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Literature Review: Pathophysiology of Tuberculous Meningitis: Mechanism of Infection and Immune Response

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Abstract

Tuberculous meningitis (TBM) is one of the tuberculosis forms that attacks the central nervous system caused by Mycobacterium tuberculosis (MTB). This illness generally happens through developed countries, especially to the kids and having high mortality levels even after modern treatment exists. The TBM happens when the MTB spreads from the lungs into the brain, crossing the brain's blood barrier, and causing inflammation. People with low-immune levels could possibly let MTB spread easily through the body. The pathophysiology of TBM is influenced by the genetics, immune responses, also the microbiota as the factors. The genetics' variation on the immune system could increase the risk of getting the illness, while the microbiota imbalance could affect the immune functions. Furthermore, this condition impacts kids and the adults. The kids get affected more severely and the people with HIV will face complications caused by immune pressure. The deeper understanding through TBM mechanisms including immune factors, also genetics are important in aim to increase prevention and treatment. The modulation immune and microbiota approaches as targeted therapy highlights a positive potential in terms of improving the patient's treatment result and decreasing the TBM's global burden.

Keywords: Tuberculous Meningitis (TBM); Mycobacterium Tuberculosis (MTB); Central Nervous System; Pathophysiology; Immune Response

1. Introduction

Tuberculous meningitis (TBM) is the tuberculosis form that caused rarely but deadly. It attacks the nervous system's center especially the meninges. This infection caused by Mycobacterium Tuberculosis (MTB) that mostly affects the lungs but also can spreading through bloodstream into the other parts like brain (1). Epidemiologically, TBM's cases are generally impacts developing countries with high tuberculosis prevalence including the Asia and Africa. The data underlines that the TBM's incidence mostly attacks the kids from those regions (2). From recent study, the mortality rates caused by TBM is in significant level, it underscores the importance of early detection and aggressive treatment even after modern treatment has exists. TBM will cause permanent brain damage without timely treatment. TBM incidence is one of the critical problems because it mostly shows up late through the detection, also the complex challenges of treatment (3). Thus, a deep understanding of TBM pathophysiology is crucial in aim to increase the prevention and treatment. This study's purposes are to exploring the mechanism of MTB infection through the nervous system and how immune responses to overcome the infections.

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2. Pathophysiology of tuberculous meningitis

The Pathophysiology of tuberculosis (TB) starts when the Mycobacterium Tuberculosis (MTB) inserting the body through inhaled droplets, mostly caused by the infected individual's contact. The body response to the infection by activates the immune system once the bacteria reached to lungs. To people with good and healthy immune system, their body could control the infection by forming the structure that includes immune cells that can isolate and limits the spreading bacteria, it's known as granuloma (4). But then, in some individuals, especially to them with immunosuppression or malnutrition, the infection could spread through bloodstream into another organs like brain (5). This process may cause bacterial infection that surrounding the brain and spinal cord, well-known as Meningeal Tuberculosis. Bacteria caused inflammation to the brain that potentially damage the brain cells and the menings, it underlines how serious it is. The symptoms include headache, seizures, and consciousness problems (6).

3. Mechanisms of infection in tuberculous meningitis

3.1. Mycobacterium tuberculosis Infection of the Central Nervous System

The infection of MTB on nervous system starts from the hematogenous or lymphogenous spread from the primary infection sources like lungs. Bacteria are able to penetrate brain's blood barrier, the protection structure that is normally prevent the pathogens to reach the brain and cerebrospinal fluid (CSF) (7). Transmission happens when the MTB entering the blood vessels and reaches the brain's capillaries. After entering blood vessels, the bacteria infect the vascular endothelial cells that caused inflammation. The bacteria are able to pass the brain's blood barrier protection, then enter cerebrospinal liquid and meninges that caused inflammation (6). This condition could be worsened by the immune system problems, including to people with HIV or other immunosuppressive conditions, it reduce the body's ability to attack the infection that allows the bacteria to grow aggressively and quickly (8).

3.2. The Role of Macrophages and Immune Cells in Invasion

Macrophages stand as an important part in body's immune response to MTB. When the bacteria reached the body, the macrophages attempt to destroy it via phagocytosis. But then, the MTB has the ability to survive inside the macrophages by preventing the elimination through the uncertain mechanism, including the production of virulence that modulate the immune responses (9). In some cases, bacteria could grow inside the macrophages and spreading to another cells, including T cells and Dendritic cells that having a role to recognize the pathogen that resulted adaptive immune respons (10). Granulomas that are shape as a response through the infection is a form of various immune cells type that are trying to limits the bacteria spreads (11). The form of granuloma in meninges could cause damaged cells and other fatal neurologic conditions (6).

4. Immune response to tuberculous meningitis

4.1. The Role of the Innate Immune System in Tuberculous Meningitis

Immune system is the first body's guard through the infection. It appears as various immune cells including neutrophils, macrophages, also natural killer cells. When the MTB reach inside the body, these cells stand to recognize and responding the bacteria. Neutrophil and macrophages take parts on the early phagocytosis as an effort to attack the MTB via phagolysis. However, directing to the TBM cases, the MTB utilize various strategies in terms to prevent attacks from the immune system. These bacteria could limit the Macrophages function such as decrease phagocytosis and pressing the macrophages killing mechanism. It potentially influences the bacteria to stays longer inside the body (12). Furthermore, the natural killer cells also take parts in recognizing and attack the infected cells. By notes, the natural killer's role through the TBM still under further research. The understanding of how NK cells contribute as an immune response through MTB inside the brain and cerebrospinal liquid still need further research to confirm it actions (13).

4.2. The Role of the Adaptive Immune System in Tuberculous Meningitis

The adaptive immune system stands as important parts in responds to the infection through the MTB. After a continuation infection, CD4+ and CD8+ T cells being a main part to control the bacteria. CD4+ T cells activate the macrophages through cytokines' release, increasing the phagocytic capabilities in aim to attack ingested bacteria (14). Furthermore, CD8+ T cells exists to eliminate host cells that are infected by the bacteria (15). Next, B cells is able to create antibodies to fight extracellular infections, also important in facing the TBM. But then, the antibodies stated as lack of effectiveness because the MTB is intracellular, it hiding inside the host cells (16). The adaptive immune response

is very important in terms of controlling the TB infection, although in some TBM cases, this response can be mis-utilization that can cause brain damage through intense inflammatory mechanisms (17)

4.3. Immune Tolerance and Immunosuppression in Tuberculous Meningitis

Both immune tolerance and immune suppression are important factors that impacting the TBM. Immune tolerance is the ability from immune system to prevent inclusive damage for itself when fighting against pathogens, on the other hand, immune suppression is a decreased condition of immune responses that caused of some factors including other infections and specific therapy. MTB strategies to avoid elimination by the immune system by inducing local immune tolerance through the infected cells, such as the brain. In chronic infections, the body tries to control the growth of bacteria by forming granulomas immune structures that aim to limits the pathogens spreads. Thus, granuloma formation can caused to inflammation that may potentially cause brain damage in TBM case. In people with bad immune systems, including HIV/AIDS conditions or immune suppressive therapy, the immune response to MTB is not optimal. It caused the bacteria can grow more quickly and led to more serious complications, like significant neurological impairment. Immune suppression leading to the immune response to these infections badly, causing to increase the diease duration, and imrpoves the risk of morbidity and mortality by much more (18)(19)(20).

5. Factors influencing the pathophysiology of tuberculous meningitis

5.1. Host Genetic Factors

Individual genetics aim to determine patient's susceptibility through TBM. Although the MTB stand as the main factor on this infection, the number-one influence of body's response to the bacteria is specific genetic components. Genes variations that control the immune response, including encoding Toll-like receptors (TLRs), can impact the body's effectiveness in recognize and fighting against the pathogen (21). Some studies have underlined that people with certain genetic variations are likely susceptible to grow the TBM. For example, mutations in genes that control the interferon gamma (IFN-γ) production, cytokine is important in aim to activate the macrophages and destroy the MTB, it limit immune response adequately. As a result, the power of body that containing the infection is decreased, increasing the potential of TBM complications (22). Furthermore, genetic factors also able in helping the granulomas formation, immune formations that limits tbacteria spreads, and the controlling the inflammation levels within central nervous system (23).

5.2. The Role of Microbiota in the Pathogenesis of Tuberculous Meningitis

The Microbiota exists to control the body's immune responses through various infection like tuberculosis, especially gastrointestinal microbiota. The recent study highlights the imbalance microbiota composition could affect the TBM grow by changing the immune response and increasing the infection susceptibility. The microbiota shift could affect the immune cells activation that includes in terms of fighting the MTB. Next, the gut microbiota have interaction with immune system that potentially affect the TBM pathogenesis and the grow infection inside the center of nervous system (25). This understanding opening the door in terms of improving the holistic therapy including the use of probiotic or diet modification in aim to increase immune response and prevent TBM growth (26).

5.3. Pathophysiological Differences in Specific Populations

The TBM pathophysiology shown significant variations between groups of people. To the kids, the body's immune system that is still developing makes them easily get infected. Furthermore, the immune response that is still growing mostly causing to shape a more aggressive TBM, with problems like seizures, low consciousness, and hypertension of intracranial that are more complex than adults. The mechanism of granuloma forming and immune response for kids is also different that affecting to the spread growing and infection levels (27). On the other hand, the adults that infected by HIV, TBM pathophysiology is very affected by their immune status. The HIV condition lowering their immune system by decreasing CD 4 T cells that caused the body powerless to fight against MTB infection. It led to harder in controlling infection and mostly growing to shape bigger. The difference of granuloma forming and immune response between HIV patients and non-HIV affects the illness phase, the neurologic complication levels, and treatment diagnosis challenges. The interaction between HIV and TBM worsen the prognosis of the disease, led to the needs of treatment approaches that is more complex (28).

6. Conclusion

Tuberculous Meningitis (TBM) refers to the bad tuberculosis form that significantly affects the center of nervous system, especially to the low-level of immune system and kids' populations. The complexities of TBM pathophysiology is on high

level, it includes the MTB hematogenous' spreads to the brain, where the bacteria caused inflammation, granuloma forming, also damage cells potential. The immune response to the MTB of TBM includes innate and adaptive immune system, with macrophages that stands to control infection. However, MTB has evolved its strategy to prevent the elimination from immune system, including immune tolerance that causing immune suppression, it worsens the illness grow and increase the death numbers.

Some of factors affects the TBM pathophysiology, including the host of genetics, immune response, also microbiota. The genetics variations of immune system component like Toll-like receptors and the interferon gamma production could shift the susceptibility of individual to the TBM. The microbiota composition also stands as the important part. This cause by the imbalance could modulate the immune response and increase the vulnerability to the infection. Furthermore, clinical presentation and TBM growth could be significantly variative through populations. The kids with unfinished body's immune system have big potential in experiencing a more-aggressive disease, while the adults with HIV faces challenges in terms of controlling the infection caused by the compromise body's immune system.

In conclusion, the TBM is being one of the critical global medical challenges. Especially to the regions with high tuberculosis and HIV levels. The deep understanding of the disease pathophysiology, immune mechanisms, and genetic factors are all important in aim to developing the diagnostic strategy, and more-effective preventive. The interdisciplinary approaches and targeted therapy including modulation of immune response and microbiota are potential to increase the result of patient's treatment and decrease the global disease that is very concerning.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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