Pathogenesis of tuberculous meningitis (TBM): a mini-review

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ABSTRACT

Background: Tuberculosis (TB) is the leading cause of death from a single infectious agent (*Mycobacterium tuberculosis*) and killed nearly 1.5 million people in 2018. TB mostly manifests as a pulmonary disease but can also affect other parts of the body, causing extrapulmonary TB. Approximately 5% of all cases of extrapulmonary TB are tuberculous meningitis (TBM), which is caused by the spread of *M. tuberculosis* to the meninges and cerebrospinal fluid (CSF).

Result: TBM is the most devastating form of TB and causes high rates of morbidity and mortality, with an estimated 50% of patients dying or suffering from neurological sequelae and complications. Meningitis is categorized as a medical emergency because it can cause death due to inflammation that occurs in the brain and spinal cord. Most meningitis patients present with fever, and signs and symptoms of meningeal inflammation include headache, neck stiffness and altered mental status. Disease management has limitations due to the limited availability of available diagnostic approaches. Until now, knowledge about the pathogenesis of TBM has been limited.

Conclusion: Further research is urgently needed to improve understanding of disease pathogenesis and diagnostic approaches based on biomarkers of disease. Current knowledge on the pathogenesis of TBM summarize the literature on diagnostic approaches based on biomarkers, which may be useful in the management of TBM.

Keywords: pathogenesis, tuberculous meningitis.

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INTRODUCTION

Tuberculous Meningitis (TBM) is an infection of the central nervous system caused by the bacterium *Mycobacterium tuberculosis,* which attacks the membranes covering the brain and spinal cord, causing an inflammatory process. Tuberculous meningitis is an infectious disease that requires prompt and appropriate treatment. Despite treatment, mortality and long-term disability rates remain very high. So that prevention, early recognition, diagnosis and treatment are fundamental to improve better outcomes. Effective early treatment is critical to the success of treatment; if late, it can worsen the prognosis and even lead to death.[1,2]

TBM is caused by the bacterium *Mycobacterium tuberculosis* complex. These acid-fast bacteria enter the host's body through inhalation droplets. Local infection in the lung becomes widespread and spreads hematogenous to the extra

lung, including the central nervous system (CNS). Hematogenous spread can occur early in infection before being controlled by the adaptive immune system. Meningitis Tuberculosis is one of the infectious diseases of the central nervous system, which is still a global challenge. This is because the mortality and morbidity rate of MTB is the highest of all forms of tuberculosis (TB). TB meningitis incidence is quite diverse in various parts of the world, including in the United States at 3% and in one of the ASEAN member countries in, the Philippines, at 28.9%. In Southeast Asia, the most common meningitis disease is tuberculous meningitis. These data indicate that most TB meningitis occurs in developing countries, including Indonesia.[3]

In the neurology department, Dr. M. Djamil Padang city 2007 found cases of TB meningitis in as many as 9 patients and in 2008 found 7 people. Cases of TBM are rare

but deadly. The mortality rate for untreated TBM patients is almost 100%. Patients infected with TBM and who survive will usually experience a neurological deficit or permanent sequelae. People infected with TBM, where the bacilli reside in the meninges or brain parenchyma as a result of the formation of small subpial or subependymal foci of metastatic caseous lesions known as rich foci. Rich focus gets bigger so that it ruptures or breaks and enters the subarachnoid space and causes meningitis.[4]

TBM is an inflammatory process in the membranes of the brain (meninges), with a duration of symptoms 6 days and has a low prodromal period such as fever, malaise, weight loss followed by a gradual onset of headache (1-2 weeks), headache worsening, vomiting, confusion, coma and also clinical findings such as neck stiffness, confusion and coma. In this condition, the classic triad of meningitis is the hallmark

of meningitis. Inflammation of the head cavity is different from inflammation in other parts of the body because if there is infection or septicemia in the brain tissue, it can cause meningeal irritation, which causes intracranial physiological changes with clinical manifestations such as sudden high fever and severe headache and can also damage the brain. Neurological symptoms from this condition can cause neck stiffness (inability to move the neck forward due to increased neck muscle tone and stiffness). Inflammation in the head cavity can cause an increase in pressure in the head cavity, and it will affect the patient's outcome. The outcome is the condition of the patient at the last follow-up before being discharged from the hospital. The outcome of patients with TBM is important to know because most of them have died.[5] The aim of this article to explain the pathogenesis of tuberculosis meningitis (TBM).

PATHOGENESIS

The blood-brain barrier protects the central nervous system. The blood-brain barrier consists of microvascular endothelial cells of the brain with tight junctions. The basal portion of these endothelial cells is supported by astrocyte processes interspersed with the extracellular matrix. Paracellular transport is limited by the tight junctions of endothelial cells, whereas transcellular movement is limited by the relatively few endothelial vesicles. This creates an impermeable barrier against many large circulating hydrophilic and pathogenic molecules. In addition, cerebrospinal fluid or cerebrospinal fluid (CSF) also protects the central nervous system and becomes a barrier so that cerebrospinal fluid becomes a spatial separator between the circulatory system and cerebrospinal fluid in the choroidal plexus. The cells lining the cerebrospinal fluid barrier are the same as the cells lining the blood-brain barrier, with more tight junctions. *Mycobacterium tuberculosis* begins to infect when a person inhales droplets containing bacteria and enters the lungs, and forms colonization of macrophages in the alveoli. During the development of active lung disease, the bacteria can spread through the lymph glands (lymphogenous) and

through the blood (hematogenous). This hematogenous spread often occurs in oxygen-rich areas, including the brain.[5,6]

The immune response to infection does not occur during the first 2-4 weeks, but after that, cell-mediated immunity is triggered. Bacterial antigens will stimulate T lymphocytes to produce lymphokines so that they will recruit and activate mononuclear phagocytes from the blood circulation. With activated macrophages, the organism can die as well as macrophages can be killed by the organism or its toxic antigenic products. Tubercles are formed consisting of macrophages, lymphocytes and other cells that surround the middle part, which is caseous necrosis.[4]

POTENTIAL BIOMARKER-BASED DIAGNOSTIC APPROACH

In order to improve TB diagnostic evaluation, recent studies have investigated several alternative approaches, including the measurement of protein concentrations in biologic fluids, transcriptional molecules, and metabolites as biomarkers for TB. Several efforts are underway to detect such biomarkers in easily obtainable specimens, such as blood, urine, and saliva, among others, with the need for a non-sputum-based approach considered a high priority by WHO.[7]

Protein in Host

Several studies have shown that the measurement of inflammatory proteins, such as cytokines, chemokines, acute phase proteins, and growth factors, can differentiate TB from other infections. Previous studies evaluated the value of alternative proteins other than IFN-γ detected in the supernatant after stimulation of blood cells with *M. tuberculosis*-specific antigen using multiplex immunoassays, particularly the Luminex platform. Because these studies were based on stimulation assays, most recent studies have focused on evaluating host markers in unstimulated specimens, including serum or plasma, urine, and saliva, given that these biomarkers can be more easily examined and interpreted in the ward.[8]

In a study conducted by Liu Q in China in adult patients with CNS infections, including TBM (n = 17), purulent

meningitis (n = 13), and cryptococcal meningitis (n = 13), CSF levels of IL-1β, TNF-α, IFN-γ, IL-6, IL-4, IL-10, IL-17A, IL-17F, and CD40L were 2-fold higher in the TBM group than in the control group, with IL-6 being reported as a potent cytokine. It is most important for distinguishing CNS infections from controls. CSF glucose and CSF/blood glucose ratios were negatively correlated with CSF IL-6 levels in patients with CNS infection, thus illustrating the potential for combined CSF IL-6 and CSF glucose as biomarkers for CNS infection. In another Chinese study by Peng T et al. that included patients with viral meningitis, encephalitis, and bacterial meningitis and patients with intracranial metastatic tumors as controls, the CSF Delta-like 1 (DLL) ligand level showed a sensitivity of 87.1%, specificity of 99.1 %, the negative predictive value (NPV) was 92.2%, and the positive predictive value (PPV) was 98.2%, at the threshold value >1.0 ng/ml in diagnosing TBM. Similarly, serum DLL levels were also higher in the TBM group and TBM was diagnosed (border value >6.0 ng/ml) with sensitivity 82.3%, specificity 91.0%, PPV 83.6%, and NPV 90.2. %. In contrast, a study by Bahr NC in Uganda conducted on HIV-infected patients reported poor sensitivity (32%) but high specificity (98%) (border value 1150 pg/ml) for DLL1 in the diagnosis of TBM. Another protein (high mobility box-1; HMGB1), a molecular pattern-associated damage protein (DAMP) that plays a role in inflammation, was also shown to have potential in the diagnosis of TBM (sensitivity and specificity 61.02% and 89.94%, respectively), at a limit value of 3.4 ng/ml in another study by Chen Y et al. Other studies evaluating the value of various protein biomarkers as diagnostic candidates for TBM include the South African study by Visser et al., who identified CSF features with three markers namely IL-13, VEGF, and cathelicidin LL-37, which showed sensitivity 52.0%, specificity 95.0%, PPV 91.0%, and NPV 66.0% in the diagnosis of TBM in children. When assessed in a more recent study, these three markers diagnosed TBM with increased sensitivity of 95.7% and specificity of 37.5%, with better results obtained (91.3% sensitivity and 100%

specificity) when IL-13 and LL-37 were replaced by IFN-γ and myeloperoxidase (MPO), which are also for the diagnosis of TBM in children. Several novel biomarkers, including the biosignature of four novel markers (soluble intracellular adhesion molecule 1 [sICAM-1], MPO, IL-8, and IFN-γ) and various individual biomarkers, including IFN-γ, MIP-4, CXCL9, CCL1, RANTES, IL-6, TNF-α, MPO, MMP-9, MMP-8, CC2, IL-10, PAI-1, CXCL8, IL-1b, A1AT, CXCL10, G-CSF, CC4, CC4b, granulocyte- macrophage-CSF (GM-CSF), platelet-derived growth factor (PDGF) AB/BB, apolipoprotein (Apo)-AI, metallo-β-lactamase (MBL), ferritin, CC5a, SAP, and CC5, were shown to have the potential for the diagnosis of childhood TBM in the same study.[9,10]

The procedure for retrieval of CSF (lumbar puncture) may be a limitation in the application of the CSF-based test due to limited resources. Blood-based biomarkers, which have shown potential and are being developed into on-site tests for the diagnosis of pulmonary TB, can be an alternative in the diagnosis of TBM. Evaluation of the diagnosis of TBM in children with adult serum (C-reactive protein [CRP], IFN-γ, IP-10, CFH, Apo-A1, SAA, and NCAM) can diagnose TBM with moderate accuracy (73.9% sensitivity and specificity 66.7%). Meanwhile, a study conducted in South Africa showed that the use of serum of three novel markers (adipsin, Aβ42, and IL-10) could diagnose TBM in children with a sensitivity value of 82.6% and specificity of 75.0%, along with several candidates identified individual biomarkers. Given the potential demonstrated in this study, further discovery and validation of similar biomarkers are needed, followed by the incorporation of the most promising candidates into on-site assays. An additional benefit of blood-based biomarkers is the possibility to detect them in finger-prick blood, as is currently being carried out for a new pulmonary TB-based prototype test (https://www.triagetb.com/).[6,11]

Transcription Marker

Transcriptomics has become a frequently used approach for the discovery of biomarkers, one of which is a TB marker, using techniques such as RNA sequencing, quantitative PCR, and microarrays. Transcriptomics is the study of the total mRNA content of an organism that can identify diagnostic, disease-associated, and response to treatment. A study by Kumar GS et al. reported up-or down-regulation of 796 genes (398 and 398) in the brain tissue of HIV-coinfected TBM patients. Four gene products are commonly found in TBM patients coinfected with HIV, namely glial fibrillary acid protein (GFAP), serpin peptidase inhibitor clade A member 3 (SERPINA3), thymidine phosphorylase (TYMP/ECGF1), and heat shock protein 8 (HSPA8).[6]

miRNA Marker

MicroRNAs (miRNAs) are a class of small non-coding RNAs (21 to 25 nucleotides long), which play important roles in the regulation of gene expression and other biological processes. These are including of cell proliferation, cell differentiation, organ development, apoptosis, immune response, and angiogenesis. Altered miRNA expression has been associated with TB. In a study involving 112 children with TBM and 130 healthy controls, miR-29a expression in Peripheral Blood Mononuclear Cells (PBMC) showed potential in the diagnosis of TBM, with a sensitivity of 67.2% and a specificity of 88.5%, in addition, a sensitivity of 81.1% and a specificity 90% when evaluated in CSF. When used in combination, expression of CSF plus PBMC miR-29a diagnosed pediatric TBM with a sensitivity of 84.4% and a specificity of 95.4%.[12]

In a genome-wide miRNA analysis study performed on adult PBMCs and CSF samples, the combination of four miRNAs (miR-126-3p, miR-130a-3p, miR-151a-3p, and miR-199a-5p) distinguished TBM from viral meningitis (VM) in PBMC (sensitivity 90.6% and specificity 86.7%) and differentiated TBM from healthy controls (sensitivity 93.5% and a specificity 70.6%). Three CSF-based miRNAs (miR-126-3p, miR-130a-3p, and miR-151a-3p) also showed potential in differentiating between TBM and VM, with miR-199a-5p levels undetectable in CSF. PBMC miRNAs with four markers (miR-126-3p, miR-130a-3p, miR-151a-3p, and miR-199a-5p) were validated in an independent sample set out in the same study (sensitivity 81.8% and specificity 90.0%) in differentiating TBM and VM as well as TBM from other non-TBM patients (sensitivity 81.8% and specificity 84.6%). Three exosome miRNAs (miR-20b, miR-191, and miR486) also demonstrated potential as biomarkers to differentiate TBM from non-TBM disease when used in combination with electronic health records (EHR) in another study, diagnosing TBM with a sensitivity of 94% and specificity 95%. Altogether, this study demonstrates that miRNA-based biosignatures have potential as candidates for TBM diagnostic biomarkers. However, further studies of their potential value are needed, including studies conducted at multiple field sites in adults and children.[12]

Metabolic Marker

Metabolomics is a powerful and advanced omics platform that may be useful in identifying new diagnostic biomarkers. This technique is used to identify metabolites associated with certain physiological or pathological conditions. Several studies have demonstrated significant differences in amino acid and energy metabolism in CSF samples from TBM patients compared with other groups, including patients with viral, bacterial, and cryptococcal meningitis. However, the diagnostic accuracy of the identified metabolites was not reported. In a study investigating urinary metabolic biomarkers in 12 children with TBM and 29 controls, the biosignature host (SUM-4) generated from the summation of urinary concentrations of methylcitric acid, 2-ketoglutaric acid, quinolinic acid, and 4-hydroxyhipuric acid, separated TBM from another group with an Area Under Curve (AUC) from the Receiver Operator Character (ROC) was 96.6%. These large or small proof-of-concept studies provide evidence that host metabolomic biomarkers may be useful in the diagnosis of TBM. However, further work is needed in this area, coupled with work focused on developing end-user-friendly detection devices for the measurement of each candidate metabolite, preferably in the treatment room.[6]

CONCLUSION

Disease management has limitations due to the limited availability of available diagnostic approaches. Until now,

knowledge about the pathogenesis of TBM has been limited. Further research is urgently needed to improve understanding of disease pathogenesis and diagnostic approaches based on biomarkers of disease.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION

The author contributes to the study from the conceptual framework, data gathering until reporting the study.

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