Neurology® Clinical Practice

Tuberculous meningitis

Diagnostic and therapeutic challenges

Jerome H. Chin, MD, PhD, MPH

Summary

Neurologists are often the first medical providers to evaluate patients with possible infectious meningitis. Knowledge of the clinical presentations and cerebrospinal fluid, microbiologic, and neuroimaging findings for different etiologies is essential to make a prompt diagnosis and initiate appropriate treatment. Tuberculosis is a common cause of meningitis in developing countries with a high prevalence of pulmonary tuberculosis. However, tuberculosis affects populations in every country and all neurologists need to be vigilant for possible cases of tuberculous meningitis presenting to their medical facilities. This article discusses the challenges of diagnosing and treating tuberculous meningitis and highlights recent advances in diagnostic technology.

Tuberculosis (TB) is a highly prevalent global human infection caused by *Mycobacterium tuberculosis* (MTB). One-third of the world's population is infected with latent TB. These individuals are not clinically affected but carry a lifetime risk of 10% for developing active disease.[1] There were an estimated 8.6 million incident cases of TB globally in 2012, with 1.3 million deaths.[2] A total of 22 high-burden countries accounted for 81% of all estimated incident cases. TB is the leading cause of death in people living with HIV, accounting for approximately 1 in 5 deaths.

The largest share of the global burden of TB is in the Southeast Asia, Western Pacific, and African regions.[2] However, TB is a global epidemic, with cases reported annually in every country. In the United States in 2012, 9,951 new cases of TB were reported, with 7.7% of cases coinfected with HIV.[3] The majority of cases (63%) were foreign-born persons. The top 5 countries of birth were Mexico, the Philippines, India, Vietnam, and China. In the United Kingdom in 2012,[4] 8,751 new cases of TB were reported, with 73% among people born in high-burden countries of South Asia and sub-Saharan Africa. In the United States and the United Kingdom, populations at higher risk for TB include racial and ethnic minorities, homeless persons, prisoners, and immunosuppressed individuals.[3,4]

School of Public Health, University of California, Berkeley.

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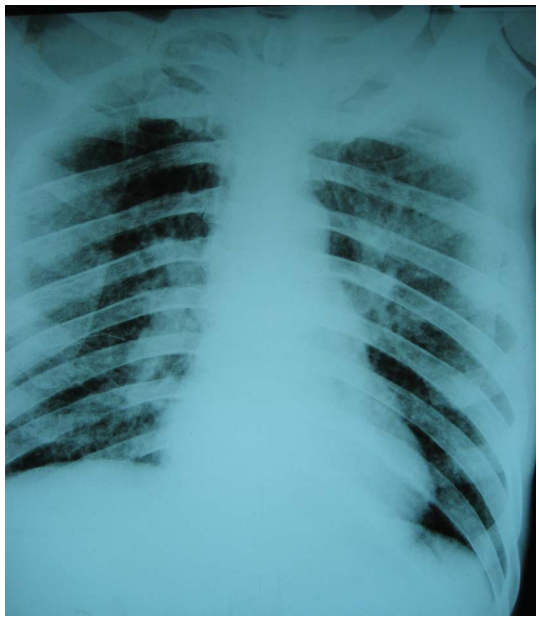
Correspondence to: chinj@asapp.org

Figure 1 Chest X-ray of pulmonary tuberculosis



Bilateral infiltrates and hilar adenopathy suggestive of active tuberculosis.

Clinical presentation of tuberculous meningitis

Tuberculous meningitis (TBM) can occur as the sole manifestation of TB or concurrent with pulmonary or other extrapulmonary sites of infection.[5–7] TBM carries a high mortality and morbidity, particularly among patients coinfected with HIV.[8–12] Delays in seeking medical care, diagnosis, and initiation of treatment are contributing factors to the high mortality and morbidity, especially in resource-limited regions. When diagnosed promptly, TBM can be cured with supervised medication administration and supportive care.

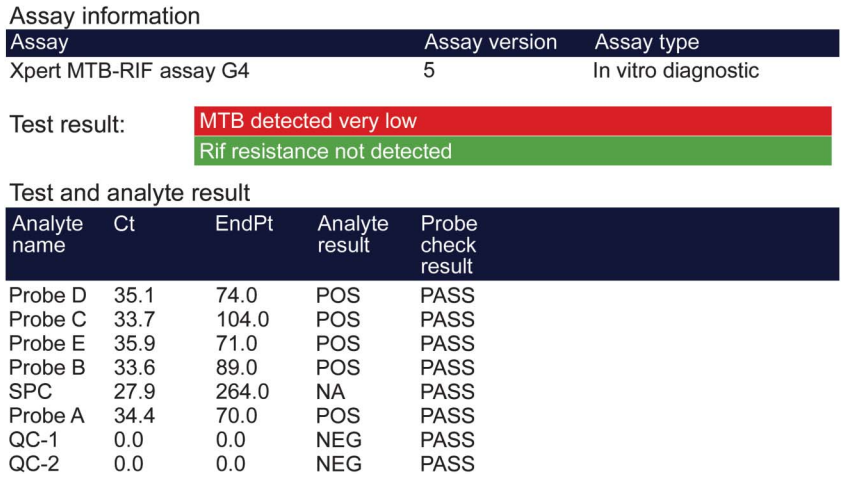
Patients with TBM develop typical symptoms and signs of meningitis including headache, fever, and stiff neck, although meningeal signs may be absent in the early stages. The duration of symptoms before presentation ranges from several days to several months.[9,10] Especially in resource-limited settings, TBM cases may present in advanced clinical stages, with Glasgow Coma Scale scores of 10 or less.[9–12] Cranial nerve (CN) palsies, hemiparesis, paraparesis, and seizures are common and should raise the possibility of MTB as the etiology of meningitis. Patients often present with multiple CN palsies, most commonly involving CN III, VI, and VII. Chest X-ray is suggestive of active or previous pulmonary TB in approximately 50% of cases (figure 1).[5]

CSF in TBM

If the clinical presentation is suggestive of TBM, cerebrospinal fluid (CSF) should be sent for routine analyses (cell counts and differential, protein level, glucose level) and microbiologic tests for bacteria, fungi, and MTB. Pleocytosis with lymphocytic predominance, high protein levels, and low glucose levels are the hallmark findings in the CSF of patients with TBM. In a consecutive series of 88 HIV-negative patients with definite TBM diagnosed by positive CSF culture,[13] the following median values were determined from CSF analyses: cell count (136/μL), mononuclear cell percentage (63%), protein concentration (160 mg/dL), and CSF glucose/blood glucose ratio (0.13). Atypical CSF findings may be obtained in HIV coinfected individuals including normal cell counts (≤5 cells/μL), polymorphonuclear cell predominance, and normal glucose levels (>2.2 mmol/L).[12]

The CSF findings noted above are not specific for TBM and can be seen in other conditions including non-MTB bacterial meningitis, fungal meningitis, carcinomatous meningitis, and

Figure 2 Xpert MTB/RIF nucleic acid amplification test



Assay information

Assay	Assay version	Assay type
Xpert MTB-RIF assay G4	5	In vitro diagnostic

Test result:

MTB detected very low

Rif resistance not detected

Test and analyte result

Analyte name	Ct	EndPt	Analyte result	Probe check result
Probe D	35.1	74.0	POS	PASS
Probe C	33.7	104.0	POS	PASS
Probe E	35.9	71.0	POS	PASS
Probe B	33.6	89.0	POS	PASS
SPC	27.9	264.0	NA	PASS
Probe A	34.4	70.0	POS	PASS
QC-1	0.0	0.0	NEG	PASS
QC-2	0.0	0.0	NEG	PASS

Xpert MTB/RIF results on the CSF of a 53-year-old patient with tuberculous meningitis and HIV coinfection. Ziehl-Neelsen stain of CSF for acid-fast bacilli was negative.

subarachnoid hemorrhage. For all patients with suspected TBM, CSF samples should be examined by Ziehl-Neelsen (ZN) staining for acid-fast bacilli, Gram staining for bacteria, India ink preparations for fungi, and antigen testing for *Cryptococcus neoformans*. In non-MTB bacterial meningitis, 60%–90% of CSF Gram stains are positive, allowing rapid identification of the causative organism for most cases.[14] In contrast, ZN staining has a very low sensitivity in cases of TBM.[9,13] For example, in a prospective observational study from Indonesia, only 11% of CSF samples taken from 207 suspected cases of TBM were positive by ZN staining.[13] In the same study, a low percentage of CSF samples yielded growth of MTB by solid culture (36%) and by liquid culture (44%). Since MTB cultures can take several weeks or longer to detect growth, a presumptive diagnosis of TBM in cases with a negative CSF ZN stain needs to be made without waiting for the results of CSF MTB culture.

A recent diagnostic advance is Xpert MTB/RIF, an automated rapid nucleic acid amplification test for MTB endorsed by the WHO in December 2010.[15] Xpert technology employs single-use sealed disposable cartridges that avoid contamination of testing equipment and requires minimal technical training to operate. The Xpert MTB/RIF assay employs 3 specific primers and 5 unique molecular probes to detect MTB and rifampicin resistance simultaneously in less than 2 hours. Molecular probes are included to detect DNA of sample processing control bacteria (figure 2). Rifampicin resistance is strongly indicative of multidrug-resistant TB (MDR-TB), defined as TB caused by organisms resistant to isoniazid and rifampicin.[15]

A 2013 Cochrane Review of Xpert MTB/RIF in pulmonary TB that included 18 unique studies reported a pooled sensitivity of the assay of 98% for smear-positive, culture-positive TB and 68% for smear-negative, culture-positive TB, and an assay specificity of 98%.[15] A prospective study from South Africa reported a sensitivity of 67% and a specificity of 94% for Xpert MTB/RIF comparing 54 HIV-infected patients with definite TBM and 65 patients with "non-TBM" meningitis.[16] A recent study of suspected TBM cases (20.8% HIV-infected) from Vietnam reported a sensitivity of 72% and a specificity of 99.5% for Xpert MTB/RIF comparing 151 definite cases of TBM with 197 cases of not TBM meningitis.[17]

Neuroimaging in TBM

Contrast-enhanced brain CT or MRI can help support a diagnosis of TBM because of the high frequency of abnormalities on initial presentation (figure 3). The most common findings in

Contrast-enhanced brain CT or MRI can help support a diagnosis of TBM because of the high frequency of abnormalities on initial presentation.

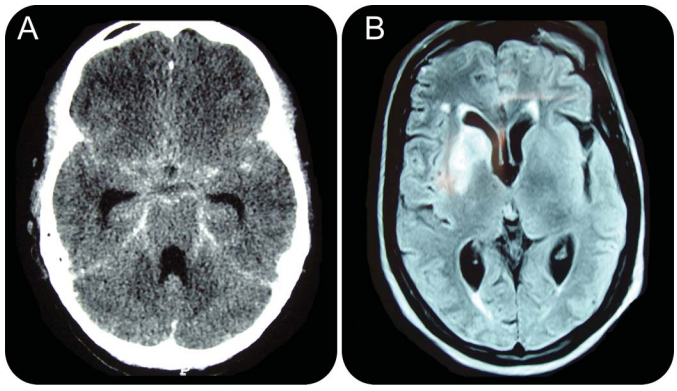
descending order are meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas.[18] Infarcts occur as a result of vasculitis affecting the vessels of the Circle of Willis, the perforating branches of the middle cerebral artery, and the vertebrobasilar circulation.

Treatment of TBM

If the clinical presentation, CSF findings, and neuroimaging studies of a patient with meningitis are compatible with TBM and other etiologies (e.g., bacterial and fungal) have been excluded by initial CSF analysis, a presumptive diagnosis of TBM should be made and treatment should be initiated promptly. Parenteral empirical antibiotics should be administered to cover non-MTB bacterial etiologies until CSF and blood cultures for bacteria are negative for >48 hours. Guidelines for the treatment of TBM in adults and children have been published by the WHO in 2010[19,20] and the British Infection Society in 2009[5] and are based on standard regimens for pulmonary TB (table). Controlled trials to determine the optimal drug regimen and treatment duration for TBM have not been conducted.

The British Infection Society guidelines recommend a first-line regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 10 months of isoniazid and rifampicin.[5] The WHO guidelines recommend a first-line regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (children) or streptomycin (adults) followed by 10 months of isoniazid and rifampicin.[19,20] Both guidelines recommend adjunctive corticosteroids based on a Cochrane review that concluded that adjunctive corticosteroids reduce the risk of death or disabling residual neurologic deficit from TBM.[8] Newer regimens combining fluoroquinolones with high-dose rifampicin show promise for improving outcomes in TBM.[21–23] For patients with suspected or confirmed MDR-TB, recently published WHO guidelines should be followed[24] and an expert in treating MDR-TB should be consulted. The Food and Drug Administration recently approved the use of bedaquiline fumarate as part of

Figure 3 Neuroimaging in tuberculous meningitis



(A) Brain CT of a 19-year-old patient with tuberculous meningitis (TBM) shows hydrocephalus and basal meningeal enhancement. (B) Brain MRI of a 56-year-old patient with TBM shows basal ganglia infarcts.

HIV-infected patients receiving treatment for TBM are at risk for clinical deterioration after initiation of antiretroviral therapy due to immune reconstitution inflammatory syndrome.

combination therapy for adults with a diagnosis of pulmonary MDR-TB. Although clinical trials of bedaquiline for the treatment of extrapulmonary MDR-TB are not available, published guidelines indicate that use on a case-by-case basis is reasonable given the high mortality rate and limited treatment options.[25]

HIV-infected patients receiving treatment for TBM are at risk for clinical deterioration after initiation of antiretroviral therapy (ART) due to immune reconstitution inflammatory syndrome (TBM-IRIS).[26,27] The rapid restoration of immune function in the presence of mycobacterial antigens provokes an intensified inflammatory reaction resulting in worsening, recurrent, or new clinical signs and symptoms. Diagnosis of TBM-IRIS requires exclusion of other causes of clinical deterioration including drug resistance, poor adherence to treatment, misdiagnosis, and other opportunistic infections. The optimal time to initiate ART is uncertain. Some guidelines recommend deferring ART to 4–6 weeks after beginning anti-TB medication.[26] Although corticosteroids do not appear to prevent TBM-IRIS,[27] restarting or increasing the dose and duration of corticosteroid treatment is recommended for the management of TBM-IRIS.[26,27]

DISCUSSION

TB is one of the most challenging causes of meningitis to diagnose because of the difficulties in rapidly identifying MTB in CSF samples. TBM should be strongly considered in any patient presenting with symptoms and signs of meningitis in regions with a high burden of TB and in high-risk individuals in regions with lower burdens of TB. Clinical, microbiologic, and radiologic findings should be used conjunctively to support a diagnosis of TBM. Empirical treatment with anti-TB drugs is the standard of care in presumptive cases with negative ZN staining of CSF for acid-fast bacilli. The Xpert MTB/RIF assay provides the ability to rapidly diagnose infection with MTB, although additional studies are needed to define the sensitivity and specificity for the diagnosis of TBM.

Table First-line drug regimens for tuberculous meningitis[5,19,20]

Drug	Daily dosage (children), mg/kg	Daily dosage (adults), mg/kg	Duration
Isoniazid	10–15 (max 300 mg)	4–6 (max 300 mg)	12 mo
Rifampicin	10–20 (max 600 mg)	8–12 (max 600 mg)	12 mo
Pyrazinamide	30–40	20–30	2 mo
Ethambutol	15–25	15–20	2 mo
Streptomycin[a]		12–18	2 mo
Dexamethasone[b]	0.6	0.4	6–8 wk

[a] WHO guidelines recommend replacing ethambutol with IM streptomycin for adults.[19]

[b] Dexamethasone should be given intravenously at first and then orally as tolerated. Dosage should be tapered weekly.[5]

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