4: Acute community-acquired meningitis and encephalitis

Miles H Beaman, Steven L Wesselingh

Empirical therapy for these conditions is a continually moving target

Abstract

- Acute meningitis and encephalitis are medical emergencies that require prompt assessment (usually by cerebral imaging and lumbar puncture) and treatment; specialist consultation is recommended.
- In acute meningitis, early administration of antibiotics can be life-saving (usually high-dose penicillin and/or a third-generation cephalosporin); antibiotics may be needed before referral to hospital.
- Emergence of penicillin and cephalosporin resistance in *Streptococcus pneumoniae* has necessitated more complex antibiotic regimens that include vancomycin or rifampicin for empirical treatment of meningitis.
- Adjunctive dexamethasone therapy may be of benefit in children with *Haemophilus influenzae* meningitis; there is no controlled evidence of its benefit in adults, but it could be considered in those with raised intracranial pressure.
- In possible encephalitis, empirical therapy with intravenous aciclovir should be given to cover herpes simplex virus (HSV) until the cause is established; HSV encephalitis may be fatal and leaves up to 50% of survivors with long-term sequelae.

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ACUTE MENINGITIS AND ENCEPHALITIS are medical emergencies that require prompt assessment and treatment.[1] We discuss these diseases in the community setting, in the absence of immunocompromised states such as AIDS. Both diseases usually manifest with acute severe headache (often described as the worst ever) and fever. Early distinction between the two conditions is critical, as their management is quite different and delay can have devastating effects.

Acute meningitis

Acute meningitis causes meningeal inflammation developing over hours to days. Symptoms include headache, photophobia, neck stiffness and, much later, confusion and coma. Disease caused by meningococcus (*Neisseria meningitidis*) may have a fulminant course over hours and may also occur without meningeal involvement. The presence of confusion, stupor or mental state changes relatively early in the course of the illness suggests encephalitis, which is also less likely to induce neck stiffness and photophobia.

Epidemiology and causative organisms

The epidemiology of meningitis varies significantly over time and between locations; up-to-date local Australian information and current management guidelines can be found at the website <http://www.health.gov.au/pubhlth/cdi/cdihtml.htm>.[2]

Viral meningitis: Studies using polymerase chain reaction (PCR) show that 85%–95% of all cases of viral meningitis are caused by enteroviruses; these are more common in summer and autumn. Less common causes include herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella–zoster virus, cytomegalovirus, Epstein–Barr virus and human herpesviruses 6, 7 and 8. Primary HIV infection can also present as acute "aseptic" meningitis.

Bacterial meningitis: The most common bacterial pathogens are *N. meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, which together account for more than 80% of cases. *Listeria monocytogenes* should also be considered, particularly in infants aged under one month, adults older than 60 years, and people with alcoholism, cancer or immunosuppression. *Staphylococcus aureus* meningitis is common after head trauma and neurosurgery. In neonates, group B streptococci (*Streptococcus agalactiae*) are the most important pathogen, but gram-negative rods such as *Escherichia coli* may also be responsible. The most significant recent change has been the dramatic decrease in bacterial meningitis caused by *H. influenzae* type b as a result of a successful childhood vaccination strategy in Australia.

Non-bacterial, non-viral acute meningitis: The most important non-bacterial, non-viral cause of meningitis in Australia is the yeast *Cryptococcus neoformans*. Cryptococcal meningitis is more common in immunocompromised patients, but can occur without obvious predisposing factors.

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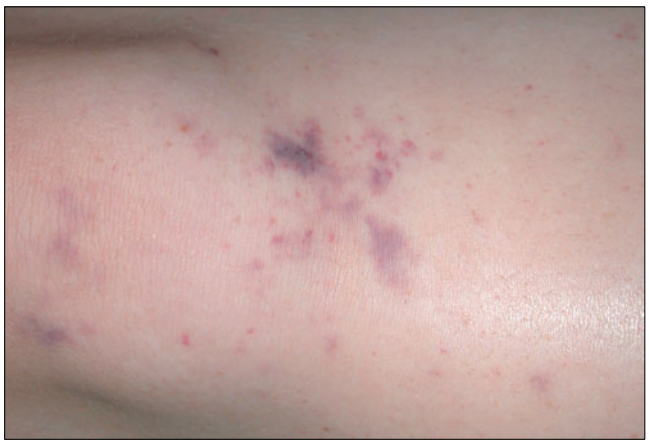
1: Rash in meningococcal meningitis



The rash in meningitis caused by Neisseria meningitidis *typically has petechial and purpuric components. (Image courtesy of Dr M Hassell, Fremantle Hospital, Fremantle, WA.)*

Pathogenesis

Viral meningitis: Virus infection of the mucosal surfaces of the respiratory or gastrointestinal tract is followed by virus multiplication in tonsillar or gut lymphatics. Viraemia with haematogenous dissemination to the central nervous system leads to meningeal inflammation.

Bacterial meningitis: Initial colonisation of mucosal surfaces, including the nasopharynx, is followed in a very small percentage of people by haematogenous or contiguous spread of bacteria. Specific antibody is an important defence. After bacterial invasion of the meninges, replication within the subarachnoid space leads to an inflammatory response. Levels of inflammatory cytokines (interleukins 1 and 6 and tumour necrosis factor-α) are proportional to the severity of symptoms and risk of adverse outcome, suggesting a role for adjunctive corticosteroids in treatment.

Clinical features[3,4]

Symptoms of acute meningitis may be subacute and non-specific. Signs of meningeal irritation are important clues; classical descriptions highlighted the importance of performing several different tests, including the Kernig and Brudzinski signs; the sensitivity of the former is increased with the patient seated.[5]

Viral meningitis: This commonly presents with non-specific constitutional symptoms and often diarrhoea and fever. Headache and photophobia may then develop. Enteroviruses may also cause vomiting, anorexia, rash, cough and myalgia. Other clues suggesting enteroviral disease are occurrence in summer or autumn or during a local epidemic. Enteroviral syndromes include pleurodynia (acute chest pain) and hand, foot and mouth disease. HSV-2 meningitis is nearly always associated with acute primary genital herpes, which may also produce urinary retention. HSV-2 also causes recurrent acute aseptic meningitis (Mollaret's meningitis).

Bacterial meningitis: This has symptoms similar to those of viral meningitis, although often more severe. Onset is often more sudden than in viral meningitis, with rapidly declining level of consciousness or cranial nerve palsies. In meningococcal meningitis, rash on the extremities may initially be macular but quickly evolves into petechiae and then purpura (Box 1). In young children and the elderly, bacterial meningitis may lack the typical signs of meningism and may present insidiously with lethargy, altered behaviour, confusion or nausea and vomiting.

Diagnosis[6,7]

Diagnostic steps in acute meningitis are outlined in Box 2. This is a simplified diagnostic algorithm; in most cases, consultation with local experts and close liaison with laboratories (to select the most useful tests) is recommended.

Critical to the diagnosis is examination of the cerebrospinal fluid (CSF). Lumbar puncture is safe in the absence of signs of raised intracranial pressure. The CSF profile may help differentiate meningitis from encephalitis and viral from bacterial meningitis (Box 3). However, the CSF profile may vary early in viral infections (with initial neutrophil predominance) and after antibiotic treatment of bacterial meningitis, which may render the Gram stain negative and protein level normal. However, these factors tend not to significantly affect the opening pressure, cell count or CSF : serum glucose ratio. The CSF profile also appears normal at presentation in about 3% of cases of bacterial meningitis.

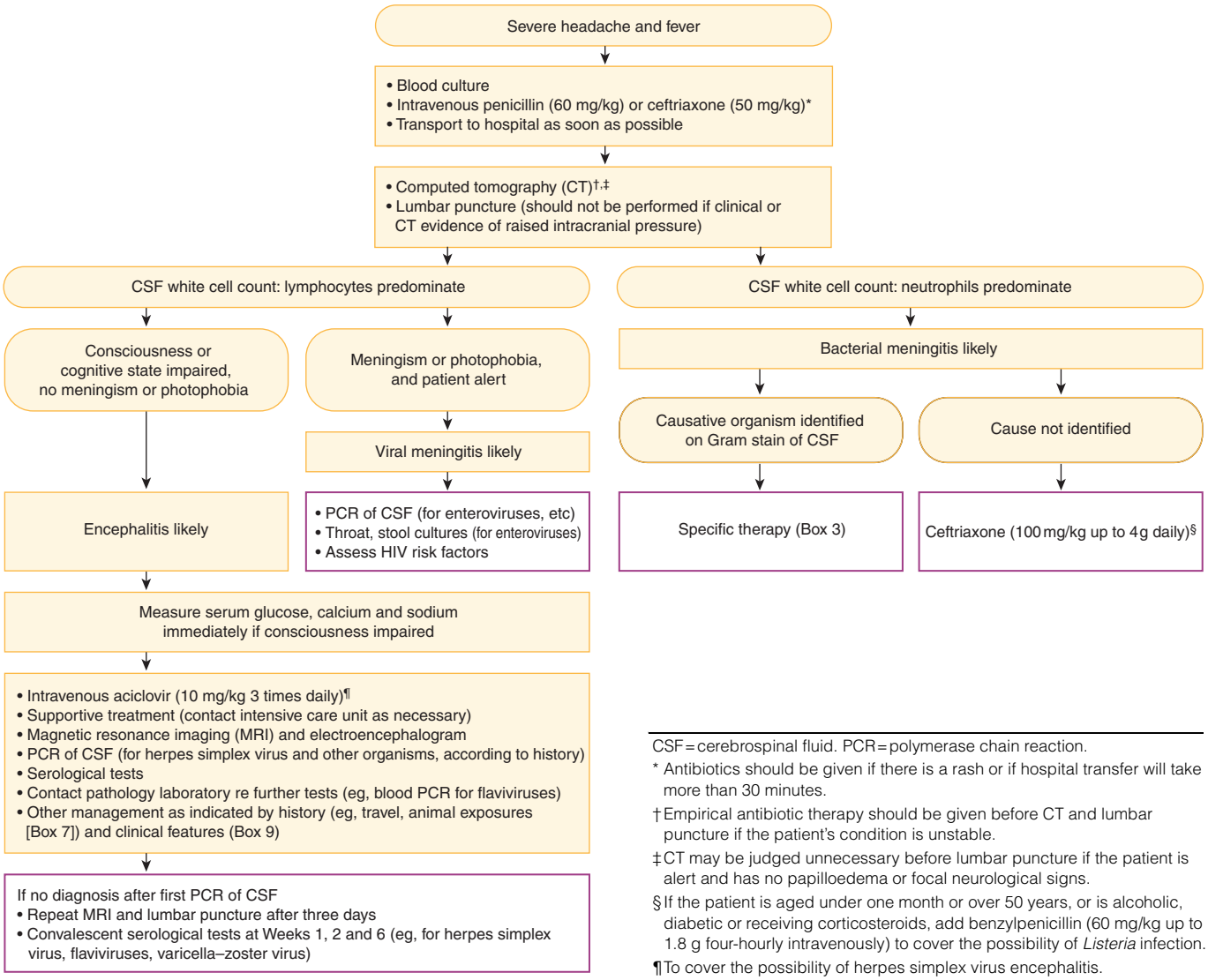
Viral meningitis: The main clue is the elevation of CSF white cell count with a predominance of lymphocytes, but there may be preceding neutrophilia. Polymerase chain reaction (PCR) tests for specific pathogens are available in most capital cities in Australia. In a patient with a typical prodrome, symptoms and lymphocytosis in the CSF, further investigation with cerebral imaging may not be necessary, but risk factors for HIV infection should be sought.

Bacterial meningitis: A predominance of neutrophils in the CSF is typical, but lymphocytes may predominate in *L. monocytogenes* and mycobacterial infections. CSF glucose concentration is decreased in about 60% of patients. If antibiotics have already been given, PCR of CSF and plasma may be helpful (especially for meningococcus).

Management

Before hospital: Early therapy of bacterial meningitis reduces mortality and morbidity. If bacterial meningitis is suspected based on history and examination of a patient in the community, then immediate intravenous administration of benzylpenicillin (3 g in adults or 60 mg/kg in children) is indicated if transport to a hospital will be delayed by more than half an hour. Any suspicion of meningococcal sepsis warrants immediate antibiotics. If practicable, blood should be taken for culture before antibiotics are given. The patient should then be transferred rapidly to hospital.

2: Diagnosis and management of acute meningitis and encephalitis



CSF = cerebrospinal fluid. PCR = polymerase chain reaction.

* Antibiotics should be given if there is a rash or if hospital transfer will take more than 30 minutes.

† Empirical antibiotic therapy should be given before CT and lumbar puncture if the patient's condition is unstable.

‡ CT may be judged unnecessary before lumbar puncture if the patient is alert and has no papilloedema or focal neurological signs.

§ If the patient is aged under one month or over 50 years, or is alcoholic, diabetic or receiving corticosteroids, add benzylpenicillin (60 mg/kg up to 1.8 g four-hourly intravenously) to cover the possibility of *Listeria* infection.

¶ To cover the possibility of herpes simplex virus encephalitis.

3: Typical profiles of cerebrospinal fluid in acute meningitis and encephalitis

		Meningitis		
Investigation	**Reference range**	**Bacterial**	**Viral**	**Encephalitis**
Opening pressure	< 30 mmH_2O	Raised	Normal	Increased
White cells				
Total count	<5 x 10^6/L	Greatly increased	Moderately increased	Moderately increased
Differential	Lymphocytes (60%–70%), monocytes (30%–50%), no neutrophils or red blood cells	Neutrophils predominate	Lymphocytes predominate	Lymphocytes predominate
Glucose concentration	2.8–4.4 mmol/L	Decreased	Normal	Normal
CSF : serum glucose ratio	>60%	Decreased	Normal	Normal
Protein concentration	<0.45 g/L	Increased	Normal or slightly increased	Normal or slightly increased

CSF = cerebrospinal fluid.

4: Antibiotic treatment of meningitis

*Treatment before hospitalisation**

Benzylpenicillin (60 mg/kg, up to) 3 g intravenously or intramuscularly

or ceftriaxone (50 mg/kg, up to) 2 g intravenously (in patients hypersensitive to penicillin or in remote areas where further parenteral therapy may be substantially delayed [over 6 h]).

Empirical treatment in hospital

Cefotaxime (child, 50 mg/kg up to) 2 g intravenously, 6-hourly

or ceftriaxone (child, 100 mg/kg up to) 4 g intravenously, daily in 1 or 2 divided doses for 7 to 10 days

plus benzylpenicillin (child, 60 mg/kg up to) 1.8 g intravenously 4-hourly for 7 to 10 days (if aged under 3 months or over 50 years).

Vancomycin (15 mg/kg up to) 500 mg four times daily intravenously or rifampicin (20 mg/kg up to) 600 mg daily should be added if *Streptococcus pneumoniae* is suspected on Gram stain, to ensure adequate cover for penicillin- or cephalosporin-intermediate or -resistant isolates before susceptibility results are available.

Specific treament (organism and susceptibility known)

Haemophilus influenzae type b

Cefotaxime (child, 50 mg/kg up to) 2 g intravenously 6-hourly

or ceftriaxone (child, 100 mg/kg up to) 4 g intravenously daily in 1 or 2 divided doses for 7 to 10 days

or, if the organism is proven to be susceptible, (amoxy)ampicillin (child: 50 mg/kg up to) 2 g intravenously, 4-hourly for 7 to 10 days.

Neisseria meningitidis

Benzylpenicillin (child: 60 mg/kg up to) 1.8 g intravenously, 4-hourly for 5 to 7 days.

For patients hypersensitive to penicillin (excluding immediate hypersensitivity), cefotaxime (child: 50 mg/kg up to) 2 g intravenously, 6-hourly *or* ceftriaxone (child: 100 mg/kg up to) 4 g intravenously daily in 1 or 2 divided doses for 5 to 7 days.

Streptococcus pneumoniae

For strains with minimum inhibitory concentration (MIC) >0.125 mg/L, vancomycin or rifampicin plus either cefotaxime or ceftriaxone.

For penicillin-susceptible strains (MIC < 0.125 mg/L), benzylpenicillin (child: 60 mg/kg up to) 1.8g intravenously 4-hourly for at least 10 days.

Listeria monocytogenes

Penicillin and (amoxy)ampicillin appear equally efficacious. In patients hypersensitive to penicillin, trimethoprim–sulfamethoxazole may be used alone.

Trimethoprim–sulfamethoxazole (child: 5/25 mg/kg up to) 160/800 mg intravenously 6-hourly

plus either benzylpenicillin (child: 60 mg/kg up to) 1.8 g intravenously, 4-hourly

or (amoxy)ampicillin (child: 50 mg/kg up to) 2 g intravenously 4-hourly.

*Blood should be collected for culture before antibiotic administration if facilities allow.

5: Case report — meningitis unresponsive to standard empirical therapy

Presentation: A 62-year-old woman recently returned from South Africa presented with a two-day history of headache, photophobia, neck stiffness and fever.

Examination: She had a fever and evidence of meningism but was initially alert.

Investigations: Cerebrospinal fluid (CSF) examination showed white cell count, 100 x 10^6 cells/L (predominantly neutrophils); protein, 2.4 g/L; glucose, 1.2 mmol/L; CSF : serum glucose ratio, 20%. Computed tomography of the brain gave normal results.

Management: Treatment was begun with ceftriaxone and aciclovir in a peripheral hospital. The patient became increasingly confused over the following 24 hours and was transferred to a tertiary referral centre. Intravenous vancomycin (1 g twice daily) was added to the treatment regimen, but not dexamethasone.

Course and outcome: CSF culture yielded *Streptococcus pneumoniae* with minimum inhibitory concentrations (MICs) of 4 mg/L for penicillin and 2 mg/L for cefotaxime. Aciclovir therapy was stopped. The patient's condition responded slowly to therapy over the subsequent four days, leaving no long-term sequelae.

Clues suggesting antibiotic-resistant S. pneumoniae *as the cause were:*

- *Poor response to initial therapy with ceftriaxone; and*
- *Exposure in a country (South Africa) with high prevalence of multiresistant* S. pneumoniae.

In a remote location where hospital transfer and diagnosis will be delayed, the choice of antibiotics should be refined according to the clinical picture (eg, penicillin if a petechial or purpuric rash is present, or ceftriaxone and aciclovir if there is papilloedema or focal signs). If computed tomography (CT) is available within an hour and the patient is clinically stable, then this should be performed before lumbar puncture.

Hospital management: Lumbar puncture should be performed initially, unless the patient's condition is unstable. In that case, blood should be collected for culture (if not already taken), and empirical antibiotic therapy administered immediately. The need for CT before lumbar puncture is controversial; we suggest that, unless the patient has depressed consciousness, papilloedema or focal neurological signs, lumbar puncture can be performed safely without a prior CT scan (especially if less than 5 mL CSF is collected via a 22-gauge needle).

Empirical antibiotic therapy for acute bacterial meningitis is outlined in Box 4. The incidence of penicillin resistance among clinical isolates of *S. pneumoniae* in Australia has risen from 1% in 1989 to 25% in 1997,[8] with recent studies showing resistance in CSF isolates ranging from 1.4% in Victoria[9] to 20.5% in Sydney (Dr P McIntyre, Deputy Director, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The New Children's Hospital, and University of Sydney, Sydney, NSW, personal communication, 2001). In view of this, patients without the typical meningococcal rash should be treated empirically with ceftriaxone plus vancomycin or rifampicin[10] (case report, Box 5). Vancomycin failures have been reported, and penetration into CSF is a concern if concurrent steroids have been given. Neither regimen has been subject to controlled clinical trial and recommendations are mainly based on in-vitro[11] and animal[12] data. Meropenem is available for hospital use and has been used successfully as an alternative, but resistance to this agent is evolving.

Duration of antibiotic therapy for bacterial meningitis is not evidence-based. Ten to 14 days of antibiotics for non-meningococcal meningitis seems reasonable, and seven to 10 days for meningococcal meningitis is appropriate for uncomplicated cases. Shorter courses have been successful in some settings.

6: Chemoprophylaxis for meningitis contacts

Prophylaxis is required for the index case and for all household and close contacts of patients with *Haemophilus influenzae* and *Neisseria meningitidis* infection. If in doubt, advice should be sought from public health authorities.

Haemophilus influenzae

Rifampicin (neonate < 1 month, 10 mg/kg; child, 20 mg/kg up to) 600 mg orally, daily for 4 days.

Alternatively, although data are limited, if rifampicin is considered unsuitable, use ceftriaxone (child: 50 mg/kg up to) 1 g intramuscularly, daily for 2 days.

Unvaccinated contacts aged under 5 years should be vaccinated as soon as possible.

Neisseria meningitidis

Rifampicin (neonate < 1 month, 5 mg/kg; child, 10 mg/kg up to) 600 mg orally, 12-hourly for 2 days.

If rifampicin is considered unsuitable, use ceftriaxone 250 mg (child, 125 mg) intramuscularly or ciprofloxacin 500 mg orally, as a single dose.

Non-pregnant adults: Ciprofloxacin 500 mg as a single dose.

Specific antivirals are currently not licensed for treatment of enteroviral meningitis in Australia. However, pleconaril (an antiviral with activity against rhinoviruses and enteroviruses) is available on compassionate use access and should be considered in the management of viral meningitis in patients with immunodeficiency.

Adjunctive immunomodulatory therapy: An aim of meningitis treatment should be to control the inflammatory response. A recent meta-analysis of dexamethasone use in meningitis showed benefit in management of childhood *H. influenzae* meningitis.[13] Some benefit was demonstrated with its use in the management of pneumococcal meningitis in children. No studies have proven its value in uncomplicated bacterial meningitis in adults or in viral meningitis. Some practitioners (in the absence of data) use corticosteroids in patients with evidence of raised intracranial pressure, focal or lateralising signs or evidence of cerebral oedema on brain imaging.

Prevention

Vaccination: Vaccination against *H. influenzae* type b with conjugate vaccine has dramatically reduced the incidence of this infection in Australia. The current polysaccharide vaccine against *N. meningitidis* can protect patients aged over two years against serogroups A, C, Y and W-135 and is useful in epidemics where these are the most common serogroups. However, as the predominant serogroup in much of Australia is group B, vaccination is less useful here. Vaccination is currently recommended for high-risk groups, including people with anatomical or functional asplenia or deficiency of the terminal components of the complement pathway, or those who travel to areas with epidemic meningococcal disease (especially sub-Saharan Africa and the Arabian peninsula during Haj). The conjugate vaccine covering serogroup C will be available in Australia shortly.

Polysaccharide vaccine against *S. pneumoniae* is currently recommended for preventing pneumococcal bacteraemia in high-risk groups, including people who are aged over 65 years, have chronic illness (eg, cardiac, pulmonary or renal disease, diabetes or alcoholism) or are immunocompromised. The age criterion is lower for Indigenous Australians (<50 years). A conjugate vaccine is currently under trial in Australia.

Chemoprophylaxis: Chemoprophylaxis for *H. influenzae* and *N. meningitidis* aims to prevent secondary disease in close contacts of infected people by eradicating nasopharyngeal colonisation. There is no evidence that chemoprophylaxis for *S. pneumoniae* is useful. Recommended chemoprophylaxis is shown in Box 6. In general, ceftriaxone is preferred in pregnant women, and ciprofloxacin in men and non-pregnant women.

Acute encephalitis

Encephalitis implies inflammation of the brain substance, parenchyma, which may coexist with inflammation of the meninges (meningoencephalitis) or spinal cord (encephalomyelitis). Encephalitis may be mild and self-limited, or may produce devastating illness. Consultation with an infectious diseases physician or neurologist is recommended in its management. A comprehensive review of this condition was published recently.[14]

Epidemiology and causative organisms

Herpes simplex virus (HSV) is the most common cause of non-seasonal encephalitis in Australia. Without treatment, HSV encephalitis is fatal in up to 80% of cases, and leaves up to 50% of survivors with long-term sequelae.[15] In the

7: Causes of encephalitis related to specific exposures

Geographic exposures

Northern Australia: arbovirus infection (Murray Valley, Kunjin),[17] scrub typhus; leptospirosis, melioidosis,[18] Japanese B encephalitis,[19] Hendra virus[20] and Australian bat lyssavirus[21] infection

South-east Asia: Japanese B encephalitis, cerebral malaria, rabies (most near neighbours of Australia, except Bali), scrub typhus,[22] typhoid encephalopathy, dengue, Nipah virus infection (Malaysia), and cysticercosis (India)

North America, Europe: Lyme disease, *Ehrlichia* infection, Rocky Mountain spotted fever, region-specific arbovirus infections (eg, West Nile, St Louis), rabies, variant Creutzfeldt–Jakob disease

Africa: cerebral malaria, tuberculosis, leptospirosis, typhoid encephalopathy, trypanosomiasis, *Borrelia* infection, brucellosis

Animal exposures

Bats (Australia): Australian bat lyssavirus

Horses (Australia): Hendra virus

Bites (overseas): rabies (especially bites by canid species in countries with endemic rabies)

Monkeys (overseas, research facilities): herpes B simiae

Cats (Australia and overseas): Bartonella henselae

Rodents (Australia and overseas): murine typhus, hantavirus

Arthropods: arbovirus infection (Murray Valley, Kunjin virus),[17] scrub typhus, Q fever

absence of particular risk factors, other common causes are enteroviruses (including enterovirus type 71, which has recently caused epidemics of meningoencephalitis[16]), influenza virus and *Mycoplasma pneumoniae*. However, the likely pathogens in encephalitis are dramatically influenced by geographic location, history of travel and animal exposures (Box 7) and vaccination.

Murray Valley encephalitis (MVE) virus causes seasonal epidemics of encephalitis at times of high regional rainfall.[17] This arthropod-borne virus is the most common flavivirus to cause encephalitis in Australia. The epicentre of endemic disease is in the east Kimberley region. Over the past five years, the distribution of Japanese B encephalitis (JE) virus has expanded into Australia via the Torres Strait Islands.[19] It causes disease clinically similar to MVE. In addition, two novel encephalitis viruses were recently identified in Australia —Hendra virus[20] and Australian bat lyssavirus.[21] They should be considered if there is a history of animal exposure (horse or bat, respectively — Box 7), or no other pathogen can be implicated.

Mycobacterium tuberculosis, the yeast *C. neoformans* and *Treponema pallidum* (syphilis) may also affect the brain parenchyma, but usually produce chronic or subacute meningitis in such circumstances.

Pathogenesis

HSV encephalitis is associated with primary HSV infection in about a third of cases; the remainder presumably represent reactivation. In immunocompromised patients, this disease may follow a chronic or relapsing course. HSV-2 encephalitis usually occurs in neonates, and accounts for fewer than 10% of cases of HSV encephalitis in adults. Risk of perinatal infection is highest when the mother develops a primary genital infection before labour; risk is less than 3% if the mother has a recurrence at delivery.

Clinical features

Encephalitis (especially if caused by HSV) may present with progressive headache, fever and alterations in cognitive state (confusion, behavioural change or dysphasia) or consciousness. Focal neurological signs (paresis) or seizures (focal or generalised) may also occur (case report, Box 8). Upper motor signs (hyperreflexia and extensor–plantar responses) are often present, but flaccid paralysis and bladder symptoms may occur if the spinal cord is involved. Associated movement disorders or the syndrome of inappropriate antidiuretic hormone secretion may be seen. Specific clinical clues as to cause are shown in Box 9.

In northern Australia, it may be desirable to distinguish MVE from Japanese encephalitis clinically. Both conditions frequently affect the brainstem and basal ganglia, but MVE often involves the spinal cord, while Japanese encephalitis may produce striking meningeal signs, with or without thalamic involvement. Both have high mortality (25%–33%) and rates of chronic sequelae in survivors (~50%).[14,17]

Diagnosis

The major differential diagnosis is meningitis or parameningeal infection, especially if meningitis is caused by atypical pathogens such as *Listeria monocytogenes*, *M. tuberculosis*, *C.*

8: Case report — sudden onset of seizures and loss of consciousness

Presentation: A 70-year-old man was taken to a hospital emergency department in a comatose state. He had become ill very suddenly while talking on the telephone — stopping in mid-sentence and having a generalised seizure.

Examination: The patient had a Glasgow Coma Score of 3, which did not respond to intravenous glucose or phenytoin. Initial computed tomography revealed no haemorrhage or focal lesion.

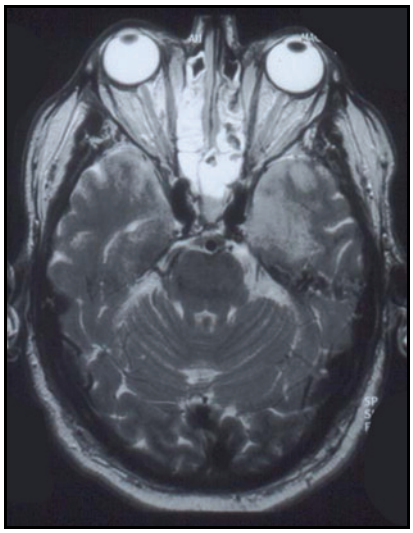
Management: He was admitted to the intensive care unit, ventilated and treated with intravenous aciclovir.

Investigations: Initial analysis of the cerebrospinal fluid (CSF) showed 7 x 10^6 lymphocytes/L; no red blood cells; protein level, 0.61 g/L; glucose level, 9 mmol/L and CSF : serum ratio, 80%. CSF was negative for cryptococcal antigen and, on polymerase chain reaction testing, for enteroviruses and Murray Valley encephalitis virus, but positive for HSV-1. An electroencephalogram showed periodic lateralising epileptiform discharges in the left temporal lobe. Magnetic resonance imaging on Day 4 showed bilateral temporal lobe abnormalities (Figure).

Diagnosis: Encephalitis caused by herpes simplex virus (HSV).

Course and outcome: Aciclovir treatment was continued, and the patient's condition improved gradually after successful treatment of complications that included aspiration pneumonia. He was transferred from the intensive care unit on Day 21. Although the patient's rehabilitation was complicated by inappropriate behaviour and memory disturbance, he was able to be discharged home on Day 50.

- *Features suggesting encephalitis were cortical signs (coma and seizure) and cerebrospinal fluid profile (*Box 3*).*
- *Patients presenting with encephalitic syndromes should receive empirical therapy with aciclovir to cover the possibility of HSV infection until an aetiological cause is identified.*
- *Temporal lobe sequelae (memory disturbance and behavioural abnormality) are characteristic of HSV encephalitis.*



Magnetic resonance image of the brain on Day 4 after presentation, showing hyperintense lesions in both temporal lobes (T2-weighted image with gadolinium enhancement).

neoformans and, during the wet season in the Northern Territory, *Burkholderia pseudomallei*.

Other causes of encephalopathy should be considered, including:

- metabolic disturbances (hypoglycaemia, hyponatraemia and hypocalcaemia);
- thiamine deficiency (Wernicke's encephalopathy);
- drugs (including neuroleptics [neuroleptic malignant syndrome], trimethoprim–sulfamethoxazole, isoniazid, non-steroidal anti-inflammatory drugs, intoxications); and
- inflammatory disorders, such as Behçet's disease, Reye's and Guillain–Barré syndromes, sarcoidosis, cerebral vasculitis (with or without a cerebral vascular accident), systemic lupus erythematosus and Wegener's granulomatosis.

Status epilepticus and malignancy (paraneoplastic syndrome) may also sometimes be confused with encephalitis.

A combination of magnetic resonance imaging (MRI) and CSF examination narrows the broad differential diagnosis. Brain biopsy is now rarely performed, but still has a place in cases which do not respond to aciclovir. As the diagnosis may be unclear, even after extensive investigation, it is worth storing extra CSF and serum for later analysis (including retrospective testing if new agents of encephalitis are discovered, or new diagnostic tests for existing pathogens become available). A staged approach may save resources, ruling out more important causes initially (HSV, enteroviruses, *M. tuberculosis* and *C. neoformans*) and rarer causes subsequently. Repeated imaging and lumbar punctures may be required.

The most sensitive type of imaging for diagnosis of encephalitis is MRI; in HSV encephalitis, CT scans may initially appear normal, but MRI usually shows involvement of the temporal lobes. Electroencephalography is less sensitive, but may be helpful if it shows characteristic features (eg, lateralising periodic sharp and slow wave patterns).

Lumbar puncture usually shows increased opening pressure (>30 cmH_2O), moderate lymphocytic pleocytosis (<50 x 10^6 cells/L), and a mild to moderate rise in protein with normal CSF : serum glucose ratio (>60%). PCR testing of CSF for HSV DNA has high sensitivity and specificity at presentation, but, if negative, should be repeated after three days, especially if red blood cells are present. In encephalitis caused by enteroviruses, PCR and culture of CSF are usually positive for the virus. If an enterovirus is suspected, throat and stool culture should also be performed at presentation.

As diagnostic methods are evolving rapidly, it is important to contact the laboratory and provide sufficient concurrent sera and CSF for the optimum test protocol.

Management

Support in an intensive care unit is often required in encephalitis to maintain ventilation, protect the airway and manage complications, such as cerebral oedema and hypoglycaemia.

HSV encephalitis should be treated with intravenous aciclovir (10 mg/kg three times daily) for two to three weeks,[23] or longer in patients who are immunocompromised or have a slow clinical response. Aciclovir-resistant strains have been reported in patients with AIDS. As HSV is a common cause of encephalitis with potentially devastating effects, it is important, in the absence of an alternative diagnosis, to use intravenous aciclovir empirically until results of specific investigations are available.

Varicella–zoster virus encephalitis also requires intravenous aciclovir;[24] ganciclovir is more potent but also more toxic. Specific therapies active against enteroviruses (pleconaril) and influenza (neuraminidase inhibitors) have recently become available, but controlled trials have not yet been undertaken in encephalitis.

9: Clinical clues as to cause of encephalitis

Herpes simplex virus: Temporal lobe signs often prominent (personality change, hallucinations)

Varicella–zoster virus: Cerebellar ataxia (children), progressive confusion (adults)

Epstein–Barr virus: Meningoencephalitis (immunocompromised)

Human herpesvirus 6: Focal encephalitis (immunocompromised adults)

Murray Valley encephalitis virus: Involvement of thalamus, brainstem, cerebellum and spinal cord

Japanese encephalitis virus: Brainstem involvement, meningeal signs may be striking, parkinsonian signs (40% overall mortality)

Cytomegalovirus: Insidiously progressive (similar to AIDS dementia)

Enteroviruses: May occur in epidemics, chronic course in patients with hypogammaglobulinaemia (enterovirus type 71 causes epidemic meningoencephalitis; brainstem involvement prominent)

Poliovirus: Involvement of spinal cord and brainstem

Rabies virus: Hyperaesthesia at inoculation site

Burkholderia pseudomallei (melioidosis): Brainstem involvement

Listeria monocytogenes: Occurs at extremes of age, brainstem involvement

Prognosis

The main prognostic sign in most types of encephalitis is conscious state on presentation — outcome is worse if coma is present initially. In MVE, lower motor signs in the limbs suggest poorer prognosis. In Japanese encephalitis, appearance of specific antibody in CSF is a good prognostic sign, whereas persistent fever, seizures or respiratory depression are adverse features.

Prevention

Routine childhood vaccinations prevent many of the diseases that can cause encephalitis (mumps, poliomyelitis, measles and rubella). Caesarean section and prophylactic aciclovir should be considered in pregnant women with active HSV-2 lesions.

Rabies immunoglobulin and vaccine should be administered to returned travellers who have been bitten by animals while in rabies-endemic regions, even if the incident was remote (latent periods of years have been described). Because Australian bat lyssavirus is related to rabies virus,

Evidence-based recommendations

- Early antibiotic treatment is associated with improved outcome from bacterial meningitis[1] ($E3_3$).
- Dexamethasone should be given to children with meningitis caused by *Haemophilus influenzae*[13] (E1).
- Intravenous aciclovir is the treatment of choice for HSV-1 encephalitis[12] (E2).

people at risk of bat bites or scratches (bat handlers, veterinarians, wildlife officers, powerline workers) have been advised to receive rabies vaccine.[25] Liaison with the local health department is important in both scenarios.

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