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Tuberculous Meningitis: A Detailed Review

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Abstract

Tuberculous meningitis (TBM) is a medical emergency. This is the most severe form of tuberculosis (TB). Appropriate therapy and early diagnosis are critical to the result. If there is a high level of clinical suspicion, empirical antituberculosis therapy ought to be initiated. HIV testing must be performed on every patient. Numerous antituberculosis medications have poor penetration into the cerebrospinal fluid, and the selection of these medications is based on the pulmonary TB regimen. To guide pharmacological therapy in TBM, more evidence is needed. The host's genotype may affect the response to steroids, which should be given as an adjuvant therapy. Complications include stroke, hyponatremia, and hydrocephalus should be actively monitored.

Keywords: Crowding, Extrapulmonary TB, Malnutrition, Tuberculosis

Introduction

A significant worldwide health concern, tuberculosis (TB) continues to be a significant public health concern in India. Although Mycobacterium TB can essentially damage any region of the body, the effects are most severe when it affects the brain. Around 1 lakh new instances of tuberculous meningitis (TBM) occur worldwide each year, making it the most debilitating and incapacitating kind. Geographical location, age group, and HIV prevalence all affect the incidence and prevalence of TBM globally. Two-thirds of all TB cases in 2017 occurred in eight countries: Bangladesh, India, China, Indonesia, the Philippines, Pakistan, Nigeria, and South Africa. urbanization, crowding, poverty, malnutrition, injectable drug use, long-term steroid usage, chronic renal failure, incarceration, HIV, diabetes, and alcoholism are the main risk factors contributing to the TB epidemic. Delays in presentation, dependence on alternative or traditional medicine, incapacity or refusal to perform lumbar puncture, lack of laboratory facilities, and the unavailability or inability to purchase antibiotics are the main causes of gaps in diagnosis and treatment. According to the Indian national guidelines for extrapulmonary TB, TBM accounts for 1% of all TB patients.[1] Because TBM is difficult to diagnose, it is typically underreported. In terms of preventing TBM, the neonatal bacillus Calmette–Guérin (BCG) vaccine may be 73% effective.[2] TBM still has a very high death rate. According to a Cochrane review, the mortality rates for TBM with and without steroids were 41% and 31%, respectively.[3] The mortality rate for TBM in HIV coinfection is approximately 40%, even with

antiretroviral therapy (ART). [4,5] When HIV-1 co-occurs with drug-resistant TBM, the death rate is almost 100%.[6]

Pathogenesis

The lung serves as the initial point of entry for Mycobacterium tuberculosis, an airborne infection. The infection spreads to the lymph nodes after first replicating it in the lungs. Extrapulmonary TB, including TBM, is caused by the spread of TB bacilli through blood. In the meninges or parameningeal regions, the bacilli settle and create a localized granuloma known as a rich focus. The bacilli spread into the subarachnoid space as a result of the rupture of the rich focus, eventually affecting the blood vessels and brain tissue. A brain abscess or tuberculoma may be the cause of parenchymal involvement. Vasculitis, an inflammation of the vessels that can lead to vascular blockage and strokes, is brought on by meningeal inflammation, which also produces basal exudates in the base of the brain. The most often affected vessels are the middle cerebral artery's perforating branches, which cause infarcts in the internal capsule and basal ganglia. Elevated intracranial pressure (ICP) and hydrocephalus brought on by basal exudates obstructing the flow of cerebrospinal fluid (CSF) may exacerbate the ischemia. TBM may be a component of the early disseminated infection in children with HIV-1 coinfection.[7] Extrapulmonary TB, particularly TBM with hidden meningeal illness, is more common in HIV-TB coinfection, and blood culture positivity is higher (40%) in HIV-1 co-infection. TBM-associated Immune Reconstitution Inflammatory Syndrome (IRIS) is more common in HIV-1 coinfected patients because antiretroviral therapy may reveal the occult meningeal illness. Both bacterial multiplication in the brain and a dysregulated host immunological response, including reactive oxygen species, are involved in the pathophysiology of TBM. Microglia absorb Mycobacterium TB bacilli after they have passed through the blood–brain barrier. The generation of cytokines and chemokines is a result of bacilli multiplying inside microglia. Given that steroids are used to treat TBM, the fact that many individuals exhibit pituitary dysfunction is noteworthy. Cytokines linked to immunology and TBM survival include interleukin-1β, matrix metalloproteinases, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). The immune response in TBM can be modulated by genetic variations in different host response genes. The balance between immunosuppressive lipoxin A4 and pro-inflammatory leukotriene B4 can be impacted by a single nucleotide variation in the leukotriene A4 hydrolase (LTA4H) promoter. The recruitment of inflammatory cells, TBM patient survival, and reaction to anti-inflammatory therapy are all correlated with the LTA4H polymorphism.

Clinical Features

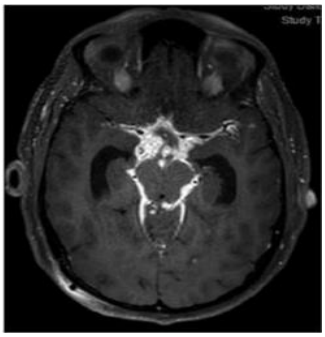
TBM's clinical manifestations are not particular. Cryptococcal meningitis and partially treated pyogenic meningitis are significant differential diagnoses. Fever, headache, vomiting, stiff neck, exhaustion, weight loss, appetite loss, altered sensorium, and focal deficits (cranial nerve palsies, vision loss, hemiparesis, and paraparesis) are typical signs and symptoms of TBM. The start is typically subtle, with a prodromal phase that lasts for days to weeks and includes symptoms like lethargy, appetite loss, and night sweats. This is followed by meningitis symptoms including fever, headache, and stiff neck. The patient may exhibit a number of problems, including hemiparesis, coma, altered sensorium, or cranial nerve palsies, if treatment is not received. TBM is a serious medical condition. The best thing a doctor can do for a patient with TBM is to treat them before a coma develops. He pretests probability of TBM is high in

endemic regions like India, and patients suspected of having TBM should be evaluated for empirical treatment. The host immunological response also affects the clinical characteristics. Extrapulmonary dissemination and TBM are frequent with HIV-1 coinfection in very young infants (less than one year of age). Additionally, they may appear with substantial morbidity and mortality in a sudden, quickly progressing coma. The result in TBM is highly predicted by the Medical Research Council's (MRC) disease severity grade. [8,9] Other significant risk factors for death include drug-resistant TB, age extremes, and HIV-1 coinfection. To determine the diagnostic predictors of TBM based on age group, setting, and HIV status, several clinical grading systems have been investigated. Not many have received external validation. But not all ratings that have been externally verified have performed well in terms of specificity and sensitivity. In the HIV-coinfected Malawian population, Thwaites score, which has been validated in several countries, performed poorly (sensitivity 78% and specificity 43%), with most false-positive cases being cryptococcal meningitis.[10,11] Published primarily for research purposes, the consensus case definition for TBM was not very helpful as a clinical diagnostic tool.

Imaging

The two most popular imaging modalities are magnetic resonance imaging (MRI) and computed tomography (CT). When it comes to identifying infarcts and tuberculomas, MRI offers superior resolution. Basal exudates, tuberculomas, and hydrocephalus are typical brain imaging findings in TBM.[12] A common appearance of tuberculomas and tubercular abscesses is ring-enhancing lesions.

The common differentials are Neurocysticercosis, fungal abscess, bacterial abscess, gliomas, metastasis, toxoplasmosis are differential diagnosis



Diagnosis

The primary technique for early TB diagnosis has been the identification of TB bacilli by Ziehl-Neelsen staining. Its sensitivity in TBM is only 10% to 20%, nevertheless. A skilled microbiologist can increase the sensitivity of CSF microscopy by taking a big volume of CSF (10 ml), centrifuging it at 3000 RPM, and then looking it over for 30 minutes.[13] In liquid media, the culture takes at least 10 days, and in solid media, it takes 8 weeks. As a result, cultures in TBM seldom assist in therapeutic decision-making. Although numerous nucleic acid amplification tests have been created, very few of them have undergone thorough validation.[14,15] Mycobacterium tuberculosis can be found in clinical specimens using the real-time polymerase chain reaction-based assay GeneXpert, which can also identify mutations linked to rifampicin resistance. The assay has a nearly 100% specificity and a 60% sensitivity. The purpose of the test should be to "rule in" rather than "rule out" the diagnosis of TBM.[16,17] According to the WHO, the second-generation assay GeneXpert Ultra has a 95% sensitivity rate and detects and amplifies a multicopy gene target. The assays for IFN-γ release in blood and CSF exhibit sensitivity of 78% and 77%, respectively, and specificity of 61% and 88%.[18] Its use in clinical practice is so limited. Adenosine deaminase (ADA) values in the CSF that are between 1 and 4 U/l have sensitivity of >93% and specificity of <80%, whereas CSF ADA values greater than 8 U/l have sensitivity of >96% and

specificity of <59%. However, these cutoff values were unable to reliably distinguish between bacterial meni and TBM. Imaging characteristics may have strong specificity, but sensitivity is still modest. While hydrocephalus, infarcts, and basal exudates on CT brain have a high specificity (95%–100%), they may not be present in the early stages of the disease, lowering the sensitivity to about 40%. More infarcts and tuberculomas may be detected by MRI. About 50% of TBM patients exhibit abnormalities on chest X-rays, and over 50% have concurrent spinal cord involvement.[19] A chest X-ray with miliary mottling indicates dispersion. Positron emission tomography, or CT, of the chest, abdomen, and pelvis can identify tuberculosis in other organs, perhaps providing a simpler biopsy site. The primary drawback of imaging as a diagnostic technique is that 15% of MRC-Grade I cases have normal brain MRIs and 30% of cases have normal CT scans. The imaging appearance is strongly impacted by age and HIV co-infection. Hydrocephalus is more common in children. Patients with HIV-coinfected TBM have lower basal exudates, particularly when their CD4 counts are low.

Management

There are three approaches to TBM management:

Using antitubercular therapy (ATT) to eradicate the TB bacilli 2. Manage the host Immune Response 3. Control the immunological response of the host supportive care while handling the issues. The start of ATT prior to the development of coma is the best indicator of survival from TBM. Regarding the optimal combination, dose, frequency of administration, or length of treatment for TBM, we currently lack high-quality evidence. The pulmonary tuberculosis (PTB) management protocols serve as the foundation for the treatment plan. The main issues with TB of the central nervous system (CNS) include rifampicin and ethambutol's limited CSF penetration. The limited CSF penetration of these medications is not taken into account in the majority of guidelines and recommendations. In TBM, it's unclear if a greater dosage of rifampicin is appropriate. An open label randomized controlled trial including 60 TBM patients in Indonesia revealed that intravenous administration of 600 mg of rifampicin could reduce mortality by half when compared to oral dose of 450 mg.[20] However, no survival effect was shown in a bigger trial involving 817 patients in Vietnam that evaluated greater doses of levofloxacin (first 2 months) and rifampicin (15 mg/kg vs. 10 mg/kg orally).[5] Higher rifampicin dosage requirements could be the likely cause of failure. In a PTB dose-ranging study, the highest dosages (30 and 35 mg/kg) demonstrated the strongest bactericidal activity, whereas doses up to 35 mg/kg were safe.[21] The fourth drug's selection is yet unclear. No comparison trials are accessible. The medications streptomycin and ethambutol are frequently used. Both show negative side effects in the form of vestibular toxicity and visual neuropathy, respectively, and have poor CSF penetration. Since isoniazid does not enhance bacterial death or improve outcome, the purpose behind drug-sensitive PTB is to prevent resistance to the antibiotic. However, as rifampicin has a low CSF penetration rate in TBM, the fourth medication's rationale also aims to improve patient survival and bacterial killing. Ethionamide penetrates the CSF more effectively (80%–90%). Additionally, levofloxacin and moxifloxacin exhibit superior penetration (70–80%) and high activity against drug-resistant and drug-susceptible TB bacilli. In a randomized controlled trial conducted in Vietnam, the intensified regimen (levofloxacin as the fifth treatment together with ethambutol and high-dose rifampicin) did not improve survival; however, patients with isoniazid-resistant TB bacilli had higher survival

rates. Therefore, the choice of the fourth drug may not affect the patient's outcome in drug-susceptible TBM, while high-dose rifampicin (15 mg/kg) and levofloxacin (as the fifth drug) may enhance the outcome in isoniazid resistance. With a death rate of over 80%, drug-resistant TBM has a very bad prognosis. Even with GeneXpert (sensitivity <60%), medication resistance is typically not detected right away. The effectiveness and CSF penetration of second-line medications are not clearly known. Two months of HRZE and seven months of HRE are advised by the Index TB guidelines. According to WHO standards, HRZS should last two months, followed by a ten-month HR continuation phase. Two months of HRZE and nine to twelve months of HRE are advised per the most recent RNTCP guidelines. These guidelines have a number of problems. In TBM, there is clinical equipoise with relation to therapy length. The majority of the recommendations in the guidelines are based on the opinions of experts. The neurologists in general and also those in the Index-TB guideline panel feel that TBM should be treated for minimum for 12–18 months. Pyrazinamide was selected above ethambutol by the Technical Advisory Subcommittee for CNS TB, which established the Index-TB guidelines. Streptomycin is preferred by many doctors and neurologists over ethambutol, particularly when TBM is a risk of vision loss and because of the possibility of ethambutol-related optic neuropathy. Both medications, however, have minimal CSF penetration.

Role of anti-inflammatory therapy

It is believed that adjunctive corticosteroids will improve patient outcomes by reducing inflammation in TBM. In 2016, the Cochrane Systematic Review and Meta-analysis found that corticosteroids improve survival in adults and children with TBM who tested negative for HIV-1.[3] The effectiveness of steroids in HIV-1 coinfection remained unclear. No group experienced a decrease in long-term impairment. However, 98 HIV-1-coinfected TBMs participated in the Vietnam trial, and in this subgroup, steroids had no discernible impact on either the combined end point of death and disability or death. A paradoxical reaction is a delayed inflammatory response that manifests weeks to months after beginning ATT.[22] IRIS occurs in HIV-coinfected people when they begin antiretroviral therapy. IRIS and paradoxical reactions can manifest as fever, convulsions, a worsening headache, or altered sensory perception. Imaging should be used to detect hydrocephalus, infarcts, or tuberculoma formation when they are suspected. TB is the paradoxical effect that is most frequently described. High-dose steroids are frequently used to treat them. Other anti-inflammatory treatments may be tried if steroids don't work or if the patient's condition worsens. This is particularly important when tuberculoma is present at the optic chiasma or when eyesight is at risk due to optochiasmatic arachnoiditis. IFN-γ, infliximab, and thalidomide have all been tested in these situations. More than fifty TBM patients who had previously received more than two months of ATT and steroids and experienced a variety of inflammatory side effects, including optochiasmatic arachnoiditis, a paradoxical increase in the size of tuberculomas, an increase in the size and number of lesions, and spinal arachnoiditis, were treated with thalidomide (at a dose of 2 mg/kg) for four to six months, according to Modi et al.[23] More than 70% of patients showed clinical and radiological improvement, according to the authors.

Pro-inflammatory and anti-inflammatory host responses can be influenced by genetic variations in some immune response genes. A lot of attention is paid to a single polymorphism in the LTA4H promotor, which affects TNF-α production by modulating eicosanoids. In the

Vietnam experiment, when steroids were administered to every participant, the TT genotype (hyperinflammatory) showed a survival benefit, while the CC genotype showed harm.[24] However, in research conducted in Indonesia, 427 HIV-negative individuals with TBM who all given corticosteroids were showed no survival benefit due to the LTA4H genotype.[25] As a result, the clinical data on the LTA4H genotype directing customized anti-inflammatory therapy is now unclear. "In hospital: intravenous dexamethasone 0.4 mg/kg/24 h in 3–4 divided doses may be preferred with a slow switch to oral therapy and taper," is the Index TB prescription for the dosage of steroids in TBM. There isn't enough data at this time to suggest a single steroid formulation or regimen over another. The only proven supplementary treatment for CNS TB, aside from steroids, is ART. When to start ART is a matter of uncertainty. There is a decision between lowering the risk of IRIS and other opportunistic infections with early ART. In TBM, a single trial comparing early versus two-month delayed ART initiation revealed serious adverse effects but no difference in survival.

Supportive management

Early detection and effective management are crucial for the many TBM consequences, which include elevated intracranial pressure, infarct, hydrocephalus, hyponatremia, and seizures. Mannitol or hypertonic saline are used as symptomatic treatments for elevated ICP. The most frequent cause of elevated ICP is hydrocephalus, and 80% of cases involve communicating hydrocephalus as a result of basal exudates disrupting CSF flow. Diuretics and repeated lumbar punctures may be used to treat communicating hydrocephalus. Endoscopic third ventriculostomy (ETV) or ventriculoperitoneal (VP) shunt are used to treat noncommunicating hydrocephalus. A comprehensive analysis of VP shunt in TBM found that the prognosis was worse for HIV-1 coinfection and that the result depends on clinical severity. In a study comparing VP shunt with ETV in 48 patients with TBM and hydrocephalus, it was found that ETV had a higher incidence of early recurrence but less long-term problems than VP shunt. [26] ETV in acute TBM hydrocephalus, with an inflammatory, dense, and opaque third ventricle, is technically challenging[30]. On the other hand, it is believed that VP shunt should be utilized for chronic burnout instances or those with communicating hydrocephalus, while ETV should be employed to treat aqueductal stenosis in early-stage TBM.[27] In the absence of solid evidence, there is still ambiguity surrounding the choice of surgery for TBM hydrocephalus. Clinically, it is challenging to distinguish between cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH), which can both cause hyponatremia in TBM patients. Fluid restriction is used to treat SIADH, whereas fluid administration is used to treat CSW. Fludrocortisone's safety and effectiveness in treating cerebral salt wasting in patients with TBM were recently evaluated in a short trial involving 36 patients.[28] A 0.9% intravenous saline solution supplemented with 5–12 g of oral salt daily, with or without the addition of 0.1–0.4 mg of fludrocortisone daily, was used in the open-label randomized controlled experiment. Although fludrocortisone caused serum sodium levels to return to normal early, it had no effect on results after six months. TB vasculitis typically causes multiple, bilateral strokes that affect deep gray matter, including the thalamus and caudate, as well as the anterior and genu of the internal capsule, or "tubercular zone." Stroke in TBM has no known cure or preventative measures. It was discovered that corticosteroids did not effectively prevent brain infarction. According to two

short trials, aspirin may help reduce stroke in TBM patients.

Prevention

Reduced Mycobacterium TB transmission, BCG immunization in newborns (which lowers the incidence of dissemination, including TBM), and ART in HIV-positive individuals are the three most effective preventive measures for TBM.

Drug resistant Tuberculous meningitis

Multidrug-resistant tuberculosis is resistant to at least rifampicin and isoniazid. The three second-line injectable ATT medications (amikacin, kanamycin, or capreomycin), as well as any fluoroquinolones and isoniazid and rifampicin, are all ineffective against extensively drug-resistant tuberculosis. There are two types of drug resistance: acquired (occurring in a person already using ATT) and primary (occurring when a drug-resistant strain was transferred from someone not on ATT). A fluoroquinolone and an injectable second-line antibiotic are among the minimum of five effective medications that should be used initially to treat multidrug-resistant TBM, according to WHO guidelines. Treatment should last between 18 and 24 months.[29] Regarding TBM, the clinical decision point of presumed treatment failure is unclear. It may not be acceptable to wait more than 3 months to decide on presumptive treatment failure.

Conclusion

TBM is a medical emergency that has a high rate of morbidity and death. If there is a high level of clinical suspicion, ATT should be used as an early empirical treatment. It is crucial to ensure adherence to the selected ATT regimen and supportive therapy. Poor CNS penetration of medications like ethambutol, streptomycin, and rifampicin is not taken into account by current ATT regimens, which are extrapolated from PTB regimens. Improving a nation's social indicators are namely, poverty, low income, and malnutrition—will be crucial to TB prevention and control.

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