5
Meningitis and encephalitis

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Meningitis

Case presentation 1

A 30-year-old male presents to the emergency department with a 24-hour history of fever and headache. The patient's symptoms began abruptly and have worsened steadily over the last day. His wife reports that in the last 6 hours he has become somewhat confused. He has no significant past medical or surgical history. He takes no medications and denies alcohol, tobacco, and drug use. His family history is likewise non-contributory.

Physical examination reveals a temperature of 38·5ºC, a pulse of 110 beats per minute, and a blood pressure of 130/70 mmHg. He does not demonstrate photophobia or neck stiffness. His neurologic exam is non-focal but he is orientated only to person. Initial laboratory evaluation is remarkable for a white blood cell count of $21{\cdot}4 \times 10^9$/liter.

You admit the patient with the presumptive diagnosis of meningitis, order two sets of blood cultures, and plan to perform a lumbar puncture (LP). You wonder whether to order a computed tomography (CT) scan prior to the LP to rule out an intracranial mass lesion, as well as whether antibiotics can be withheld until after the CT and LP have been performed.

Diagnosis

Epidemiology

The acute meningitis syndrome may be caused by a wide variety of infectious pathogens as well as by non-infectious diseases and syndromes (Box 5.1).[1–4] Given its frequency and clinical impact, this chapter will focus specifically on acute bacterial meningitis. The annual incidence of bacterial meningitis varies by geographic region, from approximately 3 per 100 000 in the United States (US), to 45·8 per 100 000 in Brazil, to 500/100 000 in Africa.[5–8] The incidence of bacterial meningitis has been profoundly affected by the introduction of the *Haemophilus influenzae* vaccine in 1987. Previously isolated in nearly 50% of cases of bacterial meningitis in the US,[8] *H. influenzae* now accounts for only about 7% of cases.[9] Comparable reductions in the incidence of *H. influenzae* meningitis have also been noted in countries in which the use of the vaccine is less comprehensive, suggesting herd immunity may be enhanced by the vaccine.[10]

Since the incidence of bacterial meningitis due to non-*Haemophilus influenzae* pathogens has remained constant during this time period, the net result of introduction of the *H. influenzae* vaccine has been a marked reduction in the overall incidence of bacterial meningitis.[9] Furthermore, the vaccine has also changed the age distribution of meningitis; the median age of persons with bacterial meningitis increased from 15 months in 1986 to 25 years in 1995,[9] such that bacterial meningitis in the US is now predominantly a disease of adults rather than children. This chapter thus focuses on bacterial meningitis in the adult population.

Box 5.1 Differential diagnosis of acute meningitis

Bacteria
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Listeria monocytogenes*
- *Hemophilus influenzae*
- *Streptococcus agalactiae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Salmonella* spp.
- *Nocardia* spp.
- *Mycobacterium tuberculosis*

Rickettsiae
- *Rickettsia rickettsii*
- *Rickettsia prowazekii*
- Rickettsiae typhi
- *Ehrlichia* spp.

Spirochetes
- *Treponema pallidum*
- *Borrelia burgdorferi*
- *Leptospira* spp.

Protozoa and helminths
- *Naegleria fowleri*
- *Angiostrongylus cantonensis*
- *Strongyloides stercoralis*
- *Toxoplasma gondii*
- *Plasmodium falciparum*

Viruses
- Nonpolio enteroviruses

Echoviruses

Coxsackieviruses
- Mumps virus
- Arboviruses
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Human immunodeficiency virus
- Adenovirus
- Parainfluenza viruses 2 and 3
- Influenza virus
- Measles virus

Fungi
- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Paracoccidioides brasiliensis*
- *Candida* spp.
- *Aspergillus* spp.
- *Sporothrix schenckii*

Neoplastic diseases
- Lymphomatous meningitis
- Carcinomatous meningitis
- Leukemia

Intracranial tumors and cysts
- Craniopharyngioma
- Dermoid/epidermoid cyst
- Teratoma

Medications
- Antimicrobial agents *
- Non-steroidal anti-inflammatory agents
- OKT3
- Azathioprine
- Cytosine arabinoside
- Immune globulin
- Ranitidine

Systemic illnesses
- Systemic lupus erythematosus
- Vogt–Koyanagi–Harada syndrome
- Sarcoidosis
- Behçet's disease
- Rheumatoid arthritis
- Polymyositis
- Wegener's granulomatosis
- Familial Mediterranean fever
- Kawasaki's syndrome

Miscellaneous
- Seizures
- Migraine
- Serum sickness
- Heavy metal poisoning

Adapted from references 1–4.

*Trimethoprim, sulfamethoxazole, ciprofloxacin, penicillin, cephalosporin, metronidazole, isoniazid, pyrazinamide.

Table 5.1 Empiric treatment of bacterial meningitis*

Patient population	Likely pathogens	Antimicrobial	Dosage and route	Duration§
Immunocompetent	*S. pneumoniae*	Cefotaxime	2 g i.v. every 6 hours, or	10–14 days
Age 18–50 years	*N. meningitidis*	Ceftriaxone	2 g i.v. every 12 hours	
Immunocompetent	*S. pneumoniae*	Cefotaxime	2 g i.v. every 6 hours, or	14–21 days
Age > 50 years	Gram-negative bacilli	Ceftriaxone	2 g i.v. every 12 hours, plus	
	L. monocytogenes	Ampicillin	2 g i.v. every 4 hours	
Impaired cellular immunity	*L. monocytogenes*	Ampicillin	2 g i.v. every 4 hours, plus	14–21 days
	Gram-negative bacilli	Ceftazidime	5–100 mg/kg every 8 hours†	
Head trauma, neurosurgery,	Staphylococci	Vancomycin	15 mg/kg every 6 hours‡, plus	21 days
cerebrospinal shunt	Gram-negative bacilli	Ceftazidime	50–100 mg/kg every 8 hours†	
	S. pneumoniae			
Geographic region with high	Multi-resistant	Cefotaxime	2 g i.v. every 6 hours, or	10–14 days
prevalence of penicillin-resistant	*S. pneumoniae*	Ceftriaxone	2 g i.v. every 12 hours, plus	
S. pneumoniae		Vancomycin	15 mg/kg every 6 hours ‡	

*Modified from references 30, 31.

†up to a total of 2 g every 8 hours.

‡up to a total of 2 g per day.

§Suggested duration of therapy for specific pathogens: *N. meningitidis* (7 days), *S. pneumoniae* (10–14 days), *L. monocytogenes* (14–21 days), gram-negative bacilli and staphylococci (21 days).

Etiology of bacterial meningitis

In an extensive surveillance project of 13 974 cases of bacterial meningitis, 80% of cases were accounted for by *Streptococcus pneumoniae, Neisseria meningitidis*, and *H. influenzae*.[8] More recent series of adult bacterial meningitis have also noted the prevalence of specific organisms: *S. pneumoniae* (20–53%) *N. meningitidis* (3–56%), *Listeria monocytogenes* (6–13%), and *H. influenzae* (4–8%).[11–13] The most likely causative organism depends on several factors including age, immunocompromise, preceding head trauma, recent neurosurgery, and site of acquisition (community-acquired *v* nosocomial) (Table 5.1).[2]

While this chapter will focus on community-acquired meningitis, nosocomial meningitis is also a significant problem. The National Nosocomial Infection Surveillance System (NNIS) noted an incidence of 5·6 non-surgical, nosocomial infections of the central nervous system (CNS) for every 100 000 patients discharged from the hospital between 1986–1993 with meningitis accounting for 91% of cases.[14] Unlike community-acquired meningitis, the most common pathogens in nosocomial meningitis are Gram-negative bacilli and staphylococci.[13]

Clinical presentation

Given the documented association between early institution of antimicrobial therapy and reduced mortality in meningitis,[15] rapid recognition and diagnosis of meningitis is imperative. The relative sensitivity of any given sign or symptom has varied across selected studies published within the past decade (Table 5.2). Fever is found in over 85% of cases, although it

Table 5.2 Symptoms and signs associated with bacterial meningitis in adults

Author/year [ref]	N*	Fever (%)	Neck stiffness (%)	Altered MS (%)	Headache (%)	Nausea/ vomiting (%)	Focal neurological signs (%)	Rash (%)
Durand 1993 [13]	259	95	88	78	NR	NR	29	11
Sigurdardottir 1997 [12]	127	97	82	66	NR	NR	10	52
Andersen 1997 [20]†	174	99	99	8	NR	52	NR	74
Hussein 2000 [11]	100	97	87	56	66	55	23	10
Rasmussen 1992 [53]	48 ‡	79	54	69	46	29	21	4

N*, number of patients (279 patient episodes in 275 patients[13]; 103 episodes in 100 patients[11]; 132 cases in 127 patients[12]).

MS, mental status

†Limited to cases of *N. meningitidis*.

‡6 cases of *Mycobacterium tuberculosis* included.

is rarely the only presenting symptom or sign.[13] Rash, particularly petechiae or purpura, are most common in meningococcal meningitis, but may also be observed in patients with meningitis caused by *S. pneumoniae*, *H. influenzae*, and *L. monocytogenes*.[13]

The classic clinical presentation of acute meningitis consists of the triad of fever, neck stiffness, and an altered mental status. Although recent reviews have found that only between 51% and 67% of patients with bacterial meningitis present with this classic triad,[11–13] 99–100% of patients have at least one of these findings.[12,13] It has thus been suggested that the diagnosis of bacterial meningitis may be effectively eliminated in a patient who presents without any of these findings.[16]

Cerebrospinal fluid culture

If the diagnosis of bacterial meningitis is a consideration, a lumbar puncture (LP) should be performed promptly. Routine morphologic and chemical analysis of the cerebrospinal fluid (CSF) in suspected bacterial meningitis should include a cell count, white blood cell differential count, glucose concentration, protein concentration, Gram stain, and bacterial culture.[2]

The appearance of the CSF in bacterial meningitis is typically turbid and/or discolored with an opening pressure ranging from 200–500 mm H_20 (Table 5.3).[2] The white blood cell count usually ranges from 1000 to 5000/mm $^{-3}$ with greater than 80% neutrophils.[2] Protein and glucose concentrations are usually 0·1–0·5 g/liter (100–500 mg/dL) and < 2·2 mol/liter (40mg/dL), respectively.[2] Recent large series of adult meningitis have noted that between 48–60% of CSF Gram stains from adults with bacterial meningitis were positive while CSF culture was positive in 65–80% of patients (Table 5.3).[11–13]

Patients partially treated with antibiotics may be less likely to have a positive CSF culture or Gram stain result, but such therapy has minimal effect on CSF indices such as leukocyte count.[17] Even after institution of appropriate antibiotics for meningitis, the CSF picture usually remains abnormal for at least 48–72 hours.[18] On the other hand, CSF pleocytosis, low CSF glucose, and elevated CSF protein may be found even in the absence of infection. Finally, the Gram stain of CSF from patients with Gram-negative bacillary or post-neurosurgery meningitis is less often as positive as for pneumococcal and meningococcal meningitis.[19]

Table 5.3 Cerebrospinal fluid analysis in bacterial meningitis in adults

Author/year [ref]	N*	Opening pressure > 300 mm H_20 (%)	Leukocyte count > 1000/mm^3 (%)	Percent neutrophils ≥ 80%	Protein > 0·2 g/ liter (%)	Glucose ≤ 2·8 mol/ liter (%)	Gram stain positive (%)	CSF culture positive (%)
Durand 1993 [13]	259	39	28 (> 5000/mm^3)	79	56	50 (> 2·2 mol/liter)	46	83
Sigurdardottir 1997 [12]	127	48	20	88	85 (> 0·5 g/liter)	89 (< 0·5 mol/liter)	57	80
Hussein 2000 [11]	100	NR	56	74	67	72	48	65

N*, number of patients (279 patient episodes in 275 patients[13]; 103 episodes in 100 patients[11]; 132 cases in 127 patients[12]).

Blood culture

Blood cultures should also be made in the evaluation of a patient with suspected bacterial meningitis, particularly if a CSF sample cannot be obtained prior to initiation of antibiotics (for example, when neuroimaging is planned prior to LP). Blood cultures in bacterial meningitis have been noted to be positive in 19–77% of patients.[12,15,20]

Other diagnostic modalities

Rapid bacterial antigen testing

The use of rapid bacterial antigen testing remains controversial. A recent review noted that of 478 CSF samples, 0·3% were positive by rapid antigen testing.[21] However, the false-positive rate exceeded the true positive rate, and therapy was not altered on the basis of any of the true-positive rapid antigen results. The false-positive results led to additional cost, prolonged hospitalisation, and some clinical complications. Furthermore, all true-positive CSF samples showed the causative micro-organisms by Gram stain.[21] In light of these and similar previous findings,[22] it has been suggested that the role of rapid antigen detection should be limited to those patients with suspected bacterial meningitis whose initial CSF Gram stain is negative and whose CSF culture is negative at 48 hours of incubation (for example, patients who received some period of antimicrobial therapy prior to examination of the CSF).[22,23] The role of antigen testing in this setting however requires further study.

Polymerase chain reaction

Polymerase chain reaction (PCR) of CSF has been used to detect microbial DNA in the CSF of patients with suspected bacterial meningitis. Primers have been developed that permit the simultaneous detection of the most common organisms, including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. While a recent study demonstrated this technique to have good sensitivity (i.e. 89%) with no false positive results,[24] the time required to perform these tests was not noted. Future studies should help to clarify the role of this technology in the diagnostic approach to bacterial meningitis.

Another important role of PCR is in the detection of viral (specifically enteroviral) meningitis. In a recent multicenter study, 476 CSF specimens were collected from patients with suspected aseptic meningitis[25]: 68 samples were positive for enterovirus by PCR (14·4%), whereas 49 samples were positive by culture (10·4%). The sensitivity and specificity of the enterovirus PCR test (using viral culture as the "gold standard") were 85·7% and 93·9%, respectively. Rapid PCR-based detection of enteroviral meningitis would facilitate early decision-making regarding

discontinuation of empiric antibacterial therapy as well as shortened hospitalization.

Neuroimaging

There exists controversy regarding the need to perform neuroimaging prior to the performance of the LP. Despite no supportive evidence, clinicians frequently perform computed tomography (CT) imaging prior to LP in order to rule out intracranial abnormalities which might increase the risk of brain herniation resulting from removal of cerebrospinal fluid during LP.[11,26] In a survey of 201 physicians who had ordered a CT prior to LP, stated reasons for this practice included suspicion that a focal brain abnormality was present (59%), belief that this practice was the standard of care (34%), and fear of litigation (5%).[27]

The risk of routine CT scanning prior to LP in patients with meningitis is that this practice is associated with a delay in performing LP and initiation of antimicrobial therapy.[27] This delay in initiation of antimicrobial therapy in turn increases the risk of a poor clinical outcome.[15]

In a study of 235 patients who underwent head CT prior to LP, clinical features associated with an abnormal finding on CT were age ≥ 60 years, immunocompromise, history of CNS disease, history of seizure within 1 week before presentation, as well as the following neurologic abnormalities: abnormal level of consciousness, inability to answer two consecutive questions correctly or to follow two consecutive comments, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language.[27] Of the 96 patients in whom none of these features was present, 93 had a normal CT scan. Although the negative predictive value of the approach was not 100%, the three patients who were misclassified underwent LP without subsequent brain herniation.[27] While these results should be validated in future studies, they suggest that a routine CT scan can safely be avoided in favor of careful evaluation of the clinical findings of patients with suspected meningitis.[28]

Possible indications for CT or magnetic resonance imaging (MRI) following initiation of therapy include persistent focal neurologic findings, persistently positive CSF cultures despite appropriate antimicrobial therapy, and persistent elevation of CSF polymorphonuclear leukocyte percentage after more than 10 days of therapy.[29] Neuroimaging is also indicated in patients with recurrent meningitis.

Therapy

Case presentation 1 (continued)

The patient undergoes LP without prior CT scanning. CSF reveals an opening pressure of 250 mm H_20, and the patient is started on ceftriaxone 2 g i.v. every 12 hours. Subsequently, the CSF demonstrates a leukocyte count of 2400/mm^3 with 70% neutrophils, protein concentration of 0·32 g/liter (320 mg/dL), and a glucose concentration of 3·4 mol/liter (62 mg/dL). The Gram stain reveals Gram-positive cocci in pairs and chains.

Antimicrobials

Earlier initiation of antimicrobial therapy is essential in the approach to bacterial meningitis. Early diagnosis and therapy reduce morbidity and mortality, particularly if antimicrobial therapy is initiated before meningitis progresses to a high severity level.[13,15] If neuroimaging prior to LP is considered, antibiotics should not be delayed until neuroimaging is complete. In this situation, blood cultures should be obtained and antibiotics then administered. The choice of empiric antibiotic depends on which organisms are most likely causative, which in turn depends on several factors including age,

immunocompromise, recent surgery or instrumentation, and local antimicrobial resistance patterns (Table 5.1).[30,31]

Corticosteroids

Adjunctive corticosteroid therapy for bacterial meningitis remains controversial. Animal studies of meningitis have shown that bacterial lysis resulting from antimicrobial therapy leads to inflammation in the subarachnoid space which in turn may contribute to poor outcomes.[32,33] These studies have also demonstrated that adjunctive corticosteroid therapy reduces cerebrospinal fluid inflammation and subsequent neurologic sequelae.[32,33] A number of randomized controlled trials have examined the possible role of corticosteroid therapy in pediatric meningitis but have come to differing conclusions. A meta-analysis of these trials showed a beneficial effect of adjunctive dexamethasone therapy in reducing severe hearing loss in children with *H. influenzae* type b meningitis and further suggested a similar benefit reducing hearing loss in those with pneumococcal meningitis.[34]

Recently, de *Gans et al*. reported the results of a multicenter trial of 301 adults with bacterial meningitis randomized to adjuvant dexamethasone vs placebo.[35] Administration of dexamethasone (10 mg) at 15 to 20 minutes before or with the first dose of antibiotic (and continued every 6 hours for 4 days) resulted in a statistically significant reduction in the risk of an unfavorable outcome (assessed with the Glasgow Outcome Scale[36]). Dexamethasone therapy was also associated with a statistically significant reduction in mortality, most pronounced for the subgroup of patients with meningitis due to *S. pneumoniae*. However, there was no significant beneficial effect of dexamethasone therapy on neurologic sequelae, including hearing loss.[35]

Given these recent results, routine adjunctive dexamethasone therapy has been recommended for those patients with suspected *S. pneumoniae* meningitis.[37] However, the ultimate role of dexamethasone in the treatment of meningitis needs to be clarified in future studies. In particular, future studies should focus on the possible impact of corticosteroids on penetration of certain antibiotics into the CNS. Dexamethasone reduces blood–brain barrier permeability and may impede the penetration of vancomycin into the subarachnoid space.[38] This issue has become increasingly important as the use of vancomycin for suspected bacterial meningitis increases because of concern regarding the continued emergence of penicillin-resistant *S. pneumoniae*.[31] Of note, while treatment with dexamethasone did not reduce vancomycin levels in the CSF in children with bacterial meningitis,[39] treatment failures have been reported in adults who received standard doses of vancomycin and adjunctive dexamethasone.[40]

Preventive therapy

H. influenzae

Currently available *H. influenzae* type b conjugate vaccines are highly immunogenic with more than 95% of infants developing protective antibody concentrations after a primary series of two or three doses. Use of this vaccine has been extremely effective at reducing the incidence of *H. influenzae* meningitis worldwide, often by more than 90%.[41] The American Academy of Pediatrics recommends that all infants should receive a primary series of *H. influenzae* vaccine beginning at 2 months of age.[42]

S. pneumoniae

Use of the 23-valent pneumococcal vaccine to prevent bacteremic pneumococcal disease is recommended in certain high risk groups.[43] The efficacy of this vaccine against meningitis due to *S. pneumoniae* has never been proven, but has been suggested to be approximately 50%.[44,45] The more recently developed pneumococcal conjugate vaccine has been demonstrated to have excellent efficacy in the prevention of

invasive pneumococcal disease in infants and children,[46] and its use is now recommended in all infants under 2 years of age.[47] Use of the conjugate vaccine is not, however, currently recommended in adults owing to limited experience in this population.

N. MENINGITIDIS

Routine vaccination with the currently available quadrivalent vaccine (covering meningococcal serotypes A, C, Y and W-135) is not recommended because of its poor immunogenicity in children under 2 years of age (i.e. the group at highest risk of sporadic meningococcal disease), and because of its relatively short duration of protection.[48,49] Use of the vaccine is recommended for certain groups:

- college freshmen, particularly those living in dormitories or residence halls
- military recruits
- persons who have terminal complement component deficiencies
- patients with anatomic or functional asplenia;
- research, industrial, and clinical laboratory personnel who are exposed routinely to *N. meningitidis*
- visitors to countries in which *N. meningitidis* is hyperendemic or epidemic (for example, the "meningitis belt" in sub-Saharan Africa).[49]

While sufficient experience exists to recommend vaccine for use in controlling outbreaks due to serogroup C meningococcal disease only, use of the vaccine may be applicable to control of outbreaks due to other vaccine preventable serogroups (A, Y, and W-135).[49] The applicability of the quadrivalent vaccine may be increased owing to recent changes in the epidemiology of meningococcus, particularly the increasing percentages of cases from serogroups covered by the vaccine.[50] Although the need for revaccination has not been determined, antibody levels decline rapidly over 2–3 years such that revaccination should be considered every 3–5 years if the patient remains at high risk.[49] The more recently developed meningococcal C conjugate vaccine has demonstrated superior immunogenicity when compared to the older polysaccharide vaccine.[51] While routine childhood immunization with the conjugate vaccine has been implemented in some countries,[52] data supporting its use in adults remains limited.

Prognosis

Case presentation 1 (continued)

The patient's CSF culture subsequently demonstrates growth of *S. pneumoniae*, which is resistant to penicillin but susceptible to ceftriaxone. The patient's fever, headache, and confusion resolve by day 3 of therapy, although the patient now complains of mild ataxia. He completes 14 days of therapy with ceftriaxone and his ataxia has resolved by the time of his hospital discharge.

While almost uniformly fatal in the pre-antibiotic era, the impact of bacterial meningitis remains great today. Mortality rates in meningitis in recent series have ranged from 17% to 37%.[11–13,15,53]

Several factors have been associated with increased mortality in patients with bacterial meningitis including advanced age,[12,13,15] obtunded mental state,[13,15] seizures,[13,15] hypotension,[15] and platelet count < 100 000/mm^3.[20] Increased fatality was also associated with absence of typical symptoms and signs and was presumably due to a delay in diagnosis.[53] Indeed, despite the recognized association between delay in administration of antibiotics and mortality,[13,15] recent evidence notes that the median duration from initial presentation to administration of antibiotics was 4 hours, with 30% of patients waiting longer than 1 hour between performance of an LP and administration of antibiotics.[15]

Mortality rates also vary substantially across infecting organisms: *S. pneumoniae* (26–28%); *N. meningitidis* (10–16%), *L. monocytogenes* (32–38%), *H. influenzae* (11–17%), and culture negative (9–10%).[12,13]

CNS sequelae occur in up to 50% of previously healthy patients following meningitis, and include dizziness, tiredness, mild memory deficits, gait ataxia, cerebral edema, intracerebral hemorrhage, and hydrocephalus.[54,55] Systemic complications may include septic shock, adult respiratory distress syndrome, and disseminated intravascular coagulation.[55]

Encephalitis

Case presentation 2

A 64-year-old woman is brought to the emergency department by her daughter after a new onset seizure. The patient had been well until 48 hours prior when she had the abrupt onset of fever and headache. Over the next 2 days, she developed confusion and exhibited bizarre behaviour, and subsequently had a seizure. She has no significant past medical history. She takes no medications and does not use alcohol, tobacco, or drugs. The season is spring. The patient is retired and spends most of her time indoors and has not travelled recently. Her daughter recalls no animal exposures.
On physical examination, she has a temperature of 38·9°C, a pulse of 100 beats per minute, and a blood pressure of 140/64 mmHg. She is minimally responsive, without nuchal rigidity or focal neurologic findings. Her Glasgow Coma Scale score is 8. A serum white blood cell count is normal. A CT scan of the head reveals no intracranial mass lesions. Evaluation of CSF demonstrates a leukocyte count of 500 cells/mm^3 with lymphocyte predominance, an elevated protein concentration of 0·98 g/liter (980 mg/dL), and a normal glucose. You admit the patient with a diagnosis of acute encephalitis and institute intravenous acyclovir for the possibility of herpes simplex virus-1 encephalitis. You wonder what other diagnostic testing should be done.

Diagnosis

Epidemiology

Encephalitis indicates inflammation of the brain, and is distinguished from meningitis by the presence of abnormality of brain function, which may manifest as altered mental status, motor or sensory deficits, or movement disorders. The incidence of acute encephalitis varies according to geographical location but has been estimated at between 3·5 and 7·4 cases per 100 000 patient years,[56] with approximately 20 000 cases of encephalitis occurring annually in the US.[57]

While almost 100 agents have been associated with encephalitis, viruses are by far the most common cause, with the most life-threatening being herpes simplex virus (HSV) and arboviruses.[56] It is important to rule out other potentially treatable conditions that may mimic viral encephalitis (Box 5.2).

Box 5.2 Diseases that may mimic viral encephalitis*

- Abscess or subdural empyema
  - bacterial
  - listerial
  - fungal
  - mycoplasmal
- Tuberculosis
- Cryptococcus
- Rickettsia
- Toxoplasmosis
- Mucormycosis
- Meningococcal meningitis
- Tumor
- Subdural hematoma
- Systemic lupus erythematosus
- Adrenal leukodystrophy
- Toxic encephalopathy
- Reye's syndrome
- Vascular disease

* Adapted from [58]

Since clinical syndromes and routine laboratory tests are often non-specific, the diagnosis of viral encephalitis may be difficult. To aid in the diagnosis, certain epidemiological features should be elicited, including: time of year, location and prevalent diseases in the area, recent travel, occupational exposures, recreational activities (for example, caving or hiking), and animal contacts (for example, insect or animal bites).[58] This chapter will focus primarily on viral encephalitis in adults in the US.

Etiology of viral encephalitis

Encephalitis resulting from viral infection can manifest as two distinct disease entities:

- acute viral encephalitis – results from direct invasion of neurons by the virus, with subsequent inflammation and neuronal destruction
- postinfectious encephalomyelitis – may occur following a variety of viral infections, usually of the respiratory tract; perivascular inflammation and demyelination of the white matter are prominent.

The most common viruses causing acute encephalitis in the US are enteroviruses, followed by HSV and arboviruses (Box 5.3).[59] Less common viral etiologies include other herpesviruses, adenovirus, measles, mumps, and the human immunodeficiency virus (HIV). Rare causes of encephalitis such as rabies would be suspected based on exposure and occupational information.

Enteroviral infections (including coxsackieviruses, echoviruses, and polioviruses) peak in the summer and fall, and children and young adults are most commonly affected (Table 5.4).[57]

HSV type 1 is the most common cause of severe non-epidemic viral encephalitis in the US, accounting for about 10% of all cases of encephalitis.[57] It has a bimodal age distribution, with most cases occurring in patients under 20 or over 50 years of age.[58] The virus has no seasonal predilection, occurring at any time of the year.

Arthropod-borne viruses (arboviruses) are a heterogeneous group of viruses transmitted by the bite of arthropod vectors (mosquitoes and

Box 5.3 Causative agents for acute viral encephalitis in the United States

Arboviruses
- La Crosse virus
- Eastern equine encephalitis virus
- Western equine encephalitis virus
- St Louis encephalitis virus
- West Nile virus
- Venezuelan equine encephalitis virus
- Powassan virus
- Snowshoe Hare virus
- Jamestown Canyon virus

Enteroviruses
- Coxsackievirus A and B
- Echoviruses
- Poliovirus

Herpesviruses
- Herpes simplex type 1
- Herpes simplex type 2
- Cytomegalovirus
- Epstein–Barr virus
- Varicella–zoster virus
- Human herpesvirus 6
- Simian herpes B virus

Other viruses
- Measles virus
- Mumps virus
- Adenovirus
- Human immunodeficiency virus
- Influenza
- Rabies virus
- JC virus
- Lymphocytic choriomeningitis

Table 5.4 Seasonal preferences of selected viruses causing encephalitis

Time of year	Virus
Summer/fall	Enteroviruses
	West Nile virus
	La Crosse virus
	Eastern equine encephalitis virus
	Western equine encephalitis virus
	St Louis encephalitis
Winter/spring	Measles virus
	Mumps virus
	Varicella–zoster virus
Any season	Herpes simplex virus type 1
	Human immunodeficiency virus
	Rabies virus

ticks). They are a common cause of sporadic and epidemic encephalitis in the USA. Arboviral infections peak in late summer and early fall when exposure to vectors is highest. First documented in the USA in 1999, West Nile virus (WNV) is now the most common cause of epidemic viral encephalitis.[60] The next most common arboviruses causing encephalitis are the California encephalitis (CE) group (La Crosse virus) and the togaviruses: western equine encephalitis (WEE), eastern equine encephalitis (EEE), and St Louis encephalitis (SLE).[59,61] Venezuelan equine encephalitis (VEE) has also caused small epidemics in Florida, Louisiana, and Texas,[62,63] and Powassan virus, which is transmitted by ticks, has caused rare cases in New England.[64]

In August 1999, an outbreak of WNV encephalitis occurred in the New York City area, representing the first known presence of this virus in the Western Hemisphere.[65] Since then, the epizootic has reappeared every summer with a rapidly expanding geographic distribution, spreading to 45 states and the District of Columbia as of November 2002.[66] A wide variety of wild and domestic birds are the typical reservoirs, and Culex mosquitos are the vectors.[65]

Epidemiologic features may help narrow the diagnosis in arboviral infections, including:

- age of the patient
- location where the infection was acquired
- incidences of other cases of arboviral infections in the area (Table 5.5).

Two paramyxoviruses, measles and mumps viruses, are rarely seen now because of effective childhood vaccines, but were significant causes of encephalitis in the pre-vaccine era.[57] These infections usually occur in the winter and spring. A postinfectious encephalitis develops in approximately 1 in 1000 cases of measles[67] and typically 4–8 days after the rash, during convalescence.[56] Subacute sclerosing panencephalitis (SSPE) is a chronic degenerative disease that presents insidiously with myoclonus and seizure activity an average of 7 years after acute measles infection.[61] CNS disease from mumps, including encephalitis, complicates

Table 5.5 Epidemiologic features of encephalitis caused by arboviruses in the United States*

Virus	Geographical distribution	Age of typical patients	Mortality rate (%)
West Nile	East, mid-west, Gulf coast, southern USA	Adults, esp. elderly	4–12
La Crosse	Central, eastern USA	< 15 years	1
Eastern equine	East, Gulf coast, southern USA	Young children and > 50 years	> 30%
Western equine	West, mid west USA	Infants and > 50 years	2–3%
St Louis	Central, western, southern USA	> 50 years	10–20%
Powassan	New England	Any age	50

*Adapted references 58, 61.

about 1% of infections,[61] and usually occurs in older children or adults. It may occur before, during, or up to 2 weeks after parotid gland swelling or in the absence of parotitis.

Seroconversion to HIV infection and primary HIV disease has been associated with acute, self-limited encephalitis syndromes.[56] Patients with the acquired immunodeficiency syndrome (AIDS) can develop CNS disease from a number of unusual organisms, such as toxoplasma, pneumocystis, cryptococcus, cytomegalovirus, and JC polyoma virus (progressive multifocal leukoencephalopathy).[68]

Rabies is transmitted by the bite of an infected animal and is a rare cause of encephalitis in the USA. Most human disease in the USA is due to bat transmission, although a history of bat bite is uncommon.[69] Other animals that are most often infected include foxes, skunks, and raccoons.

Postinfectious encephalomyelitis is an acute inflammatory demyelinating disease that accounts for approximately 10–15% of cases of acute encephalitis in the USA.[56] It most commonly develops after an infection of the respiratory tract (particularly influenza), a viral exanthem such as measles or varicella, or in the past, immunisation with vaccinia virus.[57] Worldwide, measles is the most common etiological agent.[57] The pathogenesis is thought to be an autoimmune response triggered by the viral infection, with activation of lymphocytes against myelin.[70]

Clinical presentation

The triad of fever, headache, and altered level of consciousness is the clinical hallmark of acute viral encephalitis.[58] Additional clinical findings often include disorientation, disturbances in behaviour and speech, and focal or diffuse neurologic abnormalities such as hemiparesis and seizures.

Herpes simplex type 1

The onset of HSV-1 encephalitis (HSE) is usually abrupt, although a subacute prodrome of frontal headache and malaise may occur less commonly. Fever is present in 90% of cases, headache is prominent early in the course of disease, and the majority of patients have signs suggesting a localized lesion involving one or both temporal lobes.[56,71] These findings often include dramatic personality changes, which may be the first clinical manifestation. Following these behavioural changes, patients may develop aphasia, anosmia, temporal lobe seizures, and hemiparesis. Unlike with HSV-2 meningitis, mucocutaneous herpetic lesions are rarely seen with HSV-1 encephalitis.[61]

Arboviruses

The clinical spectrum of illness due to arboviruses is broad, ranging from a mild febrile illness to aseptic meningitis to fatal encephalitis.[72] The onset of encephalitis may be abrupt or subacute and begins with non-specific symptoms of fever, headache, nausea, and vomiting. CNS symptoms usually begin on day 2 or 3, and symptoms can range widely from only mild deficits to coma. Focal abnormalities such as hemiparesis, tremors, seizures, and cranial nerve palsies can occur.[61] EEE is the most virulent of the arboviral encephalitides and produces symptomatic disease with a high frequency in all age groups and a mortality of 30%.[72,73]

In most people, infection with WNV is subclinical or causes a self-limited febrile illness.[74] Only about 1 in 150 infections results in severe neurologic illness, and advanced age (50 years of age and older) is by far the greatest risk factor for this complication.[75] Encephalitis is more common than meningitis, and symptoms of severe muscle weakness or flaccid paralysis sometimes suggestive of Guillain–Barré syndrome may provide a clue to the diagnosis of WNV.

Enteroviruses

While most enteroviral encephalitides are mild, patients with agammaglobulinemia may develop a chronic, lethal form of enteroviral encephalitis.[76]

Other herpesviruses

Cytomegalovirus and Epstein–Barr virus can cause acute encephalitis syndromes.[77] Varicella–zoster virus (VZV) infection may also be complicated by encephalitis, which usually develops a week after the exanthem begins. Acute cerebellar ataxia is the most common complication of chickenpox.[57,61] An eruption of herpes zoster may be complicated by encephalomyelitis and granulomatous arteritis, the latter of which has been associated with zoster ophthalmicus.[57]

Rabies

The common presentation of rabies is one of agitation, delirium, and hydrophobia, which ultimately progresses to coma and death.[78] The incubation period usually ranges from days to months but may be as long as a year.

Postinfectious encephalomyelitis

The clinical presentation of postinfectious encephalomyelitis resembles that of an acute viral encephalitis, except that there is usually a history of an exanthem or non-specific respiratory or gastrointestinal illness about 5 days to 3 weeks prior to the onset of CNS disease.[61]

Laboratory findings

Peripheral white blood cell counts are rarely helpful because they may be normal, slightly elevated, or slightly low.[79] Evaluation of CSF in viral encephalitis reflects the inflammatory nature of the disease, typically demonstrating a mononuclear pleocytosis, ranging from 10 to 2000 cells/mm^3, an elevated protein level, and a normal or slightly low glucose. Polymorphonuclear cells may be present early in the disease, so it may be useful to repeat the lumbar puncture in 24 hours.[80] CSF PCR to detect viral nucleic acids is the superior diagnostic test in most cases of viral encephalitis; culture of CSF for isolation of viruses has only 14%–24% sensitivity compared with PCR.[81]

In HSE, CSF may be completely normal in 3–5% of patients.[71] The presence of red blood cells in the absence of a traumatic lumbar puncture is suggestive, but not diagnostic of, necrotizing HSV-1 infection.[61] The availability of CSF PCR techniques to detect HSV DNA has revolutionized the diagnosis of HSE, allowing for rapid, sensitive, and specific diagnosis.[59] In several series, PCR was found to have a sensitivity of greater than 95% with a specificity of 94% to 100%, and it can be positive as early as 1 day after disease onset.[81–83] Studies have found no effect on PCR yield during the first week of antiviral therapy, although the sensitivity of the test declines during the second week of treatment.[82]

Antibody titers in the CSF or serum are not helpful in establishing an early diagnosis of HSE, and viral cultures are insensitive.[60] HSV antigen is detected later than HSV DNA and has a sensitivity of only 33%.[83] The historical gold standard for diagnosis has been brain biopsy with demonstration of HSV in the brain tissue; however, the sensitivity has been reported to be only 60–70%, possibly because of sampling error or improper specimen handling.[83] For this reason, as well as the less invasive nature of lumbar puncture, PCR has largely replaced the need for brain biopsy.[60]

The diagnosis of arboviral infections is usually done by serologic assays for virus-specific IgM antibodies on serum and/or CSF. Both acute and

convalescent (4 weeks) titers should be measured to confirm acute infection. Viral cultures and PCR testing of CSF, blood, or tissue samples are generally of low yield, except in the case of VEE where blood and throat cultures are frequently positive.[61]

A limitation of serologic tests is the possibility of cross-reactivity because of close antigenic relationships among the flaviviruses; for example, patients with WNV may test positive if they had recent infection with SLE or dengue, or vaccination for yellow fever or Japanese encephalitis.[75] A positive IgM test for WNV can be confirmed (eliminate positives caused by cross-reaction) by a WNV plaque-reduction neutralization antibody test (PRNT) titer of greater than 20.[60]

A case of WNV can be confirmed by any one of the following criteria:

- a 4-fold rise in the serum antibody titer
- isolation of virus, genomic sequences or antigen from tissue, blood, CSF, or other bodily fluids
- specific IgM antibody in CSF or serum by ELISA, confirmed by PRNT.[84]

When WNV infection is suspected, CSF should be obtained for PCR or IgM confirmed with PRNT, and PCR should be performed on peripheral blood if CSF is not available.[60]

The best diagnostic method for confirmation of rabies is detection of rabies virus RNA in saliva by reverse-transcriptase PCR.[58] Diagnosis may also be made by direct fluorescent antibody staining of viral antigens from a nuchal skin biopsy or brain tissue, isolation of rabies virus in a cell culture from CSF, saliva, or brain tissue, or a rabies neutralizing antibody titer of ≥ 5 in the CSF or serum in an unvaccinated person.[84]

The recommended laboratory tests for viral causes of encephalitis are listed in Table 5.6.

Other diagnostic modalities

Magnetic resonance imaging (MRI)

MRI with enhancement is superior to CT scan in detecting early lesions in the orbital–frontal and temporal lobes in HSE.[56] However, MRI has not been compared to PCR for confirmation of disease.[85] In varicella virus encephalitis, MRI may show ischemic or hemorrhagic infarctions or demyelinating lesions.[86] MRI is the most helpful test in distinguishing postinfectious encephalomyelitis from viral encephalitis since there is usually pronounced enhancement of multifocal white matter lesions.[86]

Electroencephalogram (EEG)

EEG is of value in diagnosing encephalitis, particularly in patients with HSE. Periodic high voltage spike wave activity and slow-wave complexes emanating from the temporal lobes at 2–3 second intervals are highly suggestive of HSE.[57,58,86]

Therapy

Case presentation 2 (continued)

You order PCR testing of the CSF for HSV. A MRI of the brain reveals enhancing lesions in both temporal lobes. An EEG shows diffuse slowing as well as bilateral periodic discharges in the temporal regions, suggestive of HSE.

Proven antiviral therapy is currently limited to HSV. In two separate trials comparing vidarabine to acyclovir in HSE, acyclovir was found to be superior.[87,88] The recommended dose is 10 mg/kg[1] intravenously every 8 hours for 10–14 days.[89] The dose should be adjusted in patients with renal

Table 5.6 Recommended laboratory tests in the diagnosis of viral encephalitis*

Aetiology	Diagnostic tests recommended
Herpes simplex virus type 1	PCR and cell culture of CSF and tissue
West Nile virus	PCR testing of CSF, IgM antibody of CSF and serum (with confirmation by neutralization antibody test)
Other arboviruses†	IgM and IgG antibody of serum and CSF, antigen detection and PCR (brain tissue) available for some viruses
Enterovirus	PCR and cell culture of CSF
Varicella–zoster virus	PCR and cell culture of CSF and tissue
Cytomegalovirus	PCR and cell culture of CSF and tissue
Epstein–Barr virus	PCR of CSF and tissue, serum antibody (often inconclusive)
Rabies	PCR of saliva or tissue, antigen testing of skin biopsy, brain tissue, or corneal impressions
JC polyoma virus (agent of progressive multifocal leukoencephalopathy)	PCR of CSF, PCR or in situ hybridisation of brain tissue
Colorado tick fever virus	Antibody (serum)
Human immunodeficiency virus	Laboratory tests not specific for central nervous system involvement
Herpes B virus	Cell culture or PCR of lesion (special biocontainment laboratory required)
Post-infectious encephalitis‡	Document recent infection at primary site outside CSF

*Adapted from references 59–61.

PCR, polymerase chain reaction; CSF, cerebrospinal fluid; IgM, immunoglobulin M; IgG, immunoglobulin G.

†Includes common arboviruses in North America including St Louis encephalitis, La Crosse encephalitis, eastern equine encephalitis, and western equine encephalitis.

‡Postinfectious encephalitis usually caused by measles virus, varicella–zoster virus, influenza virus, and vaccinia (pox) virus.

insufficiency. Both mortality and later sequelae can be substantially reduced if therapy is instituted before there is a major alteration in consciousness.[87] Therefore, early treatment is essential and should be initiated as soon as the diagnosis is suspected. Although several new antiviral drugs with activity against HSV are available in oral formulations with good bioavailability, none has been studied for HSV infections of the CNS.

Treatment of arboviral encephalitis is primarily supportive, as there are no proven therapies. Ribavirin and interferon-α2b have been shown to have activity against WNV *in vitro*, but no controlled trials have been done evaluating these agents.[90]

There is no specific antiviral agent for enteroviruses, but early studies of the agent pleconaril in animals have been promising.[91]

Treatment of postinfectious encephalomyelitis is largely supportive. The use of corticosteroids is often advocated, but no controlled trials have evaluated their efficacy and safety. There is no established treatment of rabies, short of supportive therapy, once symptoms have begun.

Preventive therapy

There are no human vaccines currently available for WNV. A live, attenuated Japanese encephalitis vaccine has been developed with a reported single-dose efficacy of > 99%, boding well for the possibility of a WNV vaccine in the future.[59,92] Prevention of arboviral infections rests on mosquito control and avoidance measures. The live attenuated measles and mumps vaccines, are extremely effective in preventing these

infections. Recognition of a potential exposure to an animal infected with rabies should prompt prophylactic treatment with rabies vaccine and immune globulin.[78]

Prognosis

Case presentation 2 (continued)

The patient's CSF PCR for HSV is positive and she completes a 14-day course of intravenous acyclovir. She has a slow recovery over several weeks with no clinical evidence of relapse and is transferred to a rehabilitation facility. Six months after the encephalitis, she is living independently but functioning at a lower level than previously and has short-term memory impairment and anosmia.

In the absence of therapy, mortality from HSV-1 encephalitis exceeds 70%, with only 2·5% of patients overall regaining normal function.[57,58] Even with acyclovir therapy, morbidity and mortality remain high, with a mortality of 19% and 28% at 6 months and 18 months after therapy, respectively.[87] Poorer outcome was associated with older age, a Glasgow Coma Scale score of < than 6 at presentation, and the presence of encephalitis for > 4 days prior to initiation of therapy.[87]

Many patients who survive are left with severe, debilitating sequelae, including aphasia, anosmia, problems with cognitive function, and motor and sensory deficits.[93] Relapses may also occur after completion of therapy in a small percentage (i.e. 4–7%) of patients.[87,88,94] Retreatment with acyclovir alone or combined with vidaribine is recommended for relapse.[61] Although some authors advocate a longer course of acyclovir therapy (14–21 days) to prevent relapse,[94] no definitive evidence exists that a longer duration of therapy is associated with a decreased rate of relapse.

In cases of arbovirus encephalitis, mortality rates and the presence of neurologic sequelae depend on the specific organism and age of the patient, with the extremes of age having a worse outcome.[65,72] Case fatality rates among hospitalized patients with WNV infection have ranged from 4–12%,[75] with advanced age and diabetes identified as risk factors for mortality.[65,75] Finally, rabies is uniformly fatal in non-immunized patients.[61,78]

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