TUBERCULOUS MENINGITIS

The rising incidence of HIV has seen a concomitant rise in the incidence of tuberculous meningitis.

P BILL

MB ChB, FCP (SA), FRCP(Lond)

Emeritus Professor and Consultant

Department of Neurology
Inkosi Albert Luthuli Central Hospital and
University of KwaZulu-Natal
Durban

Pierre Bill's interests are neuromuscular disorders, tropical neurology and undergraduate and postgraduate teaching. He is currently President of the College of Neurologists within the Colleges of Medicine of South Africa.

Recently there has been a resurgence of tuberculosis (TB) in developed and developing countries. This is due to the increasing prevalence of HIV, overcrowding in the urban population and in abnormal communities (prisons, refugee colonies, and concentration camps), poor nutritional status, appearance of drug-resistant strains of TB, ineffective TB control programmes, and increase in migration to the developed world from countries where TB is prevalent. Compared with pulmonary TB, which has been the subject of many clinical trials, the pathogenesis, diagnosis and treatment of tuberculous meningitis (TBM) have received little attention. How the disease kills or disables those it infects is poorly understood; the best diagnostic tests are controversial, and the optimum treatment with antituberculosis drugs is not known. The only certainties lie in the fatal consequences of missed diagnoses and management. It has been estimated that about 10% of patients with extrapulmonary TB have CNS involvement. Involvement of the CNS in TB is five times more frequent in HIV-positive than in HIV-negative patients.

EPIDEMIOLOGY

Before HIV, the most important determinant for the development of TBM was age. In populations with a high TB prevalence, the peak age for TBM is 0 - 4 years. In populations with a lower TB prevalence, most TBM cases occur in adults, risk factors being alcoholism, diabetes mellitus, malignancy, and recent corticosteroid use. Co-infection with HIV now dwarfs these risk factors, and increases the lifetime risk of developing clinical TB. HIV also increases the risk of developing extrapulmonary TB and in particular TBM – a risk which increases as the CD4 cell count diminishes.

AETIOLOGY, PATHOGENESIS AND PATHOLOGY

TBM was first described as a pathological entity in 1836, and Robert Koch demonstrated that TB was caused by *Mycobacterium tuberculosis* in 1882. *M. tuberculosis* is an aerobic Gram-positive rod that stains poorly owing to its thick cell wall that contains lipids, peptoglycans, and arabinomannans. The Ziehl-Neelsen stain uses the properties of the cell wall to form a complex that prevents decolourisation by acid or alcohol.

The development of TBM is a two-step process. *M. tuberculosis* bacilli enter the body by droplet inhalation, the initial point of infection being the alveolar macrophage. During the localised infection within the lung (primary complex) there is a short but significant bacteraemia that can seed bacilli to other organs in the body. In about 10% of cases the primary complex does not heal but progresses and tuberculous pneumonia develops, with heavier and more prolonged bacteraemia. Dissemination to the CNS is more likely, particularly if miliary TB develops. In those who develop TBM, bacilli seed to the meninges or brain parenchyma, forming small subpial or subependymal foci, called Rich foci, after the original studies of Rich and McCordick. These foci may remain dormant for many years. The second step in the development of TBM is rupture of the Rich focus into the subarachnoid space. This heralds the onset of TBM.

The release of *M. tuberculosis* bacilli into the subarachnoid space results in a local T lymphocyte-dependent response, characterised macroscopically as caseating granulomatous inflammation. The numbers and types of white cells in the CSF help differentiate TBM from other forms of meningitis, but little is known of their role in disease pathogenesis.

In 75% of children the onset of TBM is less than 12 months after the primary infection.

Three general processes produce the subsequent neurological pathology: adhesion formation, an obliterative vasculitis, and an encephalitis or a myelitis. Adhesions result from the thick, gelatinous basal meningeal exudate that develops after the inoculation of bacilli into the subarachnoid space. The exudate is particularly marked

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around the sylvian fissures, basal cisterns, brainstem and cerebellum, and contains lymphocytes, plasma cells, macrophages and fibrin. Blockage of the basal subarachnoid cisterns, 4th ventricular outlet or aqueduct can result in obstruction of the CSF and hydrocephalus. Adhesions around the interpeduncular fossa and related structures can compromise cranial nerves, particularly 2, 4 and 6, and the internal carotid artery. An obliterative vasculitis may result in infarction and stroke syndromes. These commonly occur in the territory of the internal carotid artery (ICA), proximal middle cerebral artery (MCA) and perforating vessels to the basal ganglia. Infarcts occur in about 30% of cases, causing a range of disorders ranging from hemiparesis to movement disorders. Haemorrhagic transformation of infarcted tissue is not unusual. The basal inflammatory process may extend into the parenchyma, resulting in encephalitis. Brain tissue underlying the exudate shows oedema, which can be marked throughout the hemispheres, perivascular infiltration, and a microglial reaction (known as border zone reaction).

The pathogenesis of TBM at a cellular level is poorly understood. During the first 2 - 4 weeks of infection there is no immune response to the organism. Thereafter CD4 T cells specific for mycobacterial peptides appear, enabling more efficient intracellular killing of tubercle bacilli. Activated macrophages produce interleukin 1-β and tumour necrosis factor, which promote granuloma formation. Tubercles consist of mononuclear cells surrounding a necrotic (caseous) centre. The complex cellular immune response in TB determines whether the host develops active disease. Progression and expansion of the caseous lesion may result in different types of CNS involvement. Tubercles that rupture into the subarachnoid space cause meningitis. Those deeper in the parenchyma of the brain or spinal cord cause tuberculoma or abscess.

Most CNS TB is caused by *M. tuberculosis*. Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment. They usually cause infection in persons with immunosuppression, especially patients with AIDS and very low CD4 counts (< 10 cells/μl). Atypical bacteria infrequently produce meningitis or meningoencephalitis. *Mycobacterium avium* is the most common aetiological agent of this group. *Mycobacterium fortuitum* meningitis is a complication of CNS surgery and trauma and is usually associated with abscess and foreign bodies. Less frequently NTM infections are manifested as intracranial mass lesions, or rhombencephalitis. Diagnosis is made by culture of tissue, sputum, blood or CSF. Because NTM are ubiquitous bacteria, their isolation from a sample may represent contamination. However, isolation from a sterile fluid such as CSF usually represents infection of the nervous system.

CLINICAL FEATURES

TBM is usually preceded by a prodromal period of 2 - 4 weeks of nonspecific symptoms such as fever, malaise, myalgia, and headache. Fifty per cent of patients have chest radiographic abnormalities, a history of contact with a TB patient, and a positive tuberculin skin test. In children prodromal symptoms include irritability, poor feeding, drowsiness, and abdominal pain. Eventually headache worsens and becomes continuous. Neck stiffness is reported by about 25% of patients, but meningismus is detected in a higher number. Bulging fontanelles develop in infants. Nausea, vomiting and altered sensorium may develop. A continuous low-grade fever is present in about 80% of patients.

Cranial nerve abnormalities occur in one-quarter of patients, most commonly a 6th nerve palsy. Choroidal tubercles are present in less than 10% of patients, but are diagnostic of TB. Visual loss may develop owing to optochiasmatic arachnoiditis, 3rd ventricular compression of optic chiasm from hydrocephalus, optic nerve granuloma, and ethambutol toxicity. Funduscopic examination may reveal papilloedema. Hemiplegia may occur at the onset of the disease or at a later stage. Quadriplegia secondary to bilateral infarction or severe cerebral oedema is less common. Occasionally abnormal movements may be present, including chorea hemiballismus, athetosis, generalised tremors, myoclonic jerks and ataxia. Seizures, either focal or generalised, may occur during the illness. As the disease progresses, increasing evidence of cerebral dysfunction sets in, with apathy and irritability progressing to increasing lethargy, confusion, stupor and coma. Spinal meningitis may result in root pain, spastic or flaccid paralysis and loss of sphincter control.

Although HIV-infected patients with TB are at increased risk of developing TBM, the clinical features and outcome do not seem to be altered. These patients commonly have extrameningeal TB on admission. In elderly patients with TBM, the presentation may be atypical. Signs of meningism may be absent, seizures occur more commonly, and CSF findings may be atypical, and the CSF may even be acellular.

A rare complication of TBM is tuberculous encephalopathy, usually occurring in a young child with progressive primary TB. The presentation is of reducing consciousness level with few focal signs and minimal meningism. Diffuse oedema with white matter demyelination is found pathologically. The pathogenesis is presumed to be immune mediated.

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TBM can also cause metabolic complications of which the commonest, hyponatraemia, affects more than 50% of patients with the disease. This 'cerebral salt wasting syndrome' is associated with low plasma volumes and persistent natriuresis despite normal concentrations of antidiuretic hormone (ADH). There is a stronger correlation between concentrations of atrial natriuretic peptide and sodium. Treatment with sodium and fluid replacement is probably indicated, but fludrocortisone and democycline may be useful. Hyponatraemia may also be due to inappropriate secretion of ADH.

The frequency of symptoms and signs in TBM is shown in Table I.

The severity of TBM at presentation is classified into 3 grades according to the patient's Glasgow Coma Scale (GCS) and the presence or absence of focal signs – variables that are strongly predictive of death:
Grade 1. Alert and orientated without focal neurological deficit.
Grade 2. GCS10 - 14 with or without focal neurological deficit or GCS 15 with focal neurological deficit.
Grade 3. GCS less than 10 with or without focal neurological deficit.

Relatively common causes of a chronic meningitis are listed below:

- **Infectious**
  - *M. tuberculosis*
  - Neurocyticercosis
  - *Cryptococcus neoformans*
  - *Treponema pallidum*
  - Herpes simplex viruses
  - *Borrelia burgdorferi*
  - *Brucella* species
  - *Coccidioides immitis*
  - *Histoplasma capsulatum*
  - Partially treated bacterial meningitis.
- **Non-infectious**
  - Neoplasms
  - Neurosarcoidosis
  - Vasculitis
  - Systemic lupus erythematosus
  - Behçet's disease.

DIAGNOSIS

All series of TBM stress the importance of a high level of diagnostic suspicion, as delay in treatment either results in death or substantial neurological morbidity. TBM cannot be diagnosed on history and clinical assessment alone. Useful features are a history of recent exposure to TB (particularly in children), and signs of active extrameningeal TB. A chest X-ray showing active TB is present in about 59% of patients with TBM, but lacks specificity where there is a high prevalence of pulmonary TB. Miliary TB strongly suggests multi-organ involvement. Skin testing with purified protein derivative (PPD) of *M. tuberculosis* is of limited value, except in children.

The CSF is clear or opalescent, and the opening pressure at initial lumbar puncture is elevated in about 50% of patients. A 'cobweb'-like appearance on the surface of the CSF, when allowed to stand at room temperature or in the refrigerator, is a characteristic feature but not pathognomonic of TBM. Typically there is a predominantly lymphocytic pleocytosis (60 - 1 000 cells/ml), with a high protein (0.8 - 4 g/l) and low glucose (< 50%) concentration. However, total CSF white cell count can be normal in those with depressed cell-mediated immunity, such as the elderly and people with HIV infection. Low counts have been associated with a poor outcome.

Table I. **Frequency of symptoms and signs in TBM**

Symptoms (%)	Signs (%)
Headache (50 - 80)	Neck stiffness (40 - 80)
Fever (60 - 95)	Confusion (10 - 30)
Vomiting (30 - 60)	Coma (30 - 60)
Photophobia (5 - 10)	Any cranial nerve palsy (30 - 50)
Anorexia (60 - 80)	CN3 (5 - 15)
	CN4 (30 - 40)
	CN7 (10 - 20)
	Hemiparesis (10 - 20)

Neutrophils can dominate, especially early in the disease, and have been associated with an increased likelihood of a bacteriological diagnosis and improved survival. In a small proportion of patients, neutrophils persist. When therapy is initiated, the CSF pleocytosis may change transiently from lymphocyte to neutrophil predominance, a phenomenon known as 'therapeutic paradox'. CSF examination in meningitis caused by NTM shows a mild lymphocytic pleocytosis, with nearly normal concentrations of glucose and protein.

Definitive diagnosis is based on the detection of bacilli in the CSF, either on the smear or by culture. Rates of positivity for clinically diagnosed cases range from 25% to 75%. Acid-fast bacilli may be seen on Ziehl-Neelsen stain or cultured from the CSF in up to 81% of patients. The likelihood of seeing or culturing *M. tuberculosis* from the CSF is dependent upon meticulous microscopy and culture of a large volume of CSF (> 5 ml). The limit of detection of acid-fast bacilli on CSF is 100 mycobacteria/ml. The success of the test depends on the quality and volume of the sample and the skill of the technician, and his/her persistence in examining for acid-fast bacilli. Culture of *M. tuberculosis* bacilli is the gold standard for diagnosis, but is insensitive and slow, and the decision to treat the patient should not wait for culture results.

CSF polymerase chain reaction (PCR) for *M. tuberculosis* has a sensitivity of 56% and a specificity of 98%, and should therefore not be used to exclude TBM. Molecular methods may be more useful when antituberculosis drugs have been started.

An elevated CSF adenosine deaminase level supports the diagnosis in the appropriate clinical setting.

CT and MRI changes that may be seen include basal enhancement, hydrocephalus (especially in children), tuberculoma and infarction (25 - 40% of patients). MRI may provide more information regarding cerebral miliary TB, with multiple small intraparenchymal granulomas. The

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carotid or MR angiogram may show changes in the vessels of the circle of Willis, such as segmental narrowing, irregular beaded appearance or complete occlusion (Figs. 1 and 2). Cryptococcal meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal metastases, and lymphoma may all produce similar radiological changes.

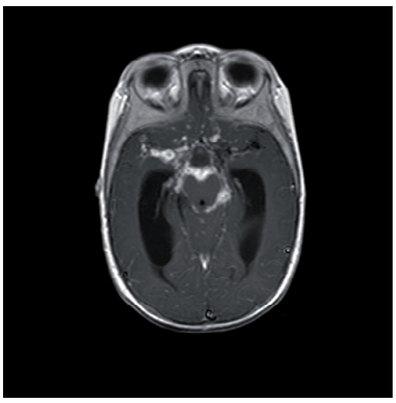

Fig. 1. Tuberculous meningitis. T1-contrasted MRI scan showing intense basal enhancement with ring-enhancing granulomas in the prepontine, and suprasellar cisterns, and along the middle cerebral artery. Hydrocephalus is present.

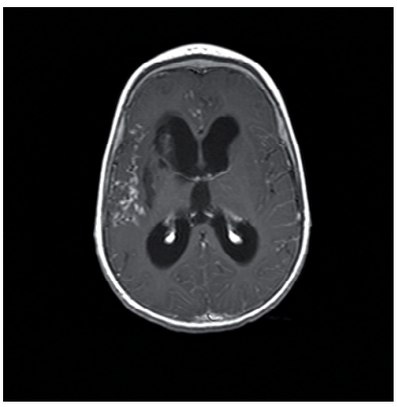

Fig. 2 . Tuberculous meningitis. T1-contrasted MRI image. Intense enhancement is seen in the right sylvian fissure with underlying right basal ganglion infarct. Hydrocephalus is present.

TREATMENT

Compared with pulmonary TB, where the optimum treatment has been developed from the results of many controlled trials, the choice of drugs, doses, and duration of treatment for TBM are unknown. There are however common principles of treatment.

Isoniazid (INH) kills most of the rapidly replicating bacilli in the first 2 weeks of treatment, with some additional help from streptomycin and ethambutol. Thereafter rifampicin and pyrazinamide become important. Rifampicin kills low or non-replicating organisms and pyrazinamide kills those in sites hostile to the penetration and action of other drugs. Empirical therapy should be instituted as early as possible to reduce morbidity and mortality. The aim of treatment is to kill both intracellular and extracellular organisms and requires the use of several drugs to avoid the development of resistance. Treatment is hindered by the difficulty of access of antituberculosis agents to the CNS compartment, drug permeability, and the complex lipids that protect the organism from the common antituberculosis drugs.

First-line drugs include INH, rifampicin, ethambutol, pyrazinamide, and streptomycin. INH diffuses readily into the CSF in the presence or absence of meningeal inflammation, with CSF concentrations of approximately 20 - 90% of serum levels. CSF levels of rifampicin are approximately 20 - 50% of serum levels in the presence of meningeal inflammation. Little or no ethambutol is detected in the CSF of patients with normal meninges. In patients with meningeal inflammation, the ethambutol level approaches 10 - 50% of serum levels. Similarly, streptomycin is not detectable in normal meninges, while in patients with meningitis CSF levels are up to 29% of serum levels. Pyrazinamide penetrates well into the CSF, both in patients with meningeal inflammation and in those with normal meninges.

Second-line drugs, which have less efficacy or greater toxicity, include para-aminosalicylic acid, ethionamide or prothionamide, cycloserine, aminoglycosides (amikacin and kanamycin) and quinolones (ofloxacin and ciprofloxacin). The first 4 penetrate well into the CSF, both in the presence or absence of meningeal inflammation. Aminoglycosides penetrate poorly into the CSF, and there is little information on the CSF penetration of quinolones. The efficacy, dosage, mode of action and major side-effects of the first-and second-line drugs are detailed further in Tables II and III.

A widely accepted regimen includes the use of 4 drugs on a daily basis in the first 2-month phase of treatment (INH, rifampicin, and pyrazinamide, and a 4th drug, either streptomycin or ethambutol). This is followed by a prolonged continuation phase with INH and rifampicin for up to 12 months or longer. Therapy should be continued for 6 months after the patient becomes asymptomatic or after the CSF culture becomes negative. In areas where resistance to INH is less than 4% and the patient does not come from an area of high prevalence of multiresistance and has not had contact with a case of multiresistance, ethambutol is not

Table II. **First-line drugs**

Drug	Dosage (mg/kg/day)			Efficacy	Major side-effects
	Children	Adult	Maximum		
INH	5 - 15	5	300	Bactericidal Both intra- and extracellular	Hepatotoxicity, peripheral neuropathy
Rifampicin	10 - 20	10	450 (< 50 kg) 600 (> 50 kg)	Bactericidal Both intra- and extracellular	Hepatotoxicity, GI, fever, cutaneous rashes
Pyrazinamide	15 - 30	1.5 g (< 50 kg) 2.0 g (> 50 kg)		Bactericidal Both intra- and extracellular	Hepatotoxicity, nausea, arthralgia
Ethambutol	15 - 20	15 - 25	1.6 g	Bacteriostatic	Optic neuritis, arthralgia
Streptomycin	15	15	1.0 g	Bacteriostatic Extracellular only	Ototoxicity, renal, vertigo, vestibular disturbances

INH, rifampicin and pyrazinamide penetrate into CSF. Ethambutol and streptomycin penetrate when the meninges are inflamed.

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Table III. **Second-line drugs**

Drug	Dosage (mg/kg/day)			Efficacy	Major side-effects
	Children	Adult	Maximum		
Ethionamide	10 - 20	15 - 20	1 g/day	Bactericidal	Hepatotoxicity, GI
Cycloserine		10 - 20	750 mg/day	Bacteriostatic	Neurotoxic (fits, depression)
Fluoroquinolones					
Ofloxacin			800 mg/day	Bacteriostatic	CNS effects, GI
Ciprofloxacin			750 mg bd	Bacteriostatic	
Aminoglycosides					
Amikacin	15	15	1.5 g/day	Bacteriostatic	Ototoxicity, vertigo
Kanamycin		15		Bacteriostatic	Renal toxicity

necessary. In children the substitution of streptomycin for ethambutol should be considered because of the difficulty in monitoring visual acuity in the paediatric group. In South Africa ethionamide is often used as the 4th drug instead of ethambutol because of poor penetration of ethambutol into the CSF. When drug resistance is unlikely, a regimen of 3 drugs (INH, rifampicin and pyrazinamide) daily for 2 months, and 2 drugs (INH and rifampicin) for an additional 4 months, may be adequate in adults. Therapy should be prolonged to 9 months or longer where there is a delayed response. For children with TBM, a 12-month regimen is recommended with daily INH, rifampicin, pyrazinamide and streptomycin for 2 months, followed by INH and rifampicin daily or twice weekly for 10 months. Pyridoxine should be given with INH.

Adjunctive corticosteroids

The use of adjunctive corticosteroids has been controversial since they were first suggested more than 50 years ago. A meta-analysis concluded that corticosteroids probably improved survival in children. There was no evidence of beneficial effects in adults or in those co-infected with HIV. A later trial in adults showed that dexamethasone was associated with reduced risk of death but did not prevent severe disability in survivors. The beneficial effect of dexamethasone was seen across all grades of severity.

Neurosurgical intervention

Hydrocephalus is a common complication of TBM, and can be treated with drugs that have a diuretic effect, serial lumbar punctures, or ventriculoperitoneal or atrial shunting. There are no data from controlled trials to indicate which is best.

M. tuberculosis resistant to antituberculosis drugs

TBM caused by resistance to one or more first-line antituberculosis drugs is an increasingly common clinical problem. The frequency of resistance varies with geographical region. In a study conducted in 35 countries, primary resistance to 1 of the 4 first-line drugs was found in 9.8% of the *M. tuberculosis* strains, most frequently to INH (7.3%) and streptomycin (6.5%), followed by rifampicin (1.8%) and ethambutol (1%). The overall prevalence was 12.6% to any of the 4 first-line drugs. In the case of primary resistance to INH, the British Thoracic Society recommend rifampicin, pyrazinamide, ethambutol and streptomycin for 2 months, followed by rifampicin and ethambutol for 7 months. In the case of secondary resistance, INH should be stopped and ethambutol and rifampicin should be administered for 12 months, together with pyrazinamide for 2 months.

Multidrug-resistant (MDR) TB is defined as resistance to at least INH and rifampicin, with or without resistance to other antituberculosis drugs. TBM caused by MDR *M. tuberculosis* has a fatality rate of 85%. Patients with MDR TBM treated with first-line drugs are likely to be dead before the results of conventional susceptibility tests (which take 6 - 8 weeks) are available, and thus timely confirmation of the diagnosis is problematic. A history of previously treated TB or recent exposure to a known case of MDR pulmonary disease may identify those at high risk. MDR is of special relevance in HIV-infected populations, because of an impaired immune response against the bacilli.

In South Africa the mean prevalence of MDR pulmonary TB is 1.6% among treatment-naïve patients, and 6.7% among patients previously treated for TB. In a study of 30 patients with MDR TB organisms, 17 died, and the rest were left with significant functional impairment. Seventy-six per cent of the patients who died were HIV positive.

Current evidence suggests MDR TBM needs treatment with second-line antituberculosis drugs, although there are insufficient data regarding the effectiveness of second-line drugs against intracellular organisms. The WHO recommends fluoroquinolones for the treatment of MDR TBM, but their published use in TBM is restricted to case reports. Data on CSF penetration and pharmacokinetics are scant. Ethionamide, prothionamide, and cycloserine are all reported to cross the blood-brain barrier well and may be effective. Aminoglycosides penetrate less well and may have to be given by intrathecal injection. Occasionally up to 5 – 7 drugs may be needed.

Until more data are available, the treatment of MDR TBM should follow the same guidelines as those used in the treatment of MDR pulmonary TB:

- Never add a single drug to a failing regimen.
- Use at least 3 previously unused drugs, 1 of which should be a fluoroquinolone.
- Streptomycin resistance does not confer resistance to other aminoglycosides, therefore amikacin or kanamycin can be used.
- Treat for at least 18 months.

The optimal regimens for the treatment of CNS TB due to atypical mycobacteria in persons with HIV infection have not been finally established, although a 4-drug regimen is needed to treat *M. avium intracellulare* infection. Current recommendations include azithromycin (500 –1 000 mg/day), and clarithromycin (500 –1 000 mg/

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day), in combination with ethambutol (15 mg/kg/day) or clofazimine (100 mg/day). Alternative regimens include the use of ciprofloxacin and rifampicin. Overall, the prognosis for meningitis caused by NTM is poor, with a mortality rate close to 70%.

PREVENTION

BCG vaccination provides the best prophylaxis against severe forms of TB, mainly meningitic and miliary. A meta-analysis of published trials on the efficacy of BCG vaccination suggests a protective effect of 64% against TBM.

HIV INFECTION AND CNS TB

HIV does not alter the clinical presentation of TBM, but may affect the number and nature of complications. Basal meningeal enhancement and hydrocephalus may be less common, and there could be more bacilli in the meninges. Active extrameningeal TB is also more common, and case fatality from TBM is higher. The prognosis of TB is poorer because of the immunosuppression resulting from the HIV infection. There is evidence that the immune response to *M. tuberculosis* enhances HIV replication, resulting in acceleration of the HIV disease. In treating HIV-infected patients, several facts should be considered. First, controlling the infection will be difficult because of the associated immune deficiency. Second, rifampicins interact with protease inhibitors, resulting in decreased activity of protease inhibitors because of induction of cytochrome P450 by rifampicin. Rifabutin has substantially less activity as an inducer of cytochrome enzymes, and may be prescribed for these patients. Conversely, if protease inhibitors, particularly ritonavir or saquinavir, which are potent cytochrome P450 inhibitors, are administered with rifabutin, blood concentrations of the latter increase markedly, as does the toxic effect. Rifabutin is efficacious in non-resistant TB and also against *M. avium*. Thirdly, HIV-infected patients can have malabsorption of antituberculosis drugs and are prone to adverse drug reactions. This makes drug monitoring particularly important. Paradoxical reactions might occur during the course of TB treatment when antiretroviral therapy restores immune function. HIV-infected patients have an increased prevalence of infections caused by NTM. Aside from classic regimens of long duration, various regimens have been proposed for HIV-infected patients:

- INH, rifabutin and pyrazinamide for 2 months, and INH and rifabutin for an additional 4 months
- INH, streptomycin, and pyrazinamide daily for 2 months, and then 2 or 3 times weekly for 7 months
- INH, rifampicin, and either ethambutol or pyrazinamide with a 4th drug, either streptomycin or clofazimine, for a period of at least 6 - 9 months.

CONCLUSION

The diagnosis and management of TBM remain a major challenge for the clinician. The current HIV epidemic contributes to the increasing TB disease burden and to consequent morbidity and mortality. CNS TB accounts for 5% of extrapulmonary TB, and meningitis is the most frequent complication.

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IN A NUTSHELL

The incidence of TB is increasing, partly because of the increasing incidence of HIV.

Compared with pulmonary TB, which has been the subject of many clinical trials, the pathogenesis, diagnosis and treatment of TBM have received little attention.

It has been estimated that about 10% of patients with extrapulmonary TB have CNS involvement.

The development of TBM is a two-step process – the bacteria first enter the lungs and then the brain. Most CNS TB is due to *M. tuberculosis*.

TBM is usually preceded by a prodromal period of 2 - 4 weeks of nonspecific symptoms such as fever, malaise, myalgia, and headache.

Neck stiffness is reported by about 25% of patients, but meningismus is detected in a higher number.

TBM can also cause metabolic complications; the commonest, hyponatraemia, affects more than 50% of patients with the disease.

TBM cannot be diagnosed on history and clinical assessment alone. Useful features are a history of recent exposure to TB (particularly in children), and signs of active extrameningeal TB.

Isoniazid kills most of the rapidly replicating bacilli in the first 2 weeks of treatment, with some additional help from streptomycin and ethambutol. Thereafter rifampicin and pyrazinamide become important. Empirical therapy should be instituted as early as possible to reduce morbidity and mortality. The aim of treatment is to kill both intracellular and extracellular organisms and requires the use of several drugs to avoid the development of resistance.

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