Meningitis and Encephalitis
Karen L. Roos, MD, FAAN; John E. Greenlee, MD, FAAN

ABSTRACT
Purpose of Review: Neurologists have a vital role in the recognition of meningitis and encephalitis, the accurate evaluation and interpretation of CSF studies, and the management and prevention of the neurologic complications of CNS infectious diseases.
Recent Findings: Although the tetravalent meningococcal glycoconjugate vaccine has decreased the incidence of meningococcal meningitis, the vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease. Thus, meningitis due to Neisseria meningitidis is still a concern in a vaccinated individual. Empiric therapy for meningitis associated with sinusitis, otitis, or mastoiditis should include antibiotic therapy for anaerobes. An organism that classically causes a subacute or chronic meningitis, such as Mycobacterium tuberculosis, may on occasion present with an acute onset of symptoms.
Summary: Unlike most other diseases, the management of patients with suspected meningitis or encephalitis begins with empiric therapy. The etiologic organism cannot always be identified. The goal is to identify those that are treatable, provide supportive care for those that are not, and, when possible, prevent the neurologic complications of these infections.

INTRODUCTION
Meningitis and encephalitis are neurologic emergencies. In the hospital setting, the initial realization that a patient has a CNS infectious disease is usually made by the emergency department physician or, if the patient is already admitted, by the primary service. For this reason, neurologic consultation may be delayed, and time is almost always of the essence in reaching an accurate diagnosis and initiating treatment.

ACUTE MENINGITIS
Bacterial Meningitis
Bacterial meningitis is most commonly caused by hematogenous spread of bacteria from a remote site of infection. Meningitis may also develop from the spread of organisms through emissary veins from infected sinuses, middle ear, or mastoid. Bacteria may enter the subarachnoid space following penetrating trauma or neurosurgical procedures or through congenital or acquired defects in the skull or spinal column. Meningitis due to entry of organisms through congenital or acquired defects in the skull or spinal column should be suspected in patients with recurrent episodes of meningitis. Acquired defects are usually the result of closed head trauma and occur at sites where the bones of the skull are thinnest: over the frontal, ethmoidal, or sphenoidal sinuses or bony structures adjacent to the middle ear or mastoid. Acquired skull base defects may be accompanied by CSF rhinorrhea or otorrhea if the meninges are breached, but not all skull base defects are associated with rhinorrhea or otorrhea. It is important to remember that an interval of many years may separate an episode of significant closed head trauma and the onset of meningitis.
Causative agents of acute bacterial meningitis. The agents causing bacterial meningitis vary with the age of the patient, the route by which infection is acquired, and the presence of associated or predisposing conditions.

The most common etiologic organism of bacterial meningitis in neonates and infants is *Streptococcus agalactiae* (group B streptococci), followed in order of frequency by *Escherichia coli*, other gram-negative bacilli, and *Listeria monocytogenes*. Meningitis due to *S. agalactiae* occurs at two points in time: within 48 hours of the postnatal period or at 7 days to 6 weeks of age. Cases occurring in the immediate postnatal period are due to acquisition of the organism from the mother at the time of birth, and meningitis often occurs as part of a systemic infection. Cases of *S. agalactiae* meningitis in older neonates are usually not accompanied by other evidence of systemic infection.

The most common causative organisms of bacterial meningitis in children and adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*. The tetravalent meningococcal glycoconjugate vaccine has decreased the incidence of meningococcal meningitis. The vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease.

Meningitis associated with sinusitis, otitis, or mastoiditis may be due to streptococci, anaerobes, *Staphylococcus aureus*, *Haemophilus*, or Enterobacteriaceae. Meningitis in the postneurosurgical patient may be due to staphylococci, gram-negative bacilli, or anaerobes. *S. aureus* is a common causative organism in patients with penetrating head trauma.

The organisms associated with bacterial meningitis in patients who are immunocompromised vary with the type of immune deficiency. Individuals with defects of cell-mediated immunity, which includes very young infants, pregnant woman, the elderly, and patients who are immunocompromised as a result of organ transplantation, malignancy, AIDS, or immunosuppressive medications, have an increased prevalence of meningitis due to *L. monocytogenes* or mycobacteria. Patients with defects of humoral immune response (and patients who have undergone splenectomy) are at risk for fulminant meningitis with *S. pneumoniae* or *N. meningitidis*. Patients with neutropenia are susceptible to meningitis caused by *Pseudomonas aeruginosa* and by gram-negative enteric bacteria.

Chronic meningitis presenting acutely. A number of etiologic organisms that typically cause a subacute or chronic meningitis may on occasion present with acute onset of symptoms. This is especially true for tuberculous meningitis but may occasionally occur with fungal meningitides due to *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, or other agents. The most urgent of these is tuberculous meningitis, and presumptive treatment should be initiated if the condition is suspected (Case 3-1).

**Case 3-1**
A 21-year-old Laotian woman presented to the emergency department with severe headache, fever, confusion, and difficulty with gait. Examination revealed confusion, nuchal rigidity, bilateral Babinski signs, and ataxia. CT scan demonstrated basilar meningeal inflammation and a mild increase in ventricular size. CSF analysis revealed 150 white blood cells/mm$^3$, 45%

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Viral Meningitis

Many of the viruses causing viral meningitis have a seasonal distribution (Table 3-1). Most cases of viral meningitis are due to enteroviruses and occur in summer or early autumn, although occasional cases may occur throughout the year. Meningitis associated with West Nile virus has a similar seasonal distribution, as does meningitis associated with other arthropod-borne viruses. The exception to this rule is Colorado tick fever, which tends to occur in late spring or early summer.

Clinical Presentation of Acute Meningitis

Bacterial meningitis may be preceded by 3 to 5 days of insidiously progressive malaise, fever, irritability, or vomiting; develop over 1 to 2 days; or have a fulminant presentation. Bacterial meningitis remains one of the few conditions in which a previously healthy young person may go to sleep with mild symptoms and never awaken. Typical symptoms are fever, headache, photophobia, vomiting, and an altered level of consciousness (Case 3-2). Patients may or may not complain of neck stiffness. Seizures may occur early in meningitis in up to 40% of affected children and may also occur in adults. Presentation with focal seizures or focal neurologic symptoms, however, should raise concern of brain abscess, cerebritis, or cerebrovascular complications. Cases of mycobacterial or fungal meningitis presenting acutely may resemble bacterial meningitis. Patients with viral meningitis are usually less overtly ill, and they never have an altered level of consciousness or new-onset seizure activity unless encephalitis has developed. Neurologists are critical in helping non-neurologists distinguish between a patient with bacterial meningitis, who should be admitted to and observed in...
the intensive care unit, and a patient with viral meningitis, who is not at risk for additional complications.

**Bedside Diagnosis of Meningitis**

Bacterial meningitis should be considered in any patient presenting with fever, alteration in consciousness, and nuchal rigidity, keeping in mind that these findings are not present in all patients. Presentation in coma is an ominous prognostic sign. The classic tests for meningeal irritation are resistance to passive flexion of the neck (nuchal rigidity), Kernig sign, and Brudzinski sign.

**Case 3-2**

A 62-year-old woman had been in good health until 4 days prior to admission, when she reported shaking chills, cough, and purulent sputum production to her husband. Two days prior to admission she reported a headache. On the day of admission, her husband found her unresponsive in the early morning hours and called an ambulance. She was brought first to an outlying facility and then transferred.

On examination, the patient was diaphoretic and unresponsive. Pulse was 108 beats/min, blood pressure was 108/84 mm Hg, and temperature was 39.8°C (103.6°F). General physical examination was unremarkable except for rales over the right lower lung field and nuchal rigidity with a positive Brudzinski sign. Fundi showed flat disks but absent venous pulsations. Blood cultures were obtained, and empiric therapy for bacterial meningitis and herpes simplex virus type 1 encephalitis was initiated with dexamethasone, ceftriaxone, vancomycin, ampicillin, and acyclovir.

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sign. Kernig sign is present when resistance to passive extension of the leg at the knee is present. Although Brudzinski developed several tests to detect meningeal irritation, the maneuver most commonly referred to as Brudzinski sign involves spontaneous flexion of the hips and knees when the neck is passively flexed. Brudzinski sign is the more sensitive of the two. Both signs, when present, are strongly suggestive of meningeal irritation; however, they were developed in the preantibiotic era when meningitis was frequently advanced at the time of presentation and may not be detected early in the course of infection. In awake patients, a more sensitive test is to ask patients to put their chin on their chest with the mouth closed. Keeping the mouth closed is important, because patients experiencing pain on flexion may hold their neck still but touch their chin to their chest by opening the jaw widely. One of the most sensitive tests of nuchal rigidity is a test that was developed during the days of the polio epidemic and involves asking the patient to kiss his or her knee (in children, who consider this request perfectly reasonable) or, in adults, to touch the forehead to the knee. This test will often detect meningeal irritation at a time when other tests are negative. It is important to keep in mind that elderly patients with extensive cervical spine disease may have neck stiffness, and occasionally patients with influenza and severe myalgias may also report neck pain. In both groups of patients, pain and resistance to movement usually occur not only upon flexion but also upon lateral rotation. Patients with meningitis, however, can usually turn the head even if neck stiffness to flexion is present. Particular attention should be paid to the presence of cutaneous rashes, petechiae, or purpura suggestive of meningococcemia; pulmonary consolidation suggestive of pneumonia due to \textit{S. pneumoniae}; or cardiac murmurs suggestive of endocarditis.

**Atypical Presentations of Meningitis**

In neonates, bacterial meningitis may present with tachypnea, apneic spells, changes in heart rate, atypical seizures, or simply vague decline. Although a feeble, high-pitched cry in an infant has been said to suggest meningitis, this is not a reliable sign. Similarly, a bulging fontanelle is a late sign, indicating significantly increased intracranial pressure. Individuals who are immunocompromised,
such as neonates, may not develop fever or nuchal rigidity. Patients with alcoholism presenting in the setting of severe inebriation may have meningitis without clearly detectable signs. Meningitis may also be deceptively asymptomatic in the elderly, and the only sign of meningitis may be confusion in a previously alert older patient or altered responsiveness in a patient who already has dementia. In these patients, as well as in neonates, the threshold for CSF analysis should be low. However, patients with alcoholism and elderly patients are also at risk for falls and subdural hematomas. In such patients, it is appropriate to begin antimicrobial therapy and obtain a head CT scan or MRI before CSF analysis. The onset of bacterial meningitis following neurosurgical procedures is often insidious, developing over hours or days. Patients in this setting are at increased risk, as an alteration of consciousness or neck stiffness may be attributed to the expected postoperative course.

**Laboratory Diagnosis of Meningitis**

Although bacterial meningitis is suspected on the basis of the clinical presentation and physical examination findings, definitive diagnosis is made by analysis of the CSF. If intracranial pressure is greatly increased, there is a risk of brain herniation independent of, but also associated with, lumbar puncture, and the likelihood of fatal herniation cannot be reliably predicted from CT or MRI. In severely ill patients in whom very high intracranial pressure is suspected, the most prudent course is to begin empiric therapy and wait until CSF pressure has been controlled before performing lumbar puncture. The organism can often be identified in blood cultures. CSF should be sent for cell count with differential, protein and glucose concentration, Gram stain, culture, and PCR. Simultaneous blood glucose should also be sent to determine the CSF:blood glucose ratio. Expeditious handling of CSF by the laboratory is important because cells may adhere to the collecting tube over time, resulting in lower CSF cell counts, and leukocytes may lyse in extremely purulent CSF.

Typical CSF findings in bacterial meningitis include elevated opening pressure, fluid that is often, but not always, turbid, elevated white blood cell count consisting predominantly of polymorphonuclear leukocytes, elevated protein concentration, and depressed CSF:blood glucose ratio. A CSF:blood glucose ratio of less than 0.3 is highly correlated with bacterial meningitis. In evaluating CSF glucose concentrations, it is important to remember that CSF glucose values will be higher in moderately to severely hyperglycemic patients and that changes in CSF glucose concentrations may lag 30 to 120 minutes behind those in blood. Protein concentrations in meningitis are a reflection of blood-brain barrier injury but usually range between 100 mg/dL and 500 mg/dL.

Specific identification of the infecting organism involves Gram stain, culture, and PCR. Gram stain provides the most rapid initial identification of the organism. Detection of organisms on Gram stain requires approximately 100,000 organisms/mm³. Errors in Gram stain may result from careless handling of CSF, inadequate efforts to resuspend bacteria if CSF has been allowed to settle, and errors in decolorization or reading of the slide. A 16S ribosomal RNA conserved sequence broad-based bacterial PCR is routinely available in most hospital laboratories. Additionally, a number of meningeal-specific PCRs detect *N. meningitidis* or *S. pneumoniae* nucleic acid in CSF, as well as a number of other meningeal pathogens, but...
specific diagnosis of the causative organism of bacterial meningitis and determination of antibiotic sensitivity require bacterial culture. Although this is routine in most hospitals, it may be helpful to alert the laboratory in advance if anaerobic infection or other unusual organisms or culture requirements are anticipated. Yield on culture can be reduced by prior antibiotic therapy. Table 3-2 is a list of the expected CSF results in meningitis due to bacteria, viruses, mycobacteria, and fungi.

Treatment of Acute Meningitis

Antibiotic therapy for bacterial meningitis. Antibiotic therapy for bacterial meningitis is initially empiric and then specific once the pathogen has been identified and the results of antimicrobial sensitivity testing are known (Table 3-3).

Therapy of chronic meningitis presenting acutely. Specific diagnosis of tuberculous meningitis can be difficult: yield by PCR approaches 50%, and sensitivity of culture (which may take up to 6 weeks) is only 70%. Thus, therapy for tuberculous meningitis should be initiated presumptively if the diagnosis is suspected (Table 3-4). Treatment of fungal meningitis is usually not begun empirically unless organisms are seen in CSF.

Treatment of viral meningitis. Most cases of viral meningitis resolve spontaneously. The headache may persist for months and can be managed with amitriptyline and nonsteroidal anti-inflammatory agents. Limited data suggest that pleconaril may shorten the...
Acyclovir is efficacious in treating herpes simplex virus type 2 (HSV-2) meningitis, and prophylactic therapy with acyclovir, valacyclovir, or famciclovir is efficacious in preventing recurrent meningitis due to HSV-2.

Corticosteroid therapy in meningitis. The realization that neurologic injury in bacterial meningitis is due to the host inflammatory response has led to a focus on controlling this aspect of meningitis. Early studies in children with Haemophilus influenzae meningitis who were treated with cefotaxime plus

| TABLE 3-3 Antibiotics for Empiric Therapy of Bacterial Meningitis |
|------------------|--------------------------|--------------------------|
| **Age and Associated Conditions** | **Probable Organism** | **Antibiotic Therapy** |
| Preterm infants  | *Staphylococcus aureus* (nosocomial) | Vancomycin plus ceftazidime |
|                  | Gram-negative bacilli     |                          |
| Neonates         | *Group B streptococci*    | Ampicillin plus cefotaxime |
|                  | *Escherichia coli*        |                          |
|                  | Other gram-negative bacilli |                         |
|                  | *Listeria monocytogenes*  |                          |
| Children and adults | *Streptococcus pneumoniae* | Third-generation (ceftriaxone or cefotaxime) or fourth-generation (cefepime) cephalosporin plus vancomycin |
|                  | *Neisseria meningitidis*  |                          |
| Adults over the age of 55 | *S. pneumoniae* | Third-generation (ceftriaxone or cefotaxime) or fourth-generation (cefepime) cephalosporin plus vancomycin plus ampicillin |
|                  | *L. monocytogenes*        |                          |
|                  | Gram-negative bacilli     |                          |
|                  | *Haemophilus influenzae*  |                          |
| Meningitis in the setting of sinusitis, otitis, or known CSF leak | *S. pneumoniae* | Third-generation (ceftriaxone or cefotaxime) or fourth-generation (cefepime) cephalosporin plus vancomycin plus meropenem or metronidazole |
|                  | *Haemophilus*             |                          |
|                  | Gram-negative bacilli     |                          |
|                  | Anaerobic or microaerophilic streptococci |                     |
|                  | *Bacteroides fragilis*    |                          |
|                  | *S. aureus*               |                          |
| Head trauma, neurosurgical procedures, shunt infections | *S. aureus* | Vancomycin plus ceftazidime or vancomycin plus meropenem |
|                  | *Staphylococcus epidermidis* |                        |
|                  | Gram-negative bacilli     |                          |
|                  | *S. pneumoniae*           |                          |
| States of impaired cellular immunity, including AIDS | *L. monocytogenes* | Third-generation (ceftriaxone or cefotaxime) or fourth-generation (cefepime) cephalosporin plus vancomycin plus ampicillin |
|                  | Gram-negative bacilli     |                          |
|                  | *S. pneumoniae*           |                          |
|                  | *H. influenzae*           |                          |
Dexamethasone demonstrated an effect on the CSF inflammatory response and a decreased incidence of deafness compared with those treated with cefotaxime alone.\textsuperscript{6} More recently, studies from Europe—including a nationwide prospective study from the Netherlands in which dexamethasone was used in all patients above 16 years of age with pneumococcal meningitis—demonstrated reduced mortality rates and neurologic sequelae in patients with pneumococcal meningitis treated with dexamethasone begun at the initiation of antibiotic therapy (class III evidence).\textsuperscript{7,8} Dexamethasone is given as 10 mg intravenously, beginning immediately prior to or with the initial dose of antibiotics, followed by 10 mg intravenously every 6 hours for 4 days. Early institution of dexamethasone and antibiotic therapy appears to be crucial, and dexamethasone has not been shown to be effective in less-developed countries where patients tend to present later in the course of their disease.\textsuperscript{8} The role of dexamethasone in tuberculous or fungal meningitides is less well established. In tuberculous meningitis, dexamethasone has been reported to decrease mortality but not neurologic sequelae in survivors.\textsuperscript{9} As with bacterial meningitis, however, the utility of dexamethasone may depend on its use early in the course of infection.

Other measures to treat cerebral edema. Patients presenting with papilledema or signs of impending brain herniation warrant emergent treatment for increased intracranial pressure. Elevation of the head of the bed to 30 degrees will often reduce pressure somewhat. Hyperventilation to a \(PCO_2\) of 27 mm Hg to 30 mm Hg will cause intracranial vasoconstriction and may be lifesaving over the short term. This usually requires intubation and paralysis, and in some cases the patient will already be hyperventilating to that level. In children, 0.5 g/kg to 2.0 g/kg of mannitol is given intravenously over 30 minutes and repeated as needed. The adult dosage is a 1.0 g/kg bolus repeated as needed every 3 to 4 hours or 0.25 g/kg every 2 to 3 hours. Pentobarbital coma has been used in extreme cases, but no controlled data exist for its use in meningitis. Decompressive craniectomy is not normally used in meningitis because the cerebral involvement is diffuse rather than focal. Surgery may be required, however, to drain an accompanying brain abscess or parameningeal focus of infection. For more information, refer to the article “Evaluation and Management of Increased Intracranial Pressure” in this issue of Continuum.

Other complications of meningitis requiring treatment. Bacterial meningitis may be accompanied by a variety

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### Table 3-4: Antimicrobial Therapy for Tuberculous Meningitis\textsuperscript{a}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Daily Dose</th>
<th>Maximum Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg to 10 mg/kg</td>
<td>300 mg</td>
<td>6 to 9 months</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg to 20 mg/kg</td>
<td>600 mg</td>
<td>6 months</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>15 mg/kg to 30 mg/kg</td>
<td>2000 mg</td>
<td>2 months</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg to 25 mg/kg</td>
<td>2500 mg</td>
<td>2 months</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg</td>
<td>1000 mg</td>
<td>2 months</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Multiple drug regimens (four or more) should be used when a high probability of drug resistance exists.
of neurologic and systemic complications, many of which may also occur in tuberculous meningitis. Bacterial meningitis arising from sinusitis or otitis may be complicated by epidural abscess, subdural empyema, brain abscess, or venous sinus thrombosis, any of which may require emergent surgery. Seizures require emergent treatment with lorazepam, phenytoin (fosphenytoin), or more aggressive therapy such as phenobarbital or pentobarbital coma in patients who fail to respond. Hyponatremia may be caused by cerebral salt wasting, the syndrome of inappropriate secretion of antidiuretic hormone, or IV fluids. Subdural effusions are common in children with meningitis; these do not usually require drainage and may be followed by CT or MRI. Patients may develop cerebral vasculitis, stroke, or spontaneous intracranial hemorrhage. Myelitis, although not usually considered a complication of bacterial meningitis, has been reported in 2.3% of patients with pneumococcal meningitis. Bacterial sepsis and shock may be present, as may disseminated intravascular coagulation, and, in the case of *N. meningitidis*, Waterhouse-Friderichsen syndrome with widespread hemorrhage and adrenal failure. Cases of meningitis associated with *S. aureus* and, less often, *S. pneumoniae* may be a complication of bacterial endocarditis. Meningitis in the presence of *S. pneumoniae* endocarditis is often accompanied by rapid destruction of the aortic valve. Basilar meningitis with basal ganglia ischemia or infarction can occur in both tuberculous meningitis and cryptococcal meningitis. The basilar meningitis that occurs in tuberculosis meningitis may produce obstructive rather than communicating hydrocephalus.

**Fungal meningitis.** Recommendations for the antimicrobial therapy of fungal meningitis are readily available, but neurologists must be vigilant about the presence and development of increased opening pressure. Opening pressure should be measured at the time of the initial lumbar puncture and any time a change in the neurologic examination occurs. A time-honored practice has been to perform daily lumbar punctures and reduce the opening pressure by 50% using a manometer. In reality, daily lumbar punctures are often not effective, and it is best to use a ventriculostomy instead.

**Prognosis**

In most series, mortality has correlated with obtundation or coma. Factors associated with poor prognosis include age older than 60 years, concomitant debilitating diseases, low Glasgow Coma Scale score on admission, focal neurologic deficits, and low CSF cell count. Seizures have predicted a worse outcome in some studies, as has low CSF:serum glucose ratio. Mortality in tuberculous meningitis is in the range of 25%, with good recovery in only 50% of patients. As in bacterial meningitis, prognosis is significantly influenced by the level of consciousness on presentation and the rapid institution of appropriate therapy. Viral meningitis is usually self-limited.

**ENCEPHALITIS**

In patients with an altered level of consciousness or an acute confusional state, the first question to ask is whether the patient has encephalitis or an encephalopathy. If the patient has encephalitis, the next question to ask is whether he or she has encephalitis that can be treated with antimicrobial agents or encephalitis that is treated with supportive care only (Case 3-3).

**Etiology**

The presence of fever and headache with an altered level of consciousness makes encephalitis more likely than...
encephalopathy. The etiologic organism of the encephalitis can be predicted based on the following: (1) the time of year, (2) prodromal symptoms (eg, flulike illness in West Nile virus infection), (3) area of residence, (4) travel and occupational and recreational activities, (5) rash (eg, varicella, meningococcemia, Rocky Mountain spotted fever), (6) contact with animals, and (7) immunosuppression from medications, malignancy, chronic corticosteroid use, or organ transplantation.

The most common identifiable etiologic organisms of encephalitis are herpesviruses (eg, herpes simplex virus type 1 or varicella-zoster virus), a tickborne bacterial infection, or an arthropodborne virus.

Neuroinvasive disease due to West Nile virus, St. Louis encephalitis virus, or Japanese encephalitis virus may present with encephalitis, a flaccid, weak limb (a poliomyelitis syndrome), or parkinsonian features.

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KEY POINTS
- The most common identifiable etiologic organisms of encephalitis are herpesviruses (eg, herpes simplex virus type 1 or varicella-zoster virus), a tickborne bacterial infection, or an arthropodborne virus.
- Neuroinvasive disease due to West Nile virus, St. Louis encephalitis virus, or Japanese encephalitis virus may present with encephalitis, a flaccid, weak limb (a poliomyelitis syndrome), or parkinsonian features.

**Case 3-3**

A 20-year-old college junior was brought to the emergency department by her boyfriend because of a 3-day history of fever, headache, and intermittent confusion. On examination, she had a temperature of 38°C (100.4°F), was oriented to self but not to date or place, and had difficulty following commands. The boyfriend denied alcohol or illicit drug use. Complete blood count with differential was normal. Noncontrast cranial CT scan was normal. CSF analysis demonstrated 100 white blood cells/mm³, lymphocytic predominance, 700 red blood cells/mm³, a glucose concentration of 47 mg/dL, and a protein concentration of 56 mg/dL.

The patient was treated empirically with acyclovir for herpes simplex virus (HSV) encephalitis based on her clinical presentation and CSF analysis. CSF PCR for HSV-1 DNA was obtained as well as serum and CSF immunoglobulin G (IgG) antibodies to determine a serum:CSF antibody ratio.

**Comment.** The CSF PCR should be positive, as she is 3 days into her illness, but it is likely too early to detect the intrathecal synthesis of antibodies. Antibodies do not appear in CSF until 8 days after symptom onset but may be detectable for up to 3 months. HSV IgG on serum and CSF should be obtained. A serum:CSF ratio of less than 20:1 is diagnostic of HSV encephalitis. Fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted imaging (DWI) magnetic resonance scans are indicated and would be expected to demonstrate an area of increased signal intensity in the temporal lobe. In 90% of adults with HSV encephalitis, an area of increased signal intensity is seen in the temporal lobe on T2-weighted images, FLAIR sequences, and DWI within 48 hours of symptom onset.

Patients with encephalitis have fever and headache and one or more of the following: confusion, behavioral abnormalities, depressed level of consciousness, focal neurologic deficits, and new-onset seizure activity.

Certain features, or a combination of features, suggest a specific etiology. Patients with West Nile virus may have a tremor, a history of diarrhea, or a maculopapular rash. The three most clinically significant flaviviruses (West Nile virus, St. Louis encephalitis virus, and Japanese encephalitis virus) may present with a flaccid, weak limb (a poliomyelitis syndrome) or parkinsonian features. Confusion and word-finding difficulty are common in HSV-1 encephalitis.
Varicella-zoster virus presents with focal neurologic deficits due to ischemic and hemorrhagic infarctions. Although varicella-zoster virus encephalitis may follow shingles, encephalitis due to varicella-zoster virus may occur in the absence of a history of shingles. The rash of Rocky Mountain spotted fever typically begins on the wrists and ankles and then spreads centrally to the face, chest, and abdomen. This is in contrast to the rash of an enterovirus, which begins on the face and chest and then spreads to the limbs. *Borrelia burgdorferi*, the causative spirochete of Lyme disease in North America, does not cause encephalitis. Thus, the appearance of a single erythematous lesion on the trunk or extremities is not a clue to the etiologic agent.

**Diagnosis**

Although the specific tests for encephalitis are magnetic resonance (MR) scan, CSF analysis, blood cultures, and complete blood count with differential and serologies, routine tests for encephalopathy should be sent as well, including serum electrolytes, glucose, creatinine, liver function test, ammonia, and serum and urine toxicology screens. An MR scan is more sensitive than a CT scan for encephalitis.

The importance of serologies (acute phase immunoglobulin M [IgM] and acute and convalescent immunoglobulin G [IgG] titers) cannot be overstated. One of the biggest impacts that PCR has had on the diagnosis of neurologic infectious diseases has been the increased awareness of other serum and CSF tests that have been available for years but were often overlooked because of the emphasis on neuroimaging abnormalities in diagnosing encephalitis.

**Herpes simplex virus type 1.** In 90% of adults with HSV encephalitis, an area of increased signal intensity is seen in the temporal lobe on T2-weighted images, fluid-attenuated inversion recovery (FLAIR) sequences, and diffusion-weighted imaging MR scan within 48 hours of symptom onset (Figure 3-1). CSF analysis demonstrates a lymphocytic pleocytosis with a normal glucose concentration. Red blood cells or xanthochromia may be seen in the CSF as this is hemorrhagic, necrotic encephalitis. The CSF PCR may be falsely negative in the first 72 hours of HSV encephalitis symptoms, and detection rates decrease 10 days after the onset of symptoms. Serum and CSF HSV IgG antibodies should be obtained to determine whether intrathecal synthesis of antibodies is present. A serum:CSF ratio of less than 20:1 is diagnostic of HSV encephalitis. It takes at least 8 days for antibodies to be detected in CSF, and antibodies may be detectable for up to 3 months. The EEG demonstrates periodic sharp-and-slow wave complexes occurring at regular 1- to 3-second intervals. These abnormalities are most typically seen between the second and fifteenth days of illness.

For HSV-1 encephalitis, CSF PCR for HSV-1 and CSF and serum antibodies should be sent.
Varicella-zoster virus. The best diagnostic test for varicella-zoster virus encephalitis is the detection of varicella-zoster virus IgM in CSF.

Mosquitoborne viruses. In encephalitis due to any of the flaviviruses, hypointense lesions may be seen in the thalami, substantia nigra, and basal ganglia on T2-weighted and FLAIR sequences. The best test for West Nile virus encephalitis is the detection of CSF IgM antibodies specific for the virus. Serum IgM and IgG antibodies cannot be used to diagnose neuroinvasive disease.

For the other mosquito-borne viral encephalitides, acute and convalescent serology remain the mainstay of diagnosis.

Epstein-Barr virus. Diagnosis of Epstein-Barr virus (EBV) depends on a combination of serology and CSF PCR. If serology demonstrates a positive virus capsid antigen (VCA) and negative Epstein-Barr nuclear antigen (EBNA) and the CSF PCR for EBV DNA is positive, a diagnosis of EBV encephalitis can be made. If serology demonstrates a negative VCA IgM and a positive EBNA and the CSF PCR is positive, a diagnosis of EBV encephalitis cannot be made, as the CSF PCR may be positive for EBV nucleic acid in an immunocompetent individual in any inflammatory CNS disorder.

Rocky Mountain spotted fever. The serologic tests for the rickettsial infections have a low sensitivity early in the disease. It is important to biopsy any skin lesions that are present and to repeatedly send serology. A number of different serologic tests are available, including the indirect fluorescent antibody test, ELISA, and flow immunoassays.

Progressive multifocal leukoencephalopathy. The CSF should be non-inflammatory. To diagnose progressive multifocal leukoencephalopathy, CSF PCR should be sent for JC virus DNA; sensitivity may only be around 60%.

Cytomegalovirus encephalitis. To diagnose cytomegalovirus encephalitis, CSF PCR for cytomegalovirus nucleic acid should be sent.

Therapy

HSV-1 encephalitis is treated with 10 mg/kg of IV acyclovir every 8 hours for 3 weeks. Varicella-zoster virus encephalitis is treated with 10 mg/kg of IV acyclovir every 8 hours for 10 to 14 days. Acyclovir is not recommended for EBV encephalitis, as it is felt to provide little or no benefit. Rocky Mountain spotted fever is treated with 100 mg of doxycycline twice daily for at least 3 days after the patient becomes afebrile. Cytomegalovirus encephalitis is treated with a combination of 60 mg/kg of IV foscarnet every 8 hours and 5 mg/kg of IV ganciclovir every 12 hours.

Noninfectious Encephalitis

Patients with noninfectious encephalitis have headache, confusion, behavioral abnormalities, gait abnormalities, and involuntary movements. CSF analysis demonstrates a lymphocytic pleocytosis with an increased protein concentration and a normal glucose concentration. The hyperintensity in the temporal lobe on T2-weighted and FLAIR MR images of paraneoplastic limbic encephalitis has a similar appearance to that of HSV-1 encephalitis. Serology and CSF should be sent for antineuronal antibodies, and, when positive, diagnostic studies should be performed for the malignancy associated with the antineuronal antibody.

Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) steroid-responsive encephalopathy (previously referred to as Hashimoto encephalopathy) has been associated with a number of antibodies, including thyroperoxidase antibodies, thyroid microsomal antibodies, thyroglobulin antibodies, extractable nuclear antigen antibodies, antistriatal antibodies, antinuclear antibodies, antiphospholipid antibodies, and gliadin antibodies.
NAIM is treated with 1000 mg of IV methylprednisolone for 5 days followed by oral prednisone therapy.

REFERENCES


