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Meningitis And Tuberculosis: A Correlation Along with Diagnosis and Management of Tuberculosis Meningitis

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Abstract

Tuberculosis, caused by Mycobacterium tuberculosis (M. tb), is a communicable disease and a leading cause of death globally, especially in developing countries. It exists in active and latent forms, affecting both pulmonary and extrapulmonary sites. The pathophysiology of TB involves interactions with various immune cells, particularly T cells, in defense against the infection. On the other hand, meningitis is the inflammation of the membranes surrounding the brain and spinal cord, and it can be caused by bacteria or viruses. Bacterial meningitis, associated with high mortality and risk of disability.

The article highlights the promulgation of TB into the brain and the immune responses within the brain, shedding light on the migration of M. tb into the central nervous system (CNS) and the innate immune responses involving microglia and cytokine secretion. The diagnostic methods for TB meningitis encompass neuroimaging, adenosine deaminase measurement in cerebrospinal fluid (CSF), microscopy, polymerase chain reaction (PCR) techniques, and enzyme-linked immunosorbent assay (ELISA). Moreover, it discusses the treatment of TB meningitis, emphasizing traditional antimicrobial therapies, systemic corticosteroid therapy, adjunctive therapy, fluid management, surgical intervention for hydrocephalus, and considerations for patients co-infected with HIV. The treatment approaches stress the importance of timely and empirical treatment, the use of newer generation fluoroquinolones, systemic corticosteroids as adjunctive therapy, and surgical interventions for hydrocephalus. The article also addresses the potential challenges and considerations for patients co-infected with HIV, such as the risk of immune reconstitution inflammatory syndrome (IRIS), drug interactions, and the efficacy of adjunctive corticosteroids.

Overall, the document provides a comprehensive overview of the correlation between TB and meningitis, covering their pathophysiology, diagnostic methods, and treatment approaches. It emphasizes the complexity of managing TB meningitis and the importance of considering various factors, including immune responses, diagnostic accuracy, and tailored treatment strategies, particularly in the context of HIV co-infection.

Keywords: Tuberculosis (TB), Mycobacterium tuberculosis (M. tb), Pulmonary tuberculosis (PTB), Extrapulmonary tuberculosis (EPTB), Central Nervous System (CNS), World Health Organization (WHO)

Introduction

Tuberculosis (TB)

*"*A scourge of the mankind from the time immemorial, the dread disease was called consumption in Dickens time had a profound social and economic effect on human existence worldwide*"*, words of Charles Dickens [3]. Tuberculosis (TB) is communicable disease caused by bacteria *Mycobacterium tuberculosis (M. tb)*. It is among one of the top leading causes of death worldwide, particularly in the developing countries [7]. A steady increase has been noted in the disease from 2020 to 2021, among which around 1.6 million people died in 2021, including 1.8 lacs suffering from Human Immunodeficiency Virus (HIV) [0]. The incidence of TB among tribal population of India is more than the urban population [1]. BCG (Bacillus Calmette- Guerin) vaccine is the most frequently used worldwide [2].

M. tb spreads through respiratory transmission, in which active form of disease shows symptoms like fever and weight loss, with localized tissue destruction at infected site, hence called as active TB. While the one-third of world's population remains asymptomatic, those who are asymptomatic for TB fall under category of latent TB [9].

Types and Stages of TB

TB is of two types, Pulmonary TB (PTB) and Extrapulmonary TB (EPTB) (involve organs other than lungs), based on clinical manifestations. PTB is caused by M. tb, which is contagious. EPTB constitutes 15-20%of all TB cases, majorly seen in HIV positive patients. EPTB is difficult to diagnose early as compared to PTB [3].

There are stages of TB, which include latency, primary disease, primary progressive disease and EPTB disease among which latent TB is usually asymptomatic with viability of bacteria remaining for years. EPTB disease occurs in more than 20% of patients, that is seen in Central Nervous System (CNS), bloodstream, lymphatic system, bones, joints, pleura and genitourinary system [15].

Pathophysiology of TB

M. tb interacts with monocytes, macrophages, dendritic cells (DC), neutrophils, natural killer cells (NK cells) through surface exposed receptors, resulting in clearing the infection or leading to granuloma formation (non- specific immunity) [2]. CD8 cytotoxic T cells, kill TB infected macrophages by perforin secretion and may kill TB bacteria by releasing granulysin [2].

The roles of T cell activation against M. tb are crucial in the immune TB. Following systemic challenge with M. tb, the initial T cell activation occurs in the draining lymph node (DLN) of the lung approximately 8-10 days after the initial challenge. This activation is correlated with the arrival of bacteria and the availability of antigen in the DLN. Once T cells become activated, they differentiate into effector T cells that migrate to the lung. By day 14 of infection, when activated T cells first arrive in the lung, bacteria are found within alveolar macrophages, myeloid DC, and neutrophils. The protective memory cells do not become activated until they encounter the antigen, which occurs more than 8 days post-infection. The T cells, particularly the Th1 (helper T cells type 1) subset, play a major role in defense against TB. They suppress Th2 (helper T cells type 2) cells and are crucial for mediating protection. Additionally, CD8 T lymphocytes produce predominantly interferons gamma (IFN-γ) and can provide protection in the absence of CD4 help. The activation of T cells and their subsequent

differentiation into effector cells are essential for controlling the growth of M. tb and initiating an effective immune response against TB [15].

Meningitis

Meninges are the layers that cover the brain and spinal cord, where outer layer is called dura mater, middle layer called arachnoid mater and the inner one is called pia mater [11]. Meningitis is the inflammation of the membranes that surround and protect the brain and spinal cord. There are various types, which includes viral meningitis, bacterial meningitis, meningococcal, pneumococcal meningitis, etc. (https://www.meningitisnow.org/).

Bacterial Meningitis

Bacterial meningitis is related to substantial mortality and risk of permanent disability for survivors. The onset symptoms are headache, fever, neck stiffness or altered mental state [10]. The complications related to this disease can be categorized as systemic including shock, respiratory failure, organ failure, coagulation disorders or intracranial complications like stroke, seizures or brain herniation [12]. The most common causes of bacterial meningitis are Streptococcus pneumoniae (S. pneumoniae), Neisseria meningitidis (N. meningitidis), Haemophilus influenzae type b, group B Streptococcus and Listeria monocytogenes [13].

Meningitis occurring due N. meningitidis starts with influenza, with symptoms like fever, muscle aches and vomiting. Meningitis due to S. pneumoniae, show conditions such as otitis media, sinusitis, mastoiditis. Cerebrospinal fluid leak, cochlear implants, asplenia and HIV. According to World Health Organization (WHO), bacterial meningitis carries highest fatality rate, with ratio of 1 in 6 deaths [10].

Pathogenesis of Bacterial Meningitis

Bacteria can enter the leptomeninges through bony defects or the bloodstream, with classical meningeal pathogens like S. pneumoniae, N. meningitidis, and group B Streptococci colonizing epithelial surfaces in the respiratory tract or lower genital tract. Sustained bacteraemia is crucial for the development of bacterial meningitis, as demonstrated by a genome-wide association analysis of invasive S. pneumoniae isolates. Sustained bacteraemia increases the likelihood of microbial exploitation of the blood-brain (BBB) or blood-cerebrospinal fluid barrier (BCSFB), which is formed of specialized endothelial cells and supporting cells like pericytes and astrocytes [23].

The cause of death due to bacterial meningitis is categorized by CNS complications, systemic complications, combination of systemic and CNS complications, sudden death, withdrawal of care and cause of death could not be ascertained [12].

Viral Meningitis

Viral meningitis is also commonly known as aseptic meningitis, usually affects young generation. Enterovirus are the causative agents for this disease. It begins with entering of virus through respiratory or gastrointestinal tract, then spreading to CNS. Inflammatory immune response plays vital role in the pathogenesis of disease. Undetected viral meningitis leads to severe encephalitic syndrome [11].

Pathogenesis of Viral Meningitis

The CNS is protected by a complex barrier system, but viral pathogens can establish infection in

cerebral vascular endothelial cells, allowing direct passage across the BBB to adjacent glia and neurons. Other mechanisms include direct infection of the choroid plexus epithelium, viral infected hematopoietic cells transported to the CNS by direct blood flow, lymphoid tissue, or inflammation-induced breakdown of the BBB. Alternatively, viral pathogens may infect and migrate to the CNS through peripheral sensory or motor neurons or olfactory sensory neurons whose dendrites are directly exposed to nasal airways [14].

Viruses that target cells of the meninges or ventricular lining, choroid plexus, and ependymal often induce meningitis, while those that infect the CNS parenchyma give rise to meningoencephalitis, encephalitis, or myelitis. Once viral tropism allows passage to the CNS, infection is characterized by the release of chemo attractants in the meninges followed by innate immune cell infiltration of neutrophils, monocytes, and antiviral CD8 lymphocytes. An intact host cell-mediated immune response, particularly T-cells, is important for clearance of viruses from the CNS [14].

How TB and Meningitis linked together?

Promulgation of TB in Brain

Promulgation of TB involves seeding of M. tb into other sites, including the CNS. Various mechanisms allow M. tb to migrate into the lymphatic system or blood stream, including cell lysis, Heparin Binding Hemagglutinin Adhesion (HBHA), invasion and traversing vascular endothelial cells, replication in Lymphatic Endothelial Cells (LEC), and trafficking to distant locations in phagocytes. M. tb can survive and replicate in infected macrophages and LEC surrounding granulomas in lymph nodes [18].

The CNS is protected from influx of potentially harmful blood-borne bacteria by two vascular barriers: BBB and BCSFB. However, M. tb bacilli migrate across these barriers, allowing them to invade and traverse brain endothelial cells in the microvasculature through rearrangement of their actin. The M. tb gene Rv0931c (pknD) has been identified as a potential virulence factor promoting CNS infection in certain TB strains [18].

Once the TB bacilli gain access to the brain, limited local innate immunity allows their survival and replication, leading to the development of silent tuberculous lesions. Postmortem studies suggest that TBM is initiated by the rupture of one of these lesions, the Rich focus, which releases M. tb bacilli into the subarachnoid space, causing a granulomatous infection of the meninges and the subsequent induction of inflammation [18].

Immune Responses of Brain

Microglia in the cerebral parenchyma are the primary CNS cells infected by M. tb, involved in immune regulation. Other CNS cells, including astrocytes and neurons, have potential roles in this process. M. tb is recognized by microglial cells via innate immune and neuro-specific receptors, including pattern recognition receptors. Internalization of M. tb by human microglia is dependent on CD14, a monocyte differentiation antigen, which binds to lipopolysaccharide with TLR-4. This receptor, along with β2-integrin CD18 and Tumor Necrosis Factor- alpha (TNF-α), is involved in the formation of multinucleated giant cells [18].

Microglia activation leads to the secretion of various cytokines, including TNF-α, which plays a crucial role in the host defence against M. tb. TNF-α is central to the pathogenesis of CNS TB, with its protective role in the immune response but also associated with pathology in vivo. Local TNF-α production in the CNS increases the permeability of the BBB and influx of other immune mediators to

the CNS. TNF-α antagonists, such as thalidomide, have been shown to down-regulate TNF-α production and improve survival in rabbit models of TB. IL-6, which is secreted by microglia in response to TBM, may also have an anti-inflammatory role by suppressing gene expression of proinflammatory cytokines. Other cytokines secreted by microglia following M. tb stimulation include IL-1β, CCL2, CCL5, and CXCL-10 [18].

Recent research has explored the pathogenic role of inflammation mediators like DAMPs (Damage associated molecular pattern) and PAMPs (Pathogen associated molecular pattern) as biomarkers of cerebral injury and potential targets for novel host-directed therapies in TBM. PAMPs are by-products released from pathogens, triggering an innate immune response. DAMPs, released by damaged host immune cells, interact with PAMPs, leading to cell death and injury. Host poly (ADP-ribose) polymerase 1 (PARP1), an ADP-ribosylating enzyme, has been suggested as a potential target in the development of host-directed therapies. S100A8/9, a protein involved in neutrophil chemoattraction and stimulation, is implicated in the pathogenesis of TB in pulmonary disease. In TBM patients with TBM and HIV infection, levels of S100A8/9 were significantly elevated two weeks after antiretroviral therapy initiation in those who developed Immune Reconstitution Inflammatory Syndrome (IRIS), which may explain the ongoing paradoxical inflammation observed in IRIS [18].

Vascular Endothelial Growth Factor (VEGF) is a potent endothelial growth factor that plays diverse roles in vasculogenesis and angiogenesis. It is now considered a useful biomarker of disease in TB and is used as an indicator of active versus latent disease activity or extrapulmonary versus primary lung disease. In TBM, VEGF disrupts the permeability of the BBB, which has been proposed as a mechanism by which dexamethasone exerts efficacy as a host-directed therapy. The release of intercellular and vascular adhesion molecules and matric metalloproteinases from inflammatory cells within the CNS has also been shown to increase the permeability of the BBB [18].

Diagnostics of TB Meningitis

TBM is sub-acute or chronic meningitis, with headache, fever and vomiting, loss of consciousness, focal neurological deficit and death [24].

Radiology

Neuroimaging can be helpful in diagnosing TBM, with an expert Consensus Case Definition (CCD). Brain Computed Tomography (CT) lacks diagnostic specificity for TBM, but can detect a combination of hydrocephalus, basal enhancement, and infarction. Magnetic Resonance Imaging (MRI) is superior to CT in defining neuroradiological features of TBM, especially when they involve the brainstem [24]. Gadolinium-enhanced MRI allows visualization of leptomeningeal tubercles, present in 90% of children and 70% of adults [20, 24].

Adenosine Deaminase

Adenosine deaminase (ADA) level measurement in CSF is a suitable test for diagnosing TBM, according to a meta-analysis by Por Mohammad et al. in 2017 [24]. ADA, a purine catabolism enzyme, is used to diagnose pleural, meningeal, and pericardial TB by assessing its presence in bodily fluids. However, its effectiveness in diagnosing TBM remains inconclusive [25]. The test has a high accuracy rate and is recommended for TBM diagnosis in guidelines [24].

A recent meta-analysis showed a sensitivity and specificity of 89% and 91% for TBM diagnosis, respectively. Some studies reported false-positive reports due to variable range, which could mimic neurological cytomegalovirus disease and probable candidal meningitis. ADA level estimation was based on the differentiation of mycobacterial meningitis from viral infections, which usually do not elevate ADA levels. The mean CSF ADA measurement for TBM cases was estimated at 14.24 IU/dL, which missed many true cases. ADA is inefficient in distinguishing TBM from other challenging clinical conditions, especially in HIV patients [25].

Microscopy

Acid-fast bacilli (AFB) microscopy is a rapid and cost-effective method for diagnosing TB in endemic countries. It provides significant sensitivity in PTB cases but is suboptimal in EPTB, particularly in TBM cases, due to issues like paucibacillary CSF specimens, faulty microscopy, and insufficient sample volumes. Sensitivity varies from 0 to 90% with slight modifications in staining procedures and extending time for light microscopy. Testing CSF centrifuged deposits for extended periods can improve sensitivity, allowing case detection up to 70% in sputum smear cases. However, large sample volumes and extended analysis time are often not feasible due to high diagnostic load on commercial laboratories [25].

Polymerase Chain Reaction (PCR)

PCR has emerged as a new diagnostic tool for diagnosing TBM, with various M. tb unique gene targets such as IS6110, devR, hsp65, pstS1, mpb-64/mpt-64, PT8/9, dnaJ, rpoB, and PPE being widely used. However, some studies reported low sensitivity, possibly due to factors like insufficient CSF volume, poor bacterial cell lysis, bacilli shortage, DNA fragment loss, and PCR inhibitors or phenol. PCR reported significant sensitivity over microbiological tests by targeting M. tb complex specific gene targets, particularly Insertion Sequence (IS), which is present in high copy numbers in the M. tb genome. Multiplex PCR (M-PCR) can improve sensitivity without the additional requirement of CSF sample volume. A study of 110 cases using M-PCR showed a sensitivity of 94.4% for confirmed TBM cases and 84.78% in suspected TBM cases over smear and culture with 100% specificity [25,28].

Real-time Polymerase Chain Reaction (RT-PCR/qPCR)

Real-time PCR (qPCR) is an automated, and quantitative method that provides results within 2 hours after DNA extraction. It has been used to detect drug resistance and M. tb simultaneously in TBM patients, with a sensitivity of 83.63%. RT-PCR has shown better results than IS6110 PCR with a detection rate of 76.36%. TBM diagnosis using CSF 'filtrates' and CSF' sediments' separately showed 87.6% and 53.1% sensitivity, respectively, using devR RT-PCR. However, NAATs (Nucleic Acid Amplification Test) do not discriminate between alive or dead bacilli, making them more prone to false-positive results. The use of CSF 'filtrate' for detecting M. tb DNA by conventional PCR targeting IS6110 and devR genes and RT-PCR targeting devR showed significant sensitivity and specificity over sediments. Simultaneous detection of M. tb antibodies using ELISA (Enzyme Linked Immunosorbent assay) using remaining filtrate may provide a clear picture of TBM diagnosis [25].

Nested Polymerase Chain Reaction

Nested PCR is a two-step process that uses two primer sets in a single tube to amplify the target sequence. It can detect 0.1 fg of M. tb DNA, which is less than the amount in a single bacterial cell. This method improves specificity and reduces the chances of amplification of non-specific products for diagnosing TBM. A study in Mexico found the highest sensitivity of 98.0% and 92.0% specificity for targeting IS6110 in TBM cases. However, some reports show unsatisfactory sensitivity of TBM detection (32% to 90%). Nested PCR results alone cannot be a sole criterion for initiating or terminating therapy, but can be used in conjunction with other clinical, radiological, cytological, and microbiological findings [25].

Gene Xpert MTB/RIF Assay

The Gene Xpert MTB/RIF assay is a real-time hemi-nested PCR test that detects M. tb bacilli and rifampicin resistance by targeting the IS6110 and 81-bp rifampin resistance-determining region (RRDR) rpoB gene. It was approved by the WHO in 2010 for investigating PTB cases and expanded its utility in 2013 for diagnosing EPTB, including TBM. A consistent review of 16 studies suggests efficient performance in diagnosing M. tb in CSF samples with a run time of around 113 minutes. However, some studies reported sub-optimal sensitivity or performance in TBM cases, ranging from 24%-86% with poor specificity of 98.6% against microbiologically confirmed cases. A study of 267 CSF samples from Indian patients with high clinical-radiological TBM notion reported a 55.1% sensitivity and 94.8% specificity against culture-confirmed cases. Mixed Mycobacterium Tuberculosis Complex (MTBC) infection and detection of dead bacilli may lead to false-positive Xpert MTB/RIF results [25].

Xpert MTB/RIF Ultra

In 2017, the WHO recommended the Xpert MTB/RIF Ultra, an ultra-sensitive version of the re-engineered Xpert MTB/RIF cartridge. This new test has improved assay chemistry and a new resistance detection algorithm for detection of M. tb and rifampin resistance rpoB genes. The next generation Xpert Ultra is considered the first TBM diagnostic tests due to its lower LOD (limit of detection) of 16 cfu/ml compared to GeneXpert 114 cfu/ml. Using CRS, TBM was detected in 17% cases, with Xpert Ultra showing 95% sensitivity. A recent prospective study from Uganda reported 76.5% sensitivity using Xpert Ultra among TBM cases provided. However, Xpert Ultra has been linked to false-positive results among patients with a previous history of TB, possibly due to the presence of M. tb DNA or intact non-viable bacilli in clinical samples. The new generation Xpert Ultra could be a game-changer in diagnosing TBM, but further testing on a larger population is needed to confirm these findings [25].

Loop-Mediated Isothermal Amplification (LAMP)

LAMP is a simple, economical, and isothermal non-assay for diagnosing TB in resource-poor countries. It uses two or three sets of primers to amplify target DNA, buffers, and DNA polymerase. Studies have reported 96% sensitivity and 100% specificity in confirmed cases, while 88% and 100% in probable cases. IS6110 LAMP showed 88.23% sensitivity and 80% specificity over nested-PCR, while multiplex LAMP showed promising results for early and rapid diagnosis. However, it is unclear whether LAMP technology will be implemented as a rule-out test in TB testing algorithms, and a large number of studies are still required to prove its efficacy in diagnosing TBM [25].

Line Probe Assay (LPA)

LPA is a strip-based technology used to detect M. tb complex and resistance to rifampin and isoniazid in multidrug-resistant tuberculosis (MDR-TB) cases. The WHO recommends the Geno-Type MTBDR plus test, which identifies mutations in rpoB, katG, and inhA promoter genes. However, this test has little significant role in identifying M. tb and drug resistance. A study in northern India evaluated Geno-Type MTBDR plus LPA for early drug resistance identification in M. tb isolates from CSF samples of confirmed TBM patients. The study found sensitivity and specificity for INH resistance (isoniazid resistance) and RIF resistance (isoniazid and rifampicin resistance), but more data is needed to establish its utility in TBM diagnosis [25].

Enzyme Linked Immunosorbent Assay (ELISA)

M. tb-specific antigen detection-based immunoassays are considered more reliable than antibody detection due to the potential for false results in patients treated with corticosteroids or immune-deficient TBM patients. Studies have shown that indirect ELISA can detect PstS1 and ESAT-6, a novel biomarker indicative of active mycobacterial replication, with 89% and 47% sensitivity, respectively, among smear-positive PTB patients. ESAT-6, an immunodominant T cell stimulatory antigen, is present in 35-92% of TB patients, while absent in non-TB controls. A prospective study in India found that 14% sensitivity and 94% specificity using novel lipoarabinomannan (LAM) detection by ELISA and combining with clinical markers could improve diagnosis up to 38%. However, antigen detection-based ELISA also carries the potential risk of false-positive and false-negative results, as well as significant variability among microtitre plates used for ELISA [25].

Interferon-Gamma Release Assays (IGRAs)

Interferon-gamma release assays measure interferon-gamma release in whole blood or Peripheral Blood Mononuclear Cells (PBMCs) in response to exposure to specific M. tb antigens. They are used in screening guidelines in low-incidence, high-income countries to diagnose latent TB due to their high specificity. However, IGRAs are not reliable for distinguishing latent from active TB. A study in China found a better outcome using peripheral blood than CSF for TBM diagnosis, with a higher specificity (97.2%). Limited data exists on the efficacy of IGRAs in TBM diagnosis among children or HIV patients. Further studies are needed to validate findings using CSF samples of definite cases [25].

Aptamer Linked Immobilized Sorbent Assay (ALISA)

ALISA is an aptamer-based ELISA used for diagnosing M. tb-specific antigens in PTB and EPTB cases. It is a cost-effective alternative to expensive molecular tests and has potential for TB diagnosis. ALISA targets a wide range of M. tb specific antigens, such as Culture Filtrate Protein (CFP10), Early Secretory Antigenic Target 6kDa (ESAT6), Heat Shock Protein (HspX), and mycobacterium species from TB (Mpt-64). Potential aptamers are selected using the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) method. ALISA showed superiority over analogous ELISA for diagnosing TBM and showed no cross-reactivity with other mycobacterial antigens. A high-affinity HspX-based DNA aptamer, H63 SL-2 M6, was developed for TBM diagnosis, revealing 100% sensitivity and 91% specificity [25].

Treatment of TB Meningitis

Traditional treatment for PTB involves RIPE [rifampin (RIF), isoniazid (INH), pyrazinamide, ethambutol] therapy for 2 months followed by RI (rifampin, isoniazid) for 10 months. Empirical treatment for TBM is similar to PTB, but with additional agents like RIPE. Fluoroquinolones and corticosteroids can enhance anti-TB performance. Thalidomide, a potent inhibitor of TNF-α, can decrease mortality in patients. Patients with past medical history conditions should be treated differently, and a thorough medical history is essential before starting therapy [29].

Antimicrobial Therapies

Timely treatment is crucial for TBM resistant patients, and empiric treatment is recommended even before microbiologic confirmation. The recommended treatment regimen for TBM consists of two months of daily INH, RIF, pyrazinamide and streptomycin or ethambutol, followed by 7-10 months of INH and RIF. Pyrazinamide has excellent CSF penetration and is a key drug in reducing the total treatment time for drug-susceptible TB. If pyrazinamide cannot be tolerated, the treatment course should be lengthened to 18 months. Newer generation fluoroquinolones such as levofloxacin and moxifloxacin, have strong activities against most M. tb strains and excellent CSF penetration and safety profiles. However, no controlled trials have been published for MDR TBM, and few studies have been published on the CSF penetrance of many second-line and newer anti-TB agents. Clinicians of patients with MDR-TBM are left to extrapolate from guidelines for MDR-PTB [26,27]

Systemic Corticosteroid Therapy

Systemic corticosteroids have been used as adjunctive treatment since the mid-20th century to reduce morbidity and mortality. Studies have shown efficacy in certain groups of patients, with dexamethasone significantly inhibiting the production of inflammatory mediators. While corticosteroids may reduce CSF penetration of anti-TB drugs, they have no effect on CSF penetration of first-line anti-TB agents. A Cochrane meta-analysis found that corticosteroids improved outcomes in HIV-negative children and adults with TBM, with treatment associated with reduced mortality at nine months. Treatment choice should be based on effective published trials. Neutralization of TNF-α may predispose individuals to TB, but it is also considered an important role in the pathogenesis of TBM [27].

Adjunctive Therapy

Immuno-adjunctive therapy has shown promise in improving clinical control of refractory mycobacterial infections. Researchers have found that individuals with active PTB exhibit a significant deficiency in glutathione (GSH), a non-protein thiol responsible for cellular homeostasis and intracellular redox balance. GSH levels are compromised in peripheral blood mononuclear cells and red blood cells, correlated with increased production of pro-inflammatory cytokines and enhanced growth of M. tb. GSH has direct antimycobacterial activity in vitro and at physiological concentrations. It enhances the functional activity of NK cells to inhibit M. tb growth inside human monocytes and activates the functions of T lymphocytes to control infection. GSH levels are also compromised in HIV-positive patients and individuals with uncontrolled type 2 diabetes. However, the underlying mechanisms of GSH-deficiency altering immune responses and increasing susceptibility to TBM remain unknown [29].

Fluid Management Therapy

TBM patients may experience a syndrome of inappropriate ADH (SIADH) release due to non-osmotic stimuli for ADH expression. This can worsen cerebral edema by shifting water from the intravascular compartment to the extra vascular space of the brain. Restricting water intake is a main stay of SIADH treatment, but hypovolemia should be avoided to prevent further ADH release. Fluid restriction to prevent cerebral edema in TBM is unjustified, and a euvolemic state should be the goal to maintain cerebral perfusion and prevent hypovolemia-induced ADH release. If symptomatic, acute hyponatremia doesn't respond to anti-TB treatment, V2 receptor antagonists may be considered [27].

Surgical Intermediation in TBM Hydrocephalus

Hydrocephalus is a common complication of TBM, affecting over 75% of patients. Surgical techniques like ventriculoperitoneal shunt placement and endoscopic third ventriculostomy can relieve elevated intracranial pressure (ICP), improving neurological outcomes. Children are at high risk for hydrocephalus and elevated ICP. A study in South Africa found 30% required ventriculo-peritoneal shunting for noncommunicating hydrocephalus or failure of medical therapy. Historically, surgical intervention was only recommended for grade 2 or 3 TBM hydrocephalus due to increased mortality and poor surgical outcomes. However, a retrospective analysis showed favourable outcomes in 33%-45% of patients with grade 4-associated hydrocephalus [27].

TBM treatment concerns in patients co-infected with HIV

HIV infection is a significant risk factor for EPTB, including meningitis. Diagnosis of TBM in HIV-infected individuals should trigger testing for HIV infection. Treatment for TBM in HIV-infected individuals is similar to non-HIV infected subjects, but there are some caveats, including the potential development of immune reconstitution inflammatory syndrome (IRIS), drug interactions and toxicities with concomitant anti-TB and antiretroviral (ARV) therapy, questionable efficacy of adjunctive corticosteroids, and higher prevalence of drug-resistant TB in HIV-positive populations [27,28]. Concurrent ARV and anti-TB therapy can result in IRIS, causing clinical exacerbation of TBM. Risk factors for IRIS include a high pathogen load, low CD4 T-cell count, and concurrent initiation of ARV and anti-TB therapy. Delaying ARV therapy in patients coinfected with HIV and TB has been associated with higher mortality. Most guidelines do not recommend simultaneous initiation of ARV and anti-TB medications due to the possibility of IRIS with ARV initiation [27].

The benefit of adjunctive corticosteroid treatment for TBM in patients coinfected with HIV has not been demonstrated, and the W-Beijing genotype is associated with HIV infection and high levels of resistance in TBM. Daily anti-TB treatment as directly observed therapy should be given to reduce relapse and treatment failure. HIV coinfection alone, even without TB drug resistance, confers worse outcomes in TBM [27].

Conclusion

TB disseminates into the brain by crossing BBB and BCSFB that invades the brain endothelial cells, leads to formation of lesions. The rupture of these lesions leads to the onset of TBM. Microglia in the cerebral parenchyma are the primary CNS cells infected by M. tb, involved in immune regulation. They secrete cytokines like TNF-α, which plays a crucial role in host defense against M. tb. Inflammation

mediators like DAMPs and PAMPs are potential targets for novel host-directed therapies in TBM. VEGF is a useful biomarker of disease in TB.

ADA has high accuracy rate in diagnostics. PCR is significant over microbiological tests. Nested PCR improves specificity and reduces chances of amplification of non- specific products in diagnosis, it can be used in conjunction with other clinical, radiological, cytological and microbiological findings. M. tb-specific antigen detection-based immunoassays are reliable due to potential false results. Studies show indirect ELISA can detect PstS1 and ESAT-6, a biomarker for active mycobacterial replication. Interferon-gamma release assays measure interferon-gamma release in whole blood or PBMCs, but not reliable for distinguishing latent TB. ALISA, an aptamer-based ELISA, targets various M. tb-specific antigens and has potential for TB diagnosis.

Timely treatment is crucial for TBM resistant patients, with a recommended regimen of INH, RIF, pyrazinamide, streptomycin, and ethambutol. Systemic corticosteroids have shown efficacy in some patients, but not in first-line anti-TB agents. Immuno-adjunctive therapy, which improves clinical control of refractory mycobacterial infections. However, the mechanisms behind GSH-deficiency altering immune responses and increasing susceptibility to TBM remain unknown. TBM patients may experience SIADH release syndrome, which can worsen cerebral edema. Fluid management therapy is essential, but hypovolemia should be avoided. Surgical intervention in TBM hydrocephalus can improve neurological outcomes. HIV infection is a significant risk factor for EPTB, and treatment in HIV-infected individuals is similar but with potential risks like immune reconstitution inflammatory syndrome (IRIS), drug interactions, and drug-resistant TB. Daily anti-TB treatment is recommended to reduce relapse and treatment failure.

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