Viral encephalitis in adults

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INTRODUCTION

Viral infections of the central nervous system (CNS) result in the clinical syndromes of aseptic meningitis or encephalitis [1-3]. The true incidence of these infections is difficult to determine because many cases are unreported, the diagnosis may not be considered, or a specific viral etiology is never confirmed. However, these disorders occur with sufficient frequency that clinicians should be familiar with the clinical manifestations, diagnostic techniques, and therapeutic options [4].

This topic will review the major distinguishing features between aseptic meningitis and viral encephalitis, as well as the viral etiologies that can cause encephalitis. Topic reviews that discuss the clinical manifestations, diagnosis, and pathogens associated with aseptic meningitis in adults and viral encephalitis in children are found elsewhere. (See "Aseptic meningitis in adults" and "Acute viral encephalitis in children: Clinical manifestations and diagnosis" and "Acute viral encephalitis in children: Treatment and prevention" and "Acute viral encephalitis in children: Pathogenesis, epidemiology, and etiology".)

MENINGITIS VERSUS ENCEPHALITIS

The presence or absence of normal brain function is the important distinguishing feature between encephalitis and meningitis. Patients with meningitis may be uncomfortable, lethargic,

or distracted by headache, but their cerebral function remains normal. In encephalitis, however, abnormalities in brain function are a differentiating feature, including altered mental status, motor or sensory deficits, altered behavior and personality changes, and speech or movement disorders. Seizures and postictal states can be seen with meningitis alone and should not be construed as definitive evidence of encephalitis. Other neurologic manifestations of encephalitis may include hemiparesis, flaccid paralysis, and paresthesias.

However, the distinction between the two entities can be frequently blurred since some patients may have both a parenchymal and meningeal process with clinical features of both. The patient is usually labeled as having meningitis or encephalitis based upon which features predominate in the illness although meningoencephalitis is also a common term that recognizes the overlap. The importance of distinguishing between encephalitis and aseptic meningitis relates to the fact that the likely cause of each syndrome is different. Some viral agents are more likely to cause aseptic meningitis, and others are more likely to cause encephalitis. (See "Aseptic meningitis in adults".)

VIRAL VERSUS POSTINFECTIOUS ENCEPHALITIS

Viral encephalitis can be either primary or postinfectious (ie, it occurs after the infection has resolved) [5].

- Primary infection is characterized by viral invasion of the central nervous system (CNS). Neuronal involvement can be identified on histologic examination, which may show inclusion bodies on light microscopy or viral particles on electron microscopy. The virus can often be cultured from brain tissue.

- In postinfectious encephalitis (also called acute disseminated encephalomyelitis, or ADEM), a virus cannot be detected or recovered, and the neurons are spared [5]. However, perivascular inflammation and demyelination are prominent in this entity. The inability to recover a virus and the type of histologic abnormalities observed suggest that postinfectious encephalitis is an immune-mediated disease [6]. (See "Acute disseminated encephalomyelitis (ADEM) in adults".)

Despite the differences in pathogenesis and histologic findings, the clinical significance of viral versus postinfectious encephalitis is often limited. It is also important to note that a number of viral infections, such as measles, varicella, or rubella, can produce either syndrome. (See 'Viral pathogens' below.)

VIRAL PATHOGENS

A wide variety of different viruses can infect the central nervous system (CNS). Most viruses are capable of causing either meningitis or encephalitis, although, in general, a given virus is more likely to cause one syndrome rather than the other. (See 'Meningitis versus encephalitis' above.)

A common cause of sporadic encephalitis is herpes simplex virus (HSV) type 1 [7]. It is important to diagnose this virus because it is treatable, and the success of treatment is related to how early therapy is initiated. (See "Herpes simplex virus type 1 encephalitis".)

Other viral pathogens may be suggested by geographic location (eg, Eastern equine encephalitis in North America and Japanese encephalitis in Asia) and epidemiologic clues, such as exposure history (eg, bat exposure or dog bite and rabies), regional outbreaks (eg, enterovirus type 71 in Denver, Colorado) [8], and clinical clues, such as profound weakness and rash with West Nile. Uncommon causes include varicella zoster virus, Epstein-Barr virus, HIV, human herpes virus-6, parvovirus, and Zika virus [9-13]. (See "St. Louis encephalitis" and "Arthropod-borne encephalitides" and "Clinical manifestations and diagnosis of rabies".)

Historical clues — The cause of viral encephalitis is apparent in some cases because of an unusual exposure history or a characteristic clinical presentation. In the absence of these findings, epidemiologic information such as seasonal occurrence or exposures may be helpful in establishing a specific diagnosis (table 1). Examples include:

- Arboviruses (eg, eastern equine, western equine, St. Louis, Venezuelan equine encephalitis, and West Nile virus) cause disease when mosquitoes are active, whereas HSV can occur at any time. In contrast, walking in woods or marshy areas with high tick populations might suggest tick-borne encephalitides seen in Eastern Europe, Colorado tick fever (western United States), and Powassan virus encephalitis. Powassan virus is transmitted by *Ixodes* ticks and should be considered in regions where these ticks are found (eg, eastern Canada and the north central and northeastern United States). Other tick-borne but nonviral etiologies include Lyme disease and Rocky Mountain spotted fever. (See "Epidemiology and pathogenesis of West Nile virus infection" and "St. Louis encephalitis" and "Arthropod-borne encephalitides" and "Epidemiology, clinical manifestations and diagnosis of Rocky Mountain spotted fever".)

- West Nile virus has been by far the most common cause of proven viral encephalitis in the United States [14,15]. West Nile virus first appeared in the United States in 1999, even though it had already been established in Africa, Asia, and Europe, and then spread rapidly across the country. The incidence of other arboviruses varies significantly based upon

geographic region. As examples, in the Northeast, there has been a steady increase in Powassan over the past several years [16], and there was a notable increase in eastern equine encephalitis in 2019 [17]. St. Louis encephalitis virus infection occurs in North America, predominantly throughout the Midwest and South in the United States. In patients with the appropriate travel history, nonviral mosquito-borne illnesses, such as cerebral malaria, may be a consideration. (See "Clinical manifestations and diagnosis of West Nile virus infection" and "St. Louis encephalitis" and "Malaria: Clinical manifestations and diagnosis in nonpregnant adults and children" and "Arthropod-borne encephalitides".)

- Both geography and animal exposure can broaden the diagnostic considerations of etiologic agents. Nipah virus encephalitis, which appeared in Malaysia and Singapore and is now present in Bangladesh, may be associated with exposure to pigs or bats [18-20]. Human infection with Hendra virus, which is seen in Australia, results from direct contact with infected horses. Avian influenza infection was associated with encephalitis in two patients from Vietnam; the source of exposure was unclear but both children swam in a canal that was frequented by ducks [21]. Lymphocytic choriomeningitis virus (LCMV) is a human-acquired zoonosis caused by a rodent-borne arenavirus, which can be transmitted through exposure to secretions of mice, rats, and hamsters. Encephalitis resulting from a bornavirus was reported in three German breeders of variegated squirrels; the virus was also detected in a squirrel from the breeding population of one of the patients [22]. (See "Nipah, Hendra, and other henipaviruses" and "Avian influenza: Epidemiology and transmission" and "Aseptic meningitis in adults".)

- Prior history of an animal exposure or bite may also suggest the possibility of rabies encephalitis; however the absence of such a history does not eliminate the diagnostic possibility of rabies. (See "Clinical manifestations and diagnosis of rabies".)

CLINICAL MANIFESTATIONS

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

The clinical presentation of aseptic meningitis is generally nonspecific, with fever, headache, nausea, and vomiting, occasionally accompanied by photophobia and a stiff neck. Physical examination characteristically reveals signs of nuchal rigidity, but its absence does not rule out the diagnosis. (See "Aseptic meningitis in adults".)

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

- Parotitis strongly suggests the diagnosis of mumps encephalitis in an unvaccinated patient with mental status changes. (See "Mumps".)
- Flaccid paralysis, a polio-like presentation, that evolves into an encephalitis strongly suggests the possibility of West Nile virus infection [23]. In fact, it has been misdiagnosed as Guillain-Barré syndrome. A maculopapular rash is also seen in approximately half of patients with this infection and is not expected in other viral encephalitides.
- Tremors of the eyelids, tongue, lips, and extremities may suggest the possibility of St. Louis encephalitis or West Nile encephalitis in the appropriate geographic location or travel history.
- Findings of hydrophobia, aerophobia, pharyngeal spasms, and hyperactivity suggest encephalitic rabies. Atypical presentations of rabies include seizures, cranial nerve palsies, and myoclonus.
- Grouped vesicles in a dermatomal pattern may suggest varicella zoster virus (VZV), which can occasionally cause encephalitis; however, the absence of rash does not eliminate VZV from consideration [24]. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster".)

Imaging — Results of imaging in patients with encephalitis may or may not demonstrate abnormal radiographic findings on computed tomography (CT) or magnetic resonance imaging (MRI) modalities. CT scanning is useful to rule out space-occupying lesions. MRI is sensitive for detecting demyelination, which may be seen in other clinical states presenting with mental status changes (eg, acute disseminated encephalomyelitis [ADEM] or possibly a relatively rapid presentation of progressive multifocal leukoencephalopathy). If present, the location of abnormal signal can sometimes be suggestive of specific etiologies:

- Temporal lobe involvement is strongly suggestive of herpes simplex virus (HSV) encephalitis, although other herpes viruses (eg, VZV, Epstein-Barr virus, human

herpesvirus 6) can also produce this clinical picture [25,26].

- Involvement of the thalamus or basal ganglia may be observed in the setting of encephalitis due to respiratory viral infection, Creutzfeldt-Jakob disease, arbovirus, and tuberculosis [27-29].

- In a study of 17 patients with confirmed West Nile infection, MRI imaging demonstrated a variety of abnormalities in the basal ganglia, thalami, mesial temporal structures, brainstem, and cerebellum in eight patients [30]. Three patients with muscle weakness also had abnormalities noted in the spinal cord and cauda equina.

- The presence of hydrocephalus may suggest nonviral etiologies such as bacteria, fungal, or parasitic agents [26].

- MRI during postinfectious encephalitis may demonstrate multifocal lesions mainly involving supratentorial white matter [6]. (See 'Viral versus postinfectious encephalitis' above.)

Electroencephalograph — Electroencephalography is often abnormal in acute encephalitis. Focality in the temporal lobe region is suggestive of HSV encephalitis, as noted above [31].

Cerebrospinal fluid findings — Examination of the cerebrospinal fluid (CSF), although not diagnostic, will usually confirm the presence of inflammatory disease of the central nervous system (CNS). The findings with aseptic meningitis and encephalitis are generally indistinguishable (although, rarely, there may be few, if any, CSF abnormalities with a pure encephalitis).

The following findings are characteristic of viral CNS infections (table 2):

- Increased white blood cell (WBC) count, but usually less than 250/mm^3. The differential shows a predominance of lymphocytes, although early infection may reveal a predominance of neutrophils. In the latter setting, a repeat CSF cell count eight hours later will generally show a shift from neutrophils to lymphocytes [32].

- Elevated protein concentration, but usually less than 150 mg/dL.

- Usually normal glucose concentration (>50 percent of blood value), but moderately reduced values are occasionally seen with HSV, mumps, or some enteroviruses.

- Red cells are usually absent (in a nontraumatic tap); their presence in the appropriate clinical setting suggests HSV-1 infection or other necrotizing encephalitides [33].

These findings are generally quite different from those associated with bacterial meningitis, which include a higher WBC count in the CSF (>2000/mm^3) with neutrophil predominance, a higher protein concentration (>200 mg/dL), and usually hypoglycorrhachia (table 2). (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Cerebrospinal fluid analysis'.)

However, exclusion of bacterial meningitis based only upon individual CSF parameters can be difficult, since the spectrum of CSF values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value (table 2). This was illustrated in a review of 296 episodes of community-acquired bacterial meningitis; 50 percent had a CSF glucose above 40 mg/dL (2.2 mmol/L), 44 percent had a CSF protein below 200 mg/dL, and 13 percent had a CSF white cell count below 100/microL [34]. In addition, if the patient received antibiotics prior to examination of the CSF, that may further confuse the clinical picture. Although prior administration of antimicrobials tends to have minimal effects on the chemistry and cytology findings, it can reduce the yield of Gram stain and culture. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'If LP is delayed or deferred'.)

DIAGNOSIS

Analysis of the cerebrospinal fluid (CSF) is required as an initial diagnostic step in patients with suspected viral encephalitis.

- The opening CSF pressure should be noted and CSF should be analyzed for cell count, glucose, and protein.
- In addition to this basic testing, the initial work-up for the etiology of a viral infection should generally include: CSF polymerase chain reaction (PCR) testing for herpes simplex virus (HSV)-1, HSV-2, VZV, and enteroviruses.
- Additional testing (eg, serology for arboviruses, HIV testing) should be considered based on geographic considerations, the clinical presentation, and the exposure history. (See 'Historical clues' above.)
- Diagnostic evaluation for nonviral infectious (eg, bacteria, fungi, and mycobacteria) and noninfectious etiologies should also be considered. (See 'Differential diagnosis' below.)

The most important viral etiology to rule out in a patient with encephalitis is HSV, since this clinical entity is usually fatal if untreated. HSV should be considered, particularly if there is temporal lobe focality suggested by symptoms, signs, or imaging studies. Diagnosis is most

readily made by detecting HSV DNA by PCR on CSF [35]. While awaiting confirmation, empiric therapy with acyclovir should be initiated. (See 'Empiric therapy' below.)

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

Rabies should also be considered in any patient with an undiagnosed encephalitis even with a negative exposure history. Diagnosis of rabies requires several specimens including saliva, skin biopsy, and CSF since the sensitivity of any single test is limited. (See "Clinical manifestations and diagnosis of rabies".)

In summary, the battery of initial diagnostic tests often includes CSF culture, PCR, and serology for the suspected pathogens. Further testing may also be required if the patient is not improving. However, even with use of PCR testing, the etiology in many cases remains undefined [35]. (See 'Definitive diagnosis' below.)

Culture — Viral culture has been routinely ordered by most clinicians after obtaining CSF samples. However, one review demonstrated that viruses were recovered from only 6 percent of 22,394 viral cultures of CSF samples [36]. Furthermore, in a subset analysis by suspected etiology, 1290 CSF samples were evaluated for HSV by PCR and culture. Of these, only nine samples were positive for HSV and all were identified only by PCR testing.

In most circumstances, PCR testing has replaced viral culture in the work-up of the CSF. Culture may still be important when rare causes of encephalitis are being considered (eg, influenza, parainfluenza, measles, mumps) for which PCR testing is unavailable.

Polymerase chain reaction — With the advent of PCR technology, significant advances have been made in the ability to diagnose viral infections of the central nervous system (CNS) [37]. CSF PCR should be performed for HSV-1, HSV-2, VZV, and enteroviruses. Identification of HSV-1 in the CSF is a rapid, sensitive, and specific diagnostic test for HSV-1 encephalitis [38]. Likewise, identification of HSV-2 in CSF is a rapid diagnostic test for HSV-2 meningitis.

PCR testing for other viruses will depend on the clinical situation, epidemiology, and availability. For West Nile virus, PCR testing is not as sensitive as IgM serology (the preferred test). (See "PCR testing for the diagnosis of herpes simplex virus in patients with encephalitis or meningitis".)

Serology — Serologic testing is most important for patients who are not improving and who do not have a diagnosis based upon PCR. Most viral etiologies require paired sera for diagnosis;

thus it is prudent to save serum in the setting of acute illness that can later be used if necessary. Convalescent serology should be obtained no sooner than three weeks after the onset of the clinical illness. As an example, the presence of IgM antibodies in a single serum provides presumptive evidence of St. Louis encephalitis; however, a significant rise or fall between appropriately timed acute convalescent or early-late convalescent sera is diagnostic.

West Nile has emerged as the most common cause of viral encephalitis in the United States. A single specimen looking for IgM antibodies in the serum or CSF is sufficient for diagnosis. A single serum specimen can also be used to diagnose mumps. Serology may also be helpful in obtaining evidence for primary Epstein-Barr virus infection, a rare cause of meningoencephalitis. (See "St. Louis encephalitis" and "Clinical manifestations and diagnosis of West Nile virus infection".)

Brain biopsy — As a last resort, brain biopsy can be considered in the patient if the etiology of encephalitis is still unknown.

Definitive diagnosis — The frequency of identification of a specific agent in patients with aseptic meningitis and encephalitis has been variable and depends upon the population studied and the mode of testing. The following illustrates the range of findings:

- In a report of 432 high-risk patients who underwent brain biopsy of presumptive herpes simplex encephalitis, 45 percent had the diagnosis confirmed, 9 percent had another virus detected, and 9 percent had another treatable cause [33]. This underscores the point that the clinical diagnosis of HSV encephalitis is often incorrect and needs to be confirmed by PCR testing.

- Among 334 patients with a case definition of encephalitis in the California Encephalitis Project, a confirmed or probable viral cause was present in 9 percent [39]; a possible cause was identified in 12 percent, a noninfectious etiology in 10 percent, and a bacterial cause in 3 percent. Despite extensive testing, 62 percent of cases were unexplained.

- In a series from the New York State Department of Health of 106 patients with presumed viral CNS infection seen in 1997 and 1998, PCR testing revealed a viral cause in 38 (36 percent) [40]. The rate of detection in earlier time periods before PCR testing was much lower (about 10 percent), employing cell culture and serologic testing.

In a later, larger series of almost 3500 patients from the same laboratory, PCR identified a viral etiology in CSF or brain tissue in only 14 percent (498 patients); selection bias may have accounted for much of the difference [41]. The most common viral causes were enterovirus (72 percent), herpes simplex (15 percent), VZV (6 percent), and West Nile virus (4 percent).

DIFFERENTIAL DIAGNOSIS

It is critical that the clinician considers a broad range of causes when evaluating patients who present with encephalitis. Only some of the causes are infectious, and not all infections are viral.

A number of noninfectious etiologies can mimic central nervous system (CNS) infections. These include primary intracranial or metastatic tumors, adverse effects of medications, and autoimmune or paraneoplastic diseases, such as those associated with vasculitis or the anti-NMDA receptor (table 3). (See "Autoimmune (including paraneoplastic) encephalitis: Clinical features and diagnosis".)

Nonviral infectious etiologies to consider in the patient with suspected CNS infection include brain abscess, syphilis, tuberculous meningitis, and fungal meningitis (eg, coccidioides), which can affect the sensorium. Amoebic encephalitis, often associated with freshwater swimming, should also be an occasional consideration. (See "Pathogenesis, clinical manifestations, and diagnosis of brain abscess" and "Central nervous system tuberculosis: An overview" and "Coccidioidal meningitis" and "Neurosyphilis".)

Knowledge of the patient's underlying immune status is also critical, since the differential diagnosis is even broader in immunocompromised hosts (eg, toxoplasmic encephalitis and cryptococcal meningitis). (See "Toxoplasmosis: Acute systemic disease" and "Epidemiology, clinical manifestations, and diagnosis of Cryptococcus neoformans meningoencephalitis in patients with HIV".)

EMPIRIC THERAPY

There are no specific therapies for most central nervous system (CNS) viral infections. However, some important exceptions apply:

- Empiric treatment for herpes simplex virus (HSV)-1 infection with acyclovir (10 mg/kg intravenously every eight hours) should always be initiated as soon as possible if the patient has encephalitis without apparent explanation [42]. Early therapy is vital because it is associated with a significant decrease in mortality and morbidity [1] (see "Herpes simplex virus type 1 encephalitis"). Acyclovir should also be administered if varicella zoster virus encephalitis is likely.

- Since a number of other treatable illnesses may present in a similar manner to viral CNS infections, consideration of alternative diagnoses, such as tuberculosis and drug-induced

delirium, is essential (table 3) [43].

A list of the major pathogens that produce the clinical syndrome of encephalitis, along with suggested initial treatment, appears in the table (table 4) [44].

INCREASED INTRACRANIAL PRESSURE

Symptoms and signs of increased intracranial pressure (ICP) include headache, vomiting, and a decreased level of consciousness. Information on the incidence or management of raised cerebrospinal fluid (CSF) pressure in patients with viral encephalitis is limited.

All of the "standard" therapeutic interventions for lowering CSF pressure (eg, steroids, mannitol) have been used in this setting, but none have been shown to be of well-established benefit. Although dexamethasone has been shown to reduce brain edema and improve neurologic outcomes in patients with pneumococcal meningitis, there are only limited retrospective data on the use of steroids in viral encephalitis [45]; extrapolating these data to patients with viral encephalitis may not be valid. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

However, serial ICP monitoring should be part of the management of a patient with encephalitis with documented elevated ICP, since this parameter has been associated with a negative prognosis [46]. Relieving elevated ICP may decrease secondary brain injury while the patient is responding to anti-infective therapy [47]. Whether any of these interventions may have a positive impact on outcome has not been determined in prospective clinical trials.

Various strategies to reduce intracranial pressure are discussed elsewhere. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'General management'.)

PROGNOSIS

Most studies of viral encephalitis are focused on short-term outcomes. As an example, one prospective study in France examined 167 surviving patients with a history of encephalitis three years after enrollment [48]. Sixty-one percent survived without sequelae, while 18 percent were mildly impaired, 14 percent were severely impaired, and 1 percent remained in a vegetative state. The most frequent sequelae included difficulties in concentration, behavioral and speech disorders, and memory loss. One-quarter of those who were previously employed had not returned to work.

In the California Encephalitis Project, more than 1500 patients with encephalitis were enrolled from 1998 through 2005 [26]. A confirmed or probable etiologic agent was identified for only 16 percent of cases. Although the vast majority of patients did not have an established diagnosis, those presenting with diffuse cerebral edema or intractable seizures had a poor neurologic recovery and increased risk of mortality. In contrast, those with self-limited seizure activity had a rapid recovery. These data suggest that future studies, which group disorders by clinical profile, may help better estimate prognosis, even if the etiologic agent is unknown.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Infectious encephalitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Encephalitis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical presentation** – Patients with encephalitis have an altered mental status ranging from subtle deficits to complete unresponsiveness. Symptoms and signs of meningeal irritation (photophobia and nuchal rigidity) are usually absent with a pure encephalitis, but often accompany a meningoencephalitis. (See 'Meningitis versus encephalitis' above.)

Other clinical features seen in patients with encephalitis include seizures and focal neurologic abnormalities (eg, hemiparesis, cranial nerve palsies, and exaggerated deep tendon and/or pathologic reflexes). (See 'Signs and symptoms' above.)

- **Evaluation** – In patients who present with encephalitis, the initial evaluation is focused on determining the etiologic agent. This includes an evaluation for viral pathogens.
  - **History and physical exam** – Clinicians should elicit a detailed sexual, travel, and exposure history (to both insects and animals). They should also examine the patient for findings (eg, rash) that may support a specific diagnosis. (See 'Historical clues' above and 'Clues on physical examination' above.)
  - **Neuroimaging** – We obtain neuroimaging in patients who present with encephalitis to assess the possibility of a localized process, which may suggest a specific etiology (eg, temporal lobe involvement and herpes simplex virus [HSV]-1). (See 'Imaging' above.)
  - **Cerebrospinal fluid evaluation** – Cerebrospinal fluid (CSF) examination is essential for diagnosis in patients with suspected encephalitis or meningoencephalitis. In addition to routine studies (cell count, glucose, protein), the initial work-up should include CSF polymerase chain reaction (PCR) testing for HSV-1, HSV-2, varicella zoster virus, and enteroviruses. Testing for other viral pathogens (eg, arboviruses) will depend on travel, as well as exposure history to insects and animals (table 4). (See 'Diagnosis' above.)
- **Empiric therapy** – In patients with encephalitis or meningoencephalitis, we recommend rapid initiation of acyclovir 10 mg/kg three times daily intravenously for empiric treatment of HSV while awaiting confirmation (**Grade 1A**). There is a high mortality associated with HSV encephalitis when treatment is delayed. (See 'Empiric therapy' above.)

  The need for other empiric agents depends upon the specific clinical scenario. A list of the major pathogens that can cause encephalitis, along with suggested initial treatment, appears in the table (table 4).

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REFERENCES

1. Whitley RJ. Viral encephalitis. N Engl J Med 1990; 323:242.

2. Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. Infect Dis Clin North Am 1990; 4:599.
3. Gluckman SJ, DiNubile MJ. Acute viral infections of the central nervous system. In: Emergen t and Urgent Neurology, Weiner WJ (Ed), Lippincott, Philadelphia 1992.
4. Tyler KL. Emerging viral infections of the central nervous system: part 1. Arch Neurol 2009; 66:939.
5. Johnson RT. The pathogenesis of acute viral encephalitis and postinfectious encephalomyelitis. J Infect Dis 1987; 155:359.
6. Sonneville R, Klein I, de Broucker T, Wolff M. Post-infectious encephalitis in adults: diagnosis and management. J Infect 2009; 58:321.
7. Mailles A, Stahl JP, Steering Committee and Investigators Group. Infectious encephalitis in france in 2007: a national prospective study. Clin Infect Dis 2009; 49:1838.
8. Pérez-Vélez CM, Anderson MS, Robinson CC, et al. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. Clin Infect Dis 2007; 45:950.
9. Torre D, Mancuso R, Ferrante P. Pathogenic mechanisms of meningitis/encephalitis caused by human herpesvirus-6 in immunocompetent adult patients. Clin Infect Dis 2005; 41:422.
10. Isaacson E, Glaser CA, Forghani B, et al. Evidence of human herpesvirus 6 infection in 4 immunocompetent patients with encephalitis. Clin Infect Dis 2005; 40:890.
11. Weinberg A, Li S, Palmer M, Tyler KL. Quantitative CSF PCR in Epstein-Barr virus infections of the central nervous system. Ann Neurol 2002; 52:543.
12. Carteaux G, Maquart M, Bedet A, et al. Zika Virus Associated with Meningoencephalitis. N Engl J Med 2016; 374:1595.
13. Jun JS, Moon J, Byun JI, et al. Clinical manifestations and treatment outcomes of parvovirus B19 encephalitis in immunocompetent adults. J Neurovirol 2017; 23:903.
14. Reimann CA, Hayes EB, DiGuiseppi C, et al. Epidemiology of neuroinvasive arboviral disease in the United States, 1999-2007. Am J Trop Med Hyg 2008; 79:974.
15. McNabb SJ, Jajosky RA, Hall-Baker PA, et al. Summary of notifiable diseases--United States, 2006. MMWR Morb Mortal Wkly Rep 2008; 55:1.
16. Centers for Disease Control and Prevention. Powassan virus. Statistics and maps. https://www.cdc.gov/powassan/statistics.html (Accessed on July 02, 2019).
17. United States Centers for Disease Control. Eastern Equine Encephalitis. https://www.cdc.gov/easternequineencephalitis/ (Accessed on October 30, 2019).

18. Chua KB, Goh KJ, Wong KT, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. Lancet 1999; 354:1257.
19. Paton NI, Leo YS, Zaki SR, et al. Outbreak of Nipah-virus infection among abattoir workers in Singapore. Lancet 1999; 354:1253.
20. Hsu VP, Hossain MJ, Parashar UD, et al. Nipah virus encephalitis reemergence, Bangladesh. Emerg Infect Dis 2004; 10:2082.
21. de Jong MD, Bach VC, Phan TQ, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 2005; 352:686.
22. Hoffmann B, Tappe D, Höper D, et al. A Variegated Squirrel Bornavirus Associated with Fatal Human Encephalitis. N Engl J Med 2015; 373:154.
23. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med 2001; 344:1807.
24. Koskiniemi M, Piiparinen H, Rantalaiho T, et al. Acute central nervous system complications in varicella zoster virus infections. J Clin Virol 2002; 25:293.
25. Wasay M, Mekan SF, Khelaeni B, et al. Extra temporal involvement in herpes simplex encephalitis. Eur J Neurol 2005; 12:475.
26. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 2006; 43:1565.
27. Lury KM, Castillo M. Eastern equine encephalitis: CT and MRI findings in one case. Emerg Radiol 2004; 11:46.
28. Deresiewicz RL, Thaler SJ, Hsu L, Zamani AA. Clinical and neuroradiographic manifestations of eastern equine encephalitis. N Engl J Med 1997; 336:1867.
29. Beattie GC, Glaser CA, Sheriff H, et al. Encephalitis with thalamic and basal ganglia abnormalities: etiologies, neuroimaging, and potential role of respiratory viruses. Clin Infect Dis 2013; 56:825.
30. Petropoulou KA, Gordon SM, Prayson RA, Ruggierri PM. West Nile virus meningoencephalitis: MR imaging findings. AJNR Am J Neuroradiol 2005; 26:1986.
31. Misra UK, Kalita J. Neurophysiological studies in herpes simplex encephalitis. Electromyogr Clin Neurophysiol 1998; 38:177.
32. Feigin RD, Shackelford PG. Value of repeat lumbar puncture in the differential diagnosis of meningitis. N Engl J Med 1973; 289:571.
33. Whitley RJ, Cobbs CG, Alford CA Jr, et al. Diseases that mimic herpes simplex encephalitis. Diagnosis, presentation, and outcome. NIAD Collaborative Antiviral Study Group. JAMA

1989; 262:234.

34. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993; 328:21.
35. Kupila L, Vuorinen T, Vainionpää R, et al. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology 2006; 66:75.
36. Polage CR, Petti CA. Assessment of the utility of viral culture of cerebrospinal fluid. Clin Infect Dis 2006; 43:1578.
37. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet 2002; 359:507.
38. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 1995; 171:857.
39. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. Clin Infect Dis 2003; 36:731.
40. Huang C, Chatterjee NK, Grady LJ. Diagnosis of viral infections of the central nervous system. N Engl J Med 1999; 340:483.
41. Huang C, Morse D, Slater B, et al. Multiple-year experience in the diagnosis of viral central nervous system infections with a panel of polymerase chain reaction assays for detection of 11 viruses. Clin Infect Dis 2004; 39:630.
42. Benson PC, Swadron SP. Empiric acyclovir is infrequently initiated in the emergency department to patients ultimately diagnosed with encephalitis. Ann Emerg Med 2006; 47:100.
43. Marinac JS. Drug- and chemical-induced aseptic meningitis: a review of the literature. Ann Pharmacother 1992; 26:813.
44. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008; 47:303.
45. Kamei S, Sekizawa T, Shiota H, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry 2005; 76:1544.
46. Kumar G, Kalita J, Misra UK. Raised intracranial pressure in acute viral encephalitis. Clin Neurol Neurosurg 2009; 111:399.
47. Kramer AH, Bleck TP. Neurocritical care of patients with central nervous system infections. Curr Treat Options Neurol 2008; 10:201.

48. Mailles A, De Broucker T, Costanzo P, et al. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin Infect Dis 2012; 54:1455.

Topic 1284 Version 31.0

GRAPHICS

Seasonal incidence of viral CNS infections

Peak time of year	Aseptic meningitis	Viral encephalitis
Summer/fall	▪ Enteroviruses: • Coxsackie • Echovirus • Poliovirus	▪ West Nile virus ▪ St Louis encephalitis virus ▪ Eastern equine encephalitis virus ▪ California encephalitis viruses ▪ Western equine encephalitis virus ▪ Powassan virus
Winter/spring	▪ Mumps ▪ Lymphocytic choriomeningitis virus	▪ Measles ▪ Mumps
Any season	▪ Herpes simplex virus type 2 ▪ HIV infection	▪ Herpes simplex virus type 1 ▪ HIV infection

Graphic 57784 Version 2.0

Typical cerebrospinal fluid findings in central nervous system infections*

	Glucose (mg/dL)		Protein (mg/dL)		Total white blood cell (cells/microL)		
	<10¶	10 to 40Δ	100 to 500◇	50 to 300§	>1000	100 to 1000	
More common	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis	Viral meningitis Nervous system Lyme disease (neuroborreliosis) Encephalitis Neurosyphilis TB meningitis¥	Bacterial meningitis	Bacterial or viral meningitis TB meningitis	Ea ba me Vir me Ne TB me
Less common	TB meningitis Fungal meningitis	Neurosyphilis Some viral infections (such as mumps and LCMV)		Early bacterial meningitis	Some cases of mumps and LCMV	Encephalitis	En

TB: tuberculosis; LCMV: lymphocytic choriomeningitis virus.

* It is important to note that the spectrum of cerebrospinal fluid values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value. Refer to the UpToDate topic reviews on bacterial meningitis for additional details.

¶ <0.6 mmol/L.

Δ 0.6 to 2.2 mmol/L.

◇ 1 to 5 g/L.

§ 0.5 to 3 g/L.

¥ Cerebrospinal fluid protein concentrations may be higher in some patients with tuberculous meningitis; concentrations >500 mg/dL are an indication of blood-brain barrier disruption or increased intracerebral production of immunoglobulins, and extremely high concentrations, in the range of 2 to 6 g/dL, may be found in association with subarachnoid block.

Graphic 76324 Version 11.0

Potentially treatable diseases mimicking viral CNS infection

Infectious
Tuberculosis
Partially treated bacterial meningitis
Listeria meningitis (occasionally)
Spirochetal infection (syphilis, Lyme disease, leptospirosis)
Rocky Mountain spotted fever
Fungal infection (cryptococcosis, coccidioidomycosis, histoplasmosis)
Mycoplasma pneumoniae
Parameningeal infection (brain abscess, epidural or subdural abscess)
Amebic infection
Trypanosomiasis
Toxoplasmosis
Cerebral malaria (*Plasmodium falciparum*)
Disseminated cat-scratch disease (*Bartonella henselae*)
Whipple's Disease (*Tropheryma whipplei*)
Legionellosis
Noninfectious
Tumor (meningeal or parenchymal)
Dural venous sinus thrombosis
Sarcoidosis
Cerebral vasculitis
Behcet syndrome
Drug-induced meningitis
▪ Nonsteroidal antiinflammatory drugs
▪ Sulfa drugs
▪ Antithymocyte globulin
▪ Intravenous immune globulin
Migrainous syndromes with pleocytosis
Autoimmune or paraneoplastic diseases (eg, those associated with vasculitis or the anti-NMDA recepto

Graphic 77933 Version 4.0

Suggested initial therapy for agents that cause encephalitis

Agent	Specific therapy
ADEM	Corticosteroids
Bacteria	
Mycoplasma pneumonia	Macrolide (eg, azithromycin, clarithromycin, erythromycin), doxycycline, or fluoroquinolone* (eg, levofloxacin, ciprofloxacin, moxifloxacin)
Listeria monocytogenes	Ampicillin plus gentamicin; trimethoprim-sulfamethoxazole
Tropheryma whipplei	Ceftiaxone, followed by either trimethoprim-sulfamethoxazole or cefixime
Fungi	
Coccidioides	Fluconazole, itraconazole, voriconazole, amphotericin B
Cryptococcus neoformans	Amphotericin B plus flucytosine
Histoplasma capsulatum	Liposomal amphotericin B
Helminths	
Baylisascaris procyonis	Albendazole plus diethylcarbamazine
Gnathostoma	Albendazole or ivermectin
Taenia solium (cycticercosis)	Albendazole and corticosteroids
Mycobacteria	
Mycobacterium tuberculosis	4-drug regimen; consider addition of corticosteroid
Protozoa	
Acanthamoeba	Trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole
Balamuthia mandrillaris	Pentamidine plus macrolide and fluconazole and sulfadiazine and flucytosine and phenothiazine
Naegleria fowleri	Amphotericin B and rifampin
Plasmodium falciparum	Quinine, quinidine or artemether
Toxoplasma gondii	Pyrimethamine plus sulfadiazine or clindamycin
Trypanosoma brucei gambiense	Eflornithine

Trypanosoma brucei rhodesiense	Melarsoprol
Rickettsioses and ehrlichioses	
Anaplasma phagocytophilum	Doxycycline
Ehrlichia chafeensis	Doxycycline
Rickettsia rickettsii	Doxycycline
Spirochetes	
Borrelia burgdorferi	Ceftriaxone, cefotaxime
Treponema pallidum	Penicillin G
Viruses	
Cytomegalovirus	Ganciclovir plus foscarnet
Epstein-Barr	No specific treatment
Herpes B virus	Valgancyclovir
Herpes simplex	Acyclovir
Human herpesvirus 6	Gancyclovir or foscarnet
Human immunodeficiency virus	Antiretroviral therapy
Influenza	Oseltamivir
JC virus	Reversal of immunosuppression if possible
Measles	Ribavirin
Nipah	Ribavirin
St. Louis encephalitis	Interferon-2 alpha
Varicella-zoster	Acyclovir
West Nile	No specific treatment

ADEM: acute disseminated encephalomyelitis.

* In pediatric patients, fluoroquinolones are not routinely used as first-line therapy, but may be a reasonable alternative for situations where no safe and effective substitute is available.

Adapted from: Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008; 47:303-27.

Graphic 69990 Version 8.0