolve into encephalitis.

Patients present with a syndrome of hyperactivity (furious rabies) in 80% of the cases, characterized by hydrophobia and aerophobia owing to spasms of the pharyngeal and nuchal muscles triggered by swallow attempts or other types of stimuli.[251] These spasms increase in frequency and are followed by agitation, hallucinations, autonomic hyperactivity, and seizures. Body temperature may be as high as 107°F. Paralytic (dumb rabies) presentations constitute 20% of cases and are characterized by paresthesias, weakness, and flaccid paralysis in the bitten limb. Diagnosis should be considered in any patient with altered consciousness and an exposure history or travel to an endemic area. Diagnosis is made with immunohistochemical staining for rabies antigen from a skin biopsy specimen in the region of the hairline at the neck.[251] Recent development of a reverse-transcription heminested PCR test on skin biopsy specimens demonstrated a sensitivity of greater than or equal to 98% and a specificity of 100%.[252] Other diagnostic methods include examination of corneal smears for rabies antigen and intracerebral inoculation of mice with patient saliva. Detection of rabies virus neutralizing antibodies in the CSF or serum is diagnostic in unimmunized patients, but antibody detection tests can lack sensitivity.

Infected patients should be isolated because body fluids can contain high titers of active virus. Treatment of rabies virus infection is largely supportive and results in a uniformly fatal outcome. One case of survival after rabies virus infection was reported in a 15-year-old girl after treatment with coma induction and EEG burst suppression using midazolam and ketamine supplemented with barbiturates and benzodiazepines.[253] Antiviral therapy included IV ribavirin (33 mg/kg load and then 16 mg/kg every 6 hours) and enteral amantadine (200 mg/day).[253] Despite this case of survival with treatment of rabies virus infection, several failures have been reported.[254]

The mainstay of rabies treatment is PEP. Wounds should be cleansed with soap and water followed by povidone-iodine. Human diploid cell rabies vaccine, rabies vaccine adsorbed, or purified chick embryo vaccine should be administered intramuscularly.[255] In 2010, new CDC recommendations for rabies PEP included vaccination on days 0, 3, 7, and 14 but no dose at day 28 as previously instructed.[256] Previously vaccinated individuals are still given vaccine on days 0 and 3. In addition to vaccination, PEP includes human rabies immunoglobulin, 20 IU/kg, administered as soon as possible after the exposure, up to 7 days after the first dose of vaccine. As much of the dose as possible should be administered at the bite wound site, and any remaining dose should be administered intramuscularly in the same limb, but distant to the vaccination site. Using the CDC- and World Health Organization–recommended rabies PEP regimen, a study of 110 rabies-exposed travelers found that only 14% received human rabies immunoglobulin and that antibody levels afterward were less than 0.5 IU/mL in 6.7% of travelers who received four doses of vaccine.[257] Thus follow-up antibody titers at day 21 after rabies PEP vaccination may be useful.[257] If the animal that caused the bite wound is available, healthy animals should be quarantined and observed for clinical illness over a 10-day period. If the animal is ill, it should be euthanized and the brain should be analyzed by the local health department for evidence of rabies infection.

Measles Virus

Measles virus remains an important cause of morbidity and mortality throughout the world (see Chapter 160).[258] In approximately 0.1% of cases, measles virus can cause an acute postinfectious measles encephalitis resulting in a 20% mortality.[246] Measles virus can also cause a chronic infection in neurons that results in subacute sclerosing panencephalitis (SSPE) or measles inclusion body encephalitis.[246,259] Measles inclusion body encephalitis is a rare and uniformly fatal condition that causes disease in young patients with defective cellular immunity.[259,260] SSPE is a slowly progressive disorder characterized by seizures, deterioration of cognitive and motor function, myoclonic movements, and death. It occurs 5 to 15 years after initial measles infection, which usually occurs in children younger than 2 years.[261] Immunization has reduced the incidence of SSPE more than 90% in developed countries; however, the rate of SSPE is 21 per 1 million population in India.[261,262] When SSPE occurs in adults, the mean age is 25 years and most patients have an undocumented or negative vaccination history for measles.

Initial symptoms may be subtle and include intellectual deterioration and behavioral changes.[261] These symptoms progress to myoclonic jerks, ataxia, dystonia, and generalized or partial seizures.[261,262] Ocular and visual symptoms occur in 10% to 50% of patients and precede neurologic disease by several years. Ocular symptoms include cortical blindness, chorioretinitis, and optic atrophy.[263,264] CSF examination findings are usually normal with a markedly increased immunoglobulin level. Neuroimaging findings are generally limited, but MRI may reveal high signal intensity on T2-weighted images in the white matter, particularly the occipital subcortical white matter, with near-uniform sparing of gray matter.

SSPE has a rapidly progressive course in adults.[265] A small, single uncontrolled trial suggested that treatment with oral inosine pranobex (Isoprinosine) and interferon-α may be effective for adult-onset SSPE,[266] but in general no adequate therapy is currently available for the treatment of SSPE.

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The complete reference list is available online at Expert Consult.

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