Encephalitis and Postinfectious Encephalitis

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ABSTRACT

Purpose of Review: Encephalitis and postinfectious encephalitis represent two important conditions for the neurologist, both in terms of their presentations as neurologic emergencies and their potential to cause death or serious neurologic impairment. This article reviews the major infectious and noninfectious causes of encephalitis and discusses postinfectious encephalitis as an indirect effect of systemic illness.

Recent Findings: Encephalitis caused by herpes simplex virus type 1 and West Nile virus are of major importance. In addition, within the past few years we have gained improved understanding of the neurologic syndromes caused by varicella-zoster virus, the recognition of enterovirus 71 as a significant human pathogen, and the realization that encephalitis may also occur by autoimmune mechanisms requiring immunosuppressive therapy. We have also learned that postinfectious encephalitis may be recurrent rather than monophasic, and that children and adults initially diagnosed with postinfectious encephalitis may later develop classic multiple sclerosis.

Summary: Encephalitis and postinfectious encephalitis present as neurologic emergencies requiring prompt diagnosis and initiation of treatment. Important concerns are to identify infectious conditions requiring antibiotic or antiviral therapy and postinfectious or other autoimmune encephalitides requiring immunosuppression.

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INTRODUCTION

In approaching patients with suspected CNS infection, the first task for the neurologist, as discussed in the article ''Acute Bacterial and Viral Meningitis,'' is to determine whether the patient has bacterial meningitis requiring emergent antibiotic therapy. When evidence of focal or diffuse parenchymal involvement is present, however, an important diagnostic consideration becomes whether the patient has encephalitis or a postinfectious illness in which systemic infection has caused an immune response directed against myelin or other antigens. In recent years, a third possibility has been recognized: encephalitis may represent an autoimmune response directed against neuronal membrane antigens or intraneuronal proteins. The clinical and radiologic features of these three entities—encephalitis, postinfectious encephalomyelitis, and autoimmune encephalopathy—may differ significantly, and recognition of these differences facilitates diagnosis. This article reviews the presentation, diagnosis, and treatment of these three important clinical entities.

ENCEPHALITIS

Although encephalitis is usually considered in terms of viral infections, other agents may involve brain parenchyma as well. The most urgent question to ask is whether the patient will require antiviral or antimicrobial

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KEY POINTS

- The most urgent question to ask in the case of a patient with suspected CNS infection is, ''Does the patient require immediate antibiotic or antiviral therapy?''
- Viral agents of primary concern are herpes simplex virus, varicella-zoster virus, and West Nile virus.
- Herpes simplex virus encephalitis remains the major cause of nonepidemic fatal encephalitis.
- Herpes simplex virus encephalitis presents with an almost universal triad of headache, fever, and alteration in mental status.
- Temporal lobe involvement in herpes simplex virus encephalitis may result in seizures characterized by olfactory or gustatory hallucinations, or déjà vu phenomena.

therapy. Three viral infections are of primary concern: herpes simplex virus (HSV) encephalitis, CNS involvement by varicella-zoster virus, and West Nile virus encephalitis. Other infectious encephalitides, although important, are less common.

Herpes Simplex Virus Encephalitis

HSV encephalitis (**Table 2-1**) represents only 10% to 15% of cases of viral encephalitis in the United States. However, it remains the most important of viral encephalitides, because it is both lethal if untreated and the only viral encephalitis for which therapy has been proven effective in clinical trials. HSV is ubiquitous in human populations. Two subtypes of HSV infect humans: HSV type 1 (HSV1) and HSV type 2 (HSV2). HSV1 is most commonly acquired in early childhood. HSV2 is more commonly sexually transmitted and thus usually acquired during adolescence or adulthood. Both agents persist in neurons within sensory ganglia. Limited evidence suggests that HSV1 may also persist within the CNS.[1] HSV1 is responsible for 90% of cases of HSV encephalitis in adults; of these cases roughly two-thirds represent reactivated infection.[2]

The pathogenesis of HSV encephalitis is not well understood. Encephalitis has been postulated to follow spread of virus from trigeminal ganglia through sensory fibers to the meninges overlying temporal lobes and orbitofrontal cortex.[3] Alternatively, encephalitis could arise following reactivation of a latent virus within the brain.[1]

HSV encephalitis affects men and women equally and may occur at any age. There is no seasonal incidence of infection. Impaired host immunity is not a risk factor for HSV encephalitis, but the infection may progress more gradually in immunocompromised individuals.[4] HSV encephalitis is usually unilateral but may also be bilateral. The virus has a predilection for orbitofrontal cortex and temporal lobes, with many cases also involving the cingulate cortex. The virus is able to infect neurons, glia, and ependyma. Vascular congestion and petechial hemorrhages may be present. Progression of the infection results in extensive, frequently hemorrhagic, destruction of the brain.[5]

HSV encephalitis presents with an almost universal triad of headache (in over 90% of cases), fever, and alteration in mental status, at times preceded by symptoms of nonspecific mild illness. Changes in mental status at presentation may range from confusion, frank psychosis, or somnolence to stupor or coma. Temporal lobe involvement may result in seizures characterized by olfactory or gustatory hallucinations, or déjà vu phenomena.[6] Examination may reveal subtle or overt corticospinal tract signs or signs suggesting temporal lobe dysfunction.[6] These may include upper-quadrant visual field defects; aphasia when the dominant hemisphere is involved; and, when the infection is bilateral, loss of ability to store and recall new information. Occasional patients will exhibit papilledema at presentation. Rare patients may present with evidence of injury to other parts of the CNS, including occipital lobes and brainstem, without temporal lobe involvement.[7] Focal or generalized seizures, however, may occur at any point during acute illness or after recovery.

CSF in HSV encephalitis typically contains a lymphocytic pleocytosis of 50 or more cells/μL (median 130 cells/μL).[6] In occasional patients, however, cell count may be normal.[6] Although HSV encephalitis is frequently hemorrhagic, the presence or absence of red blood cells in CSF does not differentiate HSV encephalitis from encephalitis due to other causes.[6] Median CSF protein concentration is 80 mg/dL but may range from normal to over 700 mg/dL; CSF glucose concentration is usually normal.[6] MRI

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TABLE 2-1 Major Infectious Agents Associated With Encephalitis

Agent (Vector)	Geographic Distribution	Peak Seasonal Incidence	High-Risk Populations	Acute Diagnosis	Treatment
Viruses					
Herpes simplex virus	Ubiquitous	No seasonal incidence	N/A; course of infection may be atypical in individuals who are immunosuppressed	CSF PCR	Acyclovir
Varicella-zoster virus	Ubiquitous	No seasonal incidence	Individuals who are immunocompromised	CSF PCR, IgM and IgG antibodies	Acyclovir
Cytomegalovirus	Ubiquitous	No seasonal incidence	Individuals who are immunocompromised, especially those with HIV	PCR	Ganciclovir; foscarnet
West Nile virus (mosquito)	Entire United States	Summer and early fall	Individuals who are immunocompromised and older adults	CSF IgM	Supportive
St Louis encephalitis virus (mosquito)	Entire United States, especially the Midwest, Mississippi River regions, and Texas	Summer and early fall	Older adults	CSF IgM	Supportive
Eastern equine encephalitis virus (mosquito)	Eastern seaboard, Gulf coast (including Texas), and the upper Midwest regions	Summer and early fall	Children and older adults	CSF IgM	Supportive
Enteroviruses	Worldwide	Summer and early fall	Individuals with IgG deficiency, including those treated with rituximab	PCR	Supportive (pleconaril)
Nonviral Agents					
Treponema pallidum	N/A	N/A	AIDS	Serology (rapid plasma reagent test, CSF, Venereal Disease Research Laboratory test, fluorescein treponema antibody test)	Penicillin or ceftriaxone

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Continued

Agent (Vector)	Geographic Distribution	Peak Seasonal Incidence	High-Risk Populations	Acute Diagnosis	Treatment
Rickettsia rickettsii (Rocky Mountain spotted fever, tick)	Entire United States; >60% of cases present in North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri	April to September	N/A	Serology (acute and convalescent sera)	Tetracyclines or chloramphenicol[a]
Listeria monocytogenes	N/A	N/A	Infants, older adults, and individuals who are immunocompromised	Bacterial culture (PCR)	Ampicillin
Mycoplasma pneumoniae	N/A	N/A	N/A	Serology (PCR)	Tetracycline, doxycycline, or erythromycin[b]

[a] Tetracyclines are usually avoided in younger children because they may stain teeth. However, because Rocky Mountain spotted fever (RMSF) has significant risk of causing fatal disease, doxycycline is recommended for both children and adults with suspected RMSF, with the assumption that a single course of antibiotics may not affect teeth to a significant degree.
[b] Tetracyclines are avoided in younger children with *M. pneumoniae* infection because of their detrimental effect on dental enamel.

with and without gadolinium administration, the initial diagnostic procedure of choice, will usually demonstrate altered signal and gadolinium enhancement within the temporal lobe and may also show involvement of insula, orbitofrontal cortex, or cingulate gyrus (**Figure 2-1**). MRI abnormalities in other regions of the cortex or brainstem without temporal lobe involvement do not exclude HSV encephalitis.[5] CT with contrast and EEG are less sensitive but, used together, may provide diagnostic information when MRI is not available.[8]

Specific diagnosis of HSV encephalitis is made by amplification of viral DNA from CSF using PCR methods. Overall diagnostic accuracy of PCR in patients with brain biopsy-proven HSV encephalitis is 98%.[9] In some patients PCR may be negative at presentation because of low copy numbers of DNA in CSF. In these cases, repeat CSF PCR in 4 to 7 days may be positive.[10] Diagnostic yield of PCR falls to 21% in patients after 2 weeks of antiviral treatment.[9] Determination of antibody titers is not of value in the acute diagnosis of HSV encephalitis. However, comparison of serum versus CSF antibodies to detect intrathecal production of antibody may be useful retrospectively and in rare cases may provide diagnostic information when PCR is negative.[11]

The advent of acyclovir revolutionized the treatment of HSV encephalitis. This agent inhibits HSV synthesis by competing with deoxyguanosine triphosphate as a substrate for DNA polymerase and causing DNA chain termination.[4] Acyclovir is converted to its pharmacologically active monophosphate form by virally encoded thymidine kinase and thus becomes active only in infected cells.[4] Acyclovir is administered at 10 mg/kg body weight every 8 hours for 3 weeks. Complications of acyclovir therapy are usually mild. The major therapeutic concern is nephrotoxicity due to deposition of drug crystals; this is avoided by both controlling the rate of

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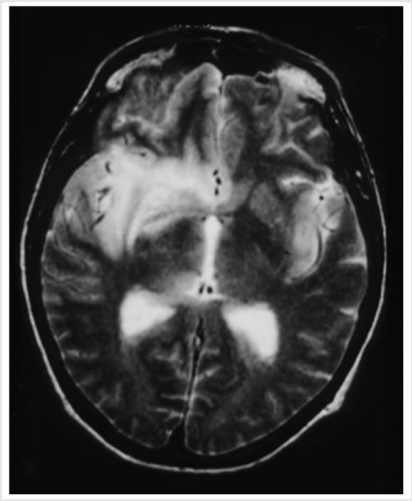

FIGURE 2-1 MRI of herpes simplex virus encephalitis with bihemispheric involvement. Greatly increased T2 signal exists in the right hippocampus and orbitofrontal cortex, as well as in the left medial temporal lobe and insula.

infusion and keeping the patient hydrated. Despite its use for more than 20 years, only a single case of acyclovir-resistant HSV encephalitis has been reported.[12]

Prior to the advent of specific antiviral therapy, mortality from HSV encephalitis was greater than 70%, with a high rate of severe neurologic sequelae among survivors. Acyclovir reduced mortality to 28%, and rapid institution of antiviral therapy has reduced 1-year mortality to 14%.[13] Patients who are alert or lethargic when treatment is initiated have excellent likelihood of survival, but mortality in patients treated when semicomatose or comatose may be as high as 25%.[6] Adverse prognostic features include coma, advanced age, delayed initiation of treatment, and evidence of extensive CNS involvement on initial MRI or CT. Approximately 30% of patients will be left with permanent neurologic deficits,[6] which may include focal or generalized seizures, impaired memory, aphasia, motor deficits, and impaired cognition.[13,14] Nonetheless, patients appearing severely impaired immediately after treatment may have good functional recovery over time[6] (**Case 2-1**).

Varicella-Zoster Virus

Varicella-zoster virus (VZV) (**Table 2-1**) may invade the CNS during primary infection (chicken pox).[15] VZV persists in sensory ganglia following initial infection, like HSV, and may cause encephalitis during reactivated infection. Prior to the advent of PCR, VZV encephalitis was considered unusual. During the past 15 years, however, neurologic complications of VZV infection have been recognized as occurring much more frequently than previously realized. VZV infection is now known to cause a protean array of syndromes of neurologic injury involving not only the brain and spinal cord, but also cranial and peripheral ganglia and nerves.[15] In one series, VZV was found to be the most common agent identified in viral meningitis and encephalitis (29% of isolates),[15,16] and studies from France and England have identified the agent in 5% to 15% of encephalitis isolates.[17,18] VZV is thought to involve the CNS following spread of virus within neurons from reactivation in latently infected trigeminal or other ganglia. In contrast to HSV, VZV infects vascular endothelial cells of large and small cerebral vessels, at times followed by spread of the infection into brain parenchyma.[19] In this process, VZV may involve large or small vessels to produce focal or multifocal ischemic injury or may cause vessel wall necrosis with arterial dissection, aneurysm formation, or hemorrhage within the subarachnoid space or brain parenchyma.[15] The classic presentation is that of herpes zoster ophthalmicus, in which initial superficial zoster is followed days to weeks later by involvement of the carotid or middle cerebral artery with stroke and contralateral hemiparesis.[15] However, VZV vasculitis may occur without preceding

KEY POINTS

- Therapy with acyclovir should be initiated at presentation in suspected herpes simplex virus encephalitis.
- In contrast to herpes simplex virus, varicella-zoster virus typically infects endothelial cells to cause a vasculitis.

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KEY POINT

- Varicella-zoster virus vasculitis may occur without preceding rash and may involve virtually any vascular territory within the brain or spinal cord.

Case 2-1

Just before traveling back to her college, a 21-year-old woman reported smelling an unusual, extremely unpleasant odor that was inapparent to everyone else in her family. Upon arriving at college, she went to bed. Her roommate was unable to waken her the next morning, and she was brought to the emergency department. Neurologic examination revealed a deeply somnolent woman who did not respond to voice but would react to pain or to loud noise. The patient was without evidence of meningeal irritation, and optic discs were flat. Neurologic examination revealed a right-sided hyperreflexia and right Babinski sign. MRI showed increased signal in the left temporal lobe, insula, and cingulate gyrus on T2 and fluid-attenuated inversion recovery (FLAIR) images, with enhancement in these areas following gadolinium. CSF contained 41 red blood cells/μL and 327 white blood cells/μL, 87% lymphocytes and 13% polymorphonuclear leukocytes, protein concentration of 271 mg/dL, and glucose concentration of 73 mg/dL. The patient was given acyclovir. PCR analysis, reported 2 days later, was positive for HSV1. Acyclovir was continued for 21 days. Over that period of time the patient regained consciousness but remained significantly cognitively impaired. She left college for 18 months and during that time had very slow improvement in intellectual function. Although psychological testing at the end of that time indicated persistent loss of cognitive abilities, she was able to return to school and resume work in her major field of study. She did well scholastically but found that retention of new information was significantly more difficult for her than had been the case prior to her illness.

Comment. This patient's initial olfactory symptoms are classic for temporal lobe seizures and in patients presenting to the emergency department should raise the question of herpes simplex virus encephalitis and suggest initiation of acyclovir if evidence of inflammation is present on CSF examination. The time course of this patient's recovery, extending over many months, is common in patients after herpes simplex virus encephalitis.

cutaneous zoster, herpes zoster ophthalmicus, or oticus and may involve virtually any vascular territory within the brain or spinal cord. VZV vasculitis may be more severe in patients with AIDS or other immunosuppression.[15] CSF usually reveals a mononuclear pleocytosis, at times with red blood cells. Hypoglycorrhachia may be present.[15,20] VZV encephalitis is diagnosed by detection of VZV IgG in CSF; in some patients anti-VZV IgM can be detected as well.[15] Oligoclonal bands are commonly present and are reactive with VZV proteins.[15] PCR has a lower diagnostic sensitivity, and although it is helpful in confirming the diagnosis, a negative PCR result does not exclude VZV.[15] Treatment of VZV encephalitis is with acyclovir, 10 mg/kg every 8 hours for a minimum of 14 days. Oral prednisone, 1 mg/kg given daily for 5 days, may be used to treat the inflammatory component of the vasculitis; more prolonged treatment is avoided to prevent steroid-induced immunosuppression.[15]

West Nile Virus

West Nile virus (WNV) (**Table 2-1**) is a single-stranded RNA virus that belongs to the family Flaviviridae.[21,22] *Culex* species mosquitoes (predominantly *Culex tarsalis* and *Culex pipiens*) serve as the primary vector for human infection. The virus infects multiple species of animals and birds, in particular birds of the family Corvidae (eg, crows, jays, magpies,

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ravens). Large "die-offs" of corvids have been reported to precede some WNV outbreaks in humans. WNV produces infection predominantly in the summer and early autumn, when mosquitoes are most active. The virus has been identified in all US states except Alaska and Hawaii, and human infections have been reported in almost all of these states. In 2011, 690 cases were reported, of which 474 cases represented neuroinvasive disease with 43 deaths (*www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount11_detailed.htm*). Only 20% of patients develop symptomatic infection, most commonly West Nile fever, which is typically characterized by malaise, fatigue, anorexia, headache, nausea, vomiting, myalgia, fever, eye pain, and a nonspecific maculopapular rash. West Nile fever usually lasts less than 7 days, although occasional patients may remain symptomatic for as long as 6 weeks.[21] Less than 1% of infected patients develop neuroinvasive disease, which is more common in elderly and transplant patients. Neuroinvasive WNV infection may present as meningitis, which is clinically indistinguishable from other viral meningitides; as encephalitis; or as a poliomyelitis with infection of spinal motor neurons (**Case 2-2**). West Nile encephalitis usually presents with fever, headache, and altered mental status, stupor, or coma. Signs of parenchymal involvement may include stupor or coma, cerebellar ataxia, or movement disorders, including tremor, myoclonus, and parkinsonian symptoms.[23] The most-feared complication of neuroinvasive WNV infection is a syndrome of acute flaccid paralysis (**Case 2-2**).[23] Occasional patients may also develop chorioretinitis or vitritis. CSF in neuroinvasive WNV infection typically shows a mild elevation in pressure (less than 250 mm H_2O), lymphocytic pleocytosis, mild elevation of protein concentration, and a normal blood to CSF ratio of glucose concentration. Cell count is usually 50 cells/μL to 260 cells/μL but may be as high as 2600 cells/μL and may be heavily polymorphonuclear, particularly at presentation.[20,23] In one series, cell count was normal in 20% of patients.[24] Occasional patients have low sodium levels indicative of the syndrome of inappropriate antidiuretic hormone secretion. MRI is often normal, although occasional patients will have areas of increased signal on T2 and FLAIR imaging in the substantia nigra, basal ganglia, and thalamus.[25] A single, acute CSF specimen positive for WNV-specific IgM antibodies is diagnostic of ongoing WNV infection.[25] PCR is less reliable. Paired sera positive for WNV-specific IgM antibodies (a fourfold or greater rise in titer from the "acute" serum, obtained 0 to 7 days after symptom onset, and the "convalescent" serum, obtained 14 to 21 days after illness onset) also provide serologic confirmation. Treatment of WNV encephalitis is supportive. Prognosis for recovery after encephalitis is good, although recovery may be extremely prolonged. The likelihood of complete recovery after West Nile flaccid paralysis is poor.[23,25]

Other Arthropod-Borne Encephalitides

A variety of other arthropod-borne agents may infect humans and cause neurologic disease (**Table 2-1**). All but two of these agents are carried by mosquitoes, and rates of infection peak in midsummer through early autumn. The exceptions to this rule are Colorado tick fever and Powassan virus encephalitis, which are most frequent in late spring and early summer. Prior to the occurrence of WNV in the United States, St Louis encephalitis had been the most common arthropod-borne cause of encephalitis, and Eastern equine encephalitis virus the most dangerous. Other, less common agents include viruses of the

KEY POINTS

- Neuroinvasive West Nile virus infection may present as meningitis, encephalitis, or a poliomyelitislike syndrome of flaccid paralysis.
- Diagnosis of neuroinvasive West Nile virus is made by detection of antiviral IgM antibody in CSF.

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KEY POINT

■ St Louis encephalitis may occur as isolated cases or as urban outbreaks.

Case 2-2

During a late-summer weekend, an emergently hospitalized 48-year-old man was diagnosed with Guillain-Barré syndrome due to Epstein-Barr virus (EBV). The patient had been in good health until 10 days prior to admission, when he had a mild systemic illness with fever and myalgias that quickly resolved. On the day of admission, he awoke with bilateral leg weakness that subsequently involved his arms. Lumbar puncture revealed 32 cells/μL, 81% lymphocytes, 11% monocytes, and 8% neutrophils, with a protein concentration of 120 mg/dL, and a glucose concentration of 72 mg/dL. CSF PCR detected EBV DNA. By the time the neurologist saw the patient, he was in respiratory distress, with normal cranial nerves and sensory examination but with flaccid upper and lower extremities. Gadolinium-enhanced MRI showed increased signal in anterior horns at several levels in cervical and thoracic spine. WNV IgM was detected in both serum and CSF, with evidence of intrathecal antibody production. The patient became ventilator dependent, could not be weaned, and died several weeks later after ventilatory support was terminated at the request of the patient and his family.

Comment. Neuroinvasive WNV infection may cause meningitis, encephalitis, or a poliomyelitis with destruction of anterior horn cells. The virus should be a diagnostic consideration in patients presenting with any of these clinical features in summer or early autumn. EBV produces latent infection of B lymphocytes, and EBV DNA can thus be present in CSF in any infection resulting in a lymphocytic pleocytosis and may not signify that EBV is the causative agent.

California/LaCrosse serogroups, Powassan virus, and Colorado tick fever virus. Although laboratories routinely test for Western equine encephalitis virus, no human case of the infection has been reported since 1994 (*diseasemaps.usgs.gov/wee_historical.html*).

St Louis encephalitis virus, like WNV, is a mosquito-borne virus that is a member of the family Flaviviridae. Cases of neuroinvasive St Louis encephalitis have been reported from almost every state, but most occur in the central Midwest and Texas. St Louis encephalitis normally occurs as scattered rural cases but may also cause periodic urban epidemics. St Louis encephalitis resembles neuroinvasive West Nile disease, with the exception that cases of poliomyelitis are uncommon. Like WNV, St Louis encephalitis virus produces more severe disease in older adults. CSF findings are similar to those seen in West Nile encephalitis. Diagnosis, as in the case of neuroinvasive WNV infection, is by CSF IgM or by rise in antibody titers.

Eastern equine encephalitis virus (EEEV) is an agent of wading and migratory birds.[26] The virus is found predominantly along the Atlantic seaboard, the Gulf of Mexico coast, and states abutting Lake Michigan (Indiana, Michigan, and Wisconsin). Incidental exposure or spread of the virus into other mosquito species facilitates the spread of the virus into humans or other species. Although the virus does not usually produce severe infection in its natural hosts, it can produce severe epizootic infection in flocks of turkeys or in exotic or game-farm birds, as well as infections in horses. EEEV encephalitis is rare in humans, and reported cases over the past 4 decades have averaged only five cases annually. EEEV infections are less likely to be asymptomatic than are infections with other arthropod-borne

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agents, in particular in individuals at the extremes of life. In individuals between 4 and 55 years of age, the ratio of inapparent EEEV infections to cases of encephalitis is 29:1. In contrast, the ratio in infants is 8:1, and the ratio in individuals over 55 years of age is 16:1.[27] EEEV encephalitis is frequently preceded by a prodromal illness, which may include fever, headache, and abdominal pain that may occasionally be severe enough to mimic an acute abdominal emergency.[28] Onset of the encephalitis is frequently abrupt and severe, particularly in children or older adults. Presentation as a meningitis is unusual, and nearly 70% of patients present in stupor or coma.[28] Focal signs of corticospinal or extrapyramidal dysfunction may be present, and the illness may be complicated by focal or generalized seizures. Overall mortality approaches 36%, with 35% of survivors having significant neurologic impairment.[28]

Enteroviral Encephalitis

Enteroviruses are small, unenveloped single-stranded RNA viruses within the family Picornaviridae (**Table 2-1**). Although over 70 serotypes of enteroviruses have been identified, coxsackievirus A9 and echoviruses E7, E9, E11, E19, and E30 have accounted for 70% of all cultured isolates from CSF. Enteroviruses are disseminated by fecal-oral spread. Enteroviral infections tend to cluster during summer months, when conditions of sanitation tend to be most relaxed, but may also occur throughout the year. Although enteroviruses are most commonly associated with viral meningitis (see preceding article), they may also cause encephalitis and, rarely, paralytic disease. Enterovirus 71 most commonly causes the childhood conditions hand, foot, and mouth disease and herpangina. Hand, foot, and mouth disease is characterized by oral ulcers and a cutaneous rash, whereas lesions in herpangina are confined to the oropharynx. In addition, however, enterovirus 71 may produce more severe disease with involvement of brainstem or, less frequently, of cortex, cerebellum, or spinal ventral roots.[29] CSF findings in enteroviral meningoencephalitis are typically a mild lymphocytic pleocytosis, mild elevation of protein concentration, and normal glucose concentration.[20] During the first 24 to 48 hours of infection, CSF may contain a mixture of polymorphonuclear leukocytes and lymphocytes.[20] MRI studies are usually unremarkable but have shown cerebral or hippocampal lesions in some patients.[30] Enterovirus 71 has been associated with MRI abnormalities in brainstem and, less frequently, cortex or cerebellum; these may be best seen on diffusion-weighted images.[31] Pleconaril, an antiviral drug that binds to a hydrophobic pocket in the major protein of the enterovirus capsid VP1, has been shown to be of modest benefit in cases of enteroviral CNS infections but is not approved for use in the United States.[32,33]

Other Viral Agents

Mumps virus was formerly a major cause of viral meningoencephalitis but has essentially disappeared as a causative agent of meningoencephalitis in the Western world following introduction of widespread immunization. The mouse arenavirus, lymphocytic choriomeningitis virus, may cause meningitis or encephalitis in individuals exposed to infected mice or hamsters (**Table 2-1**).[34] The infection is rarely fatal, but recovery can be prolonged, and the infection is one of the few viral CNS infections that may cause hypoglycorrhachia. Parvovirus B19, the agent of the childhood condition erythema infectiosum (fifth disease), may cause encephalitis in both children and adults.[35] A number of viruses typically produce infections in immunocompromised patients and do so only infrequently in healthy individuals.

KEY POINTS

- Although enteroviral encephalitis occurs predominantly during summer months, sporadic cases occur throughout the year.
- Lymphocytic choriomeningitis virus encephalitis is associated with exposure to mice or infected pet hamsters.

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KEY POINT

■ Human herpesvirus 6 is a cause of encephalitis in transplant patients.

Cytomegalovirus is classically associated with encephalitis in neonates but may also cause encephalitis in adults and was a major complication of AIDS prior to the widespread use of highly active antiretroviral therapy. The virus may also cause encephalitis in other groups of immunocompromised patients and occasionally in individuals without underlying disease.[36] Herpesviruses 6 (HHV-6, associated with roseola infantum) and HHV-7 are frequent agents of early childhood infection and in this setting may result in convulsions and, rarely, encephalopathy.[37] HHV-6 has also been associated with encephalitis, often involving limbic structures, in transplant or other immunosuppressed individuals. In one study, HHV-6 was detected in the CSF of 40% of patients with encephalitis of otherwise undetermined cause, suggesting that it is an underappreciated causative agent for viral encephalitis.[38] EBV has been associated with a wide variety of neurologic syndromes, including meningitis, encephalitis, and postinfectious encephalitis. Although the virus is almost certainly responsible for cases of encephalitis, the association of EBV with individual cases is made difficult by the fact that the virus produces latent infection of lymphocytes, so detection of EBV by PCR methods in patients with CSF pleocytosis may or may not indicate that the virus is the causative agent. Treatment of cytomegalovirus encephalitis has been with ganciclovir, with foscarnet used as an alternative agent[33] (**Table 2-2**). Controlled trials of therapy have not

TABLE 2-2 Acute Treatment of Encephalitis

Condition or Agent	Therapeutic Agent	Dose and Duration of Treatment
Herpes simplex encephalitis	Acyclovir	10 mg/kg every 8 hours for 3 weeks
Varicella-zoster encephalitis	Acyclovir	10 mg/kg every 8 hours for 10 to 14 days
Cytomegalovirus encephalitis	Ganciclovir	Ganciclovir: 5 mg/kg every 12 hours for 14 to 21 days
	Foscarnet	Foscarnet: 60 mg/kg every 8 hours for 2 to 3 weeks
Enterovirus encephalitis	Pleconaril	Not available in the United States
Syphilis	Penicillin	20 million U/d IV for 10 days
Rocky Mountain spotted fever	Doxycycline	Adults: 100 mg every 12 hours
		Children: 2.2 mg/kg every 12 hours
Listeria monocytogenes	Ampicillin	Adults: 1 g/IV to 2 g/IV every 3 to 4 hours
Mycoplasma pneumoniae	Doxycycline	Adults: 100 mg every 12 hours Children: 2.2 mg/kg every 12 hours
	Erythromycin	Adults: 250 mg to 1000 mg every 6 hours depending on severity of infection
		Children 30 mg/kg/d to 50 mg/kg/d in four divided doses

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been reported for HHV-6 encephalitis; ganciclovir, foscarnet, and acyclovir have been used in individual patients.

Rabies virus is a rare cause of viral encephalitis in Western countries but remains a significant concern in countries where dogs are not routinely vaccinated. In the United States, rabies is most frequently associated with bat bites and less often with bites from raccoons, skunks, and foxes. Treatment of animal bites includes cleaning of the infected wound, injection of rabies immunoglobulin, and immunization with human diploid cell rabies vaccine (*www.cdc.gov/rabies/exposure/*). Only five individuals are known to have survived rabies. One surviving patient was treated with induced coma using ketamine, midazolam, and phenobarbital.[39,40] The possibility of rabies should be considered in patients known to have suffered animal bites or to have been exposed to bats, and in patients from underdeveloped countries. It is important to remember that the incubation period of rabies may be up to several years and that the puncture wounds produced by bat bites may be so small as to escape detection.[41]

Encephalitis Caused by Nonviral Agents

A number of treatable bacterial and other organisms may produce brain parenchymal involvement to mimic viral encephalitis (**Table 2-1**). Meningovascular syphilis may present with subacutely or acutely progressive symptoms, and parenchymal changes that resemble HSV encephalitis may be seen on MRI (**Figure 2-2**).[42] *Listeria monocytogenes* may produce rhombencephalitis or brainstem encephalitis in both immunosuppressed and immunologically healthy individuals. *L. monocytogenes* may occasionally produce cortical encephalitis resembling HSV encephalitis on MRI.[43] *Mycoplasma* has most commonly been associated with postinfectious encephalitis (see below) but may also involve the CNS acutely. *Rickettsia rickettsii*, the agent of Rocky Mountain spotted fever, can produce a cerebral vasculopathy and may do so in the absence of a cutaneous rash.[44] The disease, spread by ticks, occurs in most states but is prevalent along the Mid-Atlantic seaboard. Cases occur throughout the year but are most common between April and September (*www.cdc.gov/rmsf/stats/*). Other rickettsial species, including *Rickettsia prowazekii*, the agent of epidemic typhus, have also been associated with human infection.[45] Treatment regimens for these infections are shown in **Table 2-2**.

KEY POINT

- Rocky Mountain spotted fever may cause systemic and CNS infection in the absence of a cutaneous rash.

Autoimmune Encephalitis

An emerging concern in the diagnosis of patients presenting with encephalitis is the recognition that paraneoplastic and other autoimmune conditions may present as limbic or other encephalitis (**Table 2-3**). An encephalitic presentation—usually limbic encephalitis—has been reported with paraneoplastic autoantibodies, such

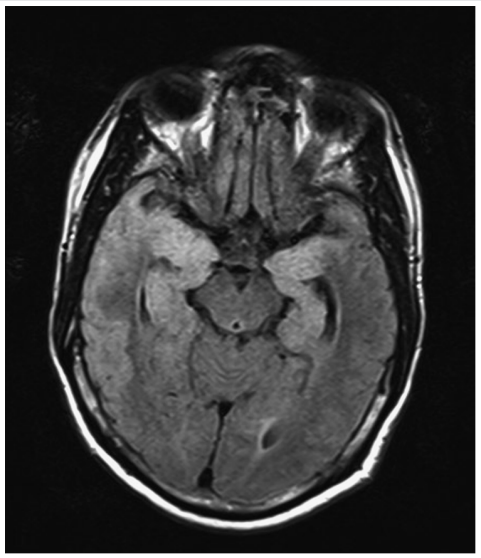

FIGURE 2-2 MRI showing temporal lobe and hippocampal involvement suggestive of herpes simplex virus encephalitis in a patient with meningovascular syphilis who presented with stupor.

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KEY POINT

■ Antibodies to neuronal surface receptors, in particular NMDA receptors, may be associated with limbic and other encephalitides.

as anti-Hu, anti-Ri, or anti-Ma1 or Ma2, as well as in patients expressing a number of autoantibodies against neural surface antigens, including the NMDA receptor (NMDAR), the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR), the metabotropic glutamate receptor subunit mGluR5, components of the voltage-gated potassium channel complex (leucine-rich, glioma inactivated 1, and contactin-associated proteinlike 2), and γ-aminobutyric acid B receptors.[46] These conditions differ from acute viral encephalitis in that their onset is usually more gradual and they tend to be progressive over time. The most frequent of these appears to be encephalitis associated with anti-NMDAR antibodies. The presence of these antibodies was initially found in patients with ovarian teratomas. However, in epidemiologic studies by the California Encephalitis Project, anti-NMDAR encephalitis was identified over 4 times more frequently

TABLE 2-3 Major Antineuronal Antibodies Associated With Encephalitis

Antibody	Major Clinical Features	Major Tumor Associations
Directed against intraneuronal antigens		
Anti-Hu[a]	Limbic, brainstem, or cerebellar encephalitis	Small cell lung cancer, other small cell or neuroendocrine tumors
Anti-Ri[a]	Limbic, brainstem, or cerebellar encephalitis	Small cell lung cancer, breast cancer
Anti-Ma 1 and 2[a]	Limbic encephalitis (especially Ma2), diencephalic or brainstem encephalitis	Varying neoplasms (Ma1), testicular neoplasms (Ma2)
Directed against neuronal receptor proteins or other neuronal antigens		
Anti-NMDAR	Limbic encephalopathy with autonomic features, seizures, respiratory failure	Ovarian teratomas (absent in most cases)
Anti-AMPAR	Limbic encephalitis	Thymus cancer, lung cancer, breast cancer
Anti-mGluR5	Limbic encephalitis	Hodgkin disease
Anti-GABA(B)	Limbic encephalitis	Small cell lung cancer, other neoplasms (~45% of patients)
Anti-VGKC complex (anti-LGi1, anti-CASPR2)	Limbic encephalitis, faciobrachial dystonic seizures or other seizures (anti-LGi1) >60% of patients may have hyponatremia	No clear tumor association

NMDAR = NMDA receptor; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; mGluR5 = metabotropic glutamate receptor 5; GABA(B) = γ-aminobutyric acid receptor type B; VGKC = voltage-gated potassium channel; LGi1 = leucine-rich, glioma inactivated 1; CASPR2 = contactin-associated proteinlike 2.

[a] The role of antibodies directed against internal neuronal proteins in disease causation has not been determined.

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than HSV1, WNV, or VZV and was the leading cause of identified encephalitis.[46] In this study, 65% of cases occurred in patients aged 18 years or younger.[46] The condition was more common in females and tended to be characterized by seizures, language dysfunction, psychosis, autonomic instability, and EEG abnormalities.[46] CSF usually showed a mild lymphocytic pleocytosis (average 23 cells/μL; range 0 to 252 cells/μL), normal or mildly elevated protein concentration, and normal glucose concentration. MRI showed temporal lobe abnormalities in 48% of patients.[46] Most patients had no teratomas or other neoplasms.

Standardized regimens of treatment for autoimmune encephalitis have not yet been developed. Treatment has relied on corticosteroids, with plasma exchange, IV immunoglobulin (IVIg), and immunosuppressive or immunomodulatory agents, such as cyclophosphamide or rituximab.[47] Patients with antibody response against cell surface antigens have, in general, responded well to treatment.[44] Patients with antibodies directed against intracellular proteins, such as anti-Hu, have tended to be much more resistant to treatment.[47]

KEY POINT

- Patients developing limbic encephalitis in association with paraneoplastic autoantibodies such as anti-Hu are less responsive to treatment than those whose encephalitis is caused by antibodies to neuronal surface antigens.

POSTINFECTIOUS ENCEPHALITIS

Postinfectious encephalitis was traditionally defined as an acute, monophasic, demyelinating illness that usually occurs within 2 to 4 weeks of viral or other illness and believed to be an immune attack on components of myelin or other related antigens (**Case 2-3**). Although postinfectious encephalitis has most frequently been associated with viral infections, cases have also been associated with infections due to a wide variety of other agents (**Table 2-4**).[48] The condition is characterized by multifocal perivenous demyelination and bears strong similarity to

Case 2-3

A 16-year-old boy had been in good health until 2 weeks prior to admission, when he developed a flulike illness characterized by fever, myalgias, and cough. He recovered from the illness without difficulty but on the morning of admission was confused upon awakening and then became unresponsive. General physical examination was normal except for very mild nuchal rigidity. Neurologic examination revealed the patient to be stuporous but able to move all four extremities in response to pain. The patient had brisk reflexes with bilateral Babinski signs. CSF contained 34 white blood cells, protein concentration of 78 mg/dL, and glucose concentration of 65 mg/dL with a simultaneous blood glucose level of 104 mg/dL. MRI revealed multiple irregular areas of increased signal on T2 and FLAIR imaging, with gadolinium enhancement of two of the lesions. All cultures were negative, as were test results for PCR, HSV, VZV, enteroviruses, EBV, and *Mycoplasma pneumoniae*. CSF and serum serology for WNV was negative, but the patient had elevated antibody titers to *M. pneumoniae*. The patient was diagnosed with postinfectious encephalomyelitis and treated with a 5-day course of IV methylprednisolone 1000 mg/d, followed by a prednisone taper. He regained consciousness over the next several days and improved steadily, returning to school on a part-time basis after 3 months. When seen in follow-up at 6 months, he was neurologically healthy.

Comment. This patient's course of an acute neurologic illness following a systemic illness is classic for postinfectious encephalitis, as were the changes seen on MRI. Prognosis for complete recovery is excellent in most cases.

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KEY POINTS

- Postinfectious encephalitis may be associated with a wide variety of preceding systemic infections.
- Postinfectious encephalitis is most common in children but may also affect adults.

two other conditions: (1) postvaccinal encephalomyelitis that follows immunization and (2) the experimental autoimmune demyelinating disease, experimental allergic encephalomyelitis.[48,49] In recent years, postinfectious and postvaccinal encephalomyelitis have been grouped under the common term acute disseminated encephalomyelitis (ADEM).[49,50] ADEM is not the consequence of a specific infection or immunization but rather a final common pathway of autoimmune CNS injury triggered by many agents or immunogens.

Postinfectious encephalitis is most common in children but can also occur in adults. The condition is rare in older adults. In children, the peak age at onset is 5 to 8 years. The disorder is more common in winter and spring months. A study from San Diego County gave a mean incidence of 0.4 per 100,000 per year among individuals younger than 20 years. Of these patients, 93% reported

TABLE 2-4 Major Infectious and Vaccine Associations of Postinfectious Encephalitis and Acute Disseminated Encephalomyelitis[a]

- **Viruses**
  - Smallpox (1:1000—historical)
  - Rubella (1:20,000)
  - Varicella (1:10,000)
  - Measles
  - Mumps
  - Influenza A (H1N1)
  - HIV
  - Human T-cell lymphotrophic virus type I
  - Hepatitis A, B, and C
  - Herpes simplex virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus type 6
  - Enteroviruses
  - Coronaviruses
  - Hantavirus (Puumala virus)
- **Bacteria**
  - Streptococcus A
  - Chlamydiae
  - Campylobacter
  - *Mycoplasma pneumoniae*
  - Legionella
  - Leptospira
  - *Rickettsia rickettsii*
  - *Salmonella typhi*
  - *Mycobacterium tuberculosis*
- **Protozoa and Other**
  - *Toxoplasma gondii*
  - Plasmodium species
- **Immunizations**
  - Rabies
    - Neural type (Semple vaccine) (1:300 to 1:7000)
    - Human diploid cell vaccine (<1:75,000)
  - Diphtheria-tetanus (0.9:100,000)
  - Poliovirus
  - Varicella (3:665,000)
  - Smallpox (0.1:100,000)
  - Japanese encephalitis (0.2:100,000)
  - Hepatitis B
  - Influenza
  - Yellow fever

[a] Adapted from Sonneville R, et al, J Infect.[48] © 2009, with permission from Elsevier. *www.sciencedirect.com/science/article/pii/S0163445309000759*.

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symptoms of infection within 21 days of the onset of illness and an additional 5% had received immunization within the preceding month.[51] The onset of ADEM may be preceded by fever, malaise, headache, nausea, or vomiting. These prodromal symptoms are followed by the abrupt—at times fulminant—onset of illness. Altered mental status, which is almost universal in children, may range from drowsiness to frank coma. Meningeal signs are common. Focal or multifocal neurologic signs may involve brain, spinal cord, or optic nerves and include unilateral or bilateral corticospinal tract signs, hemiplegia, ataxia, cranial nerve palsies, and visual loss. Hemispheric involvement may produce aphasia or parietal lobe findings of sensory loss or neglect. Focal or generalized seizures may occur; these are rare in adults but common in young children, occurring in up to 70% of children younger than 5 years, 80% of whom may develop status epilepticus.[52] In many cases, ADEM is confined to the brain and spinal cord. However, the disorder may simultaneously cause optic neuritis or involve the peripheral nervous system. The simultaneous occurrence of central and peripheral demyelinating events appears to be more common in adults than in children.[53]

Postinfectious encephalitis should be considered in the differential diagnosis of any patient—in particular any child—presenting with evidence of acute, inflammatory neurologic illness in the setting of a previous systemic illness. Making the diagnosis, however, should be preceded by ruling out actual CNS infection. The presence of multifocal neurologic signs should raise the level of suspicion of ADEM, as should the presence of signs referable to both the CNS and the peripheral nervous system. CSF typically shows a lymphocytic pleocytosis, although roughly 30% of patients will have a mixed pleocytosis with a neutrophilic predominance.[48] The frequency with which oligoclonal bands are detected is controversial.[48,54] Traditionally, the presence of oligoclonal bands was considered unusual. However, oligoclonal bands were detected in 20% of patients with ADEM in one study.[55] In another study, oligoclonal bands were reported in 65% of individuals presenting an illness initially diagnosed as ADEM; however, over 50% of these patients were subsequently diagnosed with multiple sclerosis.[54]

MRI with gadolinium enhancement is the diagnostic study of choice. T2 and FLAIR images classically show multiple, large, asymmetric, irregularly shaped lesions involving subcortical white matter and the gray-white junction of both cerebral hemispheres (**Figure 2-3**).[54] Periventricular white matter may be involved, but lesions confined to the corpus callosum are unusual.[53] Gadolinium enhancement is seen in 30% to 100% of

KEY POINTS

- Patients presenting with postinfectious encephalitis almost always have alteration in level of consciousness; meningeal signs are common.
- MRI is the diagnostic procedure of choice in patients with suspected postinfectious encephalitis.

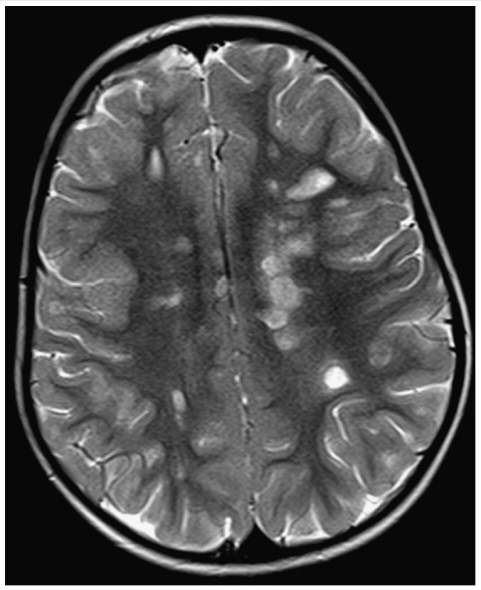

FIGURE 2-3 MRI showing multiple areas of increased T2 signal consistent with demyelination in a patient with acute disseminated encephalomyelitis.

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KEY POINTS

- Treatment of postinfectious encephalitis is with IV methylprednisolone. Plasma exchange or IV immunoglobulin should also be considered.
- Patients presenting with suspected encephalitis require presumptive treatment with antibiotics and acyclovir until bacterial infection and herpes simplex virus encephalitis have been ruled out.

patients and may vary with the stage of the disease.[51] Ring-enhancing lesions may be found but should raise particular concern about brain abscess or other CNS infection.[52] Spinal cord involvement, usually with extensive cord edema and swelling, may occur in children or adults and commonly affects the thoracic cord.[52] Despite their worrisome appearance at presentation, most lesions resolve over time.[53]

Randomized controlled trials of different therapeutic agents do not exist for ADEM in children or adults, nor do studies exist comparing one agent with another.[48,53] Class 3 evidence exists for the use of methylprednisolone, usually used as 1 g per day for 5 days.[56] Plasma exchange (usually five exchanges) or IVIg, given to a total dose of 1 g/kg to 2 g/kg during 3 to 5 days, has also been used, either in combination with methylprednisolone or after methylprednisolone failure.[48] A variety of other immunosuppressive agents, including cyclophosphamide, have been used in individual cases.

The outcome of ADEM is usually favorable. In most studies, 50% to 75% of patients undergo complete recovery over time[52,54]; up to 90% of children may undergo essentially complete recovery, although some may have persistent mild neurocognitive deficits.[52,53] The likelihood of residual deficit may also be greater in patients presenting with optic neuritis.[52] In recent years it has been realized that ADEM may be recurrent.[49] An ongoing diagnostic challenge is the recognition that a subset of patients, perhaps as high as 30%, will later develop multiple sclerosis.[49,55]

Acute Hemorrhagic Leukoencephalitis

In occasional patients (2% of a large cohort of children[52]), postinfectious encephalitis may be much more severe, presenting with fulminant hemorrhagic demyelination and cerebral edema. MRI studies, in addition to findings suggestive of demyelination, hemorrhage, and edema, may show evidence of ischemia on diffusion-weighted images.[57] This disorder has also been termed acute necrotizing hemorrhagic leukoencephalitis or Weston Hurst syndrome. Unlike postinfectious encephalitis, acute necrotizing hemorrhagic leukoencephalitis has a high rate of mortality. In individual reports, however, some patients may survive following aggressive and early treatment using combinations of methylprednisolone, IVIg, plasma exchange, or cyclophosphamide.[53]

APPROACH TO THE PATIENT WITH ENCEPHALITIS OR POSTINFECTIOUS ENCEPHALITIS

The possibility of meningitis or encephalitis should be suspected in any severely ill patient presenting with alteration in consciousness, with or without focal neurologic signs. Signs suggesting temporal lobe involvement should hint at HSV encephalitis but may occasionally be caused by other agents. The possibility of arthropod-borne encephalitis, enterovirus encephalitis, or Rocky Mountain spotted fever should be kept in mind in patients presenting during summer months. In areas of geographic prevalence, a history of tick bite may suggest Rocky Mountain spotted fever. The presence of a generalized skin rash may suggest Rocky Mountain spotted fever or WNV infection. Presentation with abrupt onset of impaired consciousness with multifocal neurologic signs following a systemic infection of almost any sort, especially in childhood, should raise the possibility of postinfectious encephalitis.

At presentation, the overriding clinical concern is that the patient may have acute bacterial meningitis, and patients should be treated with antibiotics until bacterial meningitis has been excluded.

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HSV encephalitis should be suspected—and, like bacterial meningitis, treated on suspicion—in any individual presenting with altered consciousness and evidence of inflammatory CSF response, unless some other cause for the condition is identified at presentation. MRI with gadolinium is an essential diagnostic tool in HSV encephalitis; however, it should be kept in mind that neurosyphilis and infections by other agents, including *L. monocytogenes,* may occasionally mimic MRI findings seen in HSV encephalitis.

The supportive care of patients with encephalitis or postinfectious encephalitis is both complex and demanding. Treatment of seizures is usually straightforward but may occasionally require aggressive therapy. Some patients will develop the syndrome of inappropriate antidiuretic hormone secretion and may require careful attention to electrolyte balance. Cerebral edema may become a major concern. Although dexamethasone has been used for many years to reduce cerebral edema in patients with encephalitis, its efficacy has not been established and is currently being evaluated in patients with HSV encephalitis in a multicenter trial. Decompressive craniectomy has been associated with patient survival in one case of HSV encephalitis with intractable cerebral edema.[58] In severely ill patients, survival may depend heavily on meticulous attention to details of daily care. Because recovery from encephalitis or postinfectious encephalitis may be extremely prolonged, patients may not reach optimal improvement for weeks or months. In such cases, the recovering patient and his or her family may need ongoing counseling over time.

KEY POINT

- Patient survival in encephalitis may depend on control of intracranial pressure and meticulous attention to details of electrolyte status and general patient care.

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