

NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

# Tuberculous meningitis

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Uncertainty and doubt dominate all aspects of tuberculous meningitis (TBM). The variable natural history and accompanying clinical features of TBM hinders the diagnosis. Ziehl-Neelsen staining lacks sensitivity and culture results are often insufficiently timely to aid clinical judgement. New rapid diagnostic methods are incompletely evaluated, and many are not suitable for laboratories in low income countries. The duration of chemotherapy for TBM is unclear and the benefits of adjuvant corticosteroids remain in doubt. The only uncomfortable certainties lie in the fatal consequences of missed diagnoses and delayed treatment.

This review will discuss the current uncertainties surrounding TBM. More attention will be given to diagnosis and management, as these areas have a direct bearing on patient outcome.

## Epidemiology

About 2000 million people in the world today are infected with tuberculosis,<sup>1</sup> but only 10% develop clinical disease. Why some people develop clinical disease remains unclear. The reasons are likely to be multifactorial: inherent not just to the individual person, but to their given population and environment.

Before HIV the most important determinant for the development of TBM was age. In populations with high TB prevalence TBM differs from pulmonary, and other extrapulmonary tuberculosis, in that the peak age is from 0–4 years.<sup>2</sup> In populations with lower TB prevalence, most cases of TBM are in adults. Risk factors identified for these people are alcoholism, diabetes mellitus, malignancy, and recent corticosteroid use.<sup>3–5</sup> Coinfection with HIV now dwarfs these risk factors. HIV increases the lifetime risk of developing clinical TB postinfection to 1 in 3.<sup>6</sup> HIV also predisposes to the development of extrapulmonary TB, and in particular TBM,<sup>7</sup> a risk which increases as the CD4 count declines.<sup>8</sup> The disease constitutes either reactivation of latent infection, or new infection. Evidence from DNA fingerprinting of strains using restriction fragment length polymorphism suggests that in the United States up to 40% of new disease in both HIV positive and non-HIV patients is due to recent infection.<sup>9 10</sup>

The extent to which a person's genetic constitution effects resistance or susceptibility to

infection is under debate.<sup>11</sup> Certain ethnic groups seem to be more susceptible to *M tuberculosis* than others. Studies using tuberculin conversion as a surrogate marker suggest that black skinned people are more susceptible to infection than white people.<sup>12</sup> Recently it has been proposed that certain polymorphisms in the human NRAMP1 gene may affect susceptibility to pulmonary tuberculosis in West Africans.<sup>13</sup> Whether genetic factors influence prevalence of TBM within a population is unknown.

The extent to which BCG vaccination affords protection against TBM is still debated. A meta-analysis of the published trials on the efficacy of BCG vaccination suggested a protective effect of 64% against TBM.<sup>14</sup> This figure is higher than that suggested for pulmonary TB (50%), but may only reflect more accurate case ascertainment of TBM given the universal requirement for admission to hospital. Overall, these and other studies support the view that BCG vaccination is protective against TBM.

Close correlation exists between the observed incidence of TBM in children aged 0–4 years, and the population's annual average risk of infection with *M tuberculosis*. The incidence of TBM has been calculated to represent 1% of the annual risk of infection.<sup>15</sup> Risk of infection depends on the prevalence of infectious cases in a given community. Prevalence of infectious cases is dependant not only on the risks pertinent to each person for developing disease, but to the factors inherent in the community encouraging spread of infection. The main reason for the spread of tuberculosis is poverty, with resulting homelessness, malnutrition, and breakdown of public health infrastructure.

The total number of tuberculosis cases in the world is increasing.<sup>16 17</sup> It is estimated that most of these new cases will be in south east Asia<sup>16</sup> fuelled by the rapid spread of HIV. It has been predicted that without intervention 200 million people alive today will develop TB.<sup>1</sup> The physician needs to be aware of these changes, as less common forms of tuberculosis such as TBM will be encountered more often.

## Causative agent

Tuberculous meningitis was first described as a distinct pathological entity in 1836,<sup>18</sup> and Robert Koch demonstrated that tuberculosis was caused by *Mycobacterium tuberculosis* in 1882.<sup>19</sup>

*M tuberculosis* is an aerobic gram positive rod that stains poorly due to its thick cell wall containing lipids, peptidoglycans, and arabinomannans. The Ziehl-Neelsen stain uses the properties of the cell wall to form a complex that prevents decolourisation by acid or alcohol.<sup>20</sup>

The characteristics of *M tuberculosis* enabling it to cause disease are complex and incompletely understood. It is accepted that those with active pulmonary infection vary considerably in their ability to transmit the disease to others.<sup>21</sup> Part of the variability is explained by differences in environment, infectious burden, and host immunity. Experimental evidence suggests that the virulence of individual strains is also significant, and selected gene mutations have been shown to affect virulence.<sup>22-23</sup> Whether there are strains which cause more disease of the CNS is not known. The predominance of one strain typed using restriction fragment length polymorphism has been reported from a series of patients with *M tuberculosis*,<sup>24</sup> however the mechanisms by which neurovirulence may occur is unknown.

As the contribution of strain variation and virulence becomes more apparent, so techniques are developing to determine the genetic components of mycobacterial virulence. "Molecular" Koch's postulates have been applied to advance a hypothesis for a single gene basis for a virulent phenotype. The phenotype is analogous to the disease, the gene analogous to the organism.<sup>25</sup> Only a few virulence genes have currently satisfied these methods.<sup>26</sup> The recent determination of the complete genomic sequence for *M tuberculosis* should expand our understanding in this area.<sup>27</sup>

### Pathogenesis

A discussion on the pathogenesis of tuberculous meningitis can be directed on two levels. On a macroscopic level there are the mechanisms by which the tuberculous bacilli disseminate to the CNS. This is discussed alongside the role of granulomatous inflammation, the currency of tuberculous pathology, in causing gross pathological changes within the CNS. On a microscopic level there are the cellular and immune mechanisms that can result in both the disease and its control.

The development of TBM is a two step process<sup>28</sup>; *M tuberculosis* bacilli enter the host by droplet inhalation, the initial point of infection being the alveolar macrophage. Escalating localised infection within the lung with dissemination to the regional lymph nodes produces the primary complex. During this stage there is a short but significant bacteraemia that can seed tubercle bacilli to other organs in the body. In those who develop TBM, bacilli seed to the meninges or brain parenchyma, forming small subpial or subependymal foci. These are called Rich foci, after the original pathological studies of Rich and McCordick.<sup>28</sup> In about 10% of cases, particularly in children, the primary complex does not heal but progresses. Tuberculous pneumonia develops with heavier and more prolonged

tuberculous bacteraemia. Dissemination to the CNS is more likely, particularly if miliary TB develops.

The second step in the development of TBM is rupture of a Rich focus into the subarachnoid space. This heralds the onset of meningitis, which if left untreated, will result in severe and irreversible neurological pathology. In 75% of children the onset of TBM is less than 12 months after the primary infection.<sup>29</sup>

Three general processes produce the subsequent neurological pathology: adhesion formation, an obliterative vasculitis, and an encephalitis or myelitis.<sup>30</sup> Adhesions result from a dense basal meningeal exudate that develops after inoculation of bacilli into the subarachnoid space. The exudate contains lymphocytes, plasma cells, and macrophages, with increasing quantities of fibrin. Blockage, through adhesion formation, of the basal subarachnoid cisterns can result in obstruction of the CSF and hydrocephalus. Adhesions around the interperpendicular fossa and related structures can compromise cranial nerves, particularly II, IV, and VI, and the internal carotid artery. An obliterative vasculitis of both large and small vessels develops that can result in infarction and stroke syndromes. These commonly occur in the territories of the internal carotid, proximal middle cerebral, and the perforating vessels to the basal ganglia.<sup>31</sup> Infarction through vasculitis is the mechanism by which many of the diverse clinical neurological abnormalities in TBM occur, and accounts for an appreciable part of the irreversible neurological sequelae. The intensity of the basal inflammatory process extends into the parenchyma resulting in encephalitis. Oedema occurring as a consequence can be marked throughout both hemispheres. This will contribute to rising intracranial pressure and the global clinical neurological deficit.

A rare complication of TBM is tuberculous encephalopathy.<sup>32</sup> Usually occurring in a young child with progressive primary TB, the presentation is of reducing conscious level with few focal signs and minimal meningism. Diffuse oedema and white matter pallor with demyelination are found pathologically. The pathogenesis is uncertain, but is presumed to be immune mediated. Diagnosis is important as anecdotal reports suggest a good response to corticosteroids.<sup>33</sup>

The pathogenesis of TBM at a cellular level is poorly understood. Knowledge regarding the pathogenesis of pulmonary infection is limited, but certain key principles may serve to illuminate some of the processes evident in the CNS. The formation of caseating granulomatous inflammation is fundamental.

Current theories of immunopathogenesis seek to explain the roles and interactions between the macrophage, the helper T cell, and the organism. Cell mediated immunity is central to both the control of infection and the production of tissue damage.<sup>34</sup> Lurie's experiments on tuberculosis in rabbits describe the fundamental stages of the disease.<sup>35</sup> Theories of immunopathogenesis aim to explain these stages.

The initial stage of infection is the ingestion of the inhaled tubercle bacilli by the alveolar macrophage. Depending on the ability of the macrophage to resist infection the bacilli multiply and destroy the macrophage. The innate and possibly genetically determined resistance to infection at this stage has been discussed earlier.

During the second stage bacilli grow logarithmically within newly recruited macrophages.<sup>34</sup> After about 2 weeks CD4 T cells specific for mycobacterial peptides appear. Production of  $\gamma$ -interferon activates macrophages enabling more efficient intracellular killing of tubercle bacilli. Activated macrophages produce interleukin 1- $\beta$ , and tumour necrosis factor (TNF) which promotes granuloma formation.<sup>36</sup>

The basal inflammatory exudate is central to the pathogenesis of TBM. The primary complex results in the development of cell mediated immunity; therefore, the rupture of the Rich focus with release of bacilli into the subarachnoid space will result in a local T-cell dependent response. The necrotising granulomatous response is fundamental to the subsequent pathology.<sup>30</sup> Dannenberg hypothesises that necrosis is the result of a delayed type hypersensitivity reaction to exposed tuberculoproteins.<sup>34</sup> Others propose that the granuloma architecture dictates the extent of the central necrosis: a reduced capacity for focusing T lymphocytes within a point of infection may result in failure to deliver adequate cytokine concentrations to the centres of large granulomas, resulting in degeneration and necrosis.<sup>37</sup>

Studies in bacterial meningitis have shown that CSF concentrations of TNF- $\alpha$  correlate with disease severity.<sup>38</sup> TNF- $\alpha$  concentrations in TBM are lower than they are in bacterial meningitis. In TB sensitised animals small concentrations of TNF result in substantial tissue necrosis.<sup>39</sup> Rabbit models of TBM show that CSF concentrations of TNF- $\alpha$  correlate with clinical progression.<sup>40</sup> Intervention with antibiotics and thalidomide, an anti-TNF agent, resulted in an improvement in survival and neurological outcome.<sup>40</sup> The protective role of TNF should not be forgotten, with the promotion of granuloma formation<sup>36</sup> and enhanced killing of infected cells *in vitro*.<sup>41</sup>

These models provide evidence for the important role of cytokines, in particular TNF, in the pathogenesis of TBM. They suggest alternative immunomodulatory therapeutic approaches that may supercede the blind use of corticosteroids.

### Clinical features

In textbooks TBM is described as a subacute lymphocytic meningitis.<sup>42</sup> Although this may be true in many cases, it is not helpful here to describe the classic presenting features of TBM. This is not to suggest that they do not occur, but more to emphasise the variety of clinical presentations and the requirement for a high level of diagnostic suspicion. To date all of the series of TBM reported in the literature stress the importance of early diagnosis and the

prompt institution of chemotherapy.<sup>43-49</sup> Delay in treatment either results in death, or substantial neurological morbidity.<sup>50</sup>

In those patients presenting with TBM the history will often be unhelpful. Recent contact with tuberculosis should be elucidated: several studies have shown that between 70% and 90% of children have had recent contact with TB.<sup>44-51</sup> The prodrome is usually non-specific with no one symptom predominating: 28% report headache, 25% were vomiting, and 13% had fever.<sup>43</sup> Only 2% reported meningitic symptoms.

In a review of 205 children only 38% had fever at presentation with 9% reporting photophobia.<sup>43</sup> 14% remained free from meningism throughout the illness. Recent reviews confirm the wide variety of presentations seen with TBM.<sup>44-48</sup> An Australian series of 58 patients found that on the day of admission TBM was considered a diagnosis in 36% of cases, with 6% receiving immediate treatment.<sup>44</sup> The duration of presenting symptoms varied from 1 day to 9 months, although 55% presented with less than 2 weeks of symptoms. In one quarter of patients diagnosis and treatment were delayed until clinical deterioration confirmed the diagnosis of TBM. More advanced disease, however, may be just as hard to diagnose. A review of 48 cases admitted to a French intensive care unit disclosed that on admission to the unit only 65% had fever, 52% had focal neurology, and 88% had meningism.<sup>45</sup>

The neurological complications that can occur are legion.<sup>50-52</sup> Their nature and diversity can be predicted from an understanding of the site of disease and the pathogenesis of TBM. Adhesions can result in cranial nerve palsies (particularly II, III, IV, VI, VII, and VIII), constriction of the internal carotid resulting in stroke, and obstruction of CSF flow leading to raised intracranial pressure, reduced conscious level, and hydrocephalus. Infarcts occur in about 30% of cases,<sup>53</sup> commonly in the internal capsule and basal ganglia, causing a range of disorders from hemiparesis to movement disorders. Seizures are common, especially in children and elderly people. Hydrocephalus, tuberculoma, oedema, and hyponatraemia due to inappropriate ADH secretion can all cause seizures. In those presenting with root pain, in combination with either spastic or flaccid paralysis and early loss of sphincter control, the diagnosis of spinal meningitis should not be forgotten.

Over the past 10 years there have been studies documenting the relation between HIV and TBM.<sup>46-49</sup> Although HIV infected patients with TB are at increased risk of TBM,<sup>46</sup> the clinical features and outcomes of the disease do not seem to be altered.<sup>45-49</sup> Those with TBM and HIV often have concomitant extrameningeal disease. In one report 65% had clinical or radiographic evidence of extrameningeal TB on admission.<sup>46</sup> In another series 77% of those with HIV had clinical evidence of extrameningeal TB, compared with 9% in those without HIV.<sup>49</sup> In more than half there may also be a CNS tuberculoma.<sup>47</sup> These distinguishing

characteristics may facilitate the diagnosis of TBM in those with HIV.

Elderly people with TBM are a significant group, particularly in the developed world. As with many conditions in elderly people, presentation may be atypical. Signs of meningism may be absent, seizures occur more commonly, and CSF findings may be atypical; the CSF may even be acellular.<sup>49</sup>

In summary, the diagnosis of TBM can neither be made nor excluded on clinical grounds. Coinfection with HIV does not seem to change the clinical manifestations or the outcome of TBM, although the diagnosis may be suggested by the presence of extrameningeal TB or CNS tuberculoma. Elderly people may elude diagnosis altogether unless carefully investigated. A careful search for extrameningeal TB is likely to be a useful adjunct in establishing whether meningitis is due to TB.

### Prognosis

Some studies have assessed the clinical and laboratory indices that might predict outcome. The early trials used univariate analysis—assessing prognostic variables without adjusting for the effect of covariables.<sup>54–55</sup> From these studies, some poor prognostic indicators arose—extremes of age, advanced stage of disease, concomitant extrameningeal TB, and evidence of raised intracranial pressure. Studies employing multivariate analyses that adjust for the influence of other variables are scarce. One such study in children found that the age of the patient and stage of disease were two independent variables associated with prognosis.<sup>56</sup> A more recent study looked at clinical, laboratory, and CT features in 49 adults and children with TBM.<sup>57</sup> A multivariate logistic regression model showed that the most significant variables for predicting outcome in TBM were age, stage of disease, focal weakness, cranial nerve palsy, and hydrocephalus. The message for clinicians is simple: children with advanced disease with neurological complications have poor outcomes. The intervention required is rapid diagnosis and treatment.

### Diagnosis

The rapid diagnosis of TBM is fundamental to clinical outcome. Current laboratory methods are insensitive and slow. Newer methods such as those involving the amplification of bacterial DNA by the polymerase chain reaction (PCR) and comparable systems are incompletely assessed, and are not suitable for widespread use in the developing world. The careful and repeated search for acid fast bacilli with Ziehl-Neelsen staining is still one of the most effective rapid diagnostic tests.

The diagnosis of TBM cannot be made or excluded on clinical grounds. A history of recent TB contact is helpful<sup>44–51</sup> as is the presence of extrameningeal TB.<sup>50–56</sup> Tuberculin testing is of limited value. Early studies found 22% of those with TBM were negative to 100 units PPD.<sup>38</sup> A recent study demonstrated cumulative reactivity with 10–100 units PPD to be 75%.<sup>44</sup> Some studies suggest that tuberculin testing may be more useful in

children, with 86% having greater than 15 mm of induration with 5 units purified protein derivative (PPD).<sup>51</sup>

Diagnosis is dependent on lumbar puncture and CSF examination. Abnormalities in the CSF depend on a tuberculin reaction within the subarachnoid space. Those with depressed cell mediated immunity may have atypical findings in the CSF. Acellular CSF in elderly and HIV positive patients have been reported.<sup>49</sup> Lymphocytosis of between 100 and 1000 cells/mm<sup>3</sup> is more usual, although in the first 10 days polymorphonuclear leucocytes may predominate.<sup>59</sup> A raised CSF protein occurs in most, and CSF glucose will be reduced in 70%.<sup>45–59</sup>

The search for acid fast bacilli is the most crucial part of the investigation. The limit of detection on microscopy is 100 mycobacteria/ml.<sup>60</sup> The clinician can assist the diagnostic yield in two ways: send a large volume of CSF (10 ml is recommended), and repeat the lumbar puncture if the diagnosis is suspected. Acid fast bacilli are seen in CSF smears in about 10% to 20% of those with TBM,<sup>61</sup> although this figure varies considerably. The values in recent reviews were 12.5%,<sup>45</sup> 37%,<sup>4</sup> and 87%.<sup>60</sup> The success of the test depends on the quality and volume of sample sent, the skill of the technician, and their persistence in examining for acid fast bacilli.

The culture of *M tuberculosis* from the CSF is the gold standard for diagnosis, but is insensitive and slow. Laboratories employing only solid media such as Lowenstein-Jensen may take up to 8 weeks to culture *M tuberculosis*. Semiautomated radiometric culture systems such as the Bactec 460 and automated continuously monitored systems have reduced culture times.<sup>62</sup> Although such systems do reduce the time taken for culture the decision to treat the patient should not wait for culture results.

The advent of CT and MRI has provided insight into disease progression, and gives prognostic and diagnostic information.<sup>63–64</sup> Both CT and MRI of the brain will disclose hydrocephalus, basilar meningeal thickening, infarcts, oedema, and tuberculomas.

In a CT study of 60 cases of TBM in adults and children only three had normal brain scans.<sup>65</sup> Hydrocephalus was reported in 87% of children and 12% of adults. The incidence of hydrocephalus is greater in the young, and increases with duration of the illness. In children hydrocephalus is almost always present after 6 weeks of illness.<sup>65</sup> Infarcts are seen on CT in 28%, with 83% occurring in the middle cerebral artery territory.<sup>53</sup> The basal ganglia are the most commonly affected region. Poor prognosis has been associated with enhancing basal exudates and periventricular lucency.<sup>53–64</sup>

Magnetic resonance imaging has increased sensitivity in detecting the distribution of meningeal inflammatory exudate.<sup>53</sup> Gadolinium enhanced T1 weighted images highlight the exudate, and show parenchymal infarcts as hyperintense areas; MRI may provide more

diagnostic information than CT when assessing space occupying lesions. Cerebral miliary TB, with multiple small intraparenchymal granulomas, produces moderate perilesional oedema and contrast enhancement. Larger tuberculomas are initially non-enhancing, but later demonstrate marked enhancement.

Both CT and MRI are sensitive to the changes of TBM, particularly hydrocephalus and basal meningeal exudates, but they lack specificity. The radiological differential diagnosis includes cryptococcal meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal

metastases, and lymphoma. The major role of neuroradiology has been in management and in particular in the diagnosis and follow up of those complications requiring neurosurgery.

The diagnostic dilemma faced on a daily basis in many hospitals in the developing world is illustrated in the two case histories (box). Case 1 would seem like a straightforward case of tuberculous meningitis with a lymphocytic meningitis in a patient with partially treated pulmonary tuberculosis. Case 2, with a relatively short history, normal chest radiograph, neutrophilic CSF, and recent retained placenta

### Clinical case histories

#### CASE HISTORY 1

A 57 year old woman was admitted with a 5 day history of fever, cough, neck stiffness, headache, and confusion. She was admitted to a provincial hospital where a clinical diagnosis of bacterial meningitis was made. She was treated with an unknown antibiotic and transferred to the Centre for Tropical Diseases in Ho Chi Minh City. Her medical history included partially treated pulmonary tuberculosis. On admission her temperature was 39.3°C, Glasgow coma score (GCS) 10, and she had neck stiffness, crackles in both lung fields, and bleeding from the upper gastrointestinal tract. Cerebrospinal fluid was clear with an opening pressure of 21 cm. It contained 348/mm<sup>3</sup> white cells (47% neutrophils 53% lymphocytes). The glucose CSF/blood ratio was 1.5/7.1 mmol/l, CSF lactate 6.4 mmol/l, and CSF protein 160 mg/dl. Gram and Zeihl-Neelsen stains were negative. Antigen detection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in CSF was negative. A tuberculin skin test was negative and a chest radiograph showed signs of pulmonary tuberculosis (figure). Tuberculous meningitis was considered the most likely diagnosis but she was initially started on ceftriaxone for a possible partially treated bacterial meningitis. All therapy for tuberculosis in Ho Chi Minh City is coordinated through the TB hospital and they were asked to see her. Their opinion was that this patient had dual pathology with a bacterial meningitis and pulmonary tuberculosis. There was no improvement in the clinical situation at 48 hours. At this time the result of the CSF culture became available. Enterococcus faecium resistant to ceftriaxone was isolated from the CSF. The antibiotic was changed to amoxicillin. After 3 days of amoxicillin the CSF showed 234 white cells/mm<sup>3</sup> (40% neutrophils, 60% lymphocytes). The glucose CSF/blood ratio was 3.7/6.2 mmol/l, CSF Lactate was 1.87 mmol/l, and CSF protein was 64 mg/dl. She went on to make an uneventful recovery and was discharged well.

#### CASE HISTORY 2

A 17 year old woman was admitted with an 8 day history of fever, rigors, headache, and neck stiffness. She had delivered a normal

baby 4 days before admission, the delivery being complicated by a retained placenta, for which surgical intervention was required. She received an unknown antibiotic for 3 days after this procedure. On admission her temperature was 40°C, and GCS 14 with marked neck stiffness. The chest radiograph was normal. Cerebrospinal fluid was clear with an opening pressure of 40 cm. There were 320 white cells/mm<sup>3</sup> in the CSF with 90% neutrophils and 10% lymphocytes. The glucose CSF/blood ratio was 0.7/7 mmol/l, CSF lactate was 7.8 mmol/l, and CSF protein was 62 mg/dl. Gram and Zeihl-Neelsen stains were negative. Antigen detection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *haemophilus influenzae* in CSF was negative. A tuberculin skin test was negative. The presumptive diagnosis was bacterial meningitis possibly related to the surgical procedure after the delivery. She was started on ceftriaxone, metronidazole, and tobramycin. Her clinical state remained static and a repeat CSF examination on day 4 showed white cells 560/mm<sup>3</sup> (55% neutrophils, 45% lymphocytes). The glucose CSF/blood ratio was 0.87/6 mmol/l, CSF lactate was 9.4 mmol/l, and CSF protein was 173 mg/dl. The TB hospital was asked to review her case and after 1 week elected to start antituberculous therapy. Four weeks later *Mycobacterium tuberculosis* was isolated from the admission CSF. This patient is now 5 months into a 9 month course of TB therapy.

These two cases represent the typical dilemma that confronts much of the world in the diagnosis of tuberculous meningitis. The prevalence of pulmonary tuberculosis in a country such as Viet Nam is high and patients with bacterial meningitis often have signs of TB on chest radiography. Pretreatment with antibiotics is widespread and levels of resistance to *Streptococcus pneumoniae* are very high (more than 90% of community isolates are resistant to penicillin). Consequently patients with bacterial meningitis often have negative gram stains and negative CSF culture on admission. The CSF cell counts, and glucose and protein results can be very similar in partially treated bacterial meningitis and early TBM, making a clear diagnosis often impossible as these two cases demonstrate. Making the wrong diagnosis, or delay in making the correct diagnosis can have disastrous consequences.

after delivery of a baby would certainly be consistent with bacterial meningitis. However, 4 weeks later the tubercle bacilli was cultured from Lowenstein-Jensen media. There is clearly an urgent need for a sensitive and specific affordable diagnostic test in TBM.

#### Alternative diagnostic approaches

The challenge facing new diagnostic strategies in TBM is that they must improve on the sensitivity of conventional Ziehl-Neelsen staining and culture, but maintain the specificity. In the developed world cost is less critical, but in the developing world cost considerations mandate tests that are cheap, use standard reagents with long shelf lives, and are technically undemanding.

Tuberculoesteric acid is a structural component of mycobacteria that was first detected in the CSF of a patient with TBM in 1983.<sup>65</sup> Frequency pulsed electron capture gas liquid chromatography has been used to detect femtomole quantities of tuberculoesteric acid in CSF.<sup>66</sup> The technique is unlikely to be adopted as standard diagnostic procedure due to its complexity despite 91% sensitivity and 95% specificity being reported.<sup>66</sup>

Adenosine deaminase is produced by lymphocytes and monocytes. Its detection in CSF has been reported with variable success, with sensitivities and specificities as high as 99% being suggested.<sup>67</sup> A trial comparing concentrations of adenosine deaminase in the CSF of those with aseptic meningitides found increased concentrations in 30% of those with pyogenic meningitis, and almost universally raised concentrations in TBM and neurobrucellosis.<sup>68</sup> The test lacks both sensitiv-

ity and specificity, but may be useful in narrowing the differential diagnosis in aseptic meningitides.

Serological techniques that detect the intrathecal synthesis of antimycobacterial antibodies have been studied. A good test will require an antigen with high species specificity and good immunogenicity to be sensitive. The use of crude antigens such as PPD results in low sensitivity and specificity.<sup>69</sup> Basic enzyme linked immunosorbent assays (ELISAs) have lacked sensitivity.<sup>69-70</sup> The adaptation of ELISA techniques and the identification of specific *M tuberculosis* antigens have improved results. Using a solid phase antibody competition assay with mouse monoclonal antibodies to the 38 kDa antigen (also known as antigen 5, or antigen 78), a large study was performed in pulmonary and extrapulmonary TB.<sup>71</sup> In extrapulmonary TB diagnostic sensitivity was 73%, specificity 98%, regardless of organ site.

Sensitivity improves when ELISA is used to detect anti-BCG secreting cells in the CSF of those with TBM<sup>72</sup>), but the test is technically demanding. A sensitivity of 96% and specificity of 92% is reported with this method. A cell-ELISA method allowing quantitative detection of CSF anti-PPD IgG produced similar diagnostic sensitivity and specificity.<sup>73</sup>

The differentiation of acute infection from previous exposure is problematic in antibody detection tests, and test sensitivity may be compromised in immunocompromised people. Methods to directly detect specific mycobacterial antigens in the CSF have been developed to tackle these inadequacies. Initial studies used various ELISA techniques<sup>70-74-76</sup>; most using polyclonal antibodies directed against crude antigen. Despite an expected lack of sensitivity and specificity, one retrospective study showed a sensitivity of 68% and specificity of 100% using these components.<sup>77</sup> Other studies have claimed the identification of specific TB antigens and consequently specific serological tests based on them. For example, using a preparation of 35 kDa antigen from *M tuberculosis*, 100% sensitivity (when compared with culture) and 100% specificity was reported.<sup>78</sup> The test was simple to perform and the nitrocellulose strips containing the antigen had a shelf life of 2 years. Unfortunately many assays showing early promise in highly controlled studies do not perform with high sensitivity and specificity in clinical practice.

The advent of DNA amplification techniques such as PCR has turned attention away from serological techniques. In paucibacillary TB the concept of amplifying specific genetic material to detectable levels is attractive. Use of PCR in the diagnosis of TBM is promising, but still poorly defined. The few studies to date suffer from having small numbers, different primer targets, and differing diagnostic criteria. Sensitivities vary from 33% to 90%, specificities from 88% to 100%. Much of the variability is dependent on varying definitions of the diagnostic gold standard. Many use differing clinical criteria for gold standard diagnosis, which makes interstudy comparison difficult. A set of clinical diagnostic criteria has been



Chest radiograph. Case history 1. Loss of lung volume right side. Diffuse reticular shadowing, particularly right apex. Calcification right hilar and cavitation. Findings consistent with pulmonary tuberculosis.

assessed against bacterial isolation, PCR, response to treatment, and necropsy.<sup>79</sup> The PCR was positive in 75% of those clinically adjudged to have highly probable or probable TBM, and whom improved on treatment. Future studies need to use universal and evaluated clinical diagnostic criteria.

Studies have assessed PCR against both bacterial culture, and ELISA for mycobacterial antibodies in TBM.<sup>80-82</sup> One study reported culture alone as having a sensitivity and specificity of 39% and 100%, whereas PCR had a sensitivity of 48% and a specificity of 100%.<sup>81</sup> A Vietnamese study<sup>83</sup> compared 104 patients treated for TBM on clinical grounds and the results of initial CSF microscopy, culture, and PCR. They report the sensitivities of PCR to be 32%, culture 17% and microscopy 1%. The importance of analysing adequate volumes of CSF is emphasised. Of 17 patients with culture positive TBM only 10 were PCR positive. The authors explain the result by suggesting that the small quantities of CSF used for the PCR process effectively reduces the available mycobacterial DNA to undetectable concentrations. Other authors emphasise this "aliquot phenomenon" as being an important cause of false negative PCR results.<sup>82</sup>

The use of PCR to monitor successful treatment in TBM is not yet defined. Studies have suggested that PCR could detect *M tuberculosis* up to 6 weeks after starting treatment.<sup>81</sup> A small study that performed PCR on sequential CSF samples from seven patients with TBM, found that five were negative by day 14, and only one was positive at day 28.<sup>84</sup>

Experience of PCR in respiratory samples has led to the development of commercially available tests.<sup>85</sup> A trial has evaluated the use of Roche AMPLICOR PCR in CSF samples.<sup>82</sup> Unfortunately only 37% of smear positive cases were culture positive. The reasons for this include obtaining CSF after treatment was started, and limited culture techniques. The result reduces their study to only eight cases with a gold standard diagnosis. Given these numbers, sensitivity and specificity were 87% and 100% respectively. Other commercial kits have been tested, and have been shown to produce comparable results.<sup>86</sup>

In summary, PCR has an accepted role in the detection of *M tuberculosis* in pulmonary specimens,<sup>85</sup> but is not yet fully evaluated for the diagnosis of TBM. The sensitivity of PCR on CSF samples seems to be only a moderate improvement on that of culture. The specificity is comparable, but depends on scrupulous laboratory technique to avoid DNA contamination. As with Ziehl-Neelsen staining and culture, yield is improved with greater volumes of CSF. The PCR is acknowledged to be inappropriate for the developing world<sup>82</sup> and current studies suggest that PCR does not solve the global diagnostic challenge set by TBM. There is a need for novel diagnostic approaches if sensitive and specific assay methods are to become a reality.

## Management

Before the introduction of chemotherapy TBM was almost universally fatal. Cases of transient self limiting TBM are reported in the literature,<sup>87</sup> but these are exceptional. The current United Kingdom guidelines for the management of TBM<sup>88</sup> reflect both the advances achieved by modern chemotherapy and continuing areas of uncertainty.

Streptomycin was first used to treat pulmonary TB in 1944 and in 1946 the United Kingdom Medical Research Council (MRC) began studies using streptomycin. In 1948 they published data that demonstrated a marked improvement in prognosis for those with TBM treated with streptomycin.<sup>55</sup> Mortality fell to 46% in those presenting with stage 1 (conscious, no neurological deficit), 66% in stage 2 (disturbed consciousness, with or without focal neurology), and 86% in stage 3 (comatose, with or without focal signs). The introduction of isoniazid and para-aminosalicylic acid led to further improvements in prognosis. A study documenting the changes in available chemotherapy between 1947 and 1958 shows the extent of the improvement.<sup>89</sup> Mortality fell from 64% using streptomycin alone to 27% with streptomycin and para-aminosalicylic acid, and then to 17% with the addition of isoniazid.

The addition of rifampicin and pyrazinamide produced a further improvement in prognosis with a less toxic, orally administered regime. The prognostic benefits of rifampicin have been questioned,<sup>90 91</sup> and uncertainty surrounds its penetration into the CSF. Rifampicin is 80% protein bound in plasma, enabling a maximum of 20% to penetrate the CSF in those with an intact blood-brain barrier. Studies have shown slow penetration of rifampicin into the CSF of patients with TBM, with levels just above the minimum inhibitory concentrations for *M tuberculosis*.<sup>92</sup> Meningeal inflammation enhances CSF penetration of antitubercular drugs; however, there is limited evidence to suggest that rifampicin penetration occurs independently of inflammation.<sup>93</sup>

There is no conclusive evidence to demonstrate improvement in outcome with the use of pyrazinamide. It is well absorbed orally, and has excellent penetration into the CSF.<sup>94</sup> These factors, and the sterilising effect on tubercle bacilli, have resulted in pyrazinamide being considered mandatory at the beginning of TBM treatment.<sup>88 95</sup> It has been suggested that given the uncertain benefit and penetration of rifampicin, pyrazinamide should be given for the duration of the treatment.<sup>51</sup>

The current United Kingdom guidelines<sup>88</sup> suggest treatment for the first two months with rifampicin, isoniazid, pyrazinamide, and a fourth agent. This agent can be streptomycin, ethambutol, or prothionamide. Streptomycin only penetrates the CSF to therapeutic concentrations in the presence of inflammation.<sup>96</sup> Intrathecal administration is no longer recommended, given the availability of drugs that penetrate the CSF well. The renal and ototoxicity of streptomycin, and the necessity for drug concentration monitoring, has limited its use. Ethambutol has two disadvantages that prompt

some to suggest that, “there is little to recommend its use as a first line agent” in TBM.<sup>51</sup> Firstly, it penetrates CSF poorly, and secondly the adverse effect of optic neuritis which, although rare, limits the drug’s use for those in coma. Prothionamide is strongly favoured by some, particularly in South Africa.<sup>51–95</sup> Good concentrations in CSF are achieved at a dose of 20 mg/kg.<sup>97</sup> The drawback is a foul metallic taste, commonly occurring with nausea and vomiting.

In summary, a consensus exists that isoniazid, rifampicin, and pyrazinamide constitute the best start to treatment. The addition of the fourth drug is left to local choice and experience, with little evidence to support the use of one over the other.

There is conflicting evidence for the duration of treatment. The current United Kingdom guidelines recommend 12 months in uncomplicated cases of TBM (including cerebral tuberculoma without meningitis), extending to 18 months should pyrazinamide be omitted.<sup>88</sup> No guidelines exist as to the components and duration of treatment in the case of multidrug resistant TBM.

Treatment for 12 months is probably a conservative estimate of the time required for bacterial cure. Different regimes, incomparable patient groups, and the variable use of adjuvant steroid therapy, makes meta-analysis from the trials impossible. Some suggest that TBM should be treated for a minimum of 2 years.<sup>98</sup> Evidence from 781 cases of TBM treated for 2 years showed that 35 had a recrudescence,<sup>98</sup> but nearly all patients with relapse had received less than 6 months of therapy, indicating that therapy should be in excess of this period. Evidence that 6 months of treatment can be successful was first postulated in 1960<sup>99</sup> and has been supported by more recent work.<sup>51–100</sup> Evidence from South Africa<sup>51</sup> reported on 95 children treated for 6 months with a combination of 20 mg/kg isoniazid, 20 mg/kg rifampicin, 40 mg/kg pyrazinamide, and 20 mg/kg ethionamide; 96% of these cases presented in either stage II or III TBM. Prednisolone at a dose of 4 mg/kg was randomly allocated to 40 of the children. The overall mortality was low at 16%, with only one case of recrudescence. Prednisolone made no statistical difference to morbidity or mortality. The doses of both isoniazid and rifampicin used were considerably higher than that recommended in the United Kingdom, but significant adverse reactions were not reported. The study provides good evidence for the adequacy of short course intensive chemotherapy, but the lack of a control group does not allow conclusions as to optimal dosages. Studies using 9 months chemotherapy (2 months of isoniazid, rifampicin, pyrazinamide, streptomycin, followed by 7 months of rifampicin and isoniazid) at lower doses produced comparable outcomes.<sup>101</sup>

The rationale behind the use of adjuvant corticosteroids lies in reducing the harmful effects of inflammation as the antibiotics kill the organisms. Corticosteroids do not seem to reduce the proinflammatory cytokines found in

the CSF of those with TBM.<sup>102</sup> Although the mechanism remains obscure, clinical trials suggest that corticosteroids have a beneficial effect in some groups of patients and a consensus has emerged that adjuvant corticosteroids should be used in those presenting with MRC stage II or III TBM.<sup>88–95–103</sup>

The evidence for this view is as follows. The first controlled trial to suggest benefit in using corticosteroids for TBM was published in 1955.<sup>104</sup> Of 12 patients with TBM six received steroids in addition to streptomycin and isoniazid. The white count in CSF fell faster in the steroid group, recovery from the acute phase was quicker, and none of the patients given steroids had any long term sequelae. Four of the six who did not receive corticosteroids had chronic neurological sequelae. Trials confirming these results with larger numbers were not performed until the mid-1970s when a prospective, randomised, double blind trial was performed using 72 patients.<sup>105</sup> A reduction in mortality in the steroid group was shown, but the effect on neurological morbidity could not be assessed. The largest prospective, randomised, controlled trial to date enrolled 160 patients with TBM.<sup>106</sup> Overall mortality and long term neurological sequelae were reduced in those treated with corticosteroids. The group that benefited the most were those with disease of intermediate severity. Those presenting either in a coma or with mild disease (stage I) received minimal benefit.

Raised intracranial pressure has long been considered important in the prognosis of TBM.<sup>107</sup> Reduction of intracranial pressure by steroids was thought to be one of the means by which corticosteroids exerted their beneficial effect. A recent trial assessed the efficacy of steroids with regard to CT evidence of increased intracranial pressure, parenchymal brain involvement, direct intracranial pressure measurements, and clinical outcome.<sup>108</sup> The trial showed no difference in intracranial pressure, ventricular size, or extent of infarction between those treated with or without steroids. The benefit to mortality was again found in the steroid group, and improved intellectual outcome was suggested.

It has been suggested that steroids may reduce the penetration of antituberculous drugs into the CSF by reducing inflammation. There is little evidence for this occurring. One study found no statistical difference between the plasma/CSF concentration ratios of isoniazid, pyrazinamide, rifampicin, or streptomycin, in those on or off corticosteroids.<sup>109</sup>

### Role of neurosurgery

Neurological deterioration occurring in a patient under treatment for TBM may have various causes, and requires urgent radiological assessment. Rising intracranial pressure requires active management. Hydrocephalus is a common complication that may lead to permanent neurological damage or death if left untreated. Prompt assessment by CT is of value in both diagnosis and management.<sup>64</sup> Repeated lumbar puncture or external ventricular drainage has been advocated in both



preventing and predicting the benefit of shunt surgery.<sup>110-111</sup> Studies suggest that prompt ventriculoatrial or ventriculoperitoneal shunting improves outcome, particularly in those who present with minimal neurological deficit.<sup>111</sup>

Indications for neurosurgical review include the presence of tuberculoma. These can develop or enlarge after the start of chemotherapy,<sup>112</sup> provoking much speculation as to the immunological mechanism behind this phenomenon.<sup>113</sup> In practice, surgical intervention is rarely required unless the tuberculoma is compromising a vital structure. Management is conservative, with good resolution reported with antituberculous chemotherapy in combination with steroids.<sup>114</sup>

### New developments or research avenues

The complete genome sequence of *M tuberculosis* strain H37Rv has recently been determined.<sup>27</sup> The sequence will enhance research into vaccine design, mechanisms of drug resistance, and virulence determinants. As yet specific mechanisms of neurovirulence are unknown. It is conceivable that certain isolates of *M tuberculosis* may target specific receptors facilitating meningeal involvement resulting in a neurotropism analogous to that of *Mycobacterium leprae* for peripheral nerves.

Skin testing with PPD has long been the cornerstone for assessing exposure to *M tuberculosis*. The limitations to this test have led to the development of in vitro cytokine assays assessing cell mediated immunity.<sup>115</sup> Assays first developed in cattle,<sup>116</sup> have been extended to humans, and hold many potential advantages over skin testing. The production of interferon- $\gamma$  in whole blood in response to specific *M tuberculosis* or specific *M tuberculosis* antigens shows promise. Potential applications include the detection of infection with *M tuberculosis*, differentiating exposure to *M tuberculosis* from BCG vaccine or environmental mycobacteria, and assessing response to new vaccines.

As the role of cytokines is understood, so their use in diagnosis and therapeutics is expanding. Similar substances may also exist in prokaryotic organisms. A factor has recently been characterised that promotes the resuscitation and growth of a group of gram positive bacteria including *M tuberculosis*.<sup>117</sup> In picomolar concentrations "resuscitation promoting factor (Rpf)" dramatically increases the viable cell count of dormant cultures in organisms such as *M tuberculosis*. Acting as a "bacterial cytokine" the ability of Rpf to resuscitate *M tuberculosis* has important implications for future research. A rapid increase in bacterial yield from paucibacillary disease sites such as CSF might be predicted, and may assist TBM diagnosis. If growth and latency of *M tuberculosis* is controlled in vivo by such substances, novel therapeutic strategies or vaccines might be developed.

As drug resistance becomes more prevalent so the requirement for rapid sensitivity testing becomes more urgent, particularly in TBM where inappropriate treatment can be fatal. Rapid sensitivity testing using bacteriophages

considers this problem.<sup>118-119</sup> Specific *M tuberculosis* phages carrying the firefly luciferase gene are able to infect viable *M tuberculosis* within a culture, thereby labelling them with the ability to produce light. This mechanism amplifies the detection of *M tuberculosis* allowing rapid assessment of viability on a sensitivity plate. Sensitivities of *M tuberculosis* are shown within days rather than weeks. The technique has also been used to detect *M tuberculosis* in early cultures.<sup>119-123</sup>

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