

Neurological infections

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ABSTRACT Neurological infections are a significant cause of morbidity and mortality worldwide. Increasing travel to exotic destinations and the rising HIV prevalence are resulting in increasing incidences of previously rare diseases. Timely treatment is key in determining a successful outcome. This depends upon taking a meticulous history that details the timing and presence of risks and exposures, which, with knowledge of incubation periods, enables generation of a differential diagnosis leading to focused investigations. Recent trials have generated good evidence to improve outcome in important infections: for example, artesunate has been shown to be the best drug to use in severe malaria, and the value of adjunctive steroids in pyogenic bacterial and TBM has been clearly demonstrated. However, evidence is lacking on the best treatment for other infections. The rising incidence of syphilis in the UK in the last few years has posed difficult questions regarding antibiotic choices, since good clinical data do not exist; randomised controlled trials are urgently needed. In HIV, the advent of HAART has reduced the incidence of opportunistic infections in those fortunate enough to receive it. However, central nervous system infections continue to account for considerable morbidity and mortality in these patients around the world and in patients presenting with AIDS in the UK.

KEYWORDS Central nervous system, neurological, infections, malaria, meningitis, steroids

LIST OF ABBREVIATIONS Bacterial meningitis (BM), cerebrospinal fluid (CSF), computerised tomography (CT), cryptococcal meningitis (CM), electroencephalogram (EEG), highly active anti-retroviral therapy (HAART), magnetic resonance (MR), magnetic resonance imaging (MRI), polymerase chain reaction (PCR), severe acute respiratory syndrome (SARS), *Treponema pallidum* haemagglutination test (TPHA), tuberculosis (TB), tuberculous meningitis (TBM), venereal disease research laboratory test (VDRL), World Health Organization (WHO), Zeihl–Neelsen (ZN)

DECLARATION OF INTERESTS No conflict of interests declared.

INTRODUCTION

Infectious diseases account for about a quarter of all deaths worldwide. Malaria kills a child in Africa approximately every 12 seconds, HIV and TB continue to devastate much of the world, and in recent years the world has seen the emergence of SARS, Nipah, and H5N1 avian influenza. Increased travel means that disease that emerges in one part of the world can rapidly spread to other countries, as seen with SARS. As more UK citizens holiday in exotic locations infectious diseases previously never, or rarely, seen by UK clinicians are becoming more common; 4,000 patients presented with malaria in the UK during 2004. This review outlines the clinical features and management of some of the more common infectious diseases affecting the nervous system.

MAKING THE DIAGNOSIS

Establishing the correct diagnosis is dependent upon obtaining an accurate history. In neurological infectious

diseases this often requires interviewing a third party such as a relative or friend, as the patient may be unable to give a clear history themselves. All the features of the presenting syndrome must be defined, followed by determination of the particular risks and exposures that the patient may have faced. The travel history must be detailed. Many infectious diseases have a limited geographical distribution; for example, tick-borne encephalitis is common in central Europe and parts of the USA, yet rare in South East Asia where Japanese B encephalitis is common. Malaria is very common in tropical parts of the world, but not in temperate regions, and African *trypanosomiasis* occurs in small well-defined geographical areas within particular countries. As well as a travel history it is crucial to take a detailed history of exposure to potential risks such as sexual activity, animal contact (bites and scratches), fresh or salt water activities (swimming, water skiing, diving, canoeing), hiking or camping in scrubland or forest, and failure to use protective measures such as mosquito nets. Finally, knowledge of the incubation periods (the time between possible exposure and the development of symptoms) of

Published online June 2006

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TABLE 1 Severe malaria according to WHO Guidelines 2006.

WHO criteria for severe malaria 2006	
Clinical findings	Laboratory findings
Prostration	Severe anaemia
Impaired consciousness	Hypoglycaemia
Respiratory distress (acidotic breathing)	Acidosis
Multiple convulsions	Renal impairment
Circulatory collapse	Hyperlactataemia
Pulmonary oedema (radiological)	Hyperparasitaemia
Abnormal bleeding	
Jaundice	
Haemoglobinuria	

individual diseases enables their exclusion and helps to refine the differential diagnosis.

MALARIA

This is the first diagnosis to exclude in any patient returning from an endemic region with a fever, even if the patient claims to have taken all their malaria prophylaxis and slept under a bed net every night. Up-to-date information regarding malaria risk in endemic countries is available through the WHO. There are a number of new rapid malaria detection tests available which are highly sensitive and specific, such that the diagnosis can be made even in hospitals that do not have expertise in examining blood films. However, even in the most experienced centres, diagnosis can be difficult, and at least three blood samples for thick and thin films, taken 24 hours apart, should be examined. Malaria is caused by protozoan parasites of the *Plasmodium* genus, spread by female anopheline mosquitoes. Between 1 and 3 million people die from *Plasmodium falciparum* each year, and it is increasingly seen in UK citizens returning from tropical countries. The incubation period is between seven days and one year. Clinical features include a prodromal period of lassitude, headache, muscle aches, and vague abdominal pain, followed 2–8 hours later with fever. There may be rigors. The clinical syndrome is not specific (malaria is a great imitator) and therefore diagnosis depends upon laboratory investigations. Clinically, malaria is divided according to whether it is 'uncomplicated' or 'severe'. Severe malaria is defined according to WHO criteria (see Table 1).

Severe malaria

Cerebral malaria is defined as coma (Glasgow Coma Score less than 11) due to infection with *falciparum* malaria and forms a part of the spectrum of severe malaria. It is uniformly fatal unless treated. Even when

treated, mortality remains high, at approximately 20%. There is usually a history of a few days of illness prior to developing coma, but onset can be much more sudden in children, with a prodromal illness of only a few hours. Children are much more likely to suffer fits than adults. The most common manifestation is an encephalopathy without localising neurological signs. On fundoscopy a number of abnormalities may be seen, including cotton wool spots, haemorrhages, and papilloedema and these may be associated with a worse prognosis. Deep coma, extensor posturing, seizures (which may be non-convulsive), respiratory distress, hypoglycaemia, hyperlactataemia, and a parasite load > 4% (i.e. more than 4% of all red blood cells have a malaria parasite) are all poor prognostic signs. Laboratory findings in severe malaria can include a normocytic normochromic anaemia, thrombocytopenia, normal or low white cell count, and evidence of disseminated intravascular coagulation. Hypoglycaemia may occur as a direct consequence of infection or an adverse effect of intravenous quinine therapy, and the blood glucose should be checked regularly in any unconscious or deteriorating patient. Hyponatraemia, raised urea and creatinine, and raised blood lactate may be found. Lumbar puncture may reveal an elevated opening pressure in children, but is usually normal in adults. The cerebrospinal fluid is usually normal in cerebral malaria but there may be an elevated protein or mild lymphocytosis. Cerebrospinal fluid lactate may be raised and glucose may be slightly low.

The mainstay of treatment for severe malaria in the UK is intravenous quinine followed by a second drug, usually doxycycline. The most important adverse effect of quinine is hypoglycaemia, but tinnitus, deafness, and nausea (a syndrome called cinchonism by the eighteenth century users of this drug) and, rarely, cardiac arrhythmia can occur. Artesunate is the best drug for the treatment of severe malaria and is now recommended by the WHO. Sadly, despite almost two decades of steadily accumulating evidence, this drug is still not yet manufactured according to internationally accepted Good Manufacturing Practice and is therefore only available in the UK on a named patient basis, despite the dramatic reduction in mortality when used for severe malaria as compared with the standard drug quinine.

Seizures are common in cerebral malaria, particularly in children. Phenobarbital has been shown to reduce fits in cerebral malaria, but trials in Kenya demonstrated an increased mortality in children receiving a single prophylactic injection, perhaps related to respiratory depression. The safety of other anticonvulsants such as phenytoin in the setting of severe malaria has not been determined, but adequate control of seizures is vital.

BACTERIAL MENINGITIS

Bacterial meningitis is an inflammation of the leptomeninges caused by infection of the CSF within

the subarachnoid space around the brain and spinal cord, and the ventricular system. It is a medical emergency and there is now clear evidence that all patients in the developed world should be treated with antibiotics and steroids (in adults, dexamethasone 10 mg four times daily) unless there is a very strong contraindication to the use of steroids.

Early clinical manifestations include non-specific malaise, apprehension or irritability, followed by fever, headache, myalgia, and vomiting. Seizures occur commonly in infants and children, and meningitis must always enter into the differential diagnosis of childhood febrile convulsions. Photophobia and disturbance of consciousness usually develop later. In older children and adults, the symptoms most suggestive of meningitis are irritability, severe headache, and vomiting. In meningococcal infection diarrhoea is a common non-specific symptom. Vasculitic rash is a crucial sign but may not be present early in the illness. It is most commonly reported with meningococcal disease but also occurs in pneumococcal meningitis and has been reported in meningitis due to other *Streptococcus* species, *Haemophilus influenzae*, and *Listeria monocytogenes*. Any patient with headache and a rash should be suspected of having meningitis and be treated immediately with antibacterials. Almost all adults present with at least two of the classic symptoms of bacterial meningitis: headache, fever, neck stiffness, and altered consciousness. Despite improvements in antibiotics the case fatality remains at 15–30% with neurological sequelae in a further 15–30% of patients. Co-infection with HIV can have a dramatic effect on the clinical presentation, the spectrum of bacterial infection, and the patterns of drug resistance (local knowledge is essential in guiding rational therapy).

Treatment of bacterial meningitis: antibiotics

Early diagnosis and treatment of bacterial meningitis are essential. Once suspected, empirical antibacterial treatment should be started immediately.

Treatment of bacterial meningitis should be given as soon as the diagnosis is suspected – it should not be delayed by investigations such as blood culture, lumbar puncture, or CT brain scanning. In other words the decision to treat depends upon the history and physical examination, and treatment should begin prior to performing the appropriate clinical investigations.

Cultures of blood and CSF should be taken as soon as possible (assuming there is no contraindication to the lumbar puncture) but must not delay treatment. There may be clues in the history or on examination as to the likely pathogen, but usually treatment needs to be started empirically with a broad-spectrum antibiotic (intravenous ceftriaxone) which can then be modified later with the results of CSF and blood culture. Empirical ampicillin

should be given to patients in whom listeriosis is suspected – the cephalosporins are ineffective.

Treatment of meningitis: corticosteroids

Corticosteroids are used to reduce the inflammatory response in bacterial meningitis and hence reduce mortality and morbidity. All adults presenting with suspected or proven bacterial meningitis in the UK should be given dexamethasone, 10 mg, six-hourly for four days, starting before the first dose of antibiotics if possible. If the patient has already started on antibiotics then steroids should still be given for four days as above. Steroids should be used with caution in countries where there is a high incidence of both TBM and HIV. In HIV patients, TBM can mimic bacterial meningitis, with a neutrophil-predominant CSF leucocytosis. The mistaken administration of steroids to these patients in the absence of anti-tuberculous therapy may be detrimental.

All children with suspected or proven bacterial meningitis in the UK should receive dexamethasone 0.4 mg/kg/day IV for four days, preferably with the first dose of antibiotics, but if the patient has already started on antibiotics then steroids should still be given for four days. In Africa the evidence for any benefit remains unproven. This discrepancy between the developed and developing world may reflect later presentation, frequency of co-infection with HIV, malnutrition, antimicrobial drug resistance, and sub-optimal antibiotic use.

Recurrent meningitis

Recurrent bacterial meningitis is rare in the developed world, but relatively common in the developing world, where post-traumatic meningitis is more common and the underlying CSF leak often not corrected. In any patient with recurrent meningitis a careful history is needed for previous head trauma, congenital occulta spina bifida, or fracture of the base of the skull. Rarely, recurrent bacterial meningitis is due to a genetic defect in the complement pathway.

BRAIN ABSCESS AND SUBDURAL EMPYEMA

The diagnosis of either a cerebral abscess or subdural empyema should be followed by a detailed search for the primary source of infection. Possibilities include direct spread of bacteria from contiguous anatomical structures such as the middle ear and mastoid cavities or the sinuses, skull injury or local infection, or spread from a more distant source such as the heart (endocarditis), lungs (bronchiectasis, pulmonary arteriovenous malformation), teeth, pelvis, or gastrointestinal tract. Once diagnosed, surgical drainage remains the treatment of choice in most cases, and may provide a definitive microbiological diagnosis. Antibiotic therapy is guided by consideration of the likely source of infection but should include a third-

TABLE 2 A diagnostic rule for distinguishing TBM from pyogenic bacterial meningitis in Vietnamese adults.³

Variable	Score
Age (years)	
≥36	+2
<36	0
Blood WCC (103/ml)	
≥15000	+4
<15000	0
History of illness (days)	
≥6	-5
<6	0
CSF total WCC (103/ml)	
≥900	+3
<900	0
CSF % neutrophils	
≥75	+4
<75	0
Diagnostic Rule:	Total score ≤+4 = TBM Total score >+4 = BM

generation cephalosporin (cefotaxime or ceftriaxone) and metronidazole. For abscess complicating trauma, flucloxacillin or vancomycin should be added. Treatment should continue for a minimum of six weeks.

TUBERCULOUS MENINGITIS

Tuberculous meningitis remains a difficult disease to diagnose and treat. We are still using techniques to establish a diagnosis that were developed over a hundred years ago and antibiotics that were first used 50 years ago. Tuberculous meningitis accounts for approximately 1% of all clinical presentations of TB, is increasing with the spread of HIV, and has a high case fatality (30%). Thirty per cent of survivors are left with neurological sequelae. Tuberculous meningitis usually presents with a longer history than bacterial or viral meningitis, with more than a week, of headache, fever, vomiting, and anorexia, with a stiff neck, focal neurological signs (particularly lower cranial nerves), urinary retention and reduced conscious level. Seizures are rare. Establishing a diagnosis can be helped by following a simple clinical diagnostic algorithm first described in 2002³ (see Table 2). The diagnosis is confirmed by demonstration of acid-fast bacilli by a ZN stain of the CSF. The sensitivity of this test can be improved by thorough examination of a large volume of CSF (up to 10 ml in adults) and if performed correctly is more sensitive than a PCR-based approach. Unfortunately, even then the ZN stain only has a sensitivity (at best) of 60% and culture of the CSF can take up to six weeks to become positive. The CSF is usually lymphocytic (typical range 50–900/μl CSF) with a low glucose (<50% of the blood glucose), moderate lactate (4–6 mmol/l), and high protein. However, the CSF may be neutrophilic, especially early in the illness or in those with HIV infection.

Treatment should start as early as possible with standard anti-TB drugs. All patients with TBM (adults and children) with any grade of disease should also receive dexamethasone (0.4 mg/kg/day slowly reduced over six to eight weeks⁴ with their antibiotics unless there is a clear contraindication. The most common complications of TBM are hydrocephalus, stroke-like events, encephalopathy, and secondary infections. The anti-TB drugs commonly cause severe hepatitis, and also induce liver enzymes which may interfere with other drugs, including the adjunct dexamethasone. The fact that liver enzyme induction may result in lower steroid levels than expected underlines the importance of using a dose of dexamethasone of proven benefit rather than arbitrarily choosing a dose with which physicians are comfortable. Steroid dosages and routes of administration should be based upon published evidence from randomised controlled trials.

SYPHILIS

Syphilis is caused by the bacterium *Treponema pallidum* and is a chronic systemic infectious disease usually acquired sexually, although it can also be transmitted *in utero*. The incidence of syphilis is increasing with the global spread of HIV/AIDS. The incubation period is 2–4 weeks, at which stage a primary sore develops at the site of infection, usually the genitalia, with surrounding lymphadenopathy. This is followed by the secondary bacteraemic phase with an associated symmetrical rash and generalised lymphadenopathy. If untreated, there may be a period of prolonged latency (many years) followed by a destructive late (tertiary) stage with skin, CNS, skeletal, and vascular involvement. During the late stages there is often a uveitis, choroidoretinitis, and optic atrophy.

Neurosyphilis may cause an acute or chronic meningitis, a myeloradiculopathy, space-occupying lesions in the brain or spinal cord, an arteritis leading to strokes, multiple cranial nerve palsies, Argyll–Robertson pupils, personality changes, and dementia. The dorsal roots can be affected, leading to tabes dorsalis. Early recognition and diagnosis is important as it is eminently treatable. Diagnosis is problematic but includes the use of serology and examination of the CSF. The Venereal Disease Research Laboratory test and the TPHA are the most commonly used tests of blood and CSF, but false-negatives in the blood can be seen, especially in late syphilis. The VDRL is used to monitor response to therapy.

In patients with neurosyphilis there is usually a lymphocytic pleocytosis in the CSF and an elevated protein. The sensitivity of CSF–VDRL is approximately 50% although it is highly specific. The TPHA is more sensitive but less specific. A negative CSF–TPHA is considered by some experts to exclude the diagnosis, but must be interpreted with caution in HIV infection where it is less sensitive. Common treatment regimes include

weekly intramuscular benzathine penicillin or daily intramuscular procaine penicillin (for 17 days) but there is a paucity of good data on which to base treatment choices. It is important not to miss potentially treatable disease; expert advice should be sought in patients with normal CSF who have neurological signs and positive blood syphilis serology.

VIRAL MENINGOENCEPHALITIS

There is enormous geographical variation in the viral causes of meningoencephalitis. In the developed world, the most common are herpes simplex (HSV-1), mumps, enteroviruses, herpes zoster, adenoviruses, and Epstein-Barr virus. In the USA, St Louis, West Nile, Eastern and Western Equine Encephalitis, and bunyaviruses, such as California (La Crosse) encephalitis viruses, are also relatively common. In Central and Eastern Europe, the tick-borne encephalitis virus is endemic. Herpes simplex type 2 (HSV-2) causes disease mostly in neonates and immunosuppressed patients. In Asia, Japanese encephalitis is the most common cause of encephalitis, while measles, rabies, and Nipah also occur. Rift Valley fever virus in Africa and the Middle East, and naviruses in Latin America, are other causes in various parts of the world. Post-infectious encephalomyelitis can follow almost any viral infection but has been most commonly associated with measles. People with depressed cell-mediated immunity (e.g. HIV) may develop encephalitis due to herpes zoster or cytomegalovirus. Progressive multifocal leucoencephalopathy is caused by reactivation of a common polyoma virus in patients with AIDS or other causes of immunosuppression.

The history is usually one of a few days' fever, headache, neck stiffness, myalgia and vomiting, altered consciousness, and epileptic seizures. Some viral meningoencephalitides are associated with specific clinical features; classic temporal lobe personality and behavioural changes in HSV-1, skin blisters with enteroviruses, fear of water in rabies, and abnormal movements in Japanese encephalitis; but most present with a non-specific illness. A virological cause is usually only confirmed in 30–50% of clinically suspected viral meningoencephalitis, although PCR has revolutionised the sensitivity and speed of diagnosis. Electroencephalogram is helpful as an early indicator of cortical involvement although the severity of the EEG abnormality is not a good indicator of prognosis. Magnetic resonance imaging can be helpful in demonstrating predominant temporal lobe and insular changes in HSE-1 and basal ganglia lesions in Japanese encephalitis.

Treatment is supportive in most cases. The only specific treatment is aciclovir for herpes simplex/varicella zoster infection (10 mg/kg every eight hours IV for 14 days (or 21 days in patients who are immunocompromised)). It is well tolerated and should be started in all patients with

suspected viral encephalitis; renal failure is unusual. It can be stopped if the diagnostic tests are negative and the clinical suspicion of herpes simplex infection is low. There is no proven benefit for corticosteroids, interferons, or any other adjuvant therapy in viral encephalitis.

HIV INFECTION

HIV infection of the brain and meninges may itself cause an acute meningoencephalitis at the time of seroconversion, and later patients with AIDS are at risk of a sub-acute chronic encephalopathy and dementia. The introduction and widespread use of HAART in the developed world has had a dramatic impact on the spectrum of neurological infectious diseases in individuals who are infected with HIV. Sadly, neurological opportunistic infections continue to be a major cause of mortality and morbidity in patients with HIV in the developing world where access to HAART remains poor. The index of suspicion of neurological infection on the part of the attending doctor must be high, because the immunocompromised nature of the patient often blunts symptoms and signs. For this reason, where facilities allow it, all HIV patients should have cerebral imaging prior to lumbar puncture.

Worldwide the yeast *Cryptococcus neoformans*, causing cryptococcal meningitis, is the most common opportunistic infection in HIV patients. It accounts for approximately 20% of all AIDS deaths globally, making it the second most common cause of death associated with HIV after TB. The treated case fatality rate is of the order of 10–40%. It can also occur in patients who are severely immunocompromised for other reasons, such as long-term steroid use or underlying malignancy, and very rarely affects the immunocompetent. *Cryptococcus neoformans* is distributed worldwide, although certain serotypes (B and C) are mostly found in the tropics. These tropical serotypes predominantly affect the immunocompetent. Cryptococcal meningitis usually causes a sub-acute illness with a 2–4-week history of headache and fever. Neck stiffness may be absent. Sixth nerve palsies are common. The diagnosis is made by an 'India Ink' stain of the CSF, culture, and cryptococcal antigen testing of CSF and blood. A CT scan of the brain is abnormal in approximately 50% of cases. Computerised tomography evidence of hydrocephalus is more common in HIV-negative than in HIV-positive patients. Ten to fifteen per cent of patients will have focal lesions (these may or may not enhance with contrast). Magnetic resonance scanning is probably more sensitive at detecting abnormalities. Current treatment guidelines recommend the use of amphotericin in combination with flucytosine in the initial phase of treatment, followed by fluconazole 400 mg/day for ten weeks. HIV patients then require long-term suppressive treatment with fluconazole, until their CD4 count has risen to greater than 100 cells/microL with HAART. Non-HIV patients may require many months of

treatment, and the decision to stop depends upon any other underlying immunosuppressive disease process as well as their response to anti-fungal therapy. The addition of flucytosine to amphotericin treatment seems to increase the rate of CSF sterilisation; there does not appear to be a mortality benefit. Patients may have very high intracranial pressure leading to severe and often intractable headaches, sixth nerve palsies, and blindness. This may develop weeks into treatment, and the ideal method of management is not yet determined but includes frequent lumbar punctures (daily if needed), insertion of CSF drains, or ventriculo-peritoneal shunting. There are no data to support adjunctive treatment with either mannitol or corticosteroids.

Cerebral toxoplasmosis is another important diagnosis to consider in HIV patients. Patients present with fever and may have headache or features of a space-occupying lesion. Usually the CD4 count is less than 200 cells/microL. Magnetic resonance or CT brain scanning reveals solitary or multiple lesions that show ring enhancement with intravenous contrast. The differential diagnosis includes CNS lymphoma. In the absence of brain biopsy, diagnosis is confirmed through response to appropriate treatment (e.g. combination sulfadiazine and

pyrimethamine) after the exclusion of TBM and CM. Primary CNS lymphoma remains common and must be considered in the assessment of any patient infected with HIV who presents with a neurological syndrome.

KEYPOINTS

- A careful, detailed history remains the cornerstone of establishing a diagnosis in neurological infections.
- Always consider malaria in any patient who has travelled to an endemic country. Three negative malaria blood films, taken 24 hours apart, are considered the minimal standard of care to exclude the diagnosis, and may still miss low levels of parasitaemia.
- Steroids plus appropriate antibiotics should be standard therapy in immunocompetent adults with pyogenic meningitis and immunocompetent adults with TBM.
- The incidence of syphilis is rising in the UK and should be considered in any sexually active adult with unexplained neurological symptoms.
- Cryptococcal meningitis is the second most common cause of death in HIV-positive patients. Raised intracranial pressure is common and requires CSF drainage.

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