

Management of Tuberculous meningitis – A review

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Abstract

Tuberculous Meningitis (TBM) is one of the leading causes of deaths and disabilities in the developing nations like India. Rapid diagnosis of the cases is essential to minimise the mortality and morbidity. Although clinical diagnosis is made based on the presenting symptoms, signs and radiological imaging studies, confirmation of the diagnosis is still difficult and there are significant diagnostic and treatment challenges. Cerebro spinal fluid (CSF) examination shows a lymphocytic-predominant pleiocytosis, elevated protein, and normal or low glucose. Multiple and repeated Culture and CSF examination by acid fast staining and PCR usually may show good results. Empirical treatment with at least four first-line drugs, preferably isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol is usually started in clinical suspected cases with supportive initial CSF findings. Corticosteroid can be added as adjunctive treatment, but its benefits remains doubtful. Drug interactions, possibility of drug resistant tuberculosis and development of immune reconstitution inflammatory syndrome needs to be kept in mind in initiating the TBM treatment in patients who are HIV positive. This review article throws light into the current practice in the laboratory diagnosis and management of Tuberculous meningitis.

Keywords: Tuberculous Meningitis, Tuberculosis, Diagnosis, Treatment, Prognosis.

Introduction

Tuberculous meningitis (TBM) caused by *Mycobacterium tuberculosis*, is one of the serious manifestation of extrapulmonary tuberculosis with high mortality and morbidity if not diagnosed and treated properly.^(1,2) World Health Organisation (WHO) has estimated that one third of the world's population is infected with tuberculosis (TB) among which the highest prevalence is in Asia.^(3,4) About 10% of the tuberculosis cases develop Central nervous system (CNS) disease.⁽⁵⁾ TBM remains as a serious infectious cause of chronic meningitis in the developing countries.⁽⁶⁾ In spite of the modern antituberculosis therapy, death occurs in around 20 to 50% patients with TBM.⁽⁷⁾ The estimated mortality rate of TBM cases in India is around 1.5 per 100000 population.⁽⁸⁾

This disease usually occurs when the subependymal or subpial tubercles from the bacilleamia during primary infection gets dislodged and ruptures into subarachnoid space.⁽⁹⁾ *M.tuberculosis* bacilli may be released into the meningeal space causing obstruction in the CSF flow leading to hydrocephalus or formation of tuberculomas/abscesses or occurrence of infarction and stroke syndromes due to obliterative vasculitis.⁽¹⁰⁾

The incidence and progression of primary tuberculosis to TBM is higher in young children with tuberculosis.⁽¹¹⁾ The incidence of TBM is higher in children below 5 years.⁽¹²⁾ Patients with TBM usually present with symptoms of subacute meningitic illness, which is similar to other cases of meningoencephalitis in the initial stages. Diagnosis becomes apparent in the advance stages when the neurological symptoms like coma, seizure, hemiparesis, raised intracranial tension, etc. may be present. But the prognosis becomes poor in

the advance stages. According to the British Medical Research Council TBM Grade, severity of TBM is classified into 3 grades, which helps in predicting the prognosis of the cases.⁽¹³⁾ Grade 1 includes Glasgow coma score (GCS) of 15 with no focal deficits, Grade 2 includes GCS of 15 with focal neurological deficits or GCS 11-14 and Grade 3 TBM include patients with GCS ≤ 10 .⁽¹³⁾

Literature reports the case fatality rates ranging from 20% to 32%, with permanent neurological deficits in 5% to 40% of the survivors.⁽¹⁴⁾ Human Immuno Deficiency Virus (HIV) infection also predisposes to the development of tuberculous meningitis.⁽¹⁵⁾ Case fatality rate is high in HIV coinfection cases.^(16,17) In spite of the availability of new antituberculosis drugs and modern diagnostic techniques, the mortality and morbidity of TBM remains high.⁽¹⁸⁾

Clinical manifestations of TBM

TBM usually presents as a subacute disease with symptoms for weeks prior to the diagnosis.^(19,20) Low-grade fever, malaise, headache, dizziness, vomiting, weight loss may occur in the prodromal phase which may persist for weeks. Seizures may occur rarely in TBM in adults, but common in pediatric cases with occurrence upto 50%.⁽²¹⁾ The neurological consequences in TBM include altered mental status, urinary retention, vomiting, confusion, stroke, hydrocephalus and cranial neuropathies.⁽²²⁾ Unlike bacterial meningitis, Neck stiffness and fever may sometimes be absent in TBM. In untreated cases, the disease may progress to Coma and death. On clinical evaluation, the patients may show apathy, reduced level of consciousness, bulging anterior fontanelle in infants, cranial nerve palsies, focal

neurological signs, etc. Movement disorders like tremors, chorea, ballismus, myoclonus may occur after basal ganglia infarction.⁽²³⁾ Tuberculoradiculomyelitis characterised by subacute parapareses may occur in few cases. Hyponatremia due to hypothalamic dysfunction is quite common in TBM.

Diagnosis of TBM

TBM still remains a diagnostic challenge. Diagnosis becomes difficult in unusual neurological presentations of TBM cases. Appropriate diagnosis of the cases is essential to achieve good outcomes. In majority of cases, the diagnosis of TBM is empirical and is based on the clinical, radiological and laboratory results.

Laboratory diagnosis of TBM is based on many diagnostic methods. Often, the diagnosis largely depends on CSF examination and lumbar puncture. The diagnosis of TBM in the initial stages largely depends on clinical suspicion and preliminary CSF findings. Longer duration of symptoms usually more than 6 days, raised CSF white cell count and presence of focal deficit favours the diagnosis of TBM.^(24,25) The hallmark CSF findings in TBM include high white cell count (0.05 to $1 \times 10^9/L$) with neutrophils and lymphocytes, increased protein levels (0.5 – 2.5 g/l) and normal or low glucose levels (<45 mg/dL). Acid fast staining of CSF smear has low sensitivity.⁽²⁶⁾ Several daily large volume (10 – 15 mL) lumbar punctures may increase the sensitivity to $>85\%$ when four spinal taps are performed.⁽²⁷⁾ Studies report that acid fast stains can detect up to 80% , but the results largely depend on the high volume of CSF, immediate delivery of the sample to the laboratory and prompt analysis and the expertise of the lab personnel. Studies report that sensitivity of Ziehl Neelson staining is increased when CSF leucocytes are pre-treated with triton.⁽²⁸⁾ In HIV coinfecting TBM cases, atypical CSF findings like normal cell counts with polymorphonuclear cell predominance and normal glucose levels may be present.⁽²⁹⁾

Acid fast smear remains the most common diagnostic method of TBM. For all suspected cases of TBM, the CSF sample should be screened for acid fast bacilli along with Gram staining, India ink preparation and antigen testing for *Cryptococcus neoformans*.

CSF culture may take several weeks and should be performed mainly for determining drug susceptibility rather than initial diagnosis. MODS (Microscopic Observation Drug Susceptibility Assay) is a liquid culture method found to be useful in the diagnosis of tuberculosis and drug susceptibility testing where the CSF deposit is inoculated and incubated in a microtitre plate and growth examined by an inverted microscope.⁽³⁰⁾ CSF can also be inoculated in liquid media like Mycobacterial growth indicator tube (MGIT), Becton Dickinson and should be incubated for about 6 weeks. Presence of growth can be detected by fluorescent growth indicator embedded in silicone at the bottom of MGIT tube. However, these methods require

containment level 3 facilities and experienced laboratory personnel. Studies report that the rate of recovery of *M.tuberculosis* is higher in Bactec MGIT 960 system (Becton Dickinson, Sparks, MD, USA) than the routine LJ (Lowenstein Jensen) medium.⁽³¹⁾ Radiometric Bactec460 (Becton Dickinson, Heidelberg, Germany), MB Bact (Organon Teknika, Boxtel, The Netherlands) and ESP II (Difco Laboratories, Detroit, MI, USA) are the few other automated commercially available systems for rapid detection of mycobacteria.⁽³¹⁾

Because of the relatively low sensitivity of acid fast smear and the delay in growth in culture methods, newer diagnostic methods have developed in diagnosing TBM. NAAT (Nucleic Acid Amplification Test), Line Probe assays (LPA) and the Xpert MTB/RIF can also be used in the diagnosis of TBM. The Gene Xpert MTB/RIF is a fully automated PCR (Polymerase chain reaction) which helps in diagnosis of Tuberculosis as well as detection of Rifampicin drug resistance. Line probe assays can detect common genetic mutations conferring drug resistance. However, these methods are expensive. Interferon γ release assays (IGRA) are of use in latent tuberculosis which can detect the immune response to the *M.tuberculosis* antigens, but needs large amount of CSF for diagnosing TBM.

Enzyme Linked Immuno Sorbent Assay (ELISA) helps in detecting antibodies against the CSF mycobacterial antigens.⁽²⁴⁾ Antigen-capture ELISA test helps in the detection of lipoarabinomannan (LAM) antigen in urine of TBM in children, but the sensitivity is poor.⁽³²⁾

Few studies report that CSF adenosine deaminase levels of ≥ 10 U/L has $>90\%$ sensitivity and specificity of diagnosing TBM,⁽³³⁾ but other studies have reported poor specificity of adenosine deaminase for TBM in HIV-infected adults.⁽³⁴⁾ Studies report that commercial Nucleic acid amplification (NAA) assays which utilize PCR for the diagnosis of TBM had an overall sensitivity of 56% and a specificity of 98% .⁽³⁵⁾ Mycobacterial deoxyribonucleic acid (DNA) may be detectable in the CSF for up to a month after treatment initiation.⁽³⁶⁾ PCR is considered as one of the specific methods for rapid diagnosis of tuberculous meningitis.⁽³⁶⁾

Neuro imaging helps in the diagnosis of TBM. Radiological findings include basal meningeal enhancement and hydrocephalus.⁽²⁶⁾ Magnetic Resonance Imaging (MRI) is considered superior to CT (computed tomography) scan in visualising the abnormalities associated with TBM. T2 weighted MRI imaging is good in demonstrating the brain stem pathology and diffusion weighted imaging is good in detecting acute cerebral infarcts due to TBM.⁽³⁷⁾ CT scan helps in urgent diagnosing TBM associated hydrocephalus prior to surgical intervention.

In an experimental study of proteomic analysis of CSF in TBM patients, arachidonate 5-lipoxygenase (ALOX-5), has been identified as a novel biomarker of TBM.⁽³⁷⁾

Treatment of TBM

Prompt and timely treatment may result in better outcome of TBM cases. Untreated cases are highly fatal. Initiation of empirical treatment is emphasised when the clinical suspicion and the initial CSF findings are suggestive of TBM. The drugs used in the treatment of TBM include Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Streptomycin (SM) and Ethambutol (EMB). The second line drugs which can also be used in treatment are ethionamide, cycloserine, ofloxacin and para amino salicylic acid. INH, RIF and PZA are bactericidal in nature. They are considered as the best first line drugs to begin with. Duration of treatment of the antitubercular drugs in TBM management is conflicting.⁽³⁹⁾

WHO (2010) recommends a longer therapy for TBM for about 9-12 months based on the risk of disability and mortality,⁽⁴⁰⁾ British Infection Society (2009) recommends a minimum of 12 months regimen,⁽⁴¹⁾ Indian Academy of Pediatrics (2010) recommends a continuation phase for 6-7 months which can even be extended to 8-9 months.⁽⁴²⁾ American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (2003) recommends a 9-12 months treatment regimen for TBM.⁽⁴³⁾

The common treatment regimen consists of 2 months intensive phase of daily INH, RIF, PZA and Ethambutol and followed by 7-10 months continuation phase of INH and Rifampicin.^(41,44) INH has very good CSF penetration and bactericidal activity.^(45,46) Mortality has been found to be increased in TBM patients with resistant RIF strains.⁽⁴⁷⁾ PZA also has good CSF penetrating capacity; hence in resistant cases with PZA intolerance, the treatment duration is lengthened to 18 months.⁽⁴⁸⁾ Fluoroquinolones esp levofloxacin and moxifloxacin has got excellent CSF penetration and can be used as one of the drugs in first line therapy of TBM.⁽⁴⁹⁾

MDR TBM (Multidrug Resistant Tuberculous meningitis) is defined as resistant to INH and RIF. Ethionamide, Cycloserine, Amikacin, Streptomycin, Capreomycin, Para amino salicylic acid, Thioacetazone, Linezolid are some of the second line drugs in use. bedaquiline (TMC207, a diarylquinoline) and delamanid (OPC-67683, a nitro-di-hydroimidazo-oxazole), sudoterb (LL3858, a pyrrole derivative), PA-824 (a nitroimidazo-oxazine), and SQ109 (an analogue of EMB) are few of the newer anti tuberculous drugs under clinical trials.

Corticosteroids are used as an adjunctive treatment for TBM, but its use in adults is controversial. Corticosteroid is said to improve the outcome by reducing the cerebral and spinal edema and by decreasing the inflammation in the subarachnoid space and in the small blood vessels thereby reducing the damage caused by the blood flow.⁽¹⁴⁾ It was feared that corticosteroid may decrease the penetration of anti TB

drugs into CSF.⁽⁵⁰⁾ Another study demonstrated that steroids did not have any effect on the first line anti TB drug's CSF penetration.⁽⁵¹⁾ Rock et al in his study reported that Mycobacterium tuberculosis affects the microglial cells of infected brain tissue than the astrocytes and has shown that co incubation of the steroids with the TB infected microglial cells has significantly decreased the production of inflammatory mediators.⁽⁵²⁾ Few studies showed that Corticosteroids helped in better outcome in HIV negative children and adults with TBM⁽⁵³⁾ and significantly decreases the mortality.⁽⁵⁴⁾

In few patients with TBM, there can be anti diuretic hormone (ADH) stimulation resulting in aggravation of cerebral edema indirectly due to shifting of water from intravascular compartment to extravascular compartment of the brain. Hence it was unjustified in an article that fluid intake should be restricted in cerebral edema.⁽⁵⁵⁾ Instead, it was recommended that cerebral perfusion should be maintained and hypovolemia induced ADH release should be prevented.

Hydrocephalus is one of the common complications in TBM patients with incidence of more than 75% of the cases.⁽⁵⁶⁾ Ventriculo peritoneal (VP) shunt placement and endoscopic third ventriculotomy are the surgical techniques of choice in relieving the high Intracranial pressure (ICP) in TBM.⁽⁵⁷⁾ Hydrocephalus and increased ICP are found to occur more commonly in children. Due to increase in morbidity and mortality, surgical intervention is usually recommended grade 2 or 3 TBM hydrocephalus (mild or moderately altered sensorium) and not in deeply comatose grade 4 patients. However, another study demonstrated favourable outcome of VP shunt in 33 – 45% of grade 4 TBM hydrocephalus patients.⁽⁵⁸⁾

Ravi palur et al have published about the trial of external ventricular drainage in poor grade TBM patients before selecting them for VP shunt as the prognosis for poor grade patients is very poor.⁽⁵⁹⁾

Tuberculosis (TB) is one of the commonest opportunistic infections in HIV patients. Generally, the diagnosis and management of TBM in HIV infected patients is almost similar to that of non HIV patients, but Immune reconstitution inflammatory syndrome (IRIS), efficacy of corticosteroids as adjuncts to the anti TB drugs and antiretroviral therapy, drug interactions and toxicity and drug resistance TB should be kept in mind in HIV infected patients. Concurrent treatment of TBM in HIV patients is challenging. There is a risk of drug interactions in concurrent use of anti TB drugs and anti-retroviral (ART) drugs. Concurrent treatment of both the diseases has been reported to improve survival rate,⁽⁶⁰⁾ but there is an increased risk of drug interactions and drug toxicities, high pill burden, TB-IRIS, etc. But, there is increased risk of morbidity if anti-retroviral therapy is delayed in HIV patients with TB co infection.⁽⁶¹⁾

The adjunctive use of corticosteroid treatment for HIV and TB co infected patient's remains uncertain.⁽⁵³⁾

In HIV patients who develop TB –IRIS where the other possible causes being ruled out, the use of Prednisone has been reported to be beneficial.⁽⁶²⁾ Tapering doses of Corticosteroids in TBM^(63,14) is for 6 weeks in case of stage 1 TBM and 8 weeks in case of Stage 2 and 3 TBM. Many studies reported that MDR TB is common in HIV infected patients co infected with TBM.⁽⁶⁴⁾ It is also noted that even in cases without drug resistant TB, HIV co infection alone may lead to worse prognosis.⁽⁶⁵⁾ In TBM patients with arachnoiditis, hyaluronidase administered intrathecally has been found to be beneficial.⁽⁶⁶⁾

Prognosis

Prognosis of TBM patients largely depends on severity of TBM and the neurological status at the time of clinical presentation, age of the patient, prompt initiation of treatment, etc.⁽⁶⁷⁾ Ideally empirical treatment is recommended in all suspected cases, because any delay in medication would lead to worse outcome. Mortality rate has been found to be high in patients with severe neurological involvement on admission and in extremes of ages.⁽⁶⁷⁾ Prognosis was reported to be grave in patients with lower age.⁽⁶⁷⁾ However, another study by Chang et al showed that age is not a significant prognostic factor.⁽⁶⁸⁾ Studies reported that a low CSF glucose and a high CSF protein levels may also be a significant prognostic factor.⁽⁶⁹⁾ In spite of adequate treatment of the complications, the prognosis in few patients may be poor. Studies reported that prognosis could be worse in TBM patients with obstructive hydrocephalous than the patients with communicating hydrocephalous.⁽⁷⁰⁾ This could be due to extensive tuberculous exudates causing ischemia of the cerebral vessels in the subarachnoid cisterns of the central nervous system.⁽⁷¹⁾ However, timely surgical intervention may play a critical role in the prognosis in patients with hydrocephalous.⁽⁷²⁾ Delayed diagnosis and treatment, extremes of ages, associated chronic illnesses, and advanced stage of the disease are the various precipitating factors for the high mortality and morbidity of TBM.^(73,74)

Conclusion

TBM still remains one of the most lethal complications of tuberculosis. Extremes of ages, advanced stages of illness, delay in the diagnosis and management may lead to high morbidity and mortality. Therapeutic measures which may preserve cerebral perfusion and reduce the risk of thrombosis may be helpful. In cases of HIV co infected TBM, clinicians need to be aware and monitor for the harmful toxicities of ART and TB treatment. Rapid early diagnosis and prompt treatment of TBM is the best way to improve the survival rate. Since the culture results may delay the diagnosis, the combined use of other non-culture techniques may help in early diagnosis of TBM. Smear microscopy, automated nucleic acid amplification

techniques and the use of other novel biomarkers warrant further exploration. Ideally a combination of diagnostic techniques works better than any single method. Newer Laboratory diagnostic methods are immediate requirements to improve rapid and reliable diagnosis. The use of newer anti tubercular drugs such as bidaquiline, PA – 824, etc. in the management of TBM needs to be explored. Therefore, large scale longitudinal studies involving combination of conventional culture and non-culture techniques along with newer molecular diagnostic methods are the current need for specific diagnosis of TBM.

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