European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2023 vol. 12, ISSUE N. 2, May-August

MENINGITIS: AN OLD DISEASE THAT STILL PERSISTS TODAY. NEW IMMUNE AND INFLAMMATORY ASPECTS

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ABSTRACT

Neuroinflammation is the brain's natural response mechanism to fight off potential threats and encompasses a variety of neurological diseases including meningitis. Meningitis is a serious infectious disease and devastating condition associated with high morbidity and mortality. A common method of diagnosing bacterial meningeal infection is through cerebrospinal fluid analysis. Meningococcal Neisseria (MN) menigitis is one of the most common bacterial infection affecting the central nervous system (CNS), and is characterized by infection of the arachnoid and subarachnoid spaces. The meningococcus binds to the Toll-like receptor (TLR), triggering an immune response and attracting phagocytes in the brain and systemically throughout the body. Activated immune cells produce pro-inflammatory cytokines that aggravate the disease state by destroying brain tissue, including neurons. In infection, activation of the complement system also participates in neurological damage.Therapeutic experiences against meningitis indicate that steroidal anti-inflammatory drugs, such as cortisone and other inflammatory inhibitors, reduce the meningeal pathological state. Blocking inflammation by inhibiting inflammatory cytokines could also represent a new therapeutic strategy in bacterial meningitis.

KEYWORDS: *meningitis, meningococcus, Gram-negative bacteria, immunity, inflammation, Neisseria meningitidis*

INTRODUCTION

Meningitis is a disease that has stably affected man for over 50 years. Traces of meningitis date back to 1500 BC, but the first description was given in the early 1800s (1, 2), while meningococcus, the Gram-negative bacterium responsible for the disease, was first isolated in 1887 (3).

Meningitis is an infection of the meninges that can be caused by several biological microorganisms including bacteria, viruses, and fungi, or by parasites (4). This neurological disease can be very serious and can lead to death even in hours after infection. It can cause permanent damage and 10% of those who contract it will die (5). Other bacteria such as Streptococcus pneumoniae and Haemophilus, and viruses such as herpesvirus, enterovirus, and influenza virus, can also cause meningitis (6). Immunosuppressed subjects are more prone to meningitis due to fungi (7).

Meningococcal meningitis type B is caused by the bacterium Neisseria meningitidis (NM) which is transmitted by secretions or by physical contact (8). Children, including newborns, and the elderly are at the highest risk for meningitis

Received: 22 May, 2023
Accepted: 06 July, 2023

2974-6345 (2023)

(9,10). The NM bacterium that causes the disease in humans is made up of different groups: A, B, C, Y, W135, and X (which is less present) (11,12). In Western countries, the most frequent groups are B and C (13). Meningococcal meningitis is one of the most studied and most frequent brain diseases in the African continent, in the United States, and in Europe. For about 50 years, rates of meningococcal disease in Western countries remained approximately the same, at about 1 case per 100,000 people per year (14).

DISCUSSION

The infection occurs mainly in winter and generally affects children who do not yet have their antibody system activated, but adults up to 65 years of age can also be affected. Meningococcus is a Gram-negative bacterium that causes meningitis with usually severe symptoms including headache, shock, nausea, disseminated intravascular coagulation, vomiting, photophobia, lethargy, rash, and multiple organ failure.

NM infection can affect the membranes of the brain and can infect the entire body (septicemia), including the spinal cord, by traveling in the bloodstream (15). Diagnosis should be made based on symptoms such as headache, vomiting, high fever, confusion, fatigue, sensitivity to light, and neck stiffness. In the most severe forms of septicemia, the patient may show organ damage and skin rash. Timely diagnosis and appropriate antibiotic treatment can save the life of the patient suffering from meningitis.

Severe meningococcal infection can affect the central nervous system (CNS) with brain damage and deafness and can cause scarring and even the loss of limbs (16). The infection can also be transmitted by healthy carriers. In addition to those already described above, symptoms of meningococcal meningitis include drowsiness, sudden high fever, and loss of appetite. Protection against the NM bacterium is obtained through vaccination of the patient by age and condition-appropriate doses. Meningitis vaccination can be done with various vaccines such as meningococcal type B vaccine, meningococcal quadrivalent vaccine ACWY, and meningococcal type C vaccine.

The bacterial infection affects the liquid that resides in the ventricles of the brain, causing inflammation, which is a protective response due to the phagocytes which are involved in the immune response. Meningococcus activates both innate and adaptive immunity, which should lead to the improvement of the disease (17). Therefore, meningitis infection causes inflammation of the meninges and brain parenchyma, resulting in meningoencephalitis (18). The infection can vary and affect different brain regions. Encephalitis is inflammation of the brain parenchyma that causes mental disorders and neurological dysfunction, while meningoencephalitis is the inflammation of the CNS involving both the meninges and the parenchyma (19).

In addition to bacteria and viruses, fungi, protozoa, and helminths can also cause meningitis. Bacterial meningitis causes damage to the cerebrospinal fluid and the CNS, resulting in a serious disease that can be fatal. The most common transmissible pathogen that causes the disease is Streptococcus pneumoniae, accounting for 70% of cases, along with NM and Listeria monocytogenes as other common pathogens (20,21). Pneumococcal meningitis and listeria are the most common forms of infection with a mortality rate of up to 20%, although these death rates have been dramatically lowered with vaccinations (22). The encephalitis that occurs in meningitis improves markedly after treatments with anti-inflammatories such as cortisone which reduces the rate of morbidity and mortality (23). However, this treatment is not enough, and new therapies are needed for better results.

The innate immune response participates in the elimination of pathogens and the complement system plays an important role in this reaction. In fact, complement plays a key role in the pathogenesis of neurological disease and, particularly, anaphylatoxin causes cerebral and blood pathological effects (24,25).

In bacterial meningitis, activation of the classic complement pathway begins with the binding of C1q to immune complexes formed by IgM and pneumococcal C polysaccharide (26). The alternative complement pathway occurs when C3b binds to the bacterium, setting off a chain reaction that magnifies complement activation (26). C3b opsonizes the bacterium by facilitating phagocytosis by neutrophils and macrophages, a reaction that causes the secretion of IL-1 and other monokines. Neutrophil phagocytosis of meningococcus is associated with the release of free oxygen radicals (ROS) and lysosomal proteases that cause vascular damage with increased vascular permeability, hemorrhage, and thrombosis (27). Activation of the complement system produces anaphylatoxins C3a and C5a which, by binding to their respective receptors on immune cells, participate in and amplify the inflammatory response (26). The increase in permeability exerted by the complement causes the accumulation of neutrophil granulocytes with an increase in inflammation.

Complement inhibition in bacterial meningitis drastically reduces the inflammatory reaction of the CNS which is one of the main harmful effects (28). The C5a component is the most damaging in bacterial meningitis and targeting anaphylatoxin C5a production, together with treatment with antibiotics and cortisone, is a very useful therapy (26). Neutrophils migrate to the site where bacterial multiplication occurs and participate in vascular damage. The

meningococcus releases C5a-inducing endotoxin and proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) (29).

In the disease, there is an inflammatory reaction that affects the subarachnoid space and cerebral parenchymal vessels, contributing to brain damage. In infants, the disease can lead to cerebral palsy with cognitive impairment, blindness, deafness, seizures, and hydrocephalus (30).

The bacterium crosses the blood-brain barrier (BBB) and binds to the Toll-like receptor (TLR) of antigen-presenting cells that are important mediators for the initiation of the immune reaction, triggering an inflammatory response with activation of the NF-kB or protein kinase pathway (31). This leads to the activation of leukocytes which produce immune and inflammatory mediators that damage neurons (32). The cytokines and chemokines produced in these reactions, that are activated by the NM bacterium, attract neutrophil granulocytes which produce large amounts of superoxide anion and nitric oxide, leading to oxidative stress. The resulting mitochondrial damage causes energy insufficiency and cell death, lipid peroxidation, and the breakdown of the BBB. The receptors of the microglial cells activated by the meningococcus increase the phagocytic capacity but can also damage the entire brain, including neurons (33). Microglia and macrophages of the meninges have different types of TLRs that trigger local and systemic immune responses (Fig.1). Microglia are protective cells of the brain and spinal cord that are responsible for defending brain tissue from bacterial invasion including meningococcus. Activation of TLR types 1, 2, and 4 enhances bacterial phagocytosis, whereas activation of TLR9 can cause brain tissue injury through the production of TNF and nitric oxide (NO) (34).

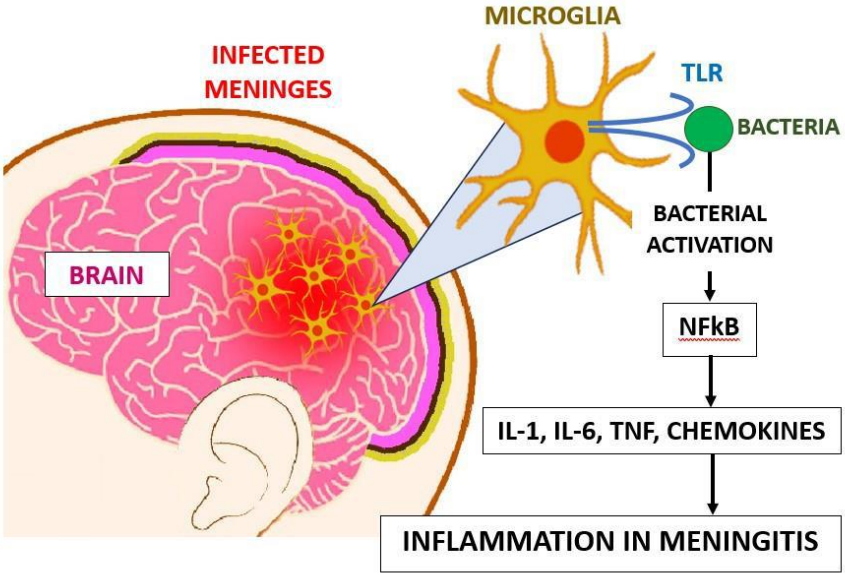

Fig. 1. *The inflammatory response in meningitis. In infected meninges, the bacterium meningitis binds to the Toll-like receptor (TLR) of microglial cells and activates the NF-kB pathway. This leads to the release of inflammatory mediators including IL-1, IL-6, tumor necrosis factor (TNF), and chemokines, resulting in inflammation which is damaging to the brain.*

CONCLUSIONS

Meningitis is caused by various biological agents, including bacteria, viruses, parasites, and fungi. Meningococcal bacterial meningitis, which we have dealt with in this paper, is a severe acute infectious disease of the CNS that causes global morbidity and mortality. The bacterium binds to the TLRs of the antigen-presenting cells and triggers the immune response. In addition, the activation of the complement system by the bacteria can also participate in brain damage. The participation of immune cells, such as macrophages, neutrophils, and lymphocytes, in the infection results in NF-KB activation, leading to the release of pro-inflammatory cytokines which cause neuronal and brain damage. The inhibition of these inflammatory products could represent a valid therapeutic mechanism for treating bacterial meningitis.

Conflict of interest

The author declares that they have no conflict of interest.

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