

# Encephalitis

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**Objectives** After completing this article, readers should be able to:

1. Understand the breadth of pathogens that cause encephalitis.
2. Describe the typical laboratory and imaging findings in encephalitis.
3. Discuss the challenge of making a specific etiologic diagnosis in patients who have encephalitis.
4. Recognize the importance of testing for treatable causes of encephalitis.
5. Explain the methods for diagnosing encephalitis caused by herpes simplex virus, Epstein–Barr virus, West Nile virus, influenza, rabies, enterovirus, *Bartonella henselae*, and *Mycoplasma pneumoniae*.

## Introduction

Encephalitis is a distressing illness for patients and their families. The onset often is acute, symptoms may progress rapidly, and previously healthy children become debilitated. In addition, even experienced physicians often are uncertain about the cause, appropriate therapy, and prognosis. A thorough and accurate review is difficult because the syndrome is complex and the number of etiologic agents and mimics of encephalitis are vast. Unfortunately, current knowledge of encephalitis is based largely on case reports and small series; high-quality evidence-based data are limited. Most important, the majority of cases have an unknown cause, which makes generalizations about encephalitis inherently problematic. This article focuses on encephalitis in immunocompetent children beyond the neonatal age group.

## Challenges and Definitions

The first challenge in discussing encephalitis is to develop practical definitions. When brain tissue is available from biopsy or autopsy, inflammatory cell infiltrate of the brain defines encephalitis. In practice, brain tissue rarely is obtained before death, and the diagnosis must be deduced from history, and physical examination plus laboratory and imaging data. This review defines encephalitis as acute central nervous system (CNS) dysfunction with radiographic or laboratory evidence of brain inflammation. CNS dysfunction includes seizures, focal neurologic findings, and alteration in mental status.

The second challenge is to determine the significance of an infectious agent found outside of the CNS in the setting of encephalitis. Many reports and series identify encephalitis pathogens by serology or by culture of non-CNS sites. If an illness is common, such as influenza or *Mycoplasma* infection, spurious associations are possible. Much encephalitis literature is composed of cases that lack detection of the putative agent from the CNS.

Finally, a number of infectious and noninfectious conditions can present with symptoms similar to those of infectious encephalitis, such as neoplasm, autoimmune disease, vasculitis, stroke, and drug reaction. Of the infectious mimics of encephalitis, bacterial meningitis is the most important because it is relatively common and treatable.

## Pathogenesis

There are at least two forms of infection-related encephalitis: primary and post- or parainfectious. A primary encephalitis results from direct CNS invasion by the offending

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agent, and the gray matter often is targeted. A post-infectious or parainfectious encephalitis presents much like a primary encephalitis, but the illness is not caused by direct CNS infection. In post/parainfectious encephalitis, neurologic effects are the consequence of the host's immune response, which often affects the white matter.

The pathogenesis of primary encephalitis is diverse and incompletely understood. Organisms infecting the brain directly first must gain entry to the CNS. Some pathogens such as arboviruses initially cause bloodstream infection, then enter the CNS via endothelial cell infection, endothelial cell transport, or carriage in cells entering the CNS. Encephalitis tends to be a rare complication after viremia because entry to the brain is carefully regulated at the blood-brain barrier. An alternative mechanism used by herpes simplex virus (HSV), rabies, and possibly poliovirus is retrograde transport in neurons. This strategy may be successful because pathogens traveling inside neurons avoid immune surveillance. An alternative mechanism used by the amoeba *Naegleria fowleri* is entry through the olfactory mucosa.

Once an organism has entered the brain, a variety of anatomic sites can become infected. For example, HSV typically infects neurons in the temporal lobe; rabies predominantly affects the pons, medulla, cerebellum, and hippocampus; and Japanese encephalitis virus affects the brainstem and basal ganglia. Neurologic signs and symptoms develop after infection as the result of direct neuronal injury, the host inflammatory response, or both. Histologically, the host response can include perivascular inflammation, gliosis, and brain edema.

Postinfectious encephalitis occurs days to weeks after the onset of an infection. Currently in the United States, a minor respiratory tract infection is likely to be the inciting event. Before the widespread use of viral vaccines, a distinctive illness such as measles or varicella was likely to be the preceding event, and encephalitis may follow these infections in regions where they remain common. Because the inciting pathogen is not detected in the CNS in postinfectious encephalitis, the illness is hypothesized to be caused by an aberrant immune response against brain antigens such as myelin basic protein. Subsequent demyelination causes focal or global CNS dysfunction. Postinfectious encephalitis often is called acute disseminated encephalomyelitis (ADEM).

## Epidemiology

An overall summary of encephalitis epidemiology is difficult because there are few population-based studies, there are many possible pathogens, and most cases are

not reported to health authorities. Only a few generalizations are possible:

1. Mosquito- and tick-borne encephalitides have distinct geographic and seasonal distributions related to their insect vectors.
2. West Nile virus (WNV) encephalitis occurs during mosquito season and is more frequent and severe in the elderly.
3. Encephalitis caused by enteroviruses, influenza virus, and varicella virus has seasonal peaks in incidence.
4. HSV encephalitis varies neither by season nor by geography. It is the most common diagnosed cause of sporadic encephalitis.
5. The majority of encephalitis cases have no etiologic agent identified.

The Centers for Disease Control and Prevention (CDC) used National Hospital Discharge Survey data to estimate the burden of hospitalization caused by encephalitis in the United States. The overall incidence of hospitalization for encephalitis was 7.3 cases/100,000 annually; on average each year, encephalitis led to more than 200,000 days of hospitalization and 1,400 deaths. Children younger than age 1 year (13.7 cases/100,000 per year) and adults older than age 65 years (10.6 cases/100,000 per year) had the highest incidence. Because these data are limited by the lack of specific diagnostic criteria, by the lack of etiologic specificity in ICD-9 codes, and by the unknown accuracy of coding, the true frequency of encephalitis in the United States is unclear.

Annual variation in vector-borne disease further complicates efforts to estimate the rate of encephalitis. In the 1990s, mosquito-borne encephalitis in the United States was uncommon, and fewer than 200 cases annually, mostly of La Crosse encephalitis, were reported in 1996 and 1997. WNV, first seen in the United States in 1999, became widespread in the summer of 2002, causing 4,156 laboratory-confirmed cases and 284 deaths. Illinois, Michigan, Ohio, Louisiana, and Indiana reported the largest number of cases. Although 96% of reported patients were older than 19 years of age, one case of congenital infection was reported, and other infections in infants were suspected to have been acquired through breastfeeding. Because WNV is an emerging cause of infection in North America, readers should refer to the CDC Web site ([www.cdc.gov](http://www.cdc.gov)) for the most up-to-date information on this disease.

## Causes

The causes of childhood encephalitis have changed over the past 30 years, as many vaccine-preventable condi-

Table 1. Pathogens of Encephalitis

## Viruses

- Adenovirus
- Arboviruses
- Encephalomyocarditis virus
- Enteroviruses
- Hepatitis A, B
- Herpesvirus (HSV) group
  - HSV 1 and 2
  - Varicella-zoster virus
  - Epstein-Barr virus
  - Cytomegalovirus
  - Human herpesvirus 6
  - Herpesvirus B
- Influenza
- Lymphocytic choriomeningitis virus
- Measles
- Mumps
- Parainfluenza
- Parvovirus
- Rabies
- Rotavirus
- Respiratory syncytial virus
- Rubella
- Smallpox
- Vesicular stomatitis virus

## Bacteria

- *Actinomyces* sp
- *Bartonella henselae*
- *Brucella* sp
- *Chlamydia* sp
- Ehrlichia (aka *Anaplasma*) sp
- *Listeria monocytogenes*
- *Mycoplasma pneumoniae*
- *Norcardia* sp
- Q fever
- *Rickettsia* sp
- Spirochetes
  - Treponema pallidum*
  - Leptospira* sp
  - Borrelia* sp
- Whipples bacillus

## Fungi

- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*

## Protozoa

- *Acanthamoeba* sp
- *Balamuthai mandrillaris*
- *Malaria* sp
- *Naegleria fowleri*
- *Toxoplasma gondii*
- *Trypanosoma* sp
  - Baylisascaris procyonis*
  - Cysticercosis
  - Schistosoma* sp
  - Strongyloides stercoralis*
  - Trichinella spiralis*

tions, such as measles, mumps, rubella, varicella, and pertussis, became uncommon. In addition, new pathogens have been identified as causes of encephalitis, and new laboratory methods provide more ways to test for infection. Families and physicians share the feeling that the treatment and prognosis of encephalitis will be optimized when the etiologic agent is identified. Unfortunately, despite intensive testing, most cases of presumed infectious encephalitis remain unexplained. Treatable causes should be pursued aggressively and infectious and postinfectious encephalitis distinguished whenever possible.

Viruses, bacteria, fungi, and parasites all can cause encephalitis (Table 1). The more common causes of encephalitis and treatable mimics along with recommended diagnostic tests are listed in Table 2. In the analysis of National Hospital Discharge data, the cause of encephalitis was unknown in 60% of cases. Herpesviruses, varicella, and arboviruses were the viral causes reported most frequently. A more recent prospective study by the California Department of Health Services attempted to define the cause of acute encephalitis in 334 immunocompetent patients between June 1998 and December 2000. Patients were studied with extensive standardized test panels using molecular detection, isolation of agents

by culture, and serology. Causes were classified as possible, probable, or confirmed. Despite this effort, a confirmed or probable diagnosis was made in only 13% of cases; a possible cause was found in an additional 12% (Table 3). The most common confirmed or probable viral pathogens were HSV, enterovirus, and Epstein-Barr virus (EBV). It is important to remember that these patients probably were not at risk for La Crosse or WNV encephalitis, based on the period and location of the study (California).

From a practical standpoint, there are too many possible causes of encephalitis for every patient to receive an exhaustive evaluation. Focused historical questions may establish the risk of specific causes and guide prioritization of testing. Some risk factors for selected encephalitis pathogens are listed in Table 4.

## Clinical Features

### History

Because encephalitis has so many underlying causes, it is impossible to generalize about clinical signs and symptoms. The first manifestations of infectious encephalitis may be fever and headache. Subsequently, altered mental status or focal neurologic signs develop. The presenting signs and symptoms may suggest whether acute enceph-

**Table 2. Commonly Diagnosed Causes and Mimics of Encephalitis**

Diagnosed Cause	Recommended Testing
<b>Sporadic</b>	
<i>Bartonella henselae</i>	Serum <i>Bartonella</i> IgG
Enterovirus (EV)	CSF EV PCR, CSF viral culture
Epstein-Barr virus (EBV)	CSF EBV PCR, serum EBV serology
Herpes simplex virus (HSV)-1	CSF HSV PCR
Measles/Subacute sclerosing panencephalitis	Serum/CSF IgG
<i>Mycoplasma pneumoniae</i> (MP)	CSF MP PCR, serum MP IgM
<b>Seasonal</b>	
West Nile virus	Serum/CSF IgM (after fourth day of illness)
La Crosse Encephalitis	Serum/CSF IgM
<b>Infectious Mimic</b>	
<b>Recommended Testing</b>	
Bacterial meningitis	CSF Gram stain and culture
Tuberculosis (MTb)	CSF AFB stain/culture CSF MTb PCR PPD
Cryptococcal meningitis	CSF/serum antigen detection CSF fungal culture
Syphilis	CSF/serum VDRL, serum FTA
Rickettsial disease	Acute/convalescent serology
<i>Ehrlichia/Anaplasma</i> sp	Peripheral blood smear Acute/convalescent serology
Malaria	Peripheral blood smear
Ig=immunoglobulin, CSF=cerebrospinal fluid, PCR=polymerase chain reaction, AFB=acid-fast bacillus, PPD=purified protein derivative, FTA=fluorescent treponemal antibody absorption.	

alitis is focal or diffuse. For example, most arboviral encephalitis has diffuse brain involvement, and early fever, vomiting, obtundation, and coma are typical. In contrast, HSV encephalitis can begin focally with hemiparesis, seizures, or cranial nerve defects. The progression from fever and headache to more profound symptoms and signs of encephalitis may occur over hours to days. Seizures may be absent at presentation but develop later in the course.

### Physical Findings

Associated physical findings outside of the nervous system occasionally give clues to the cause of encephalitis. For example, regional adenopathy should prompt consideration of cat-scratch disease; herpangina or hand, foot, and mouth disease suggests enteroviral infection. Most often, however, the results of the non-neurologic physical examination are normal or nonspecific and do not help narrow the list of possible causes. A careful initial neurologic examination is essential to establish

whether focal findings are present and to document baseline status. This examination must be interpreted in the context of seizures or the use of anticonvulsant drugs.

### Natural History

The spectrum of clinical evolution during encephalitis varies widely, and generalizations are impossible because most cases are of unknown cause. Some causes of encephalitis, such as cat-scratch disease and EBV, may have a brief course with full recovery; others, such as HSV, have a guarded long-term prognosis despite the availability of specific antiviral treatment.

### Laboratory Findings

Mild-to-moderate cerebrospinal fluid (CSF) abnormalities are typical in infectious encephalitis. Although the CSF may be completely normal, most patients have elevated white blood cell (WBC) counts ( $0.05$  to  $0.2 \times 10^3/\text{mCL}$  [ $0.05$  to  $0.2 \times 10^9/L$ ]), often with a predominance of lymphocytes. Protein concentrations can be elevated, but usually are less than  $200 \text{ mg/dL}$ , and glucose values usually are in the normal range. HSV and other causes of necrotizing encephalitis may be associated with an elevated red blood cell count and more dramatic changes in WBC and protein levels. Results of routine blood chemistry and hematology tests usually are normal.

A specific cause can be sought through laboratory testing. A possible initial evaluation (Table 5) includes the most common infectious causes of encephalitis plus important treatable mimics such as bacterial, cryptococcal, and tuberculous meningitis. Detection of pathogens in brain tissue or CSF provides convincing evidence of causation, but serology may be the best method for selected agents. For example, WNV immunoglobulin (Ig) M antibody usually is present in the serum and CSF shortly after patients become symptomatic, but the virus itself is difficult to isolate or detect by molecular methods. Infection with some agents can be detected only by comparing acute and convalescent sera. Accordingly, a

sample of acute serum always should be frozen and stored for possible use later.

Given the enormous number of possible causes of encephalitis, an exhaustive diagnostic evaluation is not practical. Evidence of treatable CNS infections such as HSV encephalitis and bacterial meningitis must be sought. Further prioritization of other testing should be guided by seasonal, geographic, and exposure information in addition to clinical details.

### Imaging and Ancillary Studies

Computed tomography (CT) scan without contrast often is performed swiftly for a patient who has an acute neurologic syndrome, but this study rarely shows an abnormality at the onset of encephalitis. Magnetic resonance imaging (MRI) is much more sensitive than CT scan for acute changes associated with encephalitis. The radiologist should be aware of the reason for the study so the appropriate sequences can be obtained to help determine whether encephalitis, postinfectious encephalitis, tumor, or abscess is the likely diagnosis.

Electroencephalography (EEG) can be a helpful adjunct in the early assessment of encephalitis. EEG may be needed to assess seizure activity and may help localize the region of encephalitic involvement. Compared with CT scan, EEG is considerably more sensitive in detecting focal encephalitis at the time of presentation.

### Treatment and Prognosis

The composition and duration of treatment for encephalitis depends on the underlying cause. Of the viral causes, only HSV and varicella have well-established therapy. In contrast, most bacterial, fungal, and parasitic causes have accepted treatments for systemic infection. The composition and dose of anti-infective therapy for

**Table 3. Causes of 334 Cases of Pediatric and Adult Encephalitis\***

Cause	Pediatric (6 mo to 18 y)	Adult (>18 y)	Total
<b>Confirmed or Probable Cases</b>			
<i>Bartonella</i> sp	5	2	7
Herpes simplex virus-1	4	7	11
Enterovirus	4	1	5
Epstein-Barr virus	3	1	4
Rotavirus	2	0	2
Subacute sclerosing panencephalitis/Measles	2	0	2
Varicella zoster	1	2	3
<i>Mycoplasma pneumoniae</i>	1	1	2
Hepatitis C	0	2	2
Rabies	0	1	1
Human herpesvirus 6	0	1	1
Baylisascaris	2	0	2
<b>Possible Cases</b>			
<i>Mycoplasma</i>	4	5	9
Enterovirus	4	9	13
<i>Chlamydia</i> sp	2	4	6
Herpes simplex virus-1	1	2	3
Varicella-zoster virus	1	1	2
Human herpesvirus 6	1	0	1
Influenza A/B	1	1	2
Parainfluenza 1 through 4	1	0	1
Respiratory syncytial virus	1	0	1
Adenovirus	1	0	1
<i>Brucella</i> sp	0	2	2
<b>Mimics</b>			
Autoimmune	6	8	14
Neoplastic	1	10	11
Infectious, nonencephalitis	1	10	11
Metabolic	2	1	3
Other (psychosis, toxin)	2	2	4
Total known or possible causes	53	73	126
Unknown cause	74	134	208
<b>Total</b>	<b>127</b>	<b>207</b>	<b>334</b>

\*From the 1998–2000 California Encephalitis Project (Glaser et al. *Clin Infect Dis*. 2003;36:731–742).

empiric or specific encephalitis should be chosen in consultation with an infectious disease specialist. Patients whose diagnosis is infectious encephalitis should receive empiric acyclovir for HSV and antibacterial agents for meningitis until bacterial and viral study results are available. In cases of suspected postinfectious encephalitis or encephalitis of unknown cause, a neurologist and an infectious disease specialist should be consulted regarding the use of intravenous immune globulin (IVIG), corticosteroids, or other immune system modulators.

The prognosis of encephalitis depends highly on cause. Some causes of encephalitis, such as rabies, are usually fatal; others, such as EBV and cat-scratch disease,

Table 4. Risk Factors for Encephalitis

Risk Factor/Exposure	Possible Cause
Mosquito bites	Alphavirus Western equine, Eastern equine, Venezuelan equine Flavivirus: St. Louis, West Nile Bunyavirus: La Crosse, California
Tick bite	Colorado tick fever, Powassan virus, <i>Anaplasma</i> (aka <i>Ehrlichia</i> ), Rocky mountain spotted fever, tick-borne encephalitis
Raccoon feces	<i>Baylisascaris procyonis</i>
Wild/domestic animals	Leptospirosis
Bats	Rabies
Pigs	Nipah virus
Cats	<i>Bartonella hensalae</i>
Rodents	Lymphochoriomeningitis virus
Sheep/goats	Q fever
Travel	
Asia	Japanese encephalitis, Nipah virus
Europe	Tick-borne encephalitis
Africa	Lassa fever
Illness-exposures	
Chickenpox	
Measles	
Influenza	
Pneumonia	<i>Mycoplasma</i>
Fresh water	<i>Naegleria fowleri</i> , leptospirosis
Soil	<i>Balamuthia mandrillaris</i>
Vaccination	Measles-mumps-rubella, vaccinia
Season	
Spring/Summer	Mosquito-borne, tick-borne
Other systemic illness	Evaluate as needed for neoplastic and rheumatologic disease

have a generally benign course. If the cause is not known, the prognosis should be guarded until the evolution of the illness becomes clear.

## Herpes Simplex Virus

### Clinical, Laboratory, and Radiologic Findings

HSV deserves special attention because it is the cause of encephalitis diagnosed most commonly. Prospective trials of acyclovir and vidarabine in the 1970s and 1980s defined the presentation and natural history of HSV encephalitis, demonstrated the efficacy of antiviral therapy, and showed that many other pathogens can mimic HSV encephalitis. Surprisingly, no clinical features distinguished biopsy-proven HSV encephalitis reliably from other causes. HSV encephalitis presentations included fever, personality change, autonomic dysfunction, and dysphagia. Most patients also developed seizures, headache, and altered level of consciousness. Although most HSV encephalitis patients have CSF characterized by mildly elevated WBC counts (average,  $0.1 \times 10^3/\text{mCL}$

[ $0.1 \times 10^9/\text{L}$ ], lymphocyte predominance) and mildly elevated protein (average, 100 mg/dL), the CSF occasionally is normal. CT and MRI studies eventually show the consequences of this infection, but images can appear normal if obtained early in the course of illness. Unilateral or bilateral temporal lobe involvement is the most common finding, but contiguous and distant areas also can be affected.

The diagnostic test of choice for HSV encephalitis is HSV DNA detection by polymerase chain reaction (PCR) on the CSF. This test is both highly sensitive and specific when performed properly. In strongly suspected cases (eg, temporal lobe involvement) that have negative results initially, the test should be repeated on a second CSF specimen.

### Treatment and Prognosis

Landmark prospective trials demonstrated the effectiveness of acyclovir in decreasing mortality and long-term morbidity

from HSV encephalitis. The currently recommended dose of acyclovir beyond the neonatal period for proven or suspected HSV encephalitis is 10 mg/kg per dose intravenously every 8 hours for 2 to 3 weeks. Prior to the availability of antiviral agents, approximately 70% of HSV encephalitis patients died; acyclovir decreased the overall mortality rate to 19%. In long-term follow-up studies of surviving acyclovir recipients, 38% were normal, 9% were moderately impaired, and 53% were severely impaired. Better outcomes were associated with an age younger than 30 years, shorter duration of symptoms before initiation of treatment, and a Glasgow coma score of greater than 10 at the time of presentation.

## Epstein-Barr Virus

### Clinical, Laboratory, and Radiographic Findings

Most patients described as having EBV encephalitis are adolescents and young adults, the most common age for acute symptomatic EBV infection. Patients typically present 1 to 3 weeks after the onset of the infectious

**Table 5. Initial Laboratory Testing for Encephalitis and Its Mimics**

#### Cerebrospinal Fluid

- Glucose, protein, cell count, differential count
- Routine bacterial culture
- Viral culture
- Herpes simplex virus polymerase chain reaction (PCR)
- Cryptococcal antigen
- Enteroviral PCR
- *Mycoplasma* PCR
- Tuberculosis culture and PCR
- Epstein-Barr virus PCR
- West Nile virus immunoglobulin (Ig) M

#### Blood

- *Bartonella henselae* Ig G
- Epstein-Barr virus serology panel
- Lyme IgG (in endemic areas if cranial neuropathy present)
- *Mycoplasma* IgM
- West Nile virus IgM (during mosquito season)
- La Crosse virus IgM (in endemic areas, during mosquito season)
- Complete blood count, differential count
- Serum to be saved for comparison with convalescent specimen

#### Other

- Viral cultures of nasopharynx and stool
- Purified protein derivative skin test

mononucleosis syndrome, although many authors emphasize that encephalitis can be the presenting complaint in EBV infection. Symptoms and signs include fever, altered mental status, headache, seizures, and focal neurologic deficits, none of which distinguishes EBV encephalitis from other causes.

EBV has been associated with encephalitis, acute cerebellar ataxia, and less commonly, with many other syndromes, including acute hemiplegia, acute psychosis, “Alice in Wonderland” syndrome, movement disorders, brainstem syndromes, transient global amnesia, acute aqueductal stenosis, syndrome of inappropriate antidiuretic hormone secretion, Guillain-Barré syndrome, and Bell palsy.

CSF and MRI findings vary widely in EBV encephalitis and can be normal. EBV encephalitis is diagnosed by detection of EBV DNA by PCR of the CSF; a serum serology consistent with acute EBV infection supports the diagnosis.

#### Treatment and Prognosis

No controlled trials support the use of antiviral agents in EBV encephalitis in the otherwise healthy host. Supportive care contributes to the generally excellent prognosis reported by most authors. Other series have found higher frequencies of neurologic sequelae and even death, suggesting that the outcome, like the CSF and MRI findings, is variable.

#### *Mycoplasma pneumoniae*

##### Clinical, Laboratory, and Radiographic Findings

*Mycoplasma pneumoniae* (MP) is known best for causing respiratory disease in children and young adults. Approximately 0.1% of MP infections are complicated by neurologic syndromes, including encephalitis, meningitis, and myelitis. Direct CNS infection and postinfectious and toxin-mediated mechanisms of disease have been described. Presenting symptoms and signs are typical of encephalitis and include fever, headache, vomiting, seizures, and altered level of consciousness. Both normal and abnormal CSF values are reported, with the most common abnormalities being mild-to-moderate increases in WBC count and elevation of the CSF protein concentrations. Many authors emphasize and caution that symptomatic respiratory tract disease frequently is absent in patients who have MP encephalitis.

In most case series of MP encephalitis, diagnosis was based on serum serologic testing. Unfortunately, this method is complicated by both false-positive and false-negative results. More convincing cases have been described using MP culture or MP PCR detection in the CNS. In two case series, CSF PCR detection was more common in patients who had prodromal syndromes of less than 1 week. Evaluation for MP encephalitis should include an attempt to detect the organism in CSF or brain tissue directly by PCR and culture plus similar evaluations of a respiratory tract specimen. Serology (IgM on acute serum and IgG on paired specimens) can support the diagnosis.

#### Treatment and Prognosis

There are no controlled trials of anti-infective therapy for MP-associated encephalitis. Outcomes are extremely variable and unpredictable, possibly reflecting the problem of accurate diagnosis. Death can occur, and the long-term prognosis is guarded because a variety of permanent defects have been described.

#### Influenza-associated Encephalitis

Influenza-associated encephalitis and encephalopathy in children have been described sporadically for many years.

For example, from 1918 to 1930, CNS disease associated with the “Spanish flu” was common. On the other hand, some cases from earlier eras probably were manifestations of Reye syndrome associated with aspirin use rather than influenza encephalitis. More recently, a 1998 to 1999 outbreak of encephalitis among Japanese children was associated with influenza A. Most of these children (80%) were younger than 5 years of age, seizures were very common, and multiorgan system failure developed in many patients. The overall mortality (32%) and long-term disability (28%) rates were high. Influenza virus was detected only rarely in CSF specimens from these children, and brain examinations from four fatal cases showed brain edema without inflammatory cell infiltration. A more widespread relationship between influenza and encephalitis is not clear. A 20-year study of children from Finland described 11 (1.6%) CNS complications, including encephalitis and status epilepticus, among 683 cases of influenza. Influenza B-associated encephalitis also has been described but is reported less frequently. Additional study is required to establish the role of influenza infection on encephalitis and encephalopathy in the United States.

### Treatment and Prevention

None of the licensed influenza drugs has established efficacy in treating encephalitis. Annual vaccination is the most important preventive measure and now is encouraged by the American Academy of Pediatrics for all children older than 6 months of age.

### West Nile Virus

In 1999, the first cases of WNV infection in birds and humans in the western hemisphere were reported in the New York City metropolitan area. Subsequently, over the next several years, the virus spread to most of the remaining continental United States, Canada, and Mexico. Because the epidemiology of WNV is changing rapidly, the reader is referred to the CDC online resources for up-to-date information ([www.cdc.gov](http://www.cdc.gov)). Birds are the primary reservoir of WNV, mosquitoes transmit the virus to humans by biting, and cases peak during the warm season. Infection also has occurred after blood transfusions and organ transplantation.

Although most infections are asymptomatic, two predominant syndromes are recognized. West Nile fever (WNF) is a nonspecific febrile illness that occurs in about 20% of those infected after an incubation period of 3 to 14 days. West Nile neuroinvasive disease (WNND) (encephalitis, meningitis, or acute flaccid paralysis) afflicts approximately 1% of those infected. Severe muscle weak-

ness, including flaccid paralysis, has been described in hospitalized patients who have WNND and may distinguish WNV from other etiologies. Other neurologic problems associated with WNND include ataxia, cranial nerve abnormalities, myelitis, optic neuritis, polyradiculitis, and seizures. Most symptomatic cases and most poor outcomes have been in the elderly.

In the pediatric age group, WNV infections generally are less common and milder than in adults. In 2002, data from the CDC identified 4,146 WNV cases nationwide: 150 (3.6%) were in individuals younger than 19 years of age, of whom 41 (27%) had WNF, 105 (70%) had WNND, and 4 (3.7%) were unknown. Risk factors for neuroinvasive disease in children are not yet understood, but immunosuppression may be a factor.

A small number of suspected cases in asymptomatic infants have been linked to breastfeeding, but the overall significance of this is not yet clear. Potentially more concerning is the infection of pregnant women and possible congenital encephalitis. In 2002, a woman who had documented WNV infection at 29 weeks estimated gestational age gave birth at term to an infant who had bilateral chorioretinitis and an abnormal MRI reading. The infant had evidence of WNV infection, suggesting that the virus was transmitted in utero. WNV may have been responsible for the abnormalities because there was no evidence of other congenital infectious causes. Data are insufficient to predict the risk in pregnant women. A registry has been established (WNV-infected pregnant women) to determine the impact of WNV on pregnancy outcomes. (Clinicians caring for WNV-infected pregnant women should contact their health department for further information.)

### Laboratory Features

A variety of nonspecific laboratory findings have been reported in WNND, including lymphocytopenia and anemia. CSF examination shows normal glucose, elevated protein, and increased WBC levels (range, 0 to  $1.782 \times 10^3/\text{mL}$  [ $1.782 \times 10^9/\text{L}$ ]). Serology is the best method to test for infection because serum and CSF IgM antibody to WNV is usually detectable within 4 days of symptom onset and nearly always within 8 days. This test is available from both commercial and public health laboratories. False-positive serology results (usually IgG) can occur after vaccination against yellow fever and Japanese encephalitis or after infection with a related virus such as St Louis encephalitis. Direct detection of WNV by viral culture of CSF rarely is positive, and PCR tests for the virus are insensitive by the time patients reach medical attention.

### Treatment and Prevention

No specific treatment is known for WNND, nor is there a human vaccine currently available. Supportive care and rehabilitation for symptomatic patients should help minimize long-term disability. Prevention of WNND depends on decreasing mosquito breeding habitats and avoiding bites. DEET-containing insect repellants are effective but should not be used on infants younger than 2 months of age; older children should use preparations containing 30% or less DEET.

### Cat-scratch Disease

*Bartonella henselae* most often causes prolonged but self-limited regional adenopathy after a cat scratch or bite. The same organism also is associated with a number of other syndromes, including encephalopathy. The mechanism of disease has not been established, but direct infectious, toxic, and postinfectious mechanisms have been suggested. CNS manifestations can develop days to months after the onset of adenopathy, and cases lacking adenopathy have been reported. Seizures occur in approximately 50% of cases and may be brief or prolonged. Although most cases are described as an encephalopathy, both the cranial nerves or the peripheral nervous system may be affected. Both CSF examination and brain imaging results usually are normal. The diagnosis is supported by detection of antibodies to *B. henselae* in the serum. Most patients recover completely without specific antimicrobial therapy, usually within 1 to 3 months.

### Enterovirus

A number of enteroviruses (coxsackie A and B, echoviruses, and other enteroviruses) are common causes of aseptic meningitis and cause encephalitis less frequently. Encephalitis patients are febrile and have a variety of CNS manifestations, including lethargy, personality change, seizures, paralysis, and coma. The presence of a rash or enanthem suggests enterovirus as the pathogen. In regions that have a distinct enteroviral infection season, onset during that time provides an additional clue. The CSF examination shows increased WBCs, normal glucose and protein concentrations, and a negative Gram stain. Specific imaging abnormalities have not been described in enteroviral encephalitis. The diagnosis can be confirmed by culture or PCR detection of enterovirus from the CSF. Growth of enterovirus from a mucosal surface supports, but does not confirm, the virus as the cause of encephalitis. An investigational antiviral drug, pleconaril, has been studied for enteroviral aseptic meningitis in children without conclusive results. Most children who have enteroviral encephalitis recover com-

pletely, but long-term complications and deaths have been reported.

Special mention should be made of Enterovirus 71 (EV 71), a well-known cause of hand, foot, and mouth disease (HFMD). Since 1998, a number of outbreaks of EV 71 with substantial neurologic morbidity and mortality have occurred among children in Asia. Three CNS syndromes have been described, including aseptic meningitis, acute flaccid paralysis, and most commonly, brainstem encephalitis. The mean age of patients was 2.5 years, and nearly all were younger than age 5 years. The illness typically began as clinically diagnosed HFMD or herpangina and was followed by CNS symptoms approximately 3 days later. The brainstem encephalitis was characterized by myoclonic jerks, tremor, and ataxia. The more severely affected patients had cranial nerve involvement plus respiratory distress, shock, and coma. Most CSF examinations showed elevated WBC counts (approximately  $0.2 \times 10^3/\text{mCL}$  [ $0.2 \times 10^9/\text{L}$ ] in brainstem encephalitis cases), and MRI imaging showed high T2 signal intensity in the brainstem. Nineteen percent of the children died in the 1998 outbreak of 405 severe cases in Taiwan.

### Rabies

Rabies is rare in the United States but deserves special mention because of its severity and worldwide importance plus the availability of protective active and passive immunization. Most of the 35,000 annual deaths occur in Asia, Africa, and Latin America, where animal rabies control and effective postexposure prophylaxis are limited. In contrast, only one to two cases are seen in the United States each year. Since 1990, most United States cases have been caused by infection with rabies virus variants associated with insectivore bats. The history of bat contact may be difficult to elicit from ill patients, and unlike bites from larger animals, trauma from a bat bite often is negligible. The incubation period for rabies is variable, ranging from a few days to more than 19 years; 75% of children develop illness within 3 months of exposure.

Rabies infection should be considered in any patient who has progressive encephalitis because identification of an animal vector and prophylaxis of other contacts can be lifesaving. The onset of rabies symptoms usually is nonspecific and may include fever, sore throat, chills, malaise, anorexia, headache, nausea, vomiting, dyspnea, cough, and weakness. Paresthesia at or near the inoculation site is a unique feature that often is present. "Paralytic" rabies constitutes the minority of cases, and the initial finding is ascending paralysis; cerebral involvement (eg, confusion)

is seen later in the illness. The “furious” form of rabies constitutes most cases, characterized by the predominant features of hydrophobia, delirium, seizures, and agitation. Pituitary, cardiac, and autonomic dysfunction also may occur. Several sensitive and specific antemortem diagnostic tests can be provided with the assistance of state and federal health authorities. With rare possible exceptions, rabies is fatal, and no effective treatment is known; once coma develops, patients usually die within 1 to 2 weeks. In October 2004, a 15-year-old female rabies patient survived after treatment with ribavirin and drug-induced coma.

Postexposure prophylaxis (PEP) with rabies vaccine and rabies immune globulin is effective if administered correctly. Persons who are bitten or scratched by any animal should wash the wound thoroughly and be evaluated for PEP in consultation with local health authorities. Essential historical points include the identity of the animal, whether the animal is available for observation and testing, and whether the bite was provoked. If contact with a bat has occurred (even without a bite), the bat should be tested for rabies. If the bat is not available, PEP should be considered in consultation with the local public health authorities. Primary prevention is more important than PEP; children should avoid direct contact with wildlife and should not handle bats.

### Acute Disseminated Encephalomyelitis

Postinfectious encephalitis often has characteristic features that permit classification as ADEM. The key historical feature is an infection that occurred days to weeks before the onset of neurologic symptoms. The infection may be memorable, such as measles, or minor, such as a respiratory tract infection. Two recent reviews of pediatric ADEM described altered levels of consciousness in most patients, fever and headache in 50%, and neck stiffness in 33%. Cranial nerve abnormalities and ataxia were common findings on neurologic examination. The diagnosis usually is considered because of the distinctive findings on MRI of the brain and spine. Multifocal, patchy, high-signal lesions are seen on T2-weighted and FLAIR images. Classically, white matter is affected more than gray matter, but basal ganglion and thalamic lesions often are described; enhancement with gadolinium is

typical. Children usually have elevated WBC counts in the CSF but rarely have oligoclonal bands suggestive of multiple sclerosis. The disease is monophasic; if symptoms wax and wane or if new lesions develop on neuroimaging, alternative diagnoses such as multiple sclerosis should be considered.

Distinguishing ADEM from other causes of acute encephalitis is important to optimize therapy. Although there have been no controlled trials, ADEM is treated with high doses of glucocorticoids to limit further, presumed immune-mediated, damage to the CNS. Alternative therapies are IVIG and plasma exchange. Most patients in the developed world who have ADEM make a clear and often complete recovery. Depending on the inciting infection, however, the prognosis should be guarded. Following measles, for example, ADEM is associated with 25% mortality and permanent neurologic deficits in 25% to 40% of survivors.

### Summary

Encephalitis is an uncommon and disturbing illness whose cause often remains enigmatic despite extensive diagnostic efforts. Clinicians should focus on testing for treatable and common causes; empiric therapy for bacterial meningitis and herpes simplex encephalitis should be started while awaiting results. Many patients will not receive a specific causative diagnosis, and the composition and duration of therapy should be decided in consultation with neurology and infectious disease specialists. Regardless of whether a specific cause is found, supportive care and early referral for rehabilitation maximize functional recovery.

### Suggested Reading

- 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;36:731–742
- Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988–1997. *Clin Infect Dis.* 2002;35:175–182
- Kolski H, Ford-Jones EL, Richardson S, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994–1995. *Clin Infect Dis.* 1998;26:398–409

## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

1. Among the following, the *most* common diagnosed cause of sporadic nonseasonal encephalitis is:
  - A. Herpes simplex virus.
  - B. La Crosse encephalitis.
  - C. Tick-borne infection.
  - D. Varicella virus.
  - E. West Nile virus.
2. For a patient who is suspected of having acute encephalitis, which of the following studies is *most* likely to be helpful?
  - A. Cerebrospinal fluid glucose level.
  - B. Computed tomography scan.
  - C. Electroencephalography.
  - D. Magnetic resonance imaging.
  - E. Viral culture.

Match the etiologic agent for encephalitis with currently recommended management (answers may be used once, more than once, or not at all).

3. Cat-scratch disease.
4. Epstein-Barr virus.
5. Herpes simplex virus.
6. Rabies.
7. West Nile virus.
  - A. Acyclovir.
  - B. Broad-spectrum antibiotics.
  - C. High-dose glucocorticoids.
  - D. Postexposure vaccination.
  - E. Supportive care.
8. Among the following, the neurologic feature that appears to distinguish encephalitis due to West Nile virus from encephalitis due to other causes is:
  - A. Ataxia.
  - B. Cranial nerve abnormalities.
  - C. Polyradiculitis.
  - D. Seizures.
  - E. Severe muscle weakness.