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Advance Laboratory Diagnosis of Tuberculous Meningitis: A Mini Review

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ABSTRACT

Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis (TB) and has very high morbidity and mortality. TBM is typically a sub acute disease with symptoms that may persist for weeks before diagnosis. Characteristic cerebrospinal fluid (CSF) findings of TBM include a lymphocytic-predominant pleiocytosis, elevated protein, and low glucose. CSF acid-fast smear and culture have relatively low sensitivity but yield is increased with multiple, large volume samples. Nucleic acid amplification of the CSF by PCR is highly specific but suboptimal sensitivity precludes ruling out TBM with a negative test.

Key words: *Tuberculous meningitidis; Tuberculous meningitidis diagnostic test; Nucleic acid assay.*

INTRODUCTION

Tuberculous meningitis is also known as TB meningitis or tubercular meningitis. Tuberculous meningitis is *Mycobacterium tuberculosis* infection of the meninges the system of membranes which envelops the central nervous system. It is the most common form of CNS tuberculosis.

Tuberculous meningitis (TBM) is caused by Mycobacterium tuberculosis (M. tuberculosis) and is the most common form of central nervous system (CNS) tuberculosis (TB). TBM is associated with a high frequency of neurologic sequelae and mortality if not treated promptly [1-5]. TBM is rare in developed countries with about 100 to 150 cases occurring annually in the US, less than 3% of the estimated 4,100 annual cases of bacterial meningitis [6-7]. The disease occurs when subependymal or subpial tubercles, also known as "Rich foci" seeded during bacillemia of primary infection or disseminated disease, rupture into the subarachnoid space [8]. Individuals with increased risk for TBM include young children with primary TB and patients with immunodeficiency caused by aging, malnutrition, or disorders such as HIV and cancer [9-10]. The use of antitumor necrosis factor-alpha (TNFα) neutralizing antibody has also been associated with increased risk of extra pulmonary TB including TBM [11]. Most have no known history of TB, but evidence of extra meningeal disease (e.g., pulmonary) can be found in about half of patients [3-4]. The tuberculin skin test is positive in only about 50% of patients' with TBM. In low TB prevalence areas, TBM is most commonly seen with reactivation TB.

Diagnosis:

The diagnosis of TBM can be difficult and may be based only on clinical and preliminary cerebrospinal fluid (CSF) findings without definitive microbiologic confirmation. Certain clinical characteristics such as longer duration of symptoms (>six days), moderate CSF pleiocytosis, and the presence of focal deficits increase the probability of TBM [12-13]. Characteristic CSF findings of TBM include the following:

(i) lymphocytic-predominant pleiocytosis. Total white cell counts are usually between 100 and 500 cells/μL. Very early in the disease, lower counts and neutrophil predominance may be present,

(ii) Elevated protein levels, typically between 100 and 500mg/dL,

(iii) Low glucose, usually less than 45mg/dL or CSF: plasma ratio<0.5.

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CSF sample should be sent for acid-fast smear with the important caveat that a single sample has low sensitivity, on the order of 20%–40% [14]. Several daily large volume (10–15mL) lumbar punctures are often needed for a microbiologic diagnosis; sensitivity increases to>85% when four spinal taps are performed [15]. Early studies demonstrated that acid-fast stains can detect up to 80% [15] although results are highly dependent on CSF volume, timeliness of sample delivery to the lab and analysis, and the technical expertise of lab personnel. While culture can take several weeks and also has low sensitivity (~40–80%), it should be performed to determine drug susceptibility. Drug-resistant strains have important prognostic and treatment implications; indeed, TBM due to isoniazid-(INH-) resistant M. tuberculosis strains have been associated with a twofold in-crease in mortality [16].

Given the relatively low sensitivity of acid-fast smear and inherent delay in culture, newer diagnostic methods for TBM have been more recently developed [14]. Although ELISA assays have been developed to detect antibodies directed against specific mycobacterium antigens in the CSF with varying sensitivities, their limited availability precludes their use as point-of-care tests in resource-poor countries [14, 17]. A recent study in children aged 6–24 months suggests that a CSF adenosine deaminase level of ≥10U/L has >90% sensitivity and specificity of diagnosing TBM [18]. However, other studies have shown poor specificity of adenosine deaminase for TBM in certain populations, particularly in HIV-infected adults with concurrent infections or cerebral lymphomas [19].

Nucleic acid amplification tests (NAAT):

This is a heterogeneous group of tests that use polymerase chain reaction (PCR) to detect mycobacterial nucleic acid. These tests vary in which nucleic acid sequence they detect and vary in their accuracy. The two most common commercially available tests are the amplified mycobacterium tuberculosis direct test (MTD, Gen-Probe) and Amplicor. In 2007, a systematic review of NAAT by the NHS Health Technology Assessment Programme concluded that for diagnosing tuberculous meningitis "Individually, the AMTD test appears to perform the best (sensitivity 74% and specificity 98%)" [20]. [In the NHS meta-analysis, they found the pooled prevalence of TB meningitis to be 29%; however there was much heterogeneity in the reported sensitivities. Using a clinical calculator, these numbers yield a positive predictive value of 94% and a negative predictive value of 90%; however the 30% prevalence may be high due to referral bias. Alternate estimates of disease prevalence can be entered into the clinical calculator to refine the predictive values. These instances vary from patient to patient according to their pathology.

Comparison of microscopy/culture of large CSF volumes to nucleic acid amplification (NAA) has shown that sensitivity of these methods for the diagnosis of TBM is similar [21]. A meta-analysis determined that commercial NAA assays utilizing polymerase chain

reaction (PCR) for the diagnosis of TBM had an overall sensitivity of 56% and a specificity of 98% [22]. The surprisingly poor sensitivity is likely due to the fact that most PCR-based studies use a single target for amplification which can result in false-negative results due to the absence of the target gene in some TB isolates [23]. Newer PCR tests amplify several target genes simultaneously and have been shown to result in much higher sensitivities in the range of 85%–95% [24]. Currently, most experts conclude that commercial NAA tests can confirm TBM but cannot rule it out [20]. Thus, it bears emphasizing that a negative CSF examination for acid-fast bacilli or *My. tuberculosis* DNA neither excludes the diagnosis of TBM nor obviates the need for empiric therapy if the clinical suspicion is high. After starting treatment, the sensitivity of CSF smear and culture decreases rapidly, while mycobacterium DNA may be detectable in the CSF for up to a month after treatment initiation [25].

CONCLUSION

Meningitis is the most deadly form of TB, particularly in persons co infected with HIV. Early diagnosis and treatment can dramatically reduce the high mortality associated with this disease. There is a need to urgently address deficiencies in the diagnostic service for tuberculosis meningitidis. There have been many advances in methodology for tuberculosis meningitides diagnosis and earlier diagnosis is of value clinically, and through the early institution of appropriate drug therapy is of public-health benefit. Nevertheless, many diagnostic tests have given promising results initially only to prove less effective in routine use. This is frequently due to bias resulting from non-independent interpretation of test results.

While, at present many of these techniques are only economically viable in the developed nations, it is to be hoped that recent advances will lead to the development of novel diagnostic strategies applicable to use in developing nations, where the burden of tuberculosis meningitidis is greatest and effective intervention most urgently required.

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