Challenges in the diagnosis of tuberculous meningitis

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ABSTRACT

Tuberculosis (TB) continues to pose a significant public health problem. Tuberculous meningitis (TBM) is the most severe form of extra-pulmonary TB. TBM carries a high mortality rate, including for those receiving treatment for TB. Diagnosis of TBM is difficult for clinicians as it can clinically present similarly to other forms of meningitis. The difficulty in diagnosis often leads to a delay in treatment and subsequent mortality. Those who survive are left with long-term sequelae leading to lifelong disability. The microbiologic diagnosis of TBM requires the isolation of Mycobacterium tuberculosis from the cerebrospinal fluid (CSF) of an infected patient. The diagnosis of tuberculous meningitis continues to be challenging for clinicians. Unfortunately, many cases of TBM cannot be confirmed based on clinical and imaging findings as the clinical findings are nonspecific, while laboratory techniques are largely insensitive or slow. Until recently, the lack of accessible and timely tests has contributed to a delay in diagnosis and subsequent morbidity and mortality for many patients, particularly those in resourcelimited settings. The availability of Xpert Ultra and point-of-care lipoarabinomannan (LAM) testing could represent a new era of prompt diagnosis and early treatment of tuberculous meningitis. However, clinicians must be cautious when ruling out TBM with Xpert Ultra due to its low negative predictive value. Due to the limitations of current diagnostics, clinicians should utilize a combination of diagnostic modalities in order to prevent morbidity in patients with TBM.

1. Background

Tuberculosis (TB) continues to pose a significant public health problem. An estimated 1.7 billion people worldwide have latent TB, and tuberculosis caused illness in 10 million people worldwide in 2018, leading to the deaths of 1.2 million HIV-negative people and 251,000 people living with HIV (PLHIV) [1]. Extrapulmonary TB accounts for ~14% of TB cases worldwide, particularly in children and PLHIV [2,3]. More specifically, tuberculous meningitis accounts for ~1% of all worldwide TB cases [3].

Tuberculous meningitis (TBM) is the most severe form of extra-pulmonary TB [4,5]. Although the peak age range for TBM is 2–5 years-old, adults who live in endemic areas or those who are immunosuppressed due to HIV or other immunosuppressive medications are susceptible to infection [3] Diagnosis of TBM is difficult for clinicians as it can clinically present similarly to other forms of meningitis. The difficulty in diagnosis often leads to a delay in treatment and subsequent mortality [4,6]. TBM carries a high mortality rate of 30–40%, including those receiving treatment for TB [4,5,7,8]. PLHIV who develop TBM have a higher mortality rate of > 60% [6,9–11]. Those who survive are left with long-term sequelae leading to lifelong

disability [3]. It is theorized that TBM disseminates when a subcortical or meningeal pocket of infection ruptures and spreads bacilli into the subarachnoid space and into the cerebrospinal fluid (CSF) [12]. The microbiologic diagnosis of TBM requires the isolation of *Mycobacterium tuberculosis* from the CSF of an infected patient [7]. Unfortunately, many cases of TBM cannot be confirmed based on clinical and imaging findings as the clinical manifestations are nonspecific, while laboratory techniques are largely insensitive or slow [3,13]. Thus, many patients are started on empiric therapy while awaiting microbiological confirmation [3,13]. Recently, immunologic tests have been developed to aid in the diagnosis of TBM [14].

2. Clinical features of tuberculosis meningitis

Clinical features of TBM are similar to those of other causes of meningitis [13]. Classically, TBM presents as a subacute meningitic illness [3]. Because TBM cannot be definitively diagnosed based on history and clinical assessment alone, there is a delay in early diagnosis and treatment initiation [3,15]. Symptoms often start with headache (50–80%) and anorexia (60–80%), leading to vomiting (30–60%), photophobia (5–10%), and fever (60–95%) [3,13]. In adults, the most

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predictive symptom for TBM is duration of illness greater than five days [3]. Approximately half of patients with TBM have an exposure to another person with sputum-smear positive pulmonary TB [12]. On initial examination, patients can have neck stiffness (40–80%), confusion (10–30%), coma (30–60%), any cranial nerve palsy (30–50%), hemiparesis (10–20%), paraparesis (5–10%), and seizures, which are more common in children (50%) compared to adults (5%) [16–21]. Additionally, patients with HIV are more likely to have evidence of TB in other organs, including the lungs, pleura, lymph nodes, genitourinary tract, vertebrae and spinal cord, and the peritoneum [9,22,23]. Chest x-rays (CXR) can demonstrate active or previous TB infections in about 50% of patients, but these findings are not specific in areas endemic to TB [16]. However, a military pattern of TB on CXR can be helpful in determining extrapulmonary dissemination of TB [24].

Patients may also continue to develop new TBM-related lesions even after the start of treatment; these are called paradoxical reactions [25]. These paradoxical clinical deteriorations are frequently seen in patients with HIV who are started on antiretroviral therapy, but they can also occur in those who are HIV-negative [26–28]. A prospective study from 2016 found that 31% of participants developed a paradoxical reaction, most within three months of initiating treatment. The most common reactions were new or worsening tuberculoma formation, new hydrocephalus, and optochiasmatic or spinal arachnoiditis [28,29]. Optochiasmatic arachnoiditis can lead to permanent blindness unless it is addressed early in the clinical course [3,30,31]. CSF analysis typically shows elevated neutrophils and protein in the CSF [29]. These new manifestations must be distinguished from treatment failure, drug-resistance or toxicity, or clinical deterioration [32]. The mechanism for these paradoxical reactions is unclear, but it is thought to be similar to the TB-associated immune reconstitution inflammatory syndrome (IRIS) that affects HIV-infected adults [26]. The primary complications of TBM are tuberculoma formation, hydrocephalus, and stroke. These complications usually appear within the first 3 months of treatment and can be deadly if they are not addressed [3].

Tuberculomas can present with or without the presence of TBM. The presentation of tuberculomas depends upon their location within the brain. As such, they may manifest as seizures, focal neurological signs, or increased intracranial pressure due to CSF flow obstruction [33,34]. Paradoxically, tuberculomas can develop or enlarge while on anti-tuberculous therapy. This phenomenon usually appears around month 3 of treatment and is usually not associated with drug resistance [35]. However, intracranial tuberculous abscesses are usually associated with drug-resistance and can have a more severe clinical course; many require surgical intervention [36].

The most common complication of TBM is hydrocephalus, occurring primarily in children [37,38]. It is usually seen as a later complication of TBM since it is caused by the block of CSF flow due to granulomatous inflammatory exudate [39]. It typically manifests with signs of increased intracranial pressure or it is visualized on imaging [40]. Of note, hydrocephalus is less likely to be present in PLHIV [21].

The major source of morbidity from TBM is from the vascular complications, particularly cerebral vasculopathy leading to localized ischemic strokes [34,39]. Patients can have vascular involvement affecting the terminal internal carotid arteries and proximal sections of the middle and anterior cerebral arteries [41,42]. The proposed mechanism of action is via inflammatory spread leading to necrotizing panarteritis and intimal proliferation with secondary thrombosis and occlusion [43,44]. The most common manifestation of ischemic stroke from TBM is hemiplegia [45–47]. It can be clinically challenging to differentiate the origin of clinical features from either tuberculomas or cerebral ischemia on examination alone [48] TBM-associated vasculopathy is typically seen in patients with chronic or partly treated TBM [44].

A characteristic finding of TBM is hyponatremia, affecting ∼ 50% of patients [20]. This finding has been originally attributed to "cerebral salt wasting syndrome"[49]. More recently, patients have been

Table 1
Clinical features of tuberculous meningitis.

Clinical features	Frequency
Presenting symptoms	
Headache	50–80%
Anorexia	60–80%
Emesis	30–60%
Photophobia	5–10%
Physical exam findings	
Fever	60–95%
Neck stiffness	40–80%
Confusion	10–30%
Coma	30–60%
Cranial nerve palsy	30–50%
Hemiparesis	10–20%
Paraparesis	5–10%
Seizures in adults	5%

diagnosed as having SIADH; however, many patients have been found to have normal levels of antidiuretic hormone [50]. A study from 2016 found that patients with severe TBM were more likely to have cerebral salt wasting [51] (Table 1).

Movement disorders can occur due to lesions in specific locations of the brain (particularly basal ganglia infarction) and can include tremor, chorea, ballismus, and myoclonus [52]. Advanced TBM can manifest as coma [3].

3. Clinical staging

There are several scales that can be used to grade the severity of TBM. The modified British Medical Research Council (BMRC) consists of three grades: grade 1 refers to patients who are alert and oriented without focal deficits; patients with grade 2 disease have a Glasgow Coma Scale (GCS) of 10–14 with or without neurological deficits or a GCS of 15 with focal deficits; and patients with grade 3 have a GCS of < 10 with or without focal neurological deficits [15,53]. The modified BMRC scale has been found to be an independent predictor of outcomes and is frequently used in research studies [5,37,54–57]. The Thwaites diagnostic scoring index, developed in 2002, is based on five features: age, length of history, white-blood-cell count, total CSF white-cell count, and CSF neutrophil proportion. The maximum possible score is 13. A patient is likely to have TBM if they have a total score of 4. The Thwaites criteria was found to have a sensitivity of 86% and specificity of 79%. It is important to note, though, that the CSF parameters may differ in PLHIV [13,58]. The Lancet consensus scoring system from 2010 is based on 20 clinical parameters including clinical features, CSF findings, imaging findings, and evidence of TB elsewhere. The maximum score is 20. Classifications in this system include: definite TBM, probable TBM, possible TBM, and not TBM. A patient has a definite diagnosis of TBM if there is evidence of AFB in CSF microscopy or culture or on CNS histopathology. For a probable diagnosis, a patient must have a total score greater than 10 points without the use of imaging or greater than 12 points if CNS imaging was acquired. For a possible TBM diagnosis, a patient must have a score between 6 and 9 without or 6–11 with imaging [58,59].

4. Cerebrospinal fluid analysis

Cerebrospinal fluid (CSF) analysis of patients with TBM include clear appearance (80–90%), low glucose in the CSF (CSF to blood glucose ratio of < 0.5 in 95%), and total CSF leukocyte count can vary from 5 to 1000 10^3/mL with a predominance of lymphocytes (30–90%) compared to neutrophils (10–70%) [13,16–20]. Neutrophils can predominate early in the disease process, and their presence is associated with improved survival [60]. Protein is usually elevated but can range from 45 to 360 mg/dL [6]. The CSF opening pressure is usually greater

than 25 cm H$_2$O in 50% of patients, particularly those with hydrocephalus [16–20,40]. Most studies report similar CSF findings in patients with HIV, except for a reduced CSF leukocyte count [10,21,61,62]. Occasionally, patients with advanced HIV and TBM may have CSF results within the normal ranges [21]. CSF changes may still be present up to 10–14 days after initiation of treatment [12].

5. Imaging findings

Brain computed tomography (CT) findings of patients with TBM may demonstrate basal meningeal enhancement, prior infarcts, hydrocephalus, and tuberculomas. These features are highly suggestive of TBM in adults [63].

Magnetic resonance imaging (MRI) can better define the neuroradiological features of TBM, particularly when evaluating brainstem disease [64]. Granulomas can be differentiated with the use of MRI. For example, non-caseating granulomas appear hypointense on T1 and hyperintense on T2. In contrast, caseating granulomas appear hypointense or isointense on T1 and isointense with rim-enhancement on T2 [65]. The appearance of tuberculomas on MRI depend on the clinical progression and maturation of the disease process [65]. Tuberculous abscesses tend to be much larger than tuberculomas (usually greater than 3 cm in diameter), solitary, thin-walled, and often multi-loculated [65]. MRI is the modality of choice for evaluating TBM-related vascular disease [44]. Diffusion-weighted imaging can better visualize early infarcts and border-zone encephalitis, identified as cytotoxic edema [64]. MRI with gadolinium enhancement can demonstrate leptomeningeal tubercles, which can be seen in 70% of adults [66]. Brain MRI also allows for the monitoring of TBM-related neuropathies, most importantly optochiasmatic arachnoiditis [67].

About 60% of adults will have vascular involvement which can be visualized on magnetic resonance angiography (MRA) [41]. Imaging findings on MRA can demonstrate a classic triad including narrowing of arteries at the base of the brain, narrowed or blocked small or medium-sized arteries with early draining veins, and a hydrocephalic pattern [68].

Single photon emission computed tomography (SPECT) can be useful to evaluate vasculitis due to TBM [69]. SPECT may show reduced blood flow in affected regions of the brain, particularly in the basal ganglia, cortical regions, and rarely midbrain [70–72]. A case series of eleven patients with TBM, found that nine patients had hypoperfusion changes on SPECT but these findings did not correlate with clinical outcomes [71].

Patients with TBM can have increased uptake in focal brain lesions, specifically in the meninges and cerebellum on FDG PET (flourodeoxyglucose positron emission tomography) [73–76]. However, one study from India found that FDG PET did not detect some granulomas that were visible on brain MRI [74]. One must have caution when using FDG PET to evaluate for TBM, as intracranial malignancy can mimic the appearance of TBM [77]. FDG PET uptake in the spine may show diffuse leptomeningeal gliomatosis or spinal arachnoiditis [78,79]. FDG PET may also be useful to evaluate for other sites of extra-pulmonary TB in patients with TBM [73,74,76,80,81].

6. Microscopy

Direct microscopy of acid-fast bacilli (AFB) smears is quick and relatively inexpensive. CSF is stained for AFB with the use of the Ziehl-Neelsen staining technique. However, traditional visualization of CSF to evaluate for AFB by microscopy has been demonstrated to have a poor sensitivity of 10–20% [7,8,82–84]. This limitation is likely due to the small number of bacilli in CSF, as TBM is a paucibacillary infection [15,85,86]. Large CSF volumes can increase sensitivity by up to 60% [84,87,88]. Because of the low sensitivity of microscopy, further diagnostic tests are usually needed.

7. Mycobacterial culture

Traditional culture methods remain the gold-standard for the diagnosis of TB.[1] Cultures have a higher sensitivity than microscopy (50–70%), but results can take several weeks to return – further delaying the diagnosis and contributing to mortality [7,8,89,90]. Chaidir et al. found that the yield of liquid culture compared to solid culture was significantly higher for HIV-negative patients (88.2% vs 74.1%) [84]. Furthermore, the use of culture methods in resource-limited settings may be challenging due to availability (usually only available in large centers), long turn-around times, laboratory safety issues, and relatively high costs [21,25].

8. Nucleic acid amplifications tests (NAAT)

Previously, PCR techniques were not possible in resource-limited settings where the majority of cases of TBM are evaluated [91,92]. Xpert MTB/RIF is a cartridge-based fully automated PCR test that has allowed for rapid (within 2 h) TB diagnostics in resource-limited settings and detection of rifampin resistance [93,94]. A 2014 WHO review of 18 Xpert MTB/RIF studies for the diagnosis of extrapulmonary TB found a pooled sensitivity of 80.5% (95% confidence interval [CI], 59.0 to 92.2%) compared to traditional culture and 62.8% (95% CI, 47.7 to 75.8%) against a combined reference standard (CRS) [95]. For TBM specifically, Xpert MTB/RIF had a sensitivity of 80.5% (95% CI 59.0–92.2%) and specificity of 97.8% (95% CI 95.2–99.0%) compared to culture results and a sensitivity of 62.8% (95% CI 47.7–75.8%) and specificity of 98.8 (95% CI 95.7–100%) compared to CRS. The sensitivity and specificity of results were not affected by HIV status or condition of the specimen. Based on these results, the WHO at that time recommended the use of Xpert MTB/RIF as the preferred initial test for the diagnosis of TBM [95]. More recently, a Cochrane review of the diagnostic utility of Xpert MTB/RIF for the diagnosis of extrapulmonary TB was completed. This study found a sensitivity of 71.1% (CI 60.9 to 80.4%) and specificity of 98% (CI 97.0 to 98.8%) for CSF samples evaluated for TBM [96]. A recent study found that CSF centrifugation had no impact on the sensitivity of Xpert MTB/RIF for the diagnosis of TBM [84]. More importantly, traditional culture methods still have a role in diagnosis due to their lower limit of detection (LOD) of ~1 to 10 cfu/mL compared to that of Xpert MTB/RIF (~116 cfu/mL) [97–100].

Apart from Xpert MTB/RIF, other NAATs have been developed for the diagnosis of TBM. A recent meta-analysis of NAATs for the diagnosis of TB meningitis compared to traditional culture methods demonstrated a sensitivity of 82% (95% confidence interval [CI], 75 to 87%), specificity of 99% (95% CI, 98 to 99%), positive likelihood ratio (PLR) of 58.6 (95% CI, 35.3 to 97.3), and negative likelihood ratio (NLR) of 0.19 (95% CI, 0.14 to 0.25) [4]. While the same review compared NAATs with combined reference standard (CRS) demonstrating a pooled sensitivity of 68% (95% CI, 41 to 87%), specificity of 98% (95% CI, 95 to 99%), PLR of 36.5 (95% CI, 15.6 to 85.3, and NLR of 0.32 (95% CI, 0.15 to 0.70) [4]. These results suggest that NAATs may have insufficient sensitivity for the diagnosis of TBM alone. However, NAATs may be beneficial due to their rapid turn-around time if they are used in addition to traditional culture methods.

A new version of the Xpert MTB/RIF test called Xpert MTB/RIF Ultra (Xpert Ultra) has been recently developed in order to improve sensitivity for *Mycobacterium tuberculosis* detection and to improve rifampin resistance detection [86]. The improved LOD of Xpert Ultra surpasses that of Xpert MTB/RIF at ~15.6 cfu/mL compared to 116 cfu/mL, respectively [86,94]. Dorman et al. found that Xpert Ultra had a superior sensitivity compared to Xpert MTB/RIF in patients with HIV and paucibacillary disease [101]. A prospective study from 2018 evaluating TBM in PLHIV found that Xpert Ultra had a higher sensitivity (90%, 95% CI 55 to 100%) than Xpert MTB/RIF (60%, 95% CI 26–88%), but the specificity of Xpert Ultra was lower (90%, 95% CI

Table 2
Limits of detection of diagnostic tests for TBM.

Diagnostic test	Limit of detection (cfu/mL)	Sensitivity (%)	Specificity (%)
GeneXpert	116	71	98
Xpert Ultra	15.6	90	90
Culture	1–10	50–70	*

* Gold-standard.

83–95%) than Xpert MTB/RIF (97%, 95% CI 92–99%) compared to culture results [93]. These results led to the updated current WHO recommendation that Xpert Ultra be used as first-line for the diagnosis of TBM. A more recent published study found that the sensitivity and specificity of Xpert Ultra was higher compared to Xpert MTB/RIF (92.9% vs 65.8%, respectively) for diagnosis of TBM in PLHIV. In this study, Xpert Ultra had a 93% negative predictive value for the diagnosis of TBM [102]. Interestingly, Donovan et al. found that Xpert Ultra was not more accurate than Xpert MTB/RIF in diagnosis of TBM in both HIV-infected and uninfected adults and that neither test had an adequate negative predictive value for ruling out TBM [103]. Xpert Ultra is not currently available in the U.S. The Tuberculous Meningitis International Research Consortium is supportive of using Xpert Ultra, given its superior sensitivity for diagnosis of TBM as compared to Xpert and culture [104] (Table 2).

9. CSF interferon-gamma release assays

Typically, interferon-gamma release assays (IGRA) are used in the diagnosis of latent TB. However, recently CSF testing via IGRA has been studied in the evaluation of TBM [3]. These tests generally require high volumes of CSF around 5–10 mL; if insufficient volumes are obtained, indeterminate results are common [105]. An initial study from 2010 found that the sensitivity of CSF IGRA is 50–70% with a specificity of 70–90%, making these tests good for ruling in the diagnosis of TBM but not adequate for ruling out TBM [105]. A recent meta-analysis on the use of IGRAs for the diagnosis of TBM found a CSF sensitivity of 78% and specificity of 88% [106]. Given the advance of molecular methods, including Xpert Ultra, it is unclear what the role of CSF IGRA testing would have, mainly due to the need for large CSF volumes [3].

10. Lipoarabinomannan testing

Patients with advanced HIV/AIDS may also be evaluated with the use of the lipoarabinomannan (LAM) testing. LAM is a glycolipid forming component of the *M. tuberculosis* cell wall and can be found in multiple body fluids of patients with TB, including CSF [107–110]. Two studies have evaluated the diagnostic potential of LAM identification with the use of enzyme-linked immunosorbent assay (ELISA). The sensitivities from these two studies ranged from 64% to 69% and the specificity from 62% to 65%, compared to either culture or PCR-confirmed cases of TBM [109]. Additionally, investigators have found higher sensitivities and specificities in HIV patients with CD4 counts below 100 cells/mm^3 compared to those with a higher CD4 count or without HIV [111]. Since these studies were performed in 2010–2011, a point-of-care lateral flow assay (LFA) for LAM has been developed [112]. In 2015, Cox et al. evaluated the use of LAM LFA in an autopsy cohort of Ugandan HIV-infected adults. They found that depending on the preparation of CSF, LAM LFA can have a sensitivity of 29% to 71% with a specificity of 70–93% for the diagnosis of TBM [113]. A study from 2019 evaluating a CSF LFA LAM test in 59 PLHIV found a sensitivity of 33% with a specificity of 96% [114]. However, this study had a small sample size and did not report CD4 counts. Some advantages of LAM LFA are cost ($1.50 per test) and speed of test (25 min per test) [113]. Since LAM LFA is a point-of-care test, it can be used at the bedside, which would be beneficial in resource-limited settings.

11. Adenosine deaminase

Adenosine deaminase (ADA) is an enzyme that is required for the conversion of adenosine to inosine. It is found primarily in T-lymphocytes [115]. Patients with tuberculosis have been found to have high levels of ADA likely due to the activation of T-lymphocytes in response to TB antigens [116]. It has traditionally been used in the diagnosis of pleural, peritoneal, and pericardial tuberculosis [117,118]. A recent review and meta-analysis including data from 20 studies found the pooled sensitivity of CSF ADA measurement for the diagnosis of TBM to be 89% (CI: 84–92%) with a specificity of 91% (CI: 87–93%). The calculated positive likelihood ratio was 9.4 (CI: 7–12.8) and a negative likelihood ratio of 0.12 (CI: 0.09–0.17) [119]. However, past studies have noted a high number of false positives in patients with HIV [120]. Given the high sensitivities and specificities, ADA CSF testing may be a reasonable test in the evaluation of TBM.

12. Conclusion

The diagnosis of tuberculous meningitis continues to be challenging for clinicians. Until recently, the lack of accessible and timely tests has contributed to a delay in diagnosis and subsequent morbidity and mortality for many patients, particularly those in resource-limited settings. The availability of Xpert Ultra and point-of-care LAM testing could represent a new era of prompt diagnosis and early treatment of tuberculous meningitis.

Ethical statement

The development of this manuscript did not involve work with human subjects or animal experiments due to the nature of this manuscript as a review article.

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