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The diagnosis and medical management of tuberculous meningitis in adults

S Marais,[1] MB ChB, FCNeurol (SA), PhD; **R J Wilkinson**,[1,2] MA, PhD, BM BCh, DTM&H, FRCP

[1] *Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, and Division of Neurology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Division of Mycobacterial Research, MRC National Institute for Medical Research, London, and Department of Medicine, Imperial College London, UK*

Corresponding author: *S Marais (marais.suzaan@gmail.com)*

Tuberculous meningitis (TBM) is a medical emergency for which tuberculosis (TB) treatment should be initiated as soon as possible after diagnosis. Owing to the low diagnostic yields of confirmatory tests, TBM is often diagnosed based on suggestive clinical and cerebrospinal fluid findings, evidence for TB outside the central nervous system (CNS), typical brain imaging features and exclusion of other causes of meningitis. TB drug regimens used in TBM may be suboptimal as they are informed by studies of TB outside the CNS, rather than being based on randomised controlled trials in TBM. TBM has a high mortality and the management of HIV-co-infected patients is further complicated by neurological TB-immune reconstitution inflammatory syndrome (IRIS), which frequently occurs after starting antiretroviral therapy (ART) during TBM treatment and contributes to the poor outcome in HIV-associated TBM. HIV-infected TBM patients due to start ART should be counselled about the risk of developing neurological TB-IRIS, typical symptoms that could be expected and need to return to hospital should any of these develop. Currently, the only evidence-based treatment for TB-IRIS is with corticosteroids, which should be considered in all cases of neurological TB-IRIS.

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Tuberculous meningitis (TBM) is a frequent cause of meningitis in South Africa (SA) and has a dismal prognosis.[1] In a study from a Cape Town hospital, TBM accounted for more than half of adult meningitis cases over a 6-month period; at 6-month follow-up mortality was 48%.[1] HIV co-infection, particularly in patients with severe immunosuppression, increases the risk of disseminated forms of tuberculosis (TB), such as meningitis, and contributes significantly to the TBM burden in high HIV/TB settings. The diagnosis of TBM is often complicated and optimal management strategies are uncertain; such challenges are likely to contribute to poor outcome in affected patients.[2]

Diagnosis

Early diagnosis and treatment initiation are crucial to improve outcome in TBM, as advanced disease, prolonged symptom duration and delayed treatment initiation are associated with increased mortality during hospitalisation, when the majority of deaths occur.[2] As discussed below, definitive microbiological tests for TBM are insensitive; therefore diagnosis and TB treatment initiation are usually based on a combination of suggestive clinical and cerebrospinal fluid (CSF) findings, evidence of TB outside the central nervous system (CNS), supportive features on brain imaging (if available) and exclusion of other common causes for meningitis.[3]

Clinical findings

TBM typically presents sub-acutely after an average of 5 - 30 days of neurological symptoms (e.g. headache, vomiting, neck pain/stiffness, seizures, focal neurological signs and confusion)[3] – unlike bacterial meningitis, which usually presents more acutely, but similar to cryptococcal meningitis (CM). However, shorter (a few days) or longer (>1 month) duration of neurological symptoms is well described and does not exclude the diagnosis of TBM. Systemic symptoms of *Mycobacterium tuberculosis* infection, such as cough, night sweats and loss of weight, may be indicative of TB, but may also be present with other causes of meningitis. Untreated HIV infection frequently results in loss of weight.

Routine CSF features

The usual CSF findings in TBM include the combination of a clear appearance, lymphocyte-predominant pleocytosis (50 - 1 000 × 10^6/L), increased protein concentrations (0.5 - >2.5 g/L) and decreased glucose (CSF/blood ratio <0.5 or absolute value <2.2 mmol/L).[2] However, atypical routine CSF findings that may cause diagnostic uncertainty are well described, including a mildly elevated or normal white cell count, normal protein or glucose concentrations, neutrophil predominance, or completely normal CSF. Atypical findings occur more frequently in the context of HIV infection, and a normal CSF white cell count is particularly common with severe immune suppression ($CD4^+$ count <50 cells/μL).[4]

Features of TB elsewhere

A search for evidence of TB outside the CNS is crucial in the diagnostic work-up of suspected TBM. Chest radiography should be performed in all cases, as abnormalities suggestive of TB are seen in a large proportion (33 - 85%) of TBM patients.[4] Further investigations such as sputum examination (smear, culture and/or Xpert), lymph node fine-needle aspiration biopsy and abdominal ultrasound should be considered, depending on the clinical presentation.

Brain imaging

The most common reason for brain imaging (usually computed tomography (CT)) in suspected TBM in SA is to rule out a contraindication to lumbar puncture (LP). Contrast-enhanced

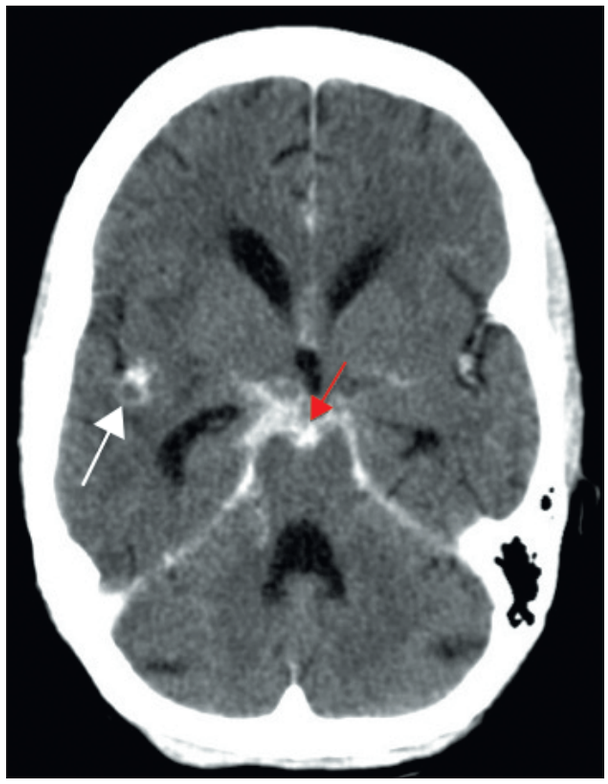

Fig. 1. Computed tomogram of a patient with tuberculous meningitis (TBM). This contrast-enhanced axial image shows three typical features of TBM, including tuberculoma (white arrow), basal meningeal enhancement (red arrow) and hydrocephalus.

brain imaging may additionally be useful in suspected TBM where diagnostic uncertainty exists. Typical imaging features, including hydrocephalus, basal meningeal enhancement, tuberculoma(s) and/or infarcts, may provide supportive evidence for a diagnosis of TBM in such cases (Fig. 1). However, brain imaging may be completely normal, especially early during the course of the disease. Furthermore, several factors may complicate the interpretation of brain imaging results in HIV-infected patients. In particular, generalised cerebral atrophy is common in the context of HIV and could be confused with communicating hydrocephalus, and a tuberculoma has a similar radiological appearance to other causes of intracranial space-occupying lesions, such as toxoplasmosis, commonly seen in HIV-infected patients.

Exclusion of other causes of meningitis

The most common differential diagnosis for TBM in SA, which predominantly affects HIV-infected patients, is CM.[1] CM cannot be distinguished from TBM by clinical or routine CSF findings and should be investigated by CSF India ink and/or cryptococcal antigen testing with or without fungal culture. CSF Gram staining and bacterial culture should be performed to exclude pyogenic bacterial meningitis. However, negative stain and culture results do not always exclude a diagnosis of bacterial meningitis, especially in patients partially treated with antibiotics before presentation, and a high index of suspicion should be maintained in such cases, as well as in those with a CSF neutrophil predominance. Meningitis due to non-opportunistic viruses (e.g. Enterovirus) that does not require specific treatment may mimic TBM. These viruses can be investigated in selected patients by CSF viral polymerase chain reaction (PCR). HIV itself is often associated with chronic CSF inflammation, including mildly increased lymphocyte counts (5 - 25 cells $\times 10^6$/L) and protein concentrations (0.46 - 1 g/L). This emphasises the importance of considering CSF results in the context of clinical and other investigative findings. Patients in whom considerable doubt regarding the diagnosis exists, such as those with atypical presentations and mild CSF abnormalities, a watch-and-wait approach could be employed with an LP repeated, if necessary, a few days after the initial LP. A limited list of other infectious differential diagnoses of HIV-associated TBM and their investigation is presented in Table 1.

Definitive diagnostic methods

Detection of acid-fast bacilli in CSF by smear examination is a rapid, inexpensive method of confirming the diagnosis of TBM. However, studies from SA report extremely low diagnostic yields by this method.[5] Culture of *M. tuberculosis* from CSF is similarly an insensitive diagnostic test and as time to positivity is at least 2 weeks, it is too slow to be clinically relevant in guiding treatment initiation in TBM.[3] Measures shown to improve the sensitivity of these microbiological tests, which can easily be implemented in our setting, include analysing large volumes of CSF (≥6 mL is advised), and performing repeated LPs.[6,7]

The Xpert MTB/RIF test (Xpert, Cepheid, Sunnyvale, CA, USA), a real-time PCR assay for *M. tuberculosis* that simultaneously detects rifampicin (RIF) resistance, is of potential value in the rapid diagnosis of TBM. In a study of TBM patients from Vietnam, the overall sensitivity of Xpert on CSF was 59.3% using clinical diagnosis as the reference standard, and the specificity was 99.5%.[8] In this study, the sensitivity of Xpert was significantly higher in HIV-infected compared with HIV-uninfected patients (sensitivity 78.8% v. 47.9%). In a predominantly HIV-infected SA TBM cohort study (87% of the 204 participants were HIV-infected), the sensitivity and specificity of Xpert were 67% and 94%, respectively; this analysis included patients with definite TBM (CSF *M. tuberculosis* culture and/or Amplicor PCR positive), compared with patients with other causes of meningitis as controls.[9] Although the overall sensitivity decreased to 36% when probable TBM was included in the reference standard, using a larger volume (3 mL) of centrifuged CSF compared with 1 mL of neat CSF increased the sensitivity markedly from 26% to 65% in this analysis.

Management

TB treatment

Similar to guidelines globally, current SA Department of Health (SA DoH) guidelines suggest RIF, isoniazid, ethambutol and pyrazinamide for 2 months, followed by RIF and isoniazid for a further 7 months as first-line treatment in adults with CNS TB. However, the principles of treating TBM are based on those developed for pulmonary TB and not informed by randomised controlled trials (RCTs) in TBM.[2] RIF is one of the backbone drugs in TBM treatment, but the evidence for the current recommended dose (10 mg/kg/day) is scant and may be too low. RIF has poor CSF penetration and TBM patients often present critically ill, vomit and receive drugs through a nasogastric tube. All these factors may further contribute to suboptimal CNS TB drug concentrations. Isoniazid and pyrazinamide have good CSF penetration and are therefore considered critical drugs in TBM treatment. However, the choice of the fourth drug during the initiation phase of TBM treatment is contentious.[2] Ethambutol crosses the meninges poorly at the recommended dose. Alternatives such as streptomycin and ethionamide are of limited use in TBM owing to poor CNS penetration, dose-limiting toxicity and intolerable

Table 1. Infective causes and their investigation in the differential diagnosis of patients with suspected HIV-associated tuberculous meningitis and/or intracerebral tuberculoma

Differential diagnosis	Investigation(s)*
Meningitis	
Cryptococcal meningitis	India ink, cryptococcal antigen testing, fungal culture
Bacterial meningitis	Gram stain, bacterial culture
Non-opportunistic viral meningitis (e.g. Enterovirus)	Viral PCR
Neurosyphilis	VDRL and TPHA or FTA tests
Herpesvirus meningoencephalitis (e.g. HSV, HZV, CMV, HHV-6)	Viral PCR
Lymphomatous meningitis	Cytology (and EBV PCR)
HIV seroconversion	Serum p24 antigen and conversion of antibody tests
Chronic HIV infection	Exclusion of other causes
Non-tuberculous mycobacteria (e.g. MAC)	Mycobacterial culture
Intracerebral space-occupying lesion(s)†	
Toxoplasmosis	Serum and CSF IgG
Primary CNS lymphoma	Brain biopsy (and EBV PCR)
Bacterial brain abscess	Brain biopsy
Cryptococcoma	India ink, cryptococcal antigen testing, fungal culture
Neurosyphilis (gumma)	VDRL and TPHA or FTA
PML-IRIS	JC virus PCR

PCR = polymerase chain reaction; VDRL = venereal disease research laboratory; TPHA = *Treponema pallidum* haemagglutination; FTA = fluorescent tryponemal antibody; HSV = herpes simplex virus; HZV = herpes zoster virus; CMV = cytomegalovirus; HHV-6 = human herpesvirus-6; EBV = Epstein-Barr virus; MAC = *Mycobacterium avium* complex; IgG = immunoglobulin G; CNS = central nervous system; PML-IRIS = progressive multifocal leucoencephalopathy immune reconstitution inflammatory syndrome; JC = John Cunningham.
*Performed on cerebrospinal fluid (CSF), unless otherwise specified.
†In addition to suggested investigations, brain biopsy may be indicated where diagnostic uncertainty persists.

gastrointestinal side-effects in adults. Fluoroquinolones such as levofloxacin and moxifloxacin have high bactericidal activity, are safe and well tolerated and have good CSF penetration; therefore they are attractive treatment options for TBM.

There is increasing interest in exploring alternative evidence-based treatment regimens for TBM. RCT findings suggest a mortality benefit from an 'intensified' treatment regimen early during TBM treatment.[10] This study investigated the safety and pharmacokinetic profiles of higher-than-normal dose, intravenous (IV) RIF and oral moxifloxacin in HIV-infected and -uninfected TBM patients. Although not powered to detect a mortality benefit, an improved outcome was observed in patients receiving IV RIF (~13 mg/kg/d) than in those on the oral standard dose during the initial 2 weeks of TB treatment. Patients who received IV RIF had a reduced mortality at 6-month follow-up (34%) compared with those who received oral RIF (65%). A further RCT assessing the use of higher doses of oral RIF (15 mg/kg/d) and oral levofloxacin in improving TBM outcome is currently ongoing in Vietnam (ISRCTN61649292). Results of this trial, which may lead to changes in treatment guidelines, are expected in 2015.

Corticosteroids

Corticosteroid treatment is associated with improved survival in HIV-uninfected patients with TBM and is recommended in all affected patients, regardless of HIV status.[11] In an RCT of adjunctive dexamethasone in TBM, this medication was associated with a reduced risk of death compared with placebo, which was significant in all patients at 9-month follow-up (relative risk: 0.69; p=0.01),[12] but only a trend for mortality benefit with dexamethasone was observed in subgroup analysis of HIV-infected patients (p=0.08). Of note, corticosteroid treatment was associated with a decrease in severe adverse events, in particular hepatitis (0/274 v. 8/271 cases in the placebo group; p=0.004).

Treatment of HIV infection in TBM patients

A large proportion of HIV-infected patients are antiretroviral therapy (ART)-naive or have defaulted ART at TBM presentation. Starting ART during TB treatment improves outcome in HIV/TB co-infected patients, and one large RCT from Vietnam has provided guidance on the timing of ART in such patients.[13] In this study of patients with HIV-associated TBM, there was no difference in 9-month mortality between severely immunosuppressed TBM patients (median $CD4^+$ count = 41 cells/μL) who started ART immediately (within 7 days of TB treatment) and those who started later (2 months after TB treatment initiation). Grade 4 adverse events were significantly more frequent in the ART group who started treatment immediately (80 v. 69%; p=0.04), suggesting that delayed treatment may be preferable. In view of these findings and the risk of CNS TB-IRIS, current SA DoH ART guidelines recommend starting ART 4 - 6 weeks after TB treatment in TBM patients, regardless of $CD4^+$ count.

Paradoxical TBM-IRIS

TB-IRIS occurs owing to an exaggerated immune response against TB antigens in HIV-infected patients after ART initiation. Paradoxical TB-IRIS occurs in patients who typically show clinical improvement after starting appropriate TB treatment, and subsequently present with new, recurrent or worsening TB symptoms after ART initiation in the context of a recovering immune system. Neurological TB-IRIS is the most life-threatening form of TB-IRIS, with an associated mortality of 13 - 75%. Neurological IRIS may present as meningitis, intracerebral tuberculoma(s), tuberculous brain abscess, radiculomyelitis or spinal epidural abscess. Patients frequently present with atypical inflammatory features such as focal meningeal enhancement on brain imaging (Fig. 2). In an observational study from Cape Town, 47% of TBM patients developed TBM-IRIS at a median of 14 days after ART initiation, while mortality due to TBM-IRIS was 12.5% (2/16).[14]

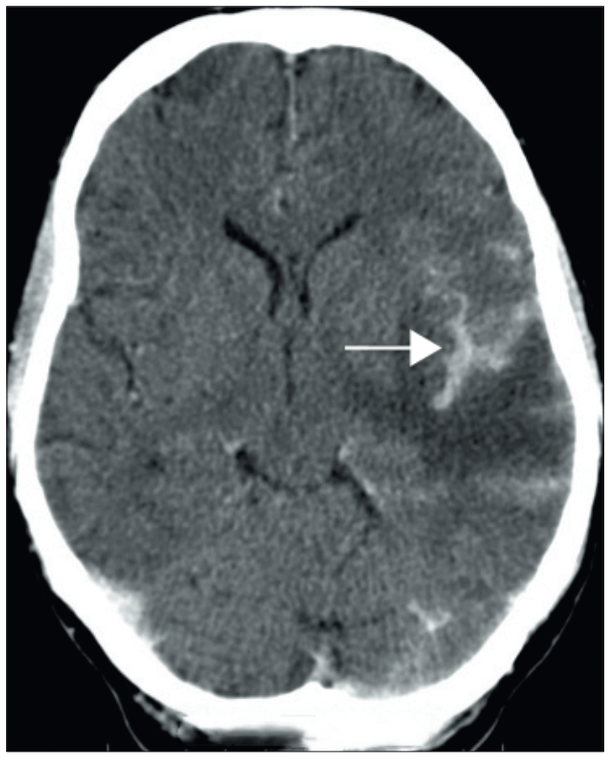

Fig. 2. Computed tomogram of a patient with tuberculous meningitis immune reconstitution inflammatory syndrome. This contrast-enhanced axial image shows focal leptomeningeal enhancement of the left hemisphere with marked involvement of the sylvian fissure (white arrow) and adjacent cerebral oedema.

Factors at TBM presentation associated with subsequent TBM-IRIS included high CSF neutrophil count and high CSF bacillary load (reflected by *M. tuberculosis* culture positivity).

Corticosteroids are the only evidence-based treatment currently available for TB-IRIS. In an RCT of prednisone for the treatment of non-life-threatening paradoxical TB-IRIS, significant benefit was demonstrated with prednisone compared with placebo. The combined endpoint was days hospitalised and outpatient therapeutic procedures. Additionally, there was also significant symptomatic improvement associated with prednisone.[15] Based on these findings and anecdotal evidence of the benefit of corticosteroids in neurological TB-IRIS, our practice is to treat all patients with neurological TB-IRIS with prednisone 1.5 mg/kg/d orally (or IV dexamethasone) for at least 2 weeks, after which the dose is reduced gradually according to clinical response. Temporary interruption of ART should only be considered in patients with a severe or persistently depressed level of consciousness and in those with severe neurological disability unresponsive to corticosteroid therapy.[16] A vital component of the management of HIV-associated TBM patients who will start ART is a comprehensive discussion with the patient, and preferably also with a family member, about the risk of developing neurological TB-IRIS, the typical symptoms that could be expected and the need to return to hospital should any of these develop.

Conclusion

Owing to a lack of rapid, sensitive diagnostic methods, the diagnosis of TBM relies strongly on suggestive clinical, laboratory and imaging features and the exclusion of common differential diagnoses. The optimal TBM treatment regimen remains to be defined and results of ongoing RCTs exploring different treatment options are eagerly awaited. Neurological TB-IRIS is a life-threatening complication in HIV-associated TBM that should be anticipated in patients who start ART during TB treatment.

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