Tuberculous Meningitis, What's New?

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Abstract

Tuberculous meningitis may not be the most common cause of bacterial meningitis in non-endemic countries, but it is certainly the most dangerous form of meningitis with a high morbidity and mortality. The diagnosis is difficult and a delay in treatment initiation can lead to poor outcomes, including severe neurological disability. In the setting of world globalization and frequent travel to endemic areas, it is important that physicians be acquainted with this disease. This review discusses the most recent advances related to diagnosis and treatment regimens, including the challenges associated with the treatment of individuals with concomitant human immunodeficiency virus infection as well as advances in vaccination against mycobacterium tuberculosis.

Keywords: Tuberculous meningitis; Diagnostic strategy; Treatment regimens; Corticotherapy; Retroviral therapy in concomitant HIV infection; New vaccines; Biomarkers

Introduction

Central nervous system tuberculosis (TB) can be viewed as three different entities: tuberculous meningitis (TBM), intracranial tuberculoma, and spinal tuberculous arachnoiditis. All three forms exist in countries with a high incidence of tuberculosis where TBM is particularly frequent in children and young adults [1]. In less endemic settings, TBM is mainly seen in adults. In some European countries, it is the third most common cause of bacterial meningitis [2]. TBM is the most severe form of Mycobacterium tuberculosis infection with a high morbidity and mortality [3]. The outcome is less favorable among vulnerable groups, such as children and patients with concomitant human immunodeficiency virus (HIV) infection [4,5]. Improvement in the sensitivity of diagnostic tools to allow a rapid confirmation of the diagnosis is therefore needed to reduce the burden of disease and delay in treatment initiation. We review here the diagnosis and treatment of TBM in non-HIV and HIV-infected individuals.

Diagnosis

The diagnosis of TBM remains a challenge because of its non-specific presentation, the low sensitivity of smear microscopy in central nervous system samples and the slow growth of M. tuberculosis in culture. Patients usually present with indolent symptoms of meningitis or meningoencephalitis, such as low grade fever, neck stiffness, photophobia, and confusion. Seizures, paresis/paraplegia, cranial nerve palsies and even coma may also occur. The cerebrospinal fluid (CSF) is usually clear and colorless with a high opening pressure (>25 cmH2O). CSF analysis mainly shows a raised white cell count (0.05–1×109/L) with neutrophils and lymphocytes (usually lymphocytic predominance; neutrophils may predominate in very early samples), raised protein (0.5–2.5 g/L), and a plasma glucose ratio <0.5 in 95% of cases [6].

A definite diagnosis can be confirmed by presence of bacilli on direct microscopy of CSF smear, positive PCR for M tuberculosis complex or a positive culture for M. tuberculosis. However, spinal fluid examination lacks sensitivity (acid-fast bacilli are seen in CSF smears in about 10-20% of individuals with TBM) [7]. Although the diagnostic yield of direct microscopy can be improved by a large sample size (10 mL of CSF is recommended) and repeating the lumbar puncture, the success of the test is dependent on many factors, including the skill of the laboratory technician [7]. Moreover, delay for positive cultures may lead to a missed diagnosis and delayed treatment. If there is evidence of TB elsewhere or if a prompt evaluation fails to establish an alternative diagnosis, empiric anti-tuberculous therapy should be started immediately in any patient with a meningeal syndrome and CSF findings of a low glucose concentration, elevated protein, and lymphocytic pleocytosis [1].

Many efforts have been made to develop a simple and rapid diagnostic test using nucleic acid amplification systems. The Xpert MTB/RIF (Cepheid, CA, USA) is an automated polymerase chain reaction (PCR) test with the advantage of detecting both M. tuberculosis complex and resistance to rifampicin within 2 hours in a single-use cartridge test (Figure 1). This test is endorsed by the World Health Organization (WHO) and used in different countries worldwide. Several studies have investigated the accuracy of the Xpert assay on CSF and showed that its specificity is consistently high, while sensitivity values depend on the sample size, tuberculosis prevalence, and the test used as a gold standard [8-10]. In the 2013, WHO policy report, the Xpert MTB/RIF had a pooled sensitivity of 79.5% (95% confidence interval [CI], 62.0–90.2) and a pooled specificity of 98.6% (95% CI, 95.8–99.6) compared to culture as a reference in detecting TB in CSF [11]. As mentioned, sensitivity can be further improved by providing a large volume sample, repeating the lumbar puncture and adding a concentration step (centrifugation or vortex) in the CSF processing before submitting to the Xpert assay [10,12,13]. However, the sensitivity of the Xpert assay is lower if a composite clinical score is considered as the gold standard [8,11]. This emphasizes the importance of starting treatment in patients with a typical clinical presentation and CSF findings, regardless of the Xpert assay results.

Identifying disease-specific biomarkers in order to help earlier diagnosis and treatment of TBM is an ongoing process. Some of the proposed biomarkers are: adenosine deaminase (ADA), CSF lactate, CSF lactate dehydrogenase and arachidonate 5lipoxygenase. None of these biomarkers have been validated for TBM diagnosis [14-18]. None the less, more recent studies are showing promising outcomes to detect new biomarkers for TBM diagnosis. Y. Yang and al [19] used iTRAQTM to identify differential proteins in the CSF of patients with TBM and healthy controls. Neural epidermal growth factorlike like 2 (NELL2) was then selected and showed the ability to distinguish between TBM subjects from healthy controls with 83.3% sensitivity and 75% specificity. Another study showed that Delta-like 1 ligand (DLL1) levels were higher in CSF and plasma of TBM patients compared to those with viral or bacterial meningitis [20]. One of the most recent studies used host Heat shock proteins (Hsps) levels in CSF as a marker of TBM using direct ELISA. Samples were collected and compared from patients with TBM, pyogenic meningitis, viral meningitis, fungal meningitis and non-infectious controls. Hsp 70 and Hsp 90 showed 89% & 88% sensitivity and 82% & 89% specificity, respectively for detection of TBM [21].

Imaging with cerebral computed tomography (CT) and cerebral magnetic resonance imaging (MRI) has improved assessment, prognostication and management in TBM. Classical findings include: tuberculomas (which are commonly supratentorial in adults), hydrocephalus, vasculitis and cerebral infarctions [22]. A retrospective study reviewing 404 TBM cases in Pakistan showed that tuberculomas were present in 50% of patients, while infarcts were present in 25%. Old age, presence of infarction and hydrocephalus were all predictors of poor outcome [23]. Paradoxical evolution defined as worsening of pre-existing lesions or appearance of new lesions in patients who showed initial improvement after anti-tuberculous therapy are now also well described. More than 50% of patients may show paradoxical neuroimaging manifestations in various forms: leptomeningeal enhancement, new tuberculomas, enlargement of pre-existing tuberculomas and new infarcts. Time to onset of paradoxical reactions after treatment initiation ranges from 1 to 9 months. Paradoxical imaging manifestations are often associated with clinical paradoxical manifestations and indicate treatment modification. Overall, outcome of TBM does not seem to be modified by paradoxical imaging manifestations even when associated with clinical manifestations [24]. Although more studies need to be done, these findings show that initial and follow-up neuroimaging is mandatory and is being increasingly used to manage patients and assess their outcome.

Treatment Regimens

Current international treatment recommendations include a four-drug regimen with anti-TB agents (rifampicin, isoniazid, pyrazinamide, and streptomycin) for two months followed by an additional seven to 10 months of bitherapy (isoniazid and rifampicin). Given the serious risk of disability and mortality, experts recommend nine to 12 months of treatment for TBM [25]. WHO recommends using streptomycin instead of ethambutol because of the doubtful penetration of ethambutol in the subarachnoid space? In Switzerland, experts recommend using amikacin instead of streptomycin (which is not available); recommendations for the rest of the regimen are as mentioned above [26].

The standard regimen used in the treatment of TBM is derived from guidelines for pulmonary TB. Current research is focused on intensified regimens and new associations to improve drug penetration in the CSF and thus lower mortality and morbidity rates. For many years, fluoroquinolones have been shown to have *in vitro* activity against M. tuberculosis [27]. Interesting results were reported in a study in Vietnam testing different fluoroquinolones in TB and their penetration in the CSF [28], with levofloxacin demonstrating a better penetration. However, patients with higher CSF concentrations of the drug had poorer outcomes than those with intermediate concentrations. These results may be biased by disease severity, as a higher CSF drug concentration is a consequence of a disrupted integrity of the blood-brain-barrier related to severity of infection (Figure 1).
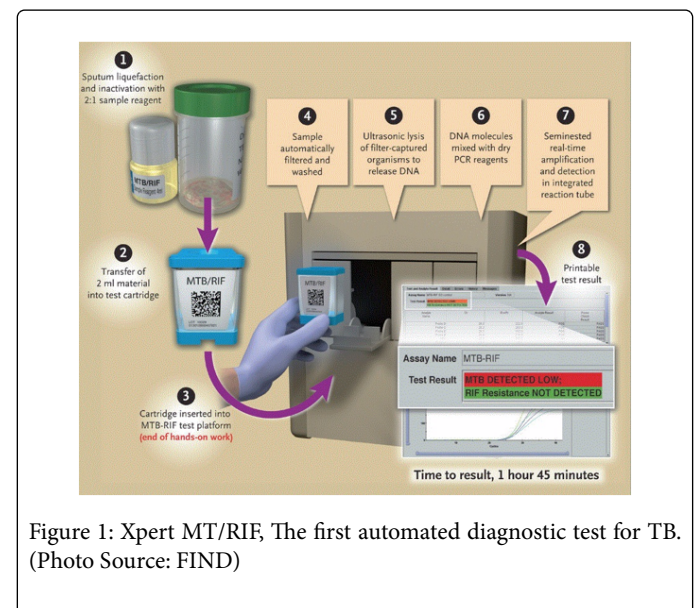

Figure 1: Xpert MT/RIF, The first automated diagnostic test for TB. (Photo Source: FIND)

Based on a previous study showing better clinical outcomes in patients with higher drug concentrations in the CSF [28], Ruslami and colleagues conducted a pharmacological-oriented study in which patients with TBM were assigned to an intensified regimen group (13 mg/kg of rifampicin intravenously) and standard therapy (approximately 10 mg/kg orally) for the first 14 days. Serial blood sampling and two samples of CSF were taken at specific times after drug administration. The results showed that higher doses of rifampicin given intravenously result in three-fold higher concentrations in plasma and CSF for up to six hours after drug administration. Although this study was not designed to evaluate clinical outcomes, there was an overall 50% reduction in the six-month mortality rate among patients in the intensified rifampicin group. Simultaneous treatment with moxifloxacin was also tested in a factorial design (designed to test all possible outcomes of multiples factors and their combinations). Results showed that doubling the moxifloxacin dose (800 mg instead of 400 mg) leads to higher concentrations in the CSF, but no reduction in mortality rates was shown with or without moxifloxacin, irrespective of the dosage [29].

A recent trial by Heemskerk and colleagues [30] compared a nine-month standard anti-TB regimen (including rifampicin 10 mg/kg/day) with an intensified regimen during the first eight weeks with higher-dose rifampicin (15 mg/kg/day) and levofloxacin (20 mg/kg/day). In contrast with previous reports [28,29], there was no difference in mortality in the two groups. Of note, the outcome was not related to the interruption of medication due to adverse events. However, a small survival benefit was observed in the subgroup with isoniazid-resistant

infection. According to the authors, this publication has some limitations that may have contributed to a negative result. The dose of rifampicin used in this study was lower than proposed by previous trials and the drug was administered orally and not intravenously, which could have had an effect on its bioavailability in the CSF.

Thus, even if these results suggest a benefit with high-dose rifampicin in TBM, the exact dosage and administration process remain unclear and more studies including a pharmacokinetic-pharmacodynamic analysis are needed before a change in current recommendations can be made. Although fluoroquinolones may be a replacement for isoniazid due to their good bactericidal activity and their benefit/adavantage in drug-resistant TB, they have not shown any effect on mortality rates. At present, the key determinants of survival from this dangerous infection remain early diagnosis and treatment [30].

Corticotherapy

Corticosteroids have long been used in addition to anti-TB treatment to decrease brain and meningeal inflammation in order to lower mortality and disabling residual neurological deficits among survivors, despite much controversy among clinicians. However, new evidence suggests that corticosteroids should become standard of care in patients with TBM, at least for those who are HIV-negative [3,31]. In a recent prospective, randomised, placebo-controlled trial, adjunctive corticotherapy (with Dexamethasone) for the treatment of TBM reduced mortality among patients over 14 years old, but there was no demonstrable effect on a combined endpoint of death and severe disability [3]. The effect of treatment was consistent across subgroups defined by disease severity (Grade I: Glasgow coma scale (GCS) of 15 with no focal neurological signs, Grade II: GCS between 11 and 14 or a GCS of 15 with a focal neurological sign; Grade III: GCS less than 10) and HIV status, although it did not reach statistical significance. The favorable effect of corticotherapy on survival may be explained by a reduction in inflammation both systemically and within the central nervous system. Reduction in inflammatory cytokine generation within the CSF may impair the diapedesis of neutrophils and mononuclear cells and prevent death from vasculitis-induced stroke and obstructive hydrocephalus. An additional explanation for the survival benefit, supported by the study findings, is the reduction of severe adverse events, including potentially fatal clinical hepatitis in patients treated with dexamethasone. Furthermore, reducing adverse events results in fewer modifications of the treatment regimen and may be an additional reason for improved overall survival [3].

A Cochrane meta-analysis of seven studies, including the above-mentioned trial, showed similar results with an overall reduction in the risk of death (relative risk [RR], 0.78; 95% CI, 0.67-0.91; 1140 participants). Data on disabling residual neurological deficits from three trials showed that corticosteroids reduce the risk of death or disabling residual deficits (RR, 0.82; 95% CI, 0.70-0.97; 720 participants) [31]. Corticotherapy regimens according to disease severity are presented in Table 1.

Concomitant HIV Infection

The combination of TBM and HIV infection are additional challenges because of the need to treat both infections and higher morbidity and mortality in concomitant HIV-infected patients [3]. In particular, the optimal timing for the initiation of anti-retroviral therapy (ART) in TB-infected patients is one of the main difficulties facing the clinician. The SAPit [32] trial conducted in South Africa compared the mortality related to two treatment strategies in patients co-infected with HIV and TB (mainly pulmonary) with CD4+ counts of <500 cells/mm^3. An integrated treatment (mean time of anti-TB treatment to ART initiation: 10 weeks) was compared to sequential treatment (mean time of anti-TB treatment to ART initiation: 37 weeks). A 56% reduction in mortality rates was observed with the earlier initiation of ART. Two recent studies demonstrated also a statistically significant reduction in the mortality rate in patients initiated on ART within the first two weeks of anti-TB therapy compared to those receiving later treatment (8-10 weeks) [33,34]. Of note, the population participating in these two studies had profound immunosuppression (mean CD4+ count <70 cell/mm^3).

Severity of disease	Corticotherapy regimen (Dexamethasone)
Grade I	**IV therapy for 2 weeks**
	• 1st week: 0.3 mg/kg/day
	• 2nd week: 0.2 mg/kg/day
	Oral therapy for 4 weeks
	• 3rd week: 0.1 mg/kg/day
	• 4th week: 3 mg/day
	• 5th week: 2 mg/day
	• 6th week: 1 mg/day (then tapering down)
Grade II & III	**IV therapy for 4 weeks**
	• 1st week: 0.4 mg/kg/day
	• 2nd week: 0.3 mg/kg/day
	• 3rd week: 0.2 mg/kg/day
	• 4th week: 0.1 mg/kg/day
	Oral therapy for 4 weeks
	• 5th week: 4 mg/day
	• 6th week: 3 mg/day
	• 7th week: 2 mg/day
	• 8th week: 1 mg/day (then tapering down)

Table 1: Corticotherapy regimens in tuberculous meningitis based on the severity of disease; Grade I: Glasgow Coma Scale (GCS) of 15 with no focal neurological signs, Grade II: GCS between 11 and 14 or a GCS of 15 with a focal neurological sign; Grade III: GCS less than 10; IV: Intravenous.

The overall risk of immune reconstruction inflammatory syndrome is higher in patients receiving early ART [32-34], although none of these reactions caused death in patients according to published trials. However, it should be taken into consideration that these studies were conducted either in patients with pulmonary TB [32] or mixed pulmonary and extra-pulmonary TB infections [33,34]. The only study comparing early ART (within two weeks) in TBM versus differed ART did not show any significant reduction in mortality and the rate of adverse events were high [35]. At present, the WHO guidelines [25] recommend the initiation of ART in adults with concomitant TB

infection after anti-TB treatment (within the first eight weeks), regardless of their CD4+ cell count.

Vaccination

Bacille-Calmette-Guérin (BCG) vaccine is a live strain of Mycobacterium bovis created nearly 100 years ago. BCG provides significant protection against severe disease (including meningitis) in children in endemic areas. Meta-analyses limited to trials in children vaccinated as neo-nates or infants showed an average protection against TB in prospective studies of 51% (RR 0.49, CI 95%: 0.34–0.70) and, in case–control studies, of 50% (OR 0.50, CI 95%: 0.39–0.64). Protection rate was 65% against TB-related death, 64% against TB meningitis and 78% against disseminated TB [36]. However, BCG has

not been proved effective in preventing tuberculosis infection in adults and controlling burden of disease worldwide. It is thus one of the highest priorities of TB research and funder community to develop new TB vaccines that are more efficient than BCG to achieve a better control of the disease [37,38]. Vaccine development has entered an accelerated phase over the last 15 years. At least 13 new "pipeline" vaccines including recombinant BCGs, whole-cell derived vaccines, recombinant viral-vectored platforms, protein and adjuvant combinations, and mycobacterial extracts [37] are currently entering human trials (Table 2). Some vaccine candidates already hold promise and signals of efficiency may be obtained over the next years: disease prevention with M72/AS01 (GSK) or *M. vaccae* product; prevention of infection with H4+IC31 (Sanofi) and disease recurrence prevention with IDRI candidate [38].

Phase I	Phase IIa	Phase IIb	Phase III
Ad5Ag85A[a] McMaster University, CanSino	RUTI [b] Archivel Farma	M72/AS01 [c] GlaxoSmithKline, Aeras	*M. vaccae* [d] AnHui, Longcom
ChAdO × 1.85A + MVA85A[a] Oxford University	ID93 + GLA-SE [c] Infectious Disease Research Institute, Aeras		
MVA85A (aerosol) [a] Oxford University	Dar-901 [d] Dartmouth University, Aeras		
MVA85A-IMX313 [a] Oxford University, Imaxio	VPM1002 [e] Serum Institue of India, Vakzine Projekt management, TBVI, Max Planck Institute for Infection Biology		
TB/FLU-04L[a] Research Institute for Biological Safety Problems	MTBVAC [e] University of Zaragoza, Biofabri, Tuberculosis Vaccine Initiative (TBVI)		
	H56 + IC31 [c] SSI, Valneva, Aeras		
	H4 + IC31 [c] Statens Serum Institute (SSI), Sanofi Pasteur, Valneva, Aeras		

Table 2: TB vaccine pipeline (Source: TAG pipeline report 2016); [a]Viral Vector; [b]Fragmented MTB; [c]Protein/adjuvant; [d]Whole Cell; [e]Live vaccine.

Conclusion

The diagnosis of TBM remains a challenging task, but clinicians can make the diagnosis based on clinical probability, including imagery and CSF analysis. Treatment should be started when suspicion is high, regardless of the diagnostic strategy chosen. The Xpert MTB/RIF platform should be used as the initial diagnostic test in CSF when TBM is suspected (strong recommendation according to WHO guidelines). Clinicians must bear in mind that the sensitivity rate of this assay (pooled sensitivity of 79%) [11] can be improved by providing larger samples, repeating the lumbar puncture, and adding a concentration step before the assay [10,12,13]. Use of biomarkers may improve early diagnosis in a near future. Although no biomarker has been validated for TBM diagnosis yet, new studies have shown good potential for progression in this field [19-21]. Neuroimaging is important in TBM for diagnosis and follow-up [22-24]. The mortality and disability rates in TBM show the importance of a rapid diagnosis and prompt treatment initiation.

The question of the benefit of high-dose rifampicin therapy and fluoroquinolone adjuvant therapy is still a subject of debate and more studies need to be performed in order to make recommendations. There is possibly a benefit in carefully selected patients [28], in

isoniazid- resistant infections [19], and using high rifampicin doses given intravenously [29]. Systemic corticosteroids should be given to all patients as an adjuvant to anti-TB therapy and the regimen should be tailored for each patient according to the individual severity of disease (Table 1).

For patients with concomitant HIV infection, there is high quality evidence showing a benefit for the early initiation of ART. WHO guidelines [26] recommend initiating ART treatment as soon as possible after anti-TB treatment (within the first eight weeks) and within the first two weeks in case of severe immunosuppression (CD4+ < 50 cell/mm^3) [39,40].

New vaccines for tuberculosis are at different stages of clinical trials (Table 2), which sheds some hope on future prevention and control of this high burden disease.

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