PART II – NEUROLOGICAL DISORDERS

CHAPTER 6
NEUROLOGICAL INFECTIONS

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NEUROLOGY IN AFRICA

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CHAPTER 6

NEUROLOGICAL INFECTIONS

Introduction

Infections of the nervous system are common in Africa and account for a significant percentage of all deaths. The causes of these infections are viral, bacterial, fungal and parasitic, protozoa and helminths. Their estimated frequency and mortality is presented in Table 6.1. These infections result in CNS illnesses characterized mainly by meningitis, focal neurological disorders and coma. Since the onset of the human immunodeficiency virus (HIV) epidemic in Africa three decades ago there has been a dramatic change in the overall pattern of CNS infections in Africa. CNS opportunistic infections related to HIV have now become commonplace and are the leading cause of death in adults in many countries. The main causes are cryptococcal meningitis (CM), cerebral toxoplasmosis (CT) and tuberculous meningitis (TBM). At the same time cerebral malaria, acute bacterial meningitis (ABM), tetanus, trypanosomiasis, neurocysticercosis and brain abscess remain as major causes of neurological illnesses. This chapter presents an overview of the main bacterial, fungal and viral infections including clinical features, diagnosis and management. After reading this chapter the student should aim to be able to diagnose, treat and prevent meningitis and know the other main CNS infections.

Table 6.1 Estimated frequency & treated mortality of main neurological infectious disease in Sub Saharan Africa

Disease	Estimated frequency per year for whole population	Mortality rates (treated patients)
Acute Bacterial Meningitis	250,000 (children) 50/100,000	5-40% (children) 10-70% (adults)
Opportunistic infections in HIV cryptococcus toxoplasmosis TB	5-700,000	50% 10-20% >50%
CNS TB (non HIV)	30,000	20-30%
Cerebral malaria	>0.5 million	10-20%
Human African trypanosomiasis	40,000-300,000	20-30%
Tetanus	100,000	40-60%
Rabies	10-20,000	100%
Leprosy	40,000	low

Meningitis

Meningitis is defined as inflammation of the pia and arachnoid meninges and the cerebrospinal fluid (CSF) that surrounds the brain and spinal cord. The main infectious causes are viral, bacterial and fungal. Meningitis is classified clinically as either acute or chronic. Acute meningitis occurs within hours or days, whereas chronic meningitis evolves over weeks. Acute meningitis is classified as aseptic which is mostly viral in origin or septic or pyogenic which is caused by bacteria.

The term **acute bacterial meningitis (ABM)** refers to acute infections caused by pyogenic bacteria. The main causes of pyogenic meningitis in Africa are *Streptococcus pneumoniae* **(pneumococcus),** *Neisseria meningitidis* **(meningococcus)** *and Haemophilus influenzae* type b **(Hib).** Chronic meningitis by definition persists for weeks (four or more). The main causes in Africa are *cryptococcal infection* and *tuberculosis.* The overall pattern of meningitis in adults has changed in Africa, whereas ABM used to be the leading cause of meningitis, cryptococcus is now the most common cause followed by tuberculous meningitis (TBM) and ABM. Their exact order depends on the geographic location, the extent of HIV epidemic and the age group affected.

ACUTE BACTERIAL MENINGITIS (ABM)

EPIDEMIOLOGY

ABM causes over a quarter of a million deaths globally each year with a large proportion of these occurring in Africa. ABM occurs mostly in young children, particularly in those <2 years but affects all age groups including adults. Africa has some of the highest rates of ABM in the world affecting as many as 1/250 of children <5 yrs, in mainly urban parts of West Africa. However as many as 1-2% of whole populations in the "meningitic belt" may be affected during cyclical meningococcal epidemics which occur every 5-10 years. It is estimated that ABM in Africa is 5-10 times more common (50/100,000/yr) as compared to high income countries. Risk factors for ABM in Africa are crowded living conditions, extremes of age, organism virulence and antibiotic resistance, and host predisposition. Individual host factors include HIV infection, malnutrition, sickle cell disease, splenectomy, a non functioning spleen, recent head injury with fracture or, post neurosurgery with CSF leak, middle ear infection and pneumonia. The overall frequency of ABM in adults in Africa appears to have remained relatively constant despite the current HIV epidemic there.

Aetiology

In children in Africa the main causative organisms of ABM are *Hib, pneumococcus* and *meningococcus.* In those countries where *Hib* vaccination has been instituted, *Hib* has now been replaced as the main cause by *pneumococcus* and *meningococcus.* Recently a new pneumococcal conjugate vaccine is being used in children in some countries, including South Africa, Gambia and Kenya. In adults the main causative organisms are *pneumococcus* and *meningococcus.* Other less common causes include *group B streptococcus, nontyphoidal salmonella, (NTS), staphylococci,* and *Escherichia coli* in neonates. *Listeria monocytogenes* may cause ABM in pregnancy and in HIV. *Gram negative bacilli* and *salmonella* may cause ABM in HIV and in the elderly.

Streptococcus pneumoniae

Pneumococcus is a gram positive coccus which exists in pairs (Fig 6.1) with many subtypes. It affects mostly infants aged <12 months, young children and adults, but all age groups may be affected. It may occasionally occur as epidemics. The main source of meningeal infection is haematogenous spread arising from the respiratory tract (pneumonia) and from otitis media, although individual host factors are also important. Sporadic invasive pneumococcal disease has increased significantly since the arrival of the HIV epidemic and is a significant cause of bacteraemia, pneumonia and death in HIV disease. It accounts for >90% of cases of ABM in adults in the main HIV affected areas in Africa. The main risk factors for ABM have already been outlined above. The case fatality rate (CFR) in Africa in treated pneumococcal meningitis is high, ranging from 30-40% in children to 50-70% in adults.

Neisseria meningitidis

Meningococcus is a gram-negative diplococcus and infection results in meningococcal disease (fig. 6.2). It is classified into serogroups with A, B, C, Y, **W**-135 and X predominating. The most common serogroup in Africa is A but there have been recent outbreaks there with serogroups W-135 and X. Epidemic strains are sometimes introduced by Hajj pilgrims returning from Mecca, where similar epidemics have occurred. Protective vaccines exist for serogroups A and C and more recently a quadrivalent vaccine for A, C, Y, and **W**-135 (meningococcal A-conjugate vaccine) but not for group B or X. The usual incubation period for meningococcal disease is 2-7 days. The peak incidence is in children with a second peak in teenagers and young adults. The main risk factor for infection is close household contact with an infected person, when the risk of contracting the disease is increased a thousand fold. While most cases are sporadic, meningococcal disease also occurs as epidemics in Africa.

Large scale epidemics occur in sub-Saharan Africa during the dry season in approximately 10 year cycles. These epidemics occur in a large *"meningitis belt"* which stretches from the Gambia and Senegal in the West to Sudan and Ethiopia in the north and as far south as Kenya and Tanzania in the east and Nigeria and Ghana in the west. The reason for epidemics is unclear but has been attributed to the loss of accumulated herd immunity and the presence of suitably dry conditions for transmission, usually from March to May. During meningococcal epidemics, outbreaks occur typically in areas of overcrowding such as towns, schools, barracks, and prisons.

The overall case fatality ratio (CFR) in adults is of around 10% but this can vary (5-20%). A lower overall CFR (5%) generally reported across parts of Africa is attributed to infection with the most common serogroup A and to meningococcal disease presenting with mostly meningitis without associated septicaemia. However a higher CFR of around 20% has been reported recently in patients infected with serogroups W-135 and X, and also with HIV infection in South Africa.

Haemophilus influenzae type b (Hib)

Hib is a small gram-negative coccobacillus. It primarily affects young children under the age of six years and is a major cause of respiratory tract infection and ABM. *Hib* related ABM primarily affects infants 1-24 months and rarely occurs in adults. The CFR in Africa in children is 20-30% and is higher in adults 30-40%.

Key points

- ABM is a major cause of mortality & morbidity in Africa
- occurs in any age group but mostly in infants & young children
- main causes are pneumococcus, meningococcus & Hib
- host risk factors are HIV, sickle cell disease, asplenia & head injury
- meningococcal infection occurs in both sporadic & epidemic forms
- CFR varies with the organism & the age group affected

Pathogenesis

All the three main bacterial causes of meningitis colonise the nasopharynx in asymptomatic carriers. Colonisation rates of around 10-20% are commonplace in schools, universities etc with higher seasonal rates in children, young adults and in case contacts. Spread is by droplets from close physical contact with asymptomatic carriers or occasionally direct from cases. The presence of a lipopolysaccharide capsule helps bacteria survive and they reach the meninges via the bloodstream or by direct invasion. Clinical disease is rare and only occurs when there is penetration across the blood-brain barrier with infection of the meninges and subarachnoid space (Fig. 6.1). This may occur in association with bacteraemia and septicaemia. The multiplication of bacteria in the sterile CSF triggers a massive host immune response with release of inflammatory cytokines, which result in activated macrophages and invasion with neutrophils, immunoglobulins and other markers of inflammation. This leads to a further breakdown in the blood brain barrier and can result in vasculitis, thrombosis, infarction, raised intracranial pressure, brain damage and death.
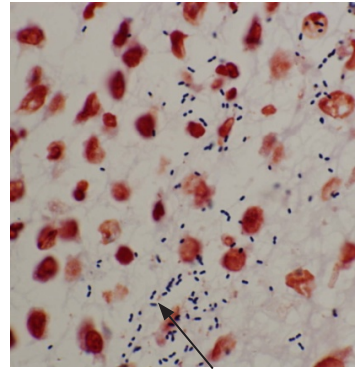
Pathology   **CSF microscopy**
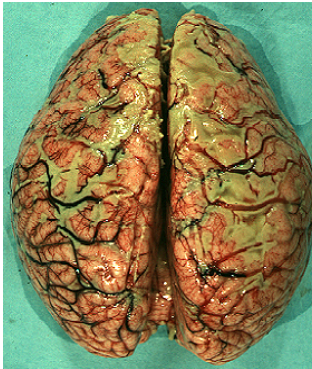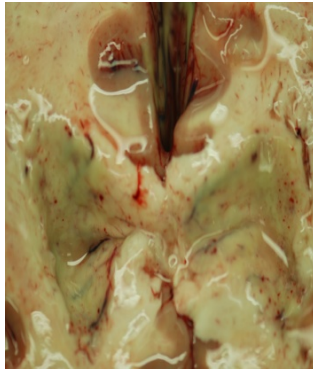
Purulent meninges   Purulent ventriculitis   Pneumococcus (Gm pos cocci)

Figure 6.1   Brain/csf in acute bacterial meningitis

Clinical diagnosis

The main clinical features of ABM are headache, fever and meningism. When this triad is accompanied by alteration in consciousness or seizures, the diagnosis is usually not in doubt. Other symptoms include photophobia, nausea, vomiting, backache and lethargy. The finding of a haemorrhagic rash on the skin is strongly suggestive of meningococcal infection. Progression occurs rapidly over 1-3 days but a smaller number may have an acute fulminant course lasting

hours. However patients with HIV infection may present with only one or two of these main features.

Seizures occur in about one third of patients, typically in children and may be the presenting complaint. Focal neurological abnormalities, status epilepticus and coma occur mainly as complications. There may also be evidence of infection outside the CNS or an underlying condition predisposing to meningitis e.g. pneumonia, HIV, middle ear infection and head injury. The differential diagnosis for ABM in adults in Africa includes the other main causes of meningitis (cryptococcus, TBM and viral), opportunistic infections in HIV, cerebral malaria, viral encephalitis, typhoid fever and other CNS infections.

Signs of meningitis

The cardinal signs of meningitis are *neck stiffness* and *Kernig's sign* (Chapter 1). **Neck stiffness** is the most important sign and is present when the neck resists passive flexion to bring the chin on to the chest. It is found in most adults and over three quarters of children with ABM. **Kernig's sign** is elicited by passively attempting to straighten the leg with the hip and knee flexed to >90 degrees. In cases of meningitis this is met with resistance and pain, caused by spasm in the hamstrings as a result of stretching inflamed nerve roots. A forward flexing of the neck elicits involuntary hip and knee flexion or *Brudzinski's sign*. **Brudzinski's sign** is found mainly in infants and young children but not in adults.

These signs of meningitis are present in most cases of established meningitis but are less likely to be present early on in the disease and in the young and the elderly. In older children and adults, in addition to the classic features, there may be back pain and myalgia and seizures in around 20%. In infants, the combination of fever, respiratory distress, irritability, crying, vomiting, drowsiness and failure to feed may be the only findings. In babies, the association of bulging fontanel, neck retraction and seizures should prompt the correct diagnosis. In the elderly, alteration in the level of consciousness and fever may be the only clinical findings. It is important to remember that whenever in doubt about the diagnosis of meningitis, to return to re-examine the patient for signs of meningitis, in particular for neck stiffness.

Pneumococcal meningitis

Patients with pneumococcal meningitis present with marked meningism. Signs of an underlying pneumonia and septicaemia may be present particularly in children. Patients tend to progress rapidly in 24-48 hours to drowsiness, confusion, seizures and coma.

Meningococcal disease

The main clinical features of meningococcal disease are those of either septicaemia with or without meningitis or meningitis alone. The proportion of patients presenting with meningitis alone appears to be greater in tropical countries. Meningococcal meningitis without septicaemia has a favourable recovery rate (95%). The clinical features of meningococcal septicaemia may vary from mildly symptomatic patients to acute fulminant infection. The onset is typically abrupt over 24-48 hours. However, symptoms can progress rapidly from drowsiness and rash to circulatory failure, coma and death within hours of onset.

The diagnostic feature of meningococcal disease is the typical haemorrhagic rash, which is non-blanching and present in the majority of patients (Fig 6.2). However it may be absent, particularly in uncomplicated meningitis in children. The rash may begin as a maculopapular rash and develops in a matter of hours into a petechial and purpuric rash all over. The

conjunctiva, palate, soles of the feet and palms of the hands should be carefully examined as the rash may be easily missed on the limbs and trunk in dark skin. The lesions do not blanch under pressure and this can be confirmed by pressure with a glass when the rash can be seen to persist. This is called the **"tumbler test"** (Fig 6.2)**.** Petechiae may later progress to larger confluent purpuric areas called purpura fulminans. Complications of meningococcal disease include skin necrosis, arthritis, gangrene and Waterhouse-Frederickson syndrome of adrenal failure.
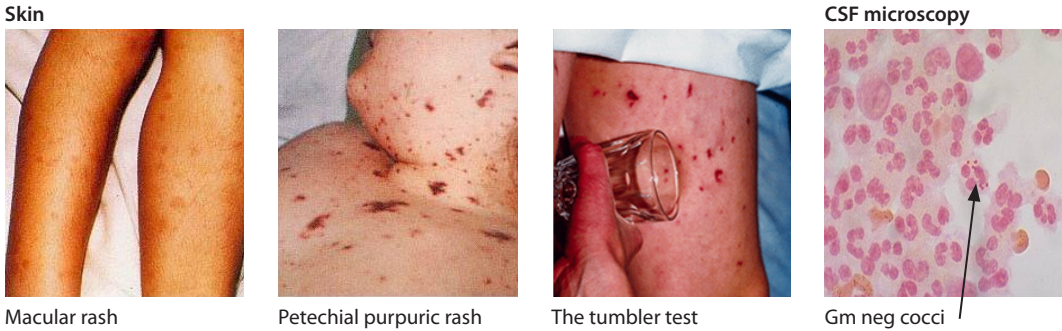
Skin   **CSF microscopy**

Macular rash   Petechial purpuric rash   The tumbler test   Gm neg cocci

Figure 6.2 Meningococcal meningitis

Hib meningitis

This has a characteristic slow onset over several days often starting with fever or respiratory tract infection. The onset of drowsiness, vomiting and convulsions in an infant in this setting may suggest the diagnosis.

Key points

- headache, fever & meningism are the cardinal clinical features of ABM
- neck stiffness is the most sensitive clinical sign
- signs are less sensitive in the young, old & in HIV infection
- meningism & bleeding into skin suggests meningococcal disease
- When in doubt about the diagnosis return & re-examine the patient

Diagnosis

The diagnosis of ABM is based on clinical and laboratory findings (Table 6.2). Laboratory tests include a full blood count, blood glucose, malaria slide, blood culture and an HIV test. A lumbar puncture (LP) is the key investigation and is an overall simple and very safe test (see appendix). It is always indicated in suspected ABM, unless there is a clear contraindication. A LP is contraindicated in the presence of suspected raised intracranial pressure (ICP). The clinical features suggestive of raised ICP in ABM are altered level of consciousness, coma, focal neurological deficit and papilloedema. These are all indications to avoid a LP and also for doing a CT scan of the head if it is available. The CT with contrast may show meningeal enhancement in ABM. If the CT of the head shows no mass lesion and there is no other evidence of raised intracranial pressure e.g. papilloedema then it is reasonable to proceed with the lumbar puncture. However it is important to note that even a normal CT may not necessarily rule out raised ICP, particularly if carried out early on in ABM.

CSF in ABM

The opening CSF pressure is typically elevated >20 cm and the colour is cloudy (Table 6.2). On analysis there is a characteristic high white cell count (>60% neutrophils), a very low glucose and an elevated protein. In HIV patients who are unable to mount a full inflammatory response, a much lower cell count is used as a cut off (>10 cells/mm³) for diagnosis of ABM and any protein elevation is also less. A similar pattern may be seen with the other causes of meningitis in HIV disease. A gram stain should always be performed on the CSF and a specimen sent for bacterial culture. Suspected cases of chronic meningitis patients should have their CSF screened for cryptococcus by India ink and cryptococcal antigen (CRAg) if available and also for tuberculosis by Ziehl-Neelsen (ZN) stain and culture.

Table 6.2 Summary CSF findings in meningitis*

	acute bacterial meningitis	tuberculous	cryptococcal	viral
opening pressure (n = <20 cm in adults)	increased	increased	increased	normal/increased
appearance (n = clear)	cloudy, purulent	yellow/cloudy	clear/cloudy	clear (cloudy)
cells/mm³* n = <5/mm³ **main type**	high >2,000/mm³ neutrophils	increased 50-500 lymphocytes	normal/increased 0-100 lymphocytes	normal/increased 0-500 lymphocytes
glucose (n = >50% plasma)	very low/absent <1 mmol/L	low	normal/low	normal
protein (n=<0.5gm/L)	elevated 1-2	high/very high 1-5	normal/elevated 0.5-2	normal/elevated 0.5-1.0
diagnosis confirmed	Gm stain & culture	ZN stain & culture	India ink stain, CRAg/culture	PCR/culture

*see appendix for exceptions

Management

The mainstay of management of ABM is prompt diagnosis and early treatment with antimicrobials (Table 6.3). It is important that antimicrobials should be given straight away (within 20-30 mins of first seeing the patient) and not to delay treatment because of ongoing investigations including a LP or CT. The early treatment is based on a presumed diagnosis of ABM and the patient is usually covered with antibiotics for the main possible bacterial causes (Table 6.3). In adults ceftriaxone or another extended-spectrum cephalosporin, cefotaxime are now the drugs of first choice. If unavailable then it is recommended to give soluble penicillin in combination with chloramphenicol. A history of anaphylaxis is a contraindication for penicillin but a history of a rash is not.

Patients at the extremes of life or with a particular risk factor may need additional antibiotic cover e.g. flucloxacillin for staphylococcal infection in neonates or gentamycin for some gram negatives in neonates and in old age. Additions or changes in antimicrobials are guided by laboratory based bacteriology stains and cultures. The use of steroids in the treatment of ABM in adults is currently not recommended in Africa as evidenced by recent prospective ABM studies in Malawi, showing no additional benefit. Supportive measures include oxygen, careful rehydration at less than 1-2 litres in the first 24 hours, maintenance of normal blood pressure, urinary output, electrolyte balance and control of pain and fever.

Table 6.3 Antimicrobial treatment of adult ABM

Drug	Dose/ route	Frequency	Duration*
ceftriaxone *or*	2 gm/iv	12 hourly	10-14 days
cefotaxime	2 gm/iv	4 hourly	10-14 days
or			
penicillin &	2.4 gm or 4 million units/iv	4 hourly	10-14 days
chloramphenicol	1 gm/iv	6 hourly	10-14 days

* children with ABM & meningococcal disease may have shorter courses of antibiotics (5-7 days)

Outcome

Death is inevitable in untreated ABM. Mortality in treated ABM varies with the age group affected, the organism causing it and in particular how early on the appropriate antimicrobial was given. The case fatality ratio (CFR) in ABM is highest in neonates and adults (50-70%). In adults in Africa, CFR is highest in pneumococcus (70%) and lowest in meningococcus (10-20%). The lowest CFR in ABM is in children with uncomplicated meningococcal meningitis (5%). The presence of underlying HIV infection significantly increases the CFR in ABM. Resistance to penicillin (20%), chloramphenicol (20%) or both (10%) and a decreased susceptibility to cephalosporins (5%) is an increasing problem particularly in Africa because of their widespread usage. Permanent neurologic deficits persist in over a quarter of all surviving ABM patients. This also varies by age group and organism. Over 50% of neonates and 40% of those who survive pneumococcal meningitis have permanent neurological deficits, in contrast to about 5-7% of those with meningococcus. The main neurological deficits after ABM are hearing loss (>25%), motor loss (12%), cognitive impairment (9%) visual disturbance (6%) and seizures.

Key points

- death is inevitable in untreated ABM
- early antibiotics is the most important treatment affecting outcome
- cephalosporins are the drugs of first choice
- over a quarter of all surviving patients have permanent neurological disabilities
- disabilities includes deafness, motor loss, cognitive impairment, mental retardation, visual disturbance & seizures

Prevention

In sporadic meningococcal infection, chemoprophylaxis should be provided for all household and close contacts of the patient within the previous 24 hours. The risk of developing meningitis in close contacts is estimated to be about 1 in 300. Adults and children over 12 yrs should receive rifampicin 600 mg orally twice daily for 2 days or ciprofloxacin or azithromycin 500 mg orally as a single dose. Rifampicin should not be given in pregnancy. For children up to the age of 12 years, use rifampicin10 mg/kg twice daily for two days or ceftriaxone 125 mg im as a single dose. Chemoprophylaxis is not indicated for close contacts of pneumococcal or Hib meningitis. Early recognition is the key to management when epidemic meningococcal meningitis is suspected. If the number of cases exceeds 15/100,000 per week or 5-10 cases per week if the population <30,000, then emergency preventative measures include alerting

the appropriate authorities, identifying the organism and use of mass chemoprophylaxis and vaccination. All three main causes of ABM are now largely preventable by vaccination.

Key points

- prevention of individual cases meningococcal infection is based on prophylaxis of close contacts
- epidemic prevention is based on early recognition, mass chemoprophylaxis & vaccination
- vaccines are available to prevent Hib & for some strains of meningococcus & pneumococcus
- ABM in SSA is largely preventable by vaccination

TUBERCULOUS MENINGITIS (TBM)

Each year there are around 10 million new cases of tuberculosis worldwide, approximately one third of which occur in Africa. TBM now accounts for 8-44% of all cases of meningitis in SSA depending on the local HIV and TB prevalence. TB of the CNS is estimated to account for <1% of all new cases of TB, but this figure is significantly higher, when there is coexisting HIV infection. Tuberculous meningitis (TBM) is the most common CNS presentation. Other CNS presentations of TB infection include focal neurological disorders in intracranial tuberculoma and paraplegia in spinal cord involvement. In Africa, non HIV associated TBM affects mostly children, in particular the age group <5 years but can affect all age groups. In contrast TBM in HIV disease mostly affects adults. TB is clinically classified as pulmonary type (85%) and extra pulmonary type (15%). Only the pulmonary type is infectious to others. TBM can arise in two main ways: either as a complication of pulmonary e.g. disseminated or miliary, or less commonly as a result of reactivation of extra pulmonary TB.

Pathogenesis

Mycobacterium tuberculosis is the main cause of TB but other members of the *M. tuberculosis* complex such as *M. bovis* and *M. africanum* may also cause human disease. TB of the CNS arises indirectly from primary infection in the lungs, from where it spreads via the blood stream to other organs including the brain and spinal cord. In the brain or spinal cord, it has a predilection for the subpial sites, where it may present either acutely as TBM or lie dormant for years and later reactivate. Under different conditions, notably immunosuppression in HIV or sometimes pregnancy these tubercles which are known as Rich foci reactivate and rupture. If they rupture into the subarachnoid space they result in TBM, into the brain a tuberculoma, or into the spinal cord a myeloarachnoiditis. The immune reaction generated is mainly inflammatory with exudates particularly around the base of the brain and in the ventricles (Fig. 6.3). This may lead to multiple cranial nerve palsies, arteritis with strokes and obstruction to CSF flow and absorption resulting in hydrocephalus.

Clinical features

TBM is a difficult condition to diagnose and confirm clinically. The clinical features are those of slowly progressive chronic meningitis frequently with associated encephalopathy. Symptoms develop gradually, usually over 1-3 weeks but can be more acute in children. Constitutional TB symptoms including fever, night sweats, weight loss and malaise may be present for a week or more early on but these may also be absent or are not specific for TB. The main neurological symptoms suggestive of TBM are headache, nausea, vomiting, irritability, behaviour change and meningism of gradual onset usually for a period of one week or usually longer in adults.
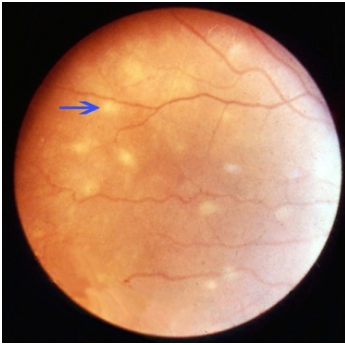
Pathology
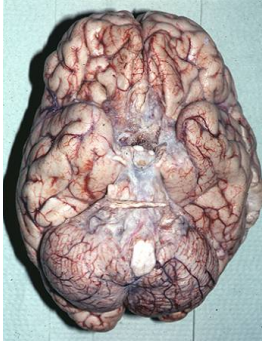
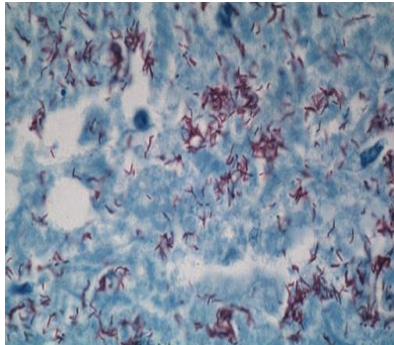Basal meningitis

Histopathology
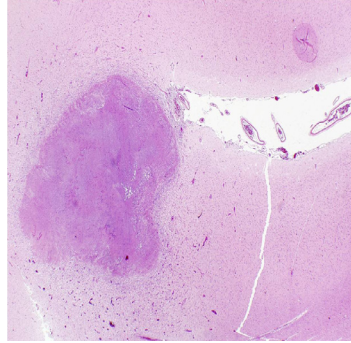
Rich focus

Endarteritis obliterans

Fundoscopy

Retinal TB

Microscopy

AFB on ZN stain

Figure 6.3   Brain/csf in tuberculous meningitis

However, headaches may be less prominent in children, fever may be absent in 10-20% of adults and the signs of meningitis are generally less prominent as compared to ABM. The main neurological signs are those of meningism including neck stiffness coupled with combinations of cranial nerve palsies (3rd, 4th, 6 th ,7th & 8th). The presence of focal neurological deficits, visual loss, papilloedema, altered level of consciousness, seizures and coma all suggest either parenchymal brain involvement or hydrocephalus. Fundoscopy may occasionally reveal typical TB retinopathy (characteristic white spots e.g. Fig 6.3). Hydrocephalus may be present early on or develop later during the course of the illness.

Other neurological presentations of TB involving the CNS are tuberculoma in the brain and spinal cord TB. Tuberculoma may be solitary or multiple presenting mainly as focal neurological deficits, seizures and occasionally raised intracranial pressure. Tuberculoma may sometimes complicate TBM and the most common site in adults is above the tentorium (supratentorium), whereas in children it is below the tentorium (infratentorium). Spinal cord TB presents as paraplegia and the site may sometimes be the source of TBM (Chapter 10). A WHO staging based on the main neurological features of TBM is outlined below (Table 6.4).

Table 6.4 WHO Staging of TBM

Disease Stage	Neurological features
Stage I	no disturbance of consciousness no *FND
Stage II	alteration in consciousness but not in coma or delirium, no FNDs, cranial nerve palsies may be present
Stage III	coma &/or FNDs

* FND focal neurological disorder

Key points

- TBM occurs either as an acute complication of pulmonary TB or as a reactivation of extra pulmonary TB
- TBM affects mostly young children whereas TBM in HIV affects mostly adults
- HIV significantly increases the risk of TBM
- symptoms of TBM include headache, fever, vomiting, & meningism for >1 week
- signs include neck stiffness, seizures & multiple cranial nerve palsies

Differential diagnosis

The differential diagnosis includes cryptococcal meningitis, partially treated ABM, cerebral malaria, brain abscess and other infectious causes of meningoencephalopathies.
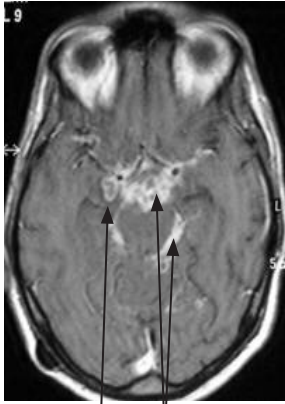
Diagnosis

The diagnosis of TBM is based on clinical suspicion and characteristic CSF findings (Table 6.2). Routine laboratory investigations are of limited value in the diagnosis of TBM. The tuberculin skin test is of little diagnostic benefit in adult populations with high levels of TB infection or previous BCG exposure and may also be negative in disseminated TB and HIV disease. The diagnosis of TBM is supported if there is evidence of concomitant TB elsewhere, most frequently pulmonary as evidenced by chest radiograph. Lumbar puncture is safe if there are no contraindications e.g., alteration in consciousness, lateralising clinical signs or signs of raised intracranial pressure (see appendix).

In TBM the opening pressure is often raised and the CSF clear in colour but may be slightly yellow in established disease. If a sample is left standing overnight in a test tube, the development of an appearance of a cobweb or lattice is supportive of TBM. The CSF white cell count in TBM is usually elevated, 50-500 cell/mm^3 mostly lymphocytes, but notably these may be absent in HIV disease or are polymorphs in early infection, particularly in young children. The CSF protein level is usually quite elevated and the glucose is low (<50% plasma glucose) but these can be normal in early disease and also in HIV infection. The organism is identified by acid-fast staining and culture. In TBM, the sensitivity of routine unconcentrated CSF staining with Ziehl-Neelsen stain is very low (<5%), but this yield can be improved markedly with increased quantity of CSF (10-20 ml in adult), by concentrating the CSF by centrifugation and by careful examination or the residue (for at least 20 mins) and by repeated CSF examinations. Polymerase chain reaction (PCR) has better sensitivity depending on bacillary load and good specificity (90-95%) but the test is not widely available in Africa and the result is no better than culture. A new automated PCR test on sputum is now available which gives a result in 4 hours but running cost is approx 20 US dollars per test which makes it relatively prohibitive

in most parts of Africa. Also it has yet to be validated on CSF. Culture is the gold standard but limitations include the fact that the result takes 4-6 weeks which is too slow to be of value clinically and this facility is again not widely available. The CRAg test in TBM is negative.

Imaging with CT/MRI (Fig. 6.4) can be very helpful. In TBM it may show evidence of hydrocephalus and after contrast generalised meningeal enhancement with irregular basilar/cisternal involvement. It may also reveal infarction or tuberculoma. A tuberculoma shows as a rounded lesion with ring enhancement with irregular walls, nodular enhancement, oedema and mass effect. They are most commonly situated near the cortex, may be multiple and accompany TBM.

MRI with contrast

CT head

Tuberculoma & basal cistern & meningeal enhancement
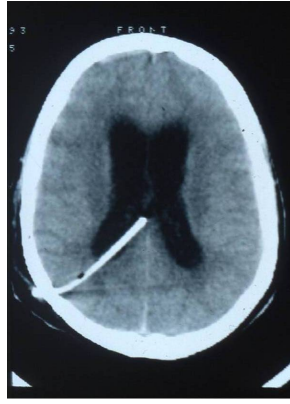
Hydrocephalus with shunt in TBM

Figure 6.4 Neuroimaging in TB CNS

Key points

- diagnosis of TBM requires a high index of clinical suspicion
- laboratory confirmation is by finding evidence of TB in CSF by ZN stain or culture
- routine CSF screening sensitivity for AFB is very low
- typical CSF findings in TBM are increased lymphocytes, elevated protein & low glucose
- CT findings in TBM include basilar meningeal enhancement & hydrocephalus

Management of TB

Treatment for CNS TB should start as early as possible with 4 drugs as any delay in treatment greatly increases mortality. These include isoniazid, rifampicin, pyrazinamide and a fourth drug ethambutol (Table 6.5). Streptomycin is also available but is a second line drug used when there is drug resistance or toxicity. The four drugs are continued for the first 2 months after which isoniazid and rifampicin are continued usually for another 10 months. In practice the standard total period of treatment is 12 months for TBM and longer for tuberculoma (18 months). A shorter period of treatment for TBM (total 9-10 months) has been proposed but is not common practice in Africa. The main side effects are hepatitis with isoniazid and rifampicin, neuropathy with isoniazid and deafness with streptomycin, and rarely optic neuritis with ethambutol (Table 6.5). Pyridoxine 20-50 mg daily should be prescribed with isoniazid

to prevent neuropathy. All HIV uninfected patients with CNS TB in WHO Stages II and III of the disease should be given steroids for the first 6 weeks of chemotherapy. The dose can be decreased gradually after the first two weeks. Hydrocephalus is a major complication of TBM occurring in >50% cases and may require ventricular peritoneal shunting or drainage as early as is clinically indicated.

Table 6.5 Treatment of CNS tuberculosis, TBM

Chemotherapy	Dose/route/frequency/duration*	Main side effects
Isoniazid *(H)*	5-10 mg/kg/po/daily/12 months (300-600 mg daily) & **pyridoxine 20-50 mg** daily to prevent neuropathy	hepatitis, neuropathy
Rifampicin *(R)*	10-12 mg/kg/po/daily/12 months (600 mg daily)	hepatitis
Pyrazinamide *(Z)*	30 mg/kg/po/daily for 2 months 1.5-2.0 gm daily	nausea & vomiting & arthralgia, hepatitis
Ethambutol *(E)* *or* **Streptomycin** *(S)***	15 mg/kg/day/po/daily for 2 months (800 mg daily) 20 mg/kg/im/daily for 2 months (1 gm daily)	optic neuritis (rare) nerve deafness, nephrotoxicity
Dexamethasone *or* **Prednisolone**	0.4 mg/kg/iv/po/daily (24 mg od) for 2 weeks and tapering over next 4 weeks 60 mg/po/daily for 2 weeks and tapering over next 4 weeks	hyperglycaemia, peptic ulcer, hypertension & psychosis

* a longer course of treatment (18/12) is recommended in tuberculoma
** second line drug

TBM in HIV

The clinical, neuroimaging and laboratory features of TBM are very similar in both HIV positive and HIV negative persons apart from decreased or no evidence of inflammation in the CSF (15-20%) and more extra meningeal TB in HIV infection. Starting ART is recommended after the first 2 weeks of TB treatment. In general steroids are not contraindicated and the indications for their use are the same as in non HIV TBM with steroid cover for the first 6 weeks of TBM treatment. However the clinical course may be complicated by drug resistant TB, co-infection, bacteraemia, immune reconstitution inflammatory syndrome (IRIS) and decreased drug compliance.

Outcome

The outcome of TBM in Africa even with treatment is poor with published CFRs varying from 13-90%. In adults TBM has a mortality rate of >50%. This is mainly related to late clinical presentation and advanced stage of disease (WHO stages II & III) or to underlying HIV infection. WHO stage I disease is associated with a good outcome. Permanent deficits occur in at least 30-40% of survivors. These include deafness, blindness, paralysis, seizures and retardation.

Prevention

Prevention of TB is based on case or patient finding and treatment. Prophylactic treatment with isoniazid is used to prevent reactivation of TB in selected patients in particular with HIV infection. The use of BCG vaccination of neonates has been shown to decrease the overall risk of TBM in children in Africa.

Key points

- delay in diagnosis greatly increases mortality in TBM
- duration of treatment in TBM is 9-12 months
- steroids are indicated in TBM for the first 6 weeks in most patients
- CFR rates and morbidity rates are very high
- prevention is by BCG & prophylaxis & active case treatment

CRYPTOCOCCAL MENINGITIS

Introduction

Cryptococcal disease is caused by *Cryptococcus neoformans,* a yeast fungus found worldwide in soil and bird excrement. It is usually acquired asymptomatically by humans via inhalation of encapsulated yeast cells, mostly during the first 5 years of life. Cryptococcal disease in immunosuppressed persons occurs mostly as a result of reactivation of latent infection. It typically presents as a chronic meningitis in patients during the later stages of HIV disease occurring with CD4 counts of <100 cells/mm^3. Since the onset of the HIV epidemic, it has become the leading cause of meningitis in large parts of Africa accounting for 33-63% of all cases depending on the individual country. After TB it is the main cause of death in HIV disease in Africa, accounting annually for over half a million deaths or around 25% of all HIV related deaths.

Clinical findings

Cryptococcal disease may present clinically as cryptococcal meningitis (CM), pulmonary infection, or uncommonly disseminated disease with skin involvement. Pneumonia is the main pulmonary presentation. While occasionally severe, pulmonary involvement is relatively uncommon and usually self limiting. Pulmonary symptoms include cough, chest pain dyspnoea and fever. CM is the main clinical disease, presenting with a sub acute or chronic illness evolving usually over 1-2 weeks or occasionally longer, 3-4 weeks. The main symptoms are headache (80-100%), fever (70%) and alteration in mental status (25-30%).

Clinical features suggestive of CM include headaches which are usually severe and associated with nausea and vomiting, and the relative absence of meningism (25-50%). Notably confusion or behaviour change with or without fever may be the only clinical feature suggestive of underlying CM. Neurological findings include isolated cranial nerve palsies (mainly 6th nerves), decreased visual acuity and papilloedema. Neck stiffness is uncommon being present in only around 25% of patients. The presence of altered level of consciousness and coma are explained by raised intracranial pressure (ICP) secondary to decreased absorption of CSF in CM by the arachnoid granulations. Raised ICP is present in about 50% of patients at diagnosis and if not properly managed is associated with a worse prognosis. Clinically CM may be indistinguishable from TBM.

Diagnosis

The diagnosis of CM requires a high index of clinical suspicion. However, the presentation of a patient with an unexplained sub acute illness with headache, fever, altered mental status and evidence of underlying HIV infection (CD4 <100 mm^3) usually suggests the diagnosis. The CSF is abnormal in >80% of CM cases but CSF chemistry remains normal in about

20%, despite the presence of the disease, usually in early CM or in advanced HIV (Table 6.2). Typical abnormal CSF findings include increased opening pressure and increased WBCs. These include mostly lymphocytes (median 10-20/mm³) but can be <5/mm³, a normal or increased protein and normal or slightly low glucose levels in around 50% of cases.

The diagnosis is confirmed by demonstrating the presence of encapsulated yeast cells in the CSF by direct staining of a centrifuged sample with Gram's or India ink staining (Fig. 6.5). It is also demonstrated by the presence of cryptococcal antigen (CRAg) in CSF or blood. While the India ink staining method is relatively easy to perform i.e., adding a few drops to CSF, and is cheap, it is less sensitive (60-80%) than CRAg which is highly sensitive (>95%). In particular all adults in Africa presenting with meningitis and India negative CSF should ideally have a CRAg test. CRAg is mostly unavailable in hospitals in Africa because of cost. However a newer rapid lateral flow assay or dipstix test for the presence of cryptococcal antigen in blood, serum or urine, costing approx 1 dollar per test offers the hope of a more affordable, rapid and accurate diagnostic test in Africa. Fungal culture is more sensitive than India ink but takes 2-5 days for results, is also more complex to perform and is available only in some specialized laboratories. CT imaging of brain is less helpful in diagnosis, being normal in over half the cases. It may show meningeal enhancement or abscess formation with contrast but its main role is to exclude other opportunistic processes. The main differential diagnosis in HIV is with TBM and toxoplasmosis.
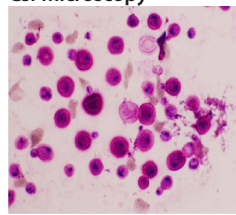
Pathology **Csf microscopy** **India ink stain**
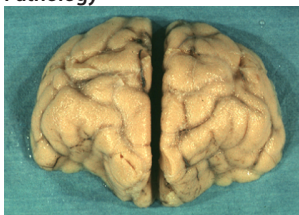
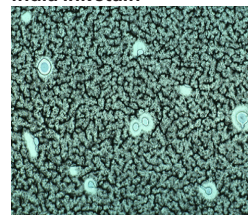Milky meninges & micro abscesses Encapsulated yeast cells
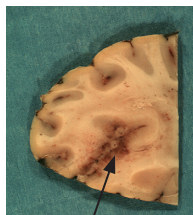
Figure 6.5 Brain/csf in cryptococcal meningitis

Key points

- CM is the leading cause of meningitis in adults in Africa
- accounts for >25% of all AIDS related deaths in Africa
- occurs mostly in patients with CD4 counts <100 cells/mm³
- symptoms include severe headache, fever and altered mental status for 1-2 weeks
- signs of meningism are frequently absent but papilloedema is common
- clinically it is often indistinguishable from TBM

Treatment

The treatment of CM in Africa is mostly based on fluconazole alone (Table 6.6). There are three phases, the induction phase lasts 2 weeks using fluconazole 1200 mg daily and the consolidation phase lasts the next 8 weeks using fluconazole 800 mg daily. The maintenance or prophylaxis phase uses fluconazole 200 mg daily until the CD4 count is >200/mm³ for >6 months. The higher treatment phase dosage of fluconazole "1200 mg daily" which is recommended here has been shown to be superior to "800 mg daily" in the induction phase

in Africa but is not yet widely adopted. The recommended first line induction treatment for CM is amphotericin B (AmB) 0.7-1mg/kg/day in saline used in combination with flucytosine 100 mg/kg/day, for the first two weeks of infection followed by the consolidation phase of fluconazole, 400 mg po daily for 8-10 weeks followed by the 200 mg daily maintenance phase. This is the most effective regime and has been shown to have highest early fungicidal activity in the CSF. However the use of AmB and flucytosine in Africa is restricted mainly because of availability, cost and the need to monitor renal function every couple of days and check for any evidence of bone marrow suppression. Combining fluconazole with either AmB or flucytosine has also been shown to be superior to fluconazole alone.

Table 6.6 Fluconazole treatment for cryptococcal meningitis in Africa

Drug	Dose/route	Duration	Side effects
Fluconazole treatment phase consolidation phase prophylaxis phase	1200 mg/po/daily 800 mg/po/daily 200 mg/po/daily	2 weeks 8 weeks until CD4 >200/mm^3 for 6/12	headache, dizziness hepatitis

Lumbar puncture in treatment

Patients with symptomatic raised ICP, papilloedema or opening CSF pressures >25 cm (normal OP is <20 cm) benefit from frequent, daily or alternate day lumbar punctures with drainage of approx 10-15 ml (max 30 ml) at each LP until symptoms clear or the CSF pressure decreases consistently to below 20 cm. Serial lumbar punctures (day 1, 3, 7, & 14) have been shown to reduce CM mortality in Africa.

CM and ART

In CM the very early initiation of ART is associated with a higher case fatality rate. A delay in initiation of ART until at least 4 weeks after the start of the treatment phase appears to have a better outcome in fluconazole treated patients. In amphotericin treated patients starting at 2 weeks is better than at 6 weeks. Further studies are underway to determine the exact optimum time to start ART. Meanwhile best practice is to follow WHO and national guidelines. Adequate secondary prophylaxis with fluconazole is essential to long term survival. Although studies from South East Asia suggest that primary prophylaxis (treating all HIV patients with fluconazole 200 mg daily) decreases CM this may not be either feasible or practical in Africa. However there is strong evidence in Africa that in HIV patients with CD4 count <100/mm^3 the presence of cryptococcal antigenaemia accurately predicts the onset of an attack of CM over the following 12 months. This highlights the need for a more targeted approach to screening of at risk HIV infected persons e.g. those starting ARTs and the treatment and chemoprophylaxis of the CRAg positives.

Prognosis

CM is fatal without treatment and has a high mortality even with treatment. In Africa the two week post treatment mortality is 20-40% and the six month mortality rate even with ART therapy is >50%. The overall high mortality rates seen in CM in Africa are ascribed to late clinical presentation, ongoing immunosuppression, concurrent infections e.g. TB, immune reconstitution syndrome (IRIS) which usually occurs within 3 months of initiating ART and high rates of relapse. The following clinical features at presentation are associated with poor prognosis, abnormal mental status, high fungal burden, increased CSF opening pressure and

poor inflammatory response (<20 cells /mm³). Relapse is common (approx 30%) and IRIS can occur months after initiating ART in patients with successfully treated CM. Management of IRIS includes excluding or treating possible CM relapse, decreasing intracranial pressure (by repeated LPs), excluding other possible opportunistic infections e.g. TBM and finally steroids if necessary.

Key points

- diagnosis is confirmed by CSF microscopy (India ink) and/or CRAg serology
- repeated lumbar punctures is critical in the management of ↑ICP in CM
- treatment is with fluconazole 1200 mg/po for 2/52 followed by 800 mg po for 8/52
- secondary prophylaxis is necessary until the CD4 count >200/mm³ for 6/12
- initiating ART for CM patients should be delayed for 4 weeks after treatment
- long-term mortality in CM is high (>50%) even with ART

VIRAL MENINGITIS

Viruses are the commonest cause of meningitis worldwide. Viral meningitis is usually a benign disease that does not require hospitalization. It is commonest in the age groups 0-1yrs and 4-15 yrs but can affect all age groups. Human enteroviruses account for >90% of cases and are classified into polioviruses, coxsackie viruses and echoviruses. Other viruses that cause meningitis include the arboviruses and adenoviruses. Young children are the usual source with spread mostly via the faecal oral route within families. It occurs throughout the year with seasonal peaks in the hotter weather. Outbreaks can occur in hospitals and schools.

Clinical features

Clinically there may be a history of a viral like illness with fever, vomiting and rash. The onset can be acute or sub acute with fever and headache occurring in most patients. Neck stiffness is mild and present in half the cases. Neurologic abnormalities are rare but febrile convulsions may occur in young children. The illness can last over a week in children and longer in adults. Clinically at onset viral meningitis may be indistinguishable from bacterial meningitis and often requires emergency antibiotics until the diagnosis is confirmed by exclusion of other causes. A lumbar puncture may be normal or show mild abnormalities including polymorphs early on and later lymphocytes (Table 6.2). Treatment is mainly symptomatic and the prognosis is generally excellent.

VIRAL ENCEPHALITIS

Encephalitis is inflammation of the brain parenchyma caused by a viral infection. It is predominantly a disease of children. The causative virus is not known in >50% of cases. The most frequent known forms are caused by an unusual manifestation of common, mainly childhood viral infections including measles, chickenpox and mumps. Herpes simplex (HSV) is the most common cause of fatal sporadic encephalitis in adults worldwide but it appears to be uncommon in Africa. Other well known viruses causing encephalitis include HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and rabies. There are great geographic variations in the causes of viral meningo-encephalitis worldwide and accounts of viruses specific to the African subcontinent including Lassa fever, Marburg disease, Ebola virus and Rift Valley Fever can be found in a larger textbook or online.

The main arthropod borne infections causing viral encephalitis are Japanese B encephalitis virus in the Far East, West Nile virus in mainly West Africa and Rift Valley Fever in East Africa. The vectors are mosquitoes and the hosts may be humans, animals or birds depending on the location and virus. Viruses enter the CNS by two distinct routes, haematogenous which is the most common route as occurs in the arthropod borne group and by local replication at the site of infection and retrograde spread to the brain via peripheral nerves as occurs in herpes and rabies. Other main ways of acquiring CNS viral infection include enteric e.g. polio and by inhalation e.g. Ebola and sexually e.g. HIV.

Clinical features

Viruses cause a variety of CNS disease including aseptic meningitis, encephalomyelitis, myelitis and myeloradiculitis. The signs and symptoms of encephalitis include fever, headache, confusion, stupor, coma, seizures, upper motor neurone signs and less commonly focal neurological deficits. Virus infections may also infrequently result in a form of autoimmune encephalitis called **acute demyelinating encephalomyelitis (ADEM)** occurring mainly in older childhood/early teens which is very responsive to high dose parenteral steroids. The clinical presentation of ADEM is that of monophasic illness and can be very similar to encephalitis. However, it is difficult to diagnose and confirm in Africa without MRI scanning.

The diagnosis of viral encephalitis is made by immunological tests, neuroimaging and EEG but the viral cause is not usually identified. Effective antiviral therapy (such as the acyclic purine nucleoside analogue, aciclovir) is available only for the herpes virus group. The mortality is variable and depends on the virus. Preventive measures include control of vectors and vaccination when available.

Key points

- viruses are leading cause of meningitis/encephalitis worldwide & mainly affect children
- enteroviruses are main causes of viral meningitis in children
- transmission is by close physical contact: inhalation, ingestion, insect bites & sexual contact
- diagnosis is clinical in combination with CSF & serology findings
- outcome is excellent in viral meningitis but variable in encephalitis depending on the virus

HERPES ENCEPHALITIS

This is the most common form of fatal sporadic encephalitis worldwide and is important because it is treatable if diagnosed early. The frequency is not known in Africa but may be less there possibly because of early exposure in childhood. There are two main types, HSV-1 and HSV-2. Humans are the reservoir for both types; HSV-1 is more common and affects mainly older adults, whereas HSV-2 affects neonates. HSV-I is spread by close physical contact and causes predominantly encephalitis, whereas HSV-2 is considered a sexually transmitted disease and predominantly causes meningitis. The source of encephalitis is mostly reactivation of latent ganglionic infection or less commonly a primary infection. It spreads in a retrograde way either via the trigeminal or olfactory nerves to the temporal and frontal areas of the brain

Clinical findings

Clinically, HSV encephalitis begins as an acute or sub acute non-specific febrile illness characterised by headache, fever, irritability, and altered mental status. Most patients go on to

experience confusion, personality change, dysphasia, focal neurological findings, memory loss and seizures affecting the temporal lobe. Herpetic skin lesions are rare. Symptoms typically evolve over several days and may take 2 to 3 weeks to reach their maximum severity. The differential diagnosis includes HIV related CNS infections, TB meningitis, partially treated acute bacterial meningitis, cerebral malaria and brain abscess.

Diagnosis

Diagnosis of HSV encephalitis is based on clinical findings and a characteristic CSF with lymphocytes, red blood cells and elevated protein. Infection in the CSF may be demonstrated by PCR, serologically and viral culture. PCR has a specificity of up to 100% and a sensitivity of 95% on CSF taken between day 2 and 10 after the onset of the illness, however serological tests are of no help in acute diagnosis of HSE, only in retrospect and then after 2 weeks. An EEG can be diagnostic. CT/MRI of the head typically shows oedema and haemorrhage in the temporal/frontal lobe (Fig. 6.6).

Pathology

Temporal lobe oedema & multiple micro haemorrhages

MRI T1
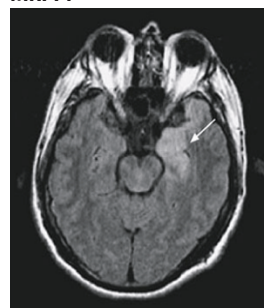
Temporal lobe oedema

Figure 6.6 Brain in herpes encephalitis

Management

The antiviral drug aciclovir 10-15 mg/kg/iv 8 hourly is given for 14 days as soon as possible after the onset of symptoms if HSE is thought to be at all likely and for 21days if HIV positive. Aciclovir is well absorbed orally if the parenteral form is unavailable. Seizures are treated as in status epilepticus. Rehabilitation includes physiotherapy, speech therapy, occupational therapy and later neuropsychological testing and support. Treated cases have a mortality of 10-20% and untreated 50-70%. Morbidity is high and includes memory loss, cognitive impairment and persistent seizures. The role of steroids is controversial but should be given at present if there is evidence of raised or increasing intracranial pressure.

RABIES

Rabies is mainly a disease of dogs, cats, jackals, mongoose and bats that is transmitted to humans. Transmission to humans in Africa is almost inevitably by the bite and saliva of a rabid dog or other animal. The severity and site of the bite from the rabid animal determines the risk of infection and 35-67% go on to develop rabies. Very rarely transmission is human to human e.g., by corneal graft. Rare cases have occurred by inhalation of bat urine in caves. There are over 50,000 deaths worldwide each year from rabies mainly in Asia but many also occur in

Africa. Post exposure prophylaxis can be 100% effective (Table 6.7) if it is given on the day of exposure or bite and the treatment precautions are rigorously adhered to.

Pathogenesis

Rabies starts with viral replication at the bite site. Then there is flow of the virus via the peripheral nerves towards the brain with replication in the brain nerve cells which gives rise to the characteristic neuronal inclusions called Negri bodies. Then there is flow back from the brain to the rest of the nervous system, in particular to the salivary glands and the clinical disease starts. Involvement of the limbic system in the brain results in furious rabies and involvement of the spinal cord results in paralytic rabies.

Clinical features

Rabies should be suspected if there are unexplained neurological, psychiatric or laryngo-pharyngeal symptoms in a patient with a history of an exposure. The usual incubation period is between 2-8 weeks but can vary from 9 days to 12 months or rarely more. The disease starts with a prodromal illness which lasts a few days, until either furious or paralytic rabies appears. The first symptom is itching, pain or paraesthesiae at the now healed bite site. Other prodromal symptoms include myalgia, fever, chills, irritability, anxiety, photophobia and headache.
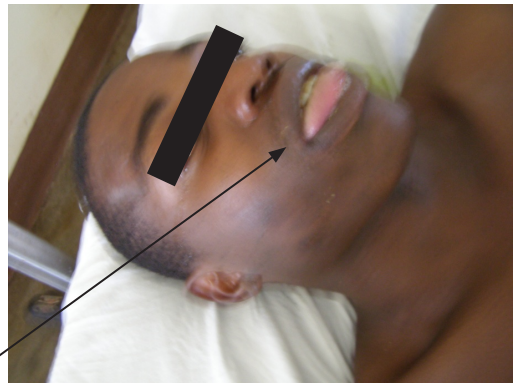
Furious rabies with tearing from the eyes, tongue protrusion & frothing

Paralytic rabies with facial scars (dog bite), hyper salivation & tongue protrusion
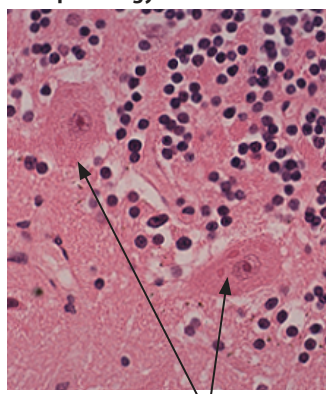
Figure 6.7 Rabies

The clinical features of furious rabies occur in 80% of cases and include hydrophobia, terror, pain, convulsions, hallucinations, aggression, cranial nerve palsies, paralysis and autonomic disturbance e.g. hyper salivation or frothing from the mouth, sweating and lacrimation (Fig 6.7). Periods of manic confusion may alternate with periods of calm and quiet. Rabies is characterised by terrifying hydrophobic spasms. These are typically provoked early on by sipping water, swallowing saliva or by blowing air onto the skin and later on by merely the sight, sound or mention of water. These are characteristically violent jerky spasms during which the neck and back are extended and the arms thrown upward. They can be very severe and end in seizures and death.

Paralytic or algid rabies occurs in about 20% of patients (Fig. 6.7). During this the patient begins with the usual prodromal symptoms followed by paralysis in the bitten limb, which eventually ascends to involve the remaining limbs and breathing. Death in rabies usually follows the onset of prodromal symptoms within 1-2 weeks and following the onset of spasms, coma and paralysis within days. The differential diagnosis includes causes of spasms including tetanus, tetany, dystonic drug reactions, poisoning and paralysis including Guillain-Barre syndrome, and CNS infections including cerebral malaria and encephalitis.

Laboratory diagnosis

The diagnosis is a clinical one based on a history of exposure and clinical findings. There are no routine laboratory or rapid tests for the diagnosis of rabies and the ante mortem diagnosis requires a reference laboratory as several tests are necessary. Antibodies are detectable in the unvaccinated patient during the second week of illness and the virus may be isolated from saliva and CSF although it may take 1-3 weeks for a result. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Skin biopsies at the nape of the neck can be examined for the presence of rabies antigen (IFA) in the cutaneous nerves. The brain of the biting animal and the patient can be examined microscopically for the presence of Negri bodies and immunofluorescent antibodies (Fig. 6.8).

Histopathology

Negri bodies (small red inclusions)
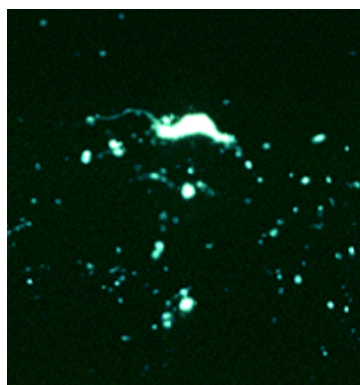
Immunofluorescence staining

Figure 6.8 Brain in rabies

Key points

- rabies is transmitted to humans mostly by the bite and saliva of a rabid dog
- diagnosis is by a history of exposure & unexplained neurological or psychiatric symptoms
- hydrophobia, terror, pain, convulsions & hallucinations occur in the majority of patients
- there are no routine clinical laboratory diagnostic tests for rabies

Treatment

Rabies patients should be nursed in a single room in isolation because the patient's saliva is potentially infective. Ideally there should be barrier nursing. Treatment is symptomatic as the disease is considered to be universally fatal once symptoms appear apart from a few isolated reports of survival with prolonged ICU care in high-income settings. Symptomatic treatment involves large doses of sedation using phenothiazines and phenobarbitone and adequate analgesia using morphine to relieve the fear and pain.

Prevention

Rabies is preventable by pre and post exposure vaccination (Table 6.7). Post exposure prophylaxis of rabies is based on using available rabies vaccines which are all equally safe and effective. These include human diploid cell vaccines (HDCV), purified vero cell vaccine (PVRV), purified chick embryo vaccine, (PCECV) and purified duck embryo vaccine (PDEV). The indications for prophylaxis are licks on skin or mucosa, scratches, abrasions and **bites** from animals in rabies endemic areas. Post exposure treatment consists of **1**) **vigorous wound debridement** and **cleaning with alcohol** or **iodine compounds, 2) starting the vaccine immediately** and **3) using rabies immunoglobulin,** if a major exposure (bites) has occurred. These measures, if carried out optimally, can reduce the risk of developing rabies to almost zero.

The vaccine should always be started as early as possible and be given regardless of the time lapse since exposure. Costs are reduced by using the intradermal route of administration. The WHO recommended vaccination schedules are presented below. *Vaccination may be discontinued if the animal, usually a dog or a cat remains healthy after 15 days of observation or if it is certain that the animal brain biopsy is negative for rabies.* The management and control of rabies in endemic areas depends on the control and immunization of dogs and the notification of the disease.

Table 6.7 WHO recommended immunization schedule for Rabies

Post exposure prophylaxis (all vaccines)	1.0 ml im (deltoid) never the buttock on day 0, 3, 7, 14, 28
Alternative regimes (where vaccine in short supply)	
8 site intradermal (HDCV & PCECV)	0.1 ml id @ eight sites* on day 0 0.1 ml id @ four sites** on day 7 0.1 ml id @ one site (deltoid) on day 28 & 90
2 site intradermal (PVRV, PCECV & PDEV)	0.2 ml id @ two sites (deltoid) on day 0, 3 & 7 & 0.2 ml id @ one site (deltoid) on day 28 & 90
Previously vaccinated (all vaccines)	1.0 ml im (deltoid) on day 0,3, &7

id = intradermal
deltoids, suprascapular, abdominal wall (lower quadrant) & lateral thighs
**deltoids & thighs*

TETANUS

Key points

- there is no effective treatment for rabies
- rabies is preventable by vaccination
- post exposure treatment consists of immediate wound cleaning, vaccination & immunoglobulin
- vaccine prophylaxis is very effective if started early (<1day) post exposure & according to schedule

TETANUS

Tetanus is caused by exposure to spores of *Clostridium tetani*, a gram positive anaerobic rod which is commonly found in soil. Tetanus follows contamination of a wound by tetanus spores. Most cases of adult tetanus follow an acute and sometimes relatively trivial injury to feet or legs. Most cases of neonatal tetanus occur as a result of contamination of the umbilical cord after birth. The disease is still prevalent in Africa despite the widespread introduction of immunization programs for neonates and pregnant women. Tetanus is estimated to cause almost a quarter of a million deaths worldwide annually, many of whom live in Africa. It is predominantly (90%) a disease of children under five years mainly affecting neonates but also affects adults, and in particular males.

Pathogenesis

The tetanus spores incubate in the wound under anaerobic conditions and mature into vegetative bacteria. They in turn produce potent neurotoxins, tetanolysin and tetanospasmin. Tetanospasmin spreads via nerves by retrograde axonal flow to the spinal cord and brain. In the spinal cord and brain, tetanospasmin binds the presynaptic terminal and produces presynaptic inhibition of gamma amino butyric acid (GABA) release. This denies the anterior horn cells and the alpha motor units of inhibition, resulting in uncontrollable spasms by both agonist and antagonist muscles. In addition a lack of neural control of the adrenal glands results in release of catecholamines, thus producing a hyper sympathetic state and widespread autonomic instability. Recovery only occurs when new terminal synapses are sprouted after 3-4 weeks.

Clinical features

The incubation period for tetanus is between 3-21 days with a median of 7 days. The clinical disease progresses over the course of the first 1-2 weeks and then continues for a total of 3-4 weeks in all. The clinical characteristic of tetanus is increased muscle tone at rest and continuing muscle spasms. On examination, there is rigidity of the muscles involving the face, neck, back and abdomen. The face may show risus sardonicus (lock jaw) and the body may be held arched in the opisthotonos like position (Fig 6.9). Reflex muscle spasms arise spontaneously and are provoked by noise, touch, and light and last from seconds to a minute. Their frequency and duration is variable from every few seconds to hours and they typically continue for most of the duration of the 3-4 week illness. Spasms are painful as full consciousness is retained. Prognosis is worse in those patients with wounds nearer the head and with a short incubation time. The main complications are pneumonia, asphyxia, hypoxia, arrhythmia and rarely fractures. Death usually occurs because of prolonged spasms provoking anoxia, pneumonia or autonomic involvement.

Figure 6.9 Tetanus. Opisthotonos, extensor spasms with arching of the back

Diagnosis

The diagnosis is made clinically as there are no confirmatory laboratory findings. The differential diagnosis includes dystonia, tetany, rabies, meningitis and poisoning (strychnine).

Management

The patient is nursed in a quiet and darkened area or room to avoid stimuli provoking spasms. The acute management involves wound debridement and exploration for foreign bodies, passive immunization with human antitetanus serum, human immunoglobulin 150 IU/kg (3-6000 iu) im, and penicillin with metronidazole to treat the infection. Diazepam is the most commonly used drug to treat muscle spasms. It may be necessary to use 10-20 mg/po or iv, initially 6 hourly increasing the frequency of administration to 4 or 2 hourly as necessary in cases of severe muscle spasms. Chlorpromazine, 50 to 100 mg/im, initially 12 hourly and increasing the frequency of administration to 6 hourly may be used in combination with diazepam. Phenobarbitone is also sometimes used in combination with diazepam. The use of regular iv magnesium sulphate has been shown to improve prognosis by decreasing the need for antispasmodics and antiarrhythmics. The choice of antispasmodic and their order, dose, frequency and duration should be according to the severity of the spasms and local treatment protocols. It is good practice to start with lower doses and over sedation should be avoided.

Beta blockers in the form of atenolol or labetolol or verapamil may be necessary to treat and prevent cardiac arrhythmias or hypertension. If there is failure to control the spasms or there is respiratory depression or pneumonia, then a tracheostomy or/and mechanical ventilation may be necessary. As the required period of intubation is usually prolonged (>7-10 days), early tracheostomy is common practice. Active immunization by tetanus toxoid is necessary when the disease has resolved as tetanus infection does not confer lasting immunity.

Prognosis

The case fatality rate with treated tetanus varies between 40-60%, more commonly the latter. Those who recover rarely have a neurological deficit.

Prevention

Primary prevention is by vaccination in early childhood as part of the routine, diphtheria, tetanus and pertussis (DTP) immunization and by booster at 4-7 years, in adolescence and once again in adulthood. For others who are non immune including pregnancy, these should

receive primary immunization followed by 10 yearly booster doses for a total of 5 doses. If a person has not been vaccinated during the last 5 years and they receive a tetanus prone injury then a booster dose should be given.

Key points

- tetanus arises from wounds contaminated by soil containing spores of *C. tetani*
- management is by passive immunoglobulin, wound debridement & antibiotics
- spasms are controlled by diazepam, chlorpromazine & magnesium sulphate
- complications are pneumonia, asphyxia, hypoxia, arrhythmia & rarely fractures
- tracheostomy and mechanical ventilation may be necessary,
- CFR is frequently >50%

SYPHILIS

Syphilis is caused by the spirochete *Treponema pallidum*. It is a sexually transmitted disease and this route of transmission accounts for most adult cases. However syphilis can be transmitted vertically *in utero* resulting in congenital syphilis or also by blood transfusion. The natural history of syphilis is divided into three stages, primary, secondary and tertiary. Primary syphilis occurs 1-6 weeks after exposure, secondary syphilis 6-8 weeks post primary and tertiary syphilis 1-45 years afterwards. It is infective during all stages and transmission rates vary from 10–60%.

Epidemiology

There are over 12 million new cases of primary syphilis worldwide annually approximately one third of which occur in Africa. The prevalence rates for syphilis serology indicating previous exposure varies from less than one in ten in pregnancy to one in two in some sex workers. Over the last decades, there has been a marked decline in neurosyphilis worldwide. This has been attributed to the widespread use of antibiotics accidentally treating syphilis. The annual incidence of neurosyphilis is low (<0.5/100,000) in high income countries. Data on the incidence of neurosyphilis is not available for Africa. There is some clinical evidence that the incidence may be higher in HIV infected adults in Africa but there is no clear epidemiological data to support that.

Pathogenesis of Neurosyphilis

The treponeme invades the CNS within 3-24 months of untreated primary infection in about 25% of cases. The pathology of neurosyphilis is made up of two main stages: a vascular stage causing endarteritis and thrombosis and a granulomatous stage causing gumma formation.

Neurological findings

Neurosyphilis is divided into two main phases, *asymptomatic* and *symptomatic*. Symptomatic neurosyphilis is divided into four distinct clinical entities. These include **acute syphilitic meningitis** which occurs in about 25% of untreated cases of primary syphilis and **meningovascular syphilis**, **tabes dorsalis** and **generalised paralysis of the insane** which occurs in <10% of untreated primary cases.

Asymptomatic

The asymptomatic phase occurs in the period 1-10 yrs after primary infection. During this phase the infection is active but there are no symptoms and the only finding is an abnormal

CSF showing lymphocytosis, elevation in protein, low glucose and positive serological tests for syphilis.

Symptomatic

Meningitis
This occurs within 2 years of primary infection. The clinical presentation ranges from an isolated aseptic meningitis with fever and rash, to an acute basal meningitis presenting with cranial nerve palsies and hydrocephalus.

Meningovascular syphilis
This occurs 5-10 years after primary infection as a result of an obliterative endarteritis affecting the small or medium sized arteries supplying the internal capsule. It presents mainly as stroke in a younger person.

Tabes Dorsalis (TD)
TD is a late manifestation of tertiary syphilis occurring 15-20 years after primary infection. It arises as result of degeneration in the posterior columns in the spinal cord and in the brain stem. It presents with unexplained lightning and abdominal pains in combination with an ataxic gait disorder. There are characteristic neurological findings including an ataxic stamping gait, positive Romberg's sign, Argyll Robertson pupils and Charcot's joints, late in the disease.

General paralysis insane (GPI)
GPI is a late manifestation occurring 10-25 years after primary infection. This is characterised by a progressive dementia with delusions of grandeur and mania, coupled with varying degrees of paralysis.

Diagnosis of neurosyphilis
The diagnosis of neurosyphilis requires a high index of clinical suspicion combined with CSF findings and serological evidence of syphilis in blood and CSF. Laboratory CSF examination shows increased lymphocytes, increased protein and a normal or reduced glucose level. Diagnosis is by specific treponemal tests; flocculation treponemal antibody (FTA) and Treponema pallidum haemagglutination assay (TPHA) and non-treponemal tests including venereal disease reference laboratory (VDRL) and rapid reagin tests (RPR). Both RPR and VDRL are used as a screening test for syphilis in Africa. VDRL is positive in the blood in nearly all cases of syphilis but false positives occur with endemic treponematoses and in other diseases e.g. tuberculosis and malaria. However VDRL is positive in the CSF in only <80% of cases of neurosyphilis, therefore a negative VDRL in CSF does not exclude the diagnosis. False negatives may occur in primary and late syphilis and also in HIV infection. A more specific antibody test is the TPHA test. A negative TPHA in the CSF excludes neurosyphilis.

HIV and Neurosyphilis
The natural history of neurosyphilis may be altered in HIV disease. There may be an accelerated progression to neurosyphilis, atypical clinical presentation, negative antibody tests and response to penicillin may be less effective. Treatment may require a longer and repeated course of penicillin.

Treatment of neurosyphilis

The treatment of neurosyphilis is with soluble penicillin 20-24 million units (4 million units 4 hourly) daily iv for 14-21 days (>17 days). Persons who are allergic to penicillin should have erythromycin 0.5 gm 6 hourly or doxycycline 200 mg bid for 28 days. Steroids are given with the first few doses of penicillin because of the rare occurrence of the Jarish-Herxheimer reaction. The prognosis depends on the stage. Treatment of asymptomatic and meningitis stages are curative. Treatment of the other tertiary stages results in an improvement in about one third and stabilization in the rest. A follow up CSF examination should be done every 6 months for 2 yrs and every year if HIV positive. If the CSF shows signs of activity (lymphocytes +++) then the patient should be retreated with penicillin. The VDRL may remain positive in CSF and become negative in serum. The principles of prevention and control include public education, screening, partner notification and treatment.

> ## Key points
>
> · syphilis is one of the most common STDs globally with 1/3 of new cases in Africa
> · neurosyphilis occurs in <10% of untreated primary syphilis
> · neurosyphilis is uncommon & is altered in HIV disease
> · confirmation relies on positive serological test in the CSF
> · treatment is with high dose penicillin iv for 14-21 days

BRAIN ABSCESS

A brain abscess is caused by infection, the main causative organism being either bacteria or protozoa. An abscess may be clinically classified as pyogenic and non pyogenic depending on the organism. Toxoplasmosis and tuberculosis are the main non pyogenic causes. The main causative organisms in pyogenic brain abscess are ***Streptococcus viridans, Staphylococcus aureus*** and ***Bacteroides fragilus***. Intracranial pyogenic abscess is a focal infection within the brain, subdural or epidural space. They are uncommon and can affect any age group. The majority arise within the brain from a purulent infection elsewhere in the body so it is important to try to find the primary source. The source of infection is either local or haematogenous. Local spread arises directly from otitis media, mastoiditis, sinusitis, dental abscess or recent head injury in particular skull fracture. Haematogenous spread arises from the heart (e.g. endocarditis), the lungs (e.g. bronchiectasis), or from any other infected source (e.g. skin abscess).

Clinical features

Most patients present with headache, fever and focal neurological disorders (FND). Headache is the most frequent initial symptom. FNDs include seizures, focal motor sensory or speech disorders or confusion or alteration in consciousness. The fever is usually low grade or absent depending on the duration being usually absent in a mature abscess. Seizures occur in about a quarter of patients. Any neurological deficit will depend on the origin, site and extent of the abscess. The time from onset to complications usually takes a couple of weeks but may occasionally occur in days. Signs of the probable source of the brain abscess may be present.

Differential diagnosis

The differential diagnosis includes any other cause of a space occupying lesion resulting in a focal CNS disorder. These include non pyogenic brain abscess e.g. toxoplasmosis or TB, parasitic cyst, intracerebral haemorrhage, subdural haematoma and brain neoplasm.

Diagnosis

The diagnosis if not already suspected clinically is made by a CT scan of the head. A CT with contrast typically shows a ring enhancing mass lesion in the brain with a central area of low density surrounded by oedema with mass effect or a subdural/epidural collection (Fig 6.10). LP is contraindicated in any suspected intracranial mass lesion.

CT scan (with contrast)
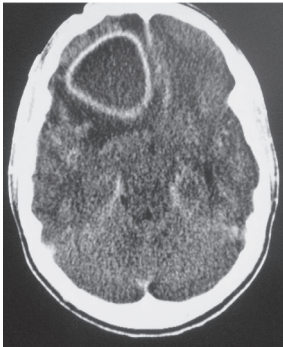
Pathology

Frontal lobe (right)

Frontal lobe (left)

Figure 6.10 Brain abscess

Management

Management is based on antibiotics and surgical drainage. The choice of antibiotics should be based on the likelihood of the primary source of infection. This includes a combined daily dose of penicillin 20-24 million units iv in divided doses 4-6 hourly, chloramphenicol 1 gm iv 6 hourly and metronidazole 500 mg iv 8 hourly. Alternately an extended-spectrum cephalosporin e.g. ceftriaxone 2 gm iv twice daily with metronidazole can also be used depending on availability and cost. Where *Staphylococcus* or gm negatives are suspected flucloxacillin or gentamycin, respectively, should be added. Ciprofloxacin intravenously is also an alternative. Surgical drainage is indicated in large abscesses or collections of pus (>3cm). This is usually done by Burr hole aspiration or by craniotomy.

All antibiotics should be given intravenously and continued for a total of not less than a period of 4-6 weeks. A follow up CT of the head is recommended to assess response to treatment. Anticonvulsants may be necessary if there are seizures. The case fatality rate in the high-income countries varies from 10% in uncomplicated cases to >50% in patients with coma. Morbidity is about 30% and includes epilepsy and focal neurological deficits.

Key points

- pyogenic brain abscesses arise from either direct or haematogenous spread
- local sources are mastoiditis, sinusitis, dental & skin infections
- haematogenous sources are skin, heart & lungs
- clinical features are headache, seizures & focal neurological deficits
- antibiotics are iv for 4-6/52 & surgical drainage is necessary for large abscesses

APPENDIX LUMBAR PUNCTURE

Indications

A lumbar puncture is indicated in the following clinical situations:

1) diagnosis of suspected CNS infections, haemorrhage and encephalopathies

2) to reduce CSF pressure e.g. in cryptococcal meningitis and benign intracranial hypertension

3) administration of intrathecal medications e.g. radio-opaque media

Contraindications

LP is a safe procedure but there is a risk of brain herniation when CSF pressure is high. A fundoscopy to exclude papilloedema should always be carried out prior to an LP. An LP is contraindicated in the following clinical situations.

1) raised intracranial pressure

2) suspected CNS mass lesion

3) bleeding disorder e.g. anticoagulation, low platelets

4) local infection at the LP site

Positioning

An LP should start with an explanation, reassurance and a warning concerning possible complications. The procedure is performed on a bed with a firm or hard edge or alternatively on a table. Proper positioning is critical to successfully completing an LP. The patient lies horizontally facing away from the operator, usually in the left lateral decubitus position with the neck firmly flexed and the knees drawn up to the chin. The back should be in line with the edge of the bed with the shoulders and hips aligned in the same vertical plane and the patient's spine maximally flexed in order to open up the lower lumbar spaces. The head may be supported by a thin pillow (Fig 6.11). If it is necessary to perform an LP with the patient sitting upright this can be done with the patient either sitting astride a chair or on the side of a bed with the spine semi flexed and head supported by a pillow and table. The site of the LP should now be identified. The spinal cord ends at L1 (L2) in adults and a line drawn down from the top of the iliac crest bisects the L3-4 interspace which is safe and avoids the danger of damaging the spinal cord. After palpating and identifying the spines, either the L3-4 or L4-5 interspace should be marked with a pen or a scratch. The LP should now be done under full sterile technique using gloves. The steps in the procedure are outlined below
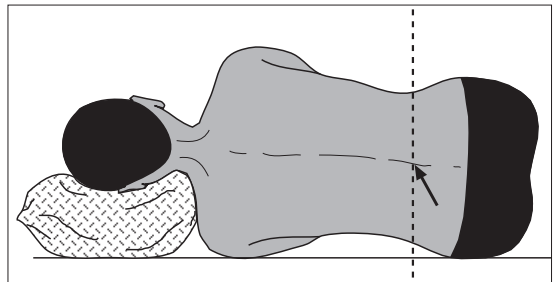

Figure 6.11 Lumbar puncture

Procedure

1) clean the L3-4 area including the iliac crest starting centrally and working outwards

2) infiltrate the skin overlying the L3-4/4-5 interspace with 2% lignocaine and wait a few minutes for it to work

3) insert the spinal 22 gauge needle in the L3-4 interspace horizontally aiming slightly towards the patient's head

4) the spinal needle is advanced slowly but firmly through the interspinous ligaments with the tip aiming for the umbilicus.

5) if the needle cannot be advanced it is likely that bone is encountered. Withdraw the needle partially and start advancing again with the needle parallel with the floor and the tip again pointing toward the umbilicus

6) the needle is advanced a short distance and continually checked until CSF obtained. Care must be taken not to advance the needle too far as it may enter the vertebral vein or disc space

7) if correctly positioned the advancing needle encounters resistance at the ligamentum flavum. After penetrating this ligament there is a sudden release as the needle enters the subarachnoid space

8) then remove the stylet from the needle to see if CSF drains, it usually does this slowly

9) CSF pressure is then measured by attaching a manometer to the needle. Ensure the patient is relaxed by slightly straightening the legs, when the column of CSF stops rising, its height is then measured (opening pressure)

10) CSF is drained from the manometer and from the spinal needle into 3 collection tubes. Approximately 2-3 ml CSF are collected into each tube and sent to the laboratory for cell count, protein, glucose concentrations and bacteriology

11) remove the LP needle and press on the LP site for about 1-2 mins and then apply a small dressing over the site

12) instruct the patient to lie flat for about 2-3 hours preferably prone to reduce the risk of post LP headache

Complications

herniation of brain or spinal cord: this is the most serious consequence of an LP. If during or after an LP the level of consciousness deteriorates or respiration alters or falls, the patient should be placed in the head down position and an infusion of 20% mannitol started. Emergency resuscitation measures should begin including possible surgical decompression.

dry or unsuccessful tap: this usually means that the technique was faulty or the disc space too narrow. In such cases another attempt should be done at either the disc space above or below. If the puncture is still unsuccessful then the LP should be attempted in the sitting position or consult a senior person with neurological or neurosurgical experience

bleeding: the spinal needle is likely to be in a vein so withdraw and try again at a different level

post LP headache: treat symptomatically with NSAIDs. Severe headaches may require a blood patch

infections: these include ABM and epidural abscess and are generally related to poor antisepsis

Interpretation of LP findings

CSF is evaluated under the following main headings *appearance, pressure, microscopy (cells mm³), protein (gms/litre) glucose (mmols/litre)* and *bacteriology* (Table 6.2).

Appearance

The normal CSF is clear and colourless. In meningitis the colour ranges from purulent or cloudy in ABM to mostly clear in viral meningitis. If in doubt the colour of CSF can be compared to water (which is the same as normal CSF) against a background of white sheet of paper when even the slightest opaqueness or yellowness (xanthochromia) in CSF is always abnormal.

Bloody CSF

It is important to distinguish between a traumatic tap and SAH. The following points are helpful. In SAH the CSF remains uniformly blood stained throughout the procedure and the opening pressure is usually elevated. In contrast in traumatic tap the bleeding into the CSF lessens as it flows and pressure is normal. This will have been evident as the CSF leaves the spinal needle and when comparing the 1st and 3rd collection tubes which show a clearing or lessening of blood. Blood in CSF can persist for up to one week but is gradually replaced by bilirubin (xanthochromia) which stays for >2 weeks. A bloody spinal tap will falsely elevate the CSF WCC and protein.

Xanthochromia (yellow discolouration)

This is seen from 24 hours to >2 weeks after a bleed, usually a SAH. It may also be seen in a subdural haematoma, high CSF protein, jaundice and rifampicin treatment.

Pressure

The normal CSF opening pressure in adults is 8-16 cm. The normal CSF pressure should never be over 20 cm water. CSF pressure is elevated in brain swelling in infections (e.g. meningitis), mass lesions, hydrocephalus and trauma. *Suspected elevation in intracranial pressure is the main contraindication to an LP.*

Cell count

The normal CSF contains up to five WBC/ml, either lymphocytes or monocytes. The count may be higher in children. Increased white cells in CSF usually indicate infection until proved otherwise. The presence of predominant neutrophils indicates pyogenic infection, in particular **ABM** and presence of lymphocytes indicates **TBM** or **CM** in HIV or viral infection. However neutrophils can predominate in early **TBM** and in some viral and fungal infections **(CM)** and lymphocytes can predominate in partially treated ABM, particularly in the very young. The presence of a small number of RBCs may be related to the trauma of the LP but if persisting in all 3 samples suggest a CNS source.

Protein

The normal CSF protein is <0.5gm/litre. Elevation in CSF protein is a common abnormality in neurological disorders. Moderate elevations 0.5-1gm/litre suggests infection e.g. meningitis, cerebral malaria, abscess, infarction and tumours whereas a more marked elevations in protein can be a feature of TBM, Guillain Barre Syndrome or spinal block.

Glucose

The normal CSF glucose is >50% blood glucose. *A concurrent blood glucose (ideally fasting) should be checked at the time of the LP.* CSF glucose can be reduced, very low or even absent in CNS infections. Very low or absent glucose is a characteristic of ABM and may also occur in TBM.

Microbiology

Normal CSF is sterile. Gram's stain for bacteria, acid fast stain for TB and India ink stain for cryptococcus are indicated in all suspected cases of meningitis. If India ink is negative then a cryptococcal antigen test (CRAg) should be carried out on all patients in whom the diagnosis of cryptococcal infection is possible. Microbiological screening includes appropriate cultures.

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