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Disruption of the Blood–CSF Barrier in Tuberculous and Non-Tuberculous Meningitis: Mechanisms, Diagnosis, and Clinical Impact

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Abstract

The blood–cerebrospinal fluid barrier (BCSFB) is an important interface in the central nervous system (CNS), controlling immune surveillance, waste removal, and pathogen invasion. Breakdown of the BCSFB is a characteristic of meningitis, such as tuberculous meningitis (TBM) and non-tuberculous meningitis (non-TBM), due to bacterial, viral, fungal, or parasitic infection. This review examines the physiology and function of the BCSFB, its contribution to CNS homeostasis, and the mechanisms with which neurotropic pathogens violate the barrier to cause meningitis. We explain the differential pathophysiological profiles of TBM, including granulomatous inflammation, and non-TBM, having purulent or lymphocytic reactions, and their corresponding cerebrospinal fluid (CSF) profiles. Diagnostic issues are discussed, pointing out novel biomarker-based methods, like CSF metabolomics, to distinguish TBM from non-TBM. Clinical implication of the disruption of BCSFB, such as neuroinflammation, neuronal dysfunction, and elevated mortality, is assessed, stressing the necessity for more effective diagnostic and therapeutic interventions in order to reduce the global burden of meningitis.

Introduction

Numerous physical barriers exist in the central nervous system (CNS) that aid in halting the infiltration of neurotropic microbes into the brain tissues[1, 2]. These barriers contain blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (BCSFB), meninges and nasal epithelium-olfactory bulb interface. Together, these obstacles create sophisticated structures that hinder neurotropic organisms from invading the central nervous system (CNS) through the blood-borne dissemination, cerebral spinal fluid (CSF) or through nasal epithelium. Besides these physical blockades, native immune cells also proactively safeguard these locations, providing an additional degree of defense [1, 3].

BBB in conjunction with a group of receptors, transporters, efflux pumps, and other cellular elements, regulates the entry and exit of molecules from the vascular system into the brain, thus, maintaining homeostasis. The majority of blood-borne chemicals are stopped from entering the brain by an intact blood-brain barrier [4-6]. The BCSFB serves as a regulatory gate for immune surveillance and neuroimmune communication. The BCSFB is a biophysical and biochemical barrier that serves as an immunosurveillance system, aids in CNS waste clearance, and a physical blockade to peripheral transmission [7]. There are occasions in which neurotropic pathogens penetrate the central nervous system and induce a neuroinflammation, even in the presence of immunologically patrolled barriers [1]. An increasing amount of data indicates that the B-CSF barrier is essential for the transmission of inflammatory responses from the peripheral to the central nervous system and is involved in the pathogenesis and development of many neurological conditions. Neurotoxicity and neuronal dysfunction might arise if hematogenous pathogens disseminate to CSF through the BCSFB [8].

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When microbes interact with, penetrate the blood-brain barrier (BBB) and cause inflammation, this condition is known as meningoencephalitis/meningitis which is a potentially lethal infection of the central nervous system (CNS). Numerous fungal, viral, or bacterial pathogens can cause infectious meningoencephalitis/meningitis, although viruses and bacteria are the most frequent perpetrators [9]. For instance, Mycobacterium tuberculosis, a frequent cause of lung disease but it also, has the potential to infect the CNS resulting in a lethal form of tuberculosis termed as tuberculosis meningitis [10]. In this comprehensive review, we tend to discuss blood-CSF barrier integrity, its physiology and function, its dysfunction in TB and non-TB meningitis and different pathways employed by the neurotropic pathogens to breach the BCSF barrier to induce meningitis.

The Blood–CSF Barrier: Physiology and Function

The blood-CSF barrier keeps apart the blood and the CSF [11]. Choroid plexus (CP) epithelial cells and tight junctions that join these cells and the basal membrane are what constitute the BCSF barrier. This barrier limits the access of solutes into the CSF. The richly vascularized structures located in the ventricles that produce the CSF are called choroid plexus [12]. CP possesses peculiar structural organization, which consists of tight layer of epithelial cells that encase the connective stroma and large fenestrated capillary loops are formed by blood vessels penetrating this stroma [13]. For immunosurveillance purposes, stroma also harbors various populations of immune cells such as macrophages, dendritic cells and T cells [14]. The ChP acts as both a specific entry point and an obstacle against infectious pathogens because it is an interface between the central nervous system (CNS) and a vascularized stroma that contains a range of immune cells [15]. Any pathogens that penetrate this barrier and enter the CSF have direct access to the brain parenchyma and can significantly affect the homeostatic state [14].

What differentiates blood-CSF barrier from blood brain barrier is that, BBB comprises of highly vascularized endothelial cells containing tight junctions, basal lamina, pericytes, and perivascular space encompassed by the astrocyte endfeet and is found in all over the brain [16]. To stop water-soluble molecules from moving paracellularly, these endothelial cells are connected by adherens and tight junctions. Adherens junctions between the BBB's endothelial cells control cellular adhesion and the movement of chemicals between the blood and brain, preserving the barrier's integrity [17, 18]. For the brain's 86 billion neurons to function at their best, the BBB oversees the movement of substances into and out of the central nervous system (CNS), maintaining the chemical stability of the neuronal microenvironment and promoting regular neuronal metabolism. The equilibrium of the brain's microenvironment is disrupted by BBB impairments [19, 20]. Attributed to these functions, this barrier is considered as an 'absolute' or 'true' barrier [7].

Meningitis: Pathophysiology and Classification

- **Overview of Meningitis Types**

Neurological infections are among the deadliest illnesses and account for a large number of fatalities globally. WHO reports that these deadly diseases claim the lives of almost 200,000 people, including newborns [21]. Inflammation of the meninges is called meningitis which is horrific and potentially lethal infection and it is mostly caused by bacteria, viruses and fungi [22, 23]. The meninges are the three-layered structures: dura mater, arachnoid mater and the pia mater. Leptomeninges is a term refers to arachnoid and pia mater collectively [24, 25]. These structures encase the brain and the spinal cord and every structure has discernible cellular and functional properties [24, 26]. The meninges control the growth of the skull, brain blood vasculature, and forebrain and hindbrain. They also support the upkeep of the pial basement membrane and the survival, migration, and positioning of neurons in the brain [27, 28].

Meningitis can be caused by a variety of pathogens as well as autoimmune, neoplastic and drug associated conditions [29]. In this review our discussion will be on tuberculosis (TB) meningitis and non-TB meningitis which can be of bacterial, viral, fungal and parasitic origin excluding mycobacterial meningitis.

Tuberculous Meningitis

One of the most frequent causes of morbidity and death for TB patients is tuberculosis meningitis (TBM), a severe form of TB that affects the central nervous system [30]. WHO reported that 10.8 million people acquired tuberculosis in 2023. According to a recent study on the burden of disease in adults, the worldwide incidence of tuberculous meningitis was estimated to be between 129 000 and 199 000 cases, with up to 70 000 cases (35–54%) co-infected with HIV. The mortality rate calculated by the model was 27% [10]. TBM exacerbates the global burden of tuberculosis by disproportionately affecting immunocompromised populations, especially those with HIV [31].

Following a systemic infection, M. tuberculosis spreads through the bloodstream and penetrates the blood-brain barrier (BBB), which allows bacteria to enter the central nervous system (CNS) through macrophages. BBB crossing is facilitated by bacterial virulence factors, such as those that promote actin rearrangement and adhesion. Once inside the central nervous system, M. tuberculosis forms a "Rich focus," or leptomeningeal or cortical granuloma, which can burst into the subarachnoid space, causing severe inflammation and infection. This immune response strikes a balance between tissue damage and bacterial control, as evidenced by neutrophil-induced inflammation and cytokine release. TBM relies heavily on macrophages and microglia. Microglia are CNS resident immune cells that release pro-inflammatory cytokines like TNF-α and IL-1β in response to M. tuberculosis invasion. These cytokines regulate bacterial replication but can also cause tissue damage and neuroinflammation.

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Extended microglia activation can cause neurotoxicity and cognitive problems. A characteristic of TBM is the formation of granulomas, which are caused by immune cells clumping together around M. tuberculosis and frequently result in vascular damage in later stages [31, 32].

Acute Bacterial Meningitis

High rates of mortality and morbidity, as well as an accelerated onset and potential for outbreak and epidemic, characterize acute bacterial meningitis (ABM) [33]. Three pathogens: Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type B are the main culprits behind community-acquired bacterial meningitis. Additionally, certain groups, such as neonates, pregnant women, transplant recipients, and older adults, are susceptible to meningitis due to Streptococcus suis in Southeast Asia, Listeria monocytogenes, Group B streptococci, and Gram-negative bacteria like Escherichia coli and Klebsiella pneumonia [33-36].

Viral Meningitis

When a virus invades the meninges, it causes viral meningitis, the most prevalent infection of the central nervous system. It is prevalent in immunocompromised individuals, including children and the elderly [37]. Known viruses that cause meningoencephalitis include herpes simplex virus, human herpesviruses 6 and 7, enteroviruses, Japanese encephalitis virus, West Nile virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, human immunodeficiency virus, and rabies virus [9].

Fungal Meningitis

Fungal infections of the central nervous system can cause meningitis. This condition can be caused by a variety of fungi, including filamentous fungi like Aspergillus spp., Penicillium spp., and Pseudallescheria spp.; dimorphic fungi like Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides spp., and Sporothrix spp.; dematiaceous fungi like Cladophialophora bantiana and Exophiala dermatitidis [38]. The most common cause of fungal meningitis in the globe, especially among HIV-positive people, is Cryptococcus species. The majority of cases of cryptococcal meningitis in the Cryptococcus genus are caused by C. neoformans. People in high-risk categories are particularly vulnerable to brain infections brought on by pathogenic fungus, including those with AIDS, recipients of organ transplants, immunocompromised by corticosteroid medications and chemotherapy, and patients with cancers of the blood [38].

- **CNS Entry Routes**

Pathogens can enter the central nervous system (CNS) through the BBB and BCSFB, either by paracellular or transcellular penetration, or by infecting leukocytes from the peripheral circulation (the "Trojan horse" mechanism). The bacterial attachment to endothelium or epithelial cells is followed by transcellular penetration. After that, bacteria are moved past these barriers by receptor-mediated processes or pinocytosis. By breaking the tight connections between cells that compose the BBB and/or BCSFB, pathogens can instead enter the central nervous system (CNS) paracellularly, increasing permeability [39].

Disruption of the Blood–CSF Barrier in Meningitis

A breach of BCSFB could be explained by the increased CSF cells and protein. A variety of proinflammatory cytokines and chemokines can compromise the integrity of BCSFB. Proinflammatory cytokines, including interleukin (IL)-1β, IL-8, IL-6, and tumor necrosis factor (TNF)-α, recruit immune cells, trigger the formation of matrix metalloproteinases (MMPs), and start the immune system's inflammatory pathways. The breakdown of the extracellular matrix brought on by these inflammatory indicators may further compromise the BBB and BCSF, enabling cell migration to the infection site. Cerebral endothelial cell permeability is increased in vitro and in vivo by proinflammatory cytokines like TNF-α and IL-6 [40].

Pathological Profiles of TBM and Non-TB Meningitis

Granulomatous inflammation in the leptomeninges is a characteristic of tuberculous meningitis (TBM), a severe form of extrapulmonary tuberculosis caused by Mycobacterium tuberculosis. This inflammation is frequently caused by the rupture of subpial or subependymal Rich foci into the subarachnoid space. Histopathologically, TBM is characterized by a thick basal exudate that includes fibroblasts, lymphocytes, plasma cells, Langhans giant cells, and epithelioid macrophages. Vasculitis and caseous necrosis cause endarteritis, infarcts, and hydrocephalus, especially in the cranial nerves and basal cisterns [41]. Forms of meningitis that are non-TB-related differ significantly from this granulomatous reaction. The pathology of acute bacterial meningitis (BM) includes purulent exudates with an abundance of neutrophilic infiltration, which results in rapid meningeal inflammation without granulomas. This frequently causes diffuse brain edema and elevated intracranial pressure, but less chronic vasculopathy. Conversely, viral meningitis (VM) exhibits lymphocytic pleocytosis with little exudate or necrosis, indicating a less severe, self-limiting inflammatory process that mostly involves mononuclear cells without caseation [42]. These variations are further outlined by cerebrospinal fluid (CSF) profiles: Cell counts frequently surpass 500 × 10^6/L, and TBM is characterized by lymphocytic pleocytosis (>50% lymphocytes), elevated protein (>1 g/L), low glucose (<2.2 mmol/L), and reduced chloride (<120 mmol/L) [42]. While VM maintains normal or slightly elevated protein and glucose levels with lymphocytic dominance but lower cell counts, BM CSF exhibits neutrophilic predominance, significantly elevated protein, and profoundly low glucose [43].

Table 1.0 Comparisons of TB and Non-TB Meningitis Pathological Profiles

Type of Meningitis	Characteristic Inflammation	Key Cell Types	Cerebrospinal Fluid (CSF) Profile	Protein	Glucose	Cell Count
Tuberculous Meningitis (TBM)	Granulomatous inflammation	Lymphocytes, Plasma cells, Langhans giant cells, Epithelioid macrophages	Lymphocytic pleocytosis (>50% lymphocytes)	>1 g/L	<2.2 mmol/L	>500 × 10^6/L
Acute Bacterial Meningitis (BM)	Purulent exudates	Neutrophils	Neutrophilic predominance	Significantly elevated	Profoundly low	Not specified
Viral Meningitis (VM)	Lymphocytic pleocytosis with little exudate	Mononuclear cells	Normal or slightly elevated	Normal or slightly elevated	Not significantly low	Lower cell counts

Differential Diagnosis of TB and Non-TB Meningitis

Due to overlapping clinical features, tuberculous meningitis (TBM) and non-TBM, such as bacterial (BM) and viral (VM), pose diagnostic challenges. Therefore, advanced clinical and biomarker-based approaches are required for differentiation, especially across age groups. In contrast to BM, which exhibits acute onset and high neutrophil counts, and VM, which has milder CSF abnormalities, TBM frequently manifests with weight loss, prolonged symptom duration (>5 days), and cerebrospinal fluid (CSF) findings such as elevated protein, low glucose (<2.2 mmol/L), and a high lymphocyte percentage (>50%) [44, 45]. A study found distinct ventricular CSF biomarkers, such as elevated neuronal excitotoxicity markers, that differentiate pediatric TBM from non-TB infections. Pediatric TBM, especially in children under five, frequently manifests with vague symptoms like irritability [46]. Compared to conventional diagnostics like Ziehl-Neelsen (10–20% sensitivity) or GeneXpert (55–80% sensitivity), advanced biomarker techniques, such as CSF metabolomics, show elevated citrulline and lactate in TBM across all ages, improving specificity [32, 47]. These biomarker-based and age-specific clinical approaches improve the diagnostic precision of TBM versus non-TBM in a variety of contexts [45, 47].

Table 1.1 Differential diagnosis of TB and non-TB meningitis across age groups

Meningitis Type	Age Group	Onset	Symptoms	CSF Findings	Sensitivity
Tuberculous	All Ages	Prolonged	Weight loss	Elevated protein, Low glucose (<2.2 mmol/L), High lymphocyte percentage (>50%)	CSF metabolomics: high citrulline and lactate
Non-TB Bacterial	All Ages	Acute	High neutrophil counts	Milder CSF abnormalities	Ziehl-Neelsen: 10-20%, GeneXpert: 55-80%
Non-TB Viral	All Ages	Milder	Vague symptoms (irritability in pediatric)	Milder CSF abnormalities	Ziehl-Neelsen: 10-20%, GeneXpert: 55-80%
Tuberculous	Under 5	Prolonged	Irritability	Elevated protein, Low glucose (<2.2 mmol/L), High lymphocyte percentage (>50%)	CSF metabolomics: high citrulline and lactate

Discussion

The blood–cerebrospinal fluid barrier (BCSFB) is a critical component in CNS homeostasis, but its dysregulation by neurotropic pathogens forms the basis of meningitis pathogenesis. In tuberculous meningitis (TBM), Mycobacterium tuberculosis-induced granulomatous inflammation produces devastating complications such as vasculitis, infarcts, and hydrocephalus due to the breakdown of Rich foci into the subarachnoid space. This is in contrast to non-TBM, in which acute bacterial meningitis (ABM) has marked neutrophilic invasion and viral meningitis (VM) displays less pronounced lymphocytic reaction. These different pathological profiles are paralleled by cerebrospinal fluid (CSF) patterns, with TBM having lymphocytic pleocytosis, increased protein, and decreased glucose, as opposed to the neutrophil predominance seen in ABM and less pronounced CSF abnormalities in VM. Differential TBM and non-TBM diagnosis

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is still problematic because it shares overlapping clinical presentations, especially among immunocompromised individuals and children. New diagnostic technologies like CSF metabolomics that detects increased citrulline and lactate levels provide better specificity than the older methods like Ziehl-Neelsen staining or GeneXpert, which are not sensitive enough.

Pathogens cross the BCSFB by transcellular, paracellular, or "Trojan horse" pathways with the help of proinflammatory cytokines (e.g., TNF-α, IL-6) and matrix metalloproteinases (MMPs) to enhance barrier permeability. These pathways emphasize the interaction of microbial virulence determinants with host immune mechanisms, which have the potential to worsen neuroinflammation and neuronal injury. High morbidity and mortality due to TBM, especially among HIV-co-infected patients, highlight the imperative to identify targeted therapies that modulate BCSFB impairment and prevent inflammatory damage. Elucidation of pathogen-specific BCSFB entry pathways and identification of new biomarkers that improve early diagnosis, particularly in resource-poor settings where prevalence is high, remain essential areas of future research. Moreover, therapeutic interventions on cytokine-driven inflammation and barrier healing may diminish the clinical burden of meningitis, enhancing outcomes in a broad array of populations.

Conclusion

Disruption of the blood–cerebrospinal fluid barrier (BCSFB) is a key process in the pathogenesis of tuberculous and non-tuberculous meningitis by allowing entry of the pathogen and subsequent neuroinflammatory responses. TBM offers distinct challenges owing to its granulomatous pathology and high mortality, especially in the immunocompromised host, whereas non-TBM shows diverse inflammatory patterns based on the causative pathogen. Technological advances in diagnosis, including CSF metabolomics, present promising pathways to distinguish TBM from non-TBM and overcome the deficiencies of traditional approaches. Insight into the molecular and cellular processes underlying BCSFB dysfunction is necessary to design effective treatment strategies to mitigate the global health burden of meningitis. Improved diagnostic accuracy and directed therapies have the potential to enhance clinical outcomes and minimize the catastrophic neurological effects of infection.

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Declarations:

Authors' Contribution:

- All Authors contributed equally in conceptualizing, research, data collection and compilation of the manuscript
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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Core Tip:

This review elucidates the critical role of the blood–cerebrospinal fluid barrier (BCSFB) in the pathogenesis of tuberculous meningitis (TBM) and non-tuberculous meningitis (non-TBM). It details the mechanisms by which pathogens breach the BCSFB, the distinct pathological and cerebrospinal fluid (CSF) profiles of TBM and non-TBM, and the diagnostic challenges addressed by advanced biomarker-based approaches like CSF metabolomics. The clinical impact of BCSFB disruption, including neuroinflammation and high mortality, underscores the need for improved diagnostics and targeted therapies to reduce the global burden of meningitis.

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