Neuroinflammatory Disorders and The Involvement of the Microglia: A Literature Review

Henry Nielson Koch

Received March 16, 2024
Accepted May 04, 2024
Electronic access May 15, 2024

Alzheimer's disease, multiple sclerosis, meningitis, and mad cow disease are diseases in the brain for which the brain activates its defense. The microglia are a part of an inflammatory response in the brain that, if uncontrolled, could cause severe, irreparable damage. These cells have been revealed to play a crucial role in responding to any issues or problems that could arise in the body. The present literature review, via PubMed and Google, of the literature regarding the involvement of microglia in the above diseases, indicates that the microglia directly attack the pathogens in meningitis and mad cow disease. However, in Alzheimer's disease, the microglia work against the buildup of brain plaque in an immune response that may be a result or cause of the disease. In the case of multiple sclerosis, the problem is an inflammatory immune response in which the microglia target brain myelin. After further research, inflammation is also a significant part of Alzheimer's Disease, indicating specific study and understanding of the microglia response to create the most beneficial treatments for those with the disease.

Keywords: Alzheimer's Disease, Microglia, Inflammation, Multiple Sclerosis, Central Nervous System, Brain

Introduction

Alzheimer's disease is known to be a neurodegenerative disease that is quite common among elderly citizens[1]. In this disease, multiple proteins start the buildup of amyloid plaques that will spread throughout the brain[2]. This spread of plaques activates the immune response of the central nervous system, which mainly entails the microglia. The microglia are the resident cells that mitigate most toxic substances inside the central nervous system, and this plaque applies as something problematic inside the brain. The microglia are a part of an inflammatory response in the brain that, if uncontrolled, could cause severe, irreparable damage. This prompts the issue of finding a treatment to specifically target the inflammatory aspect of Alzheimer's disease, as microglial inflammation can exacerbate damage caused by other sources of nerve lesions which can lead to the exacerbation of some neurological diseases. As such, in this paper, the microglia and neuroinflammatory disorders are explored, and the link can be made with the microglia's involvement in these diseases.

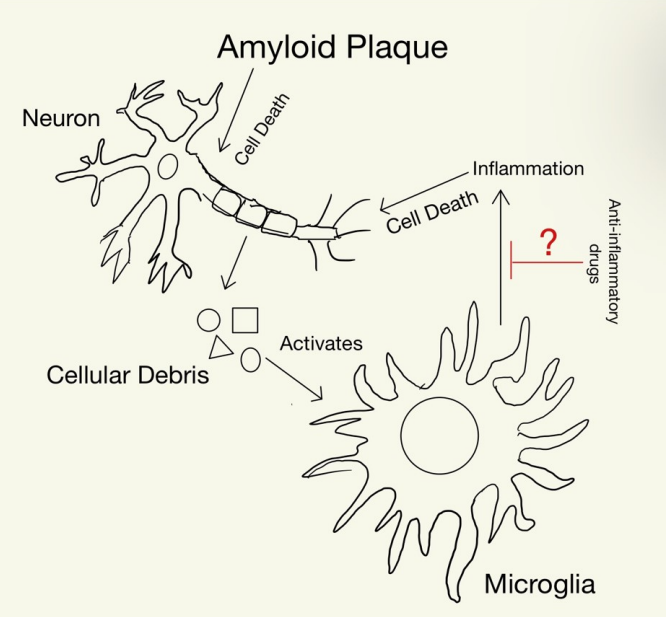

Fig. 1 Microglial involvement in the buildup of Amyloid Plaque, causing cell death and inflammation in the brain.

The Microglia

As our circulatory system contains mobile immune cells, so does our central nervous cell contains phagocytic microglia that can "remain stationary or become mobile to facilitate the cleanup process"[3]. In the central nervous system (CNS), the parenchymal sentinels' microglia profoundly impact the immune response[3]. Previously only classified as phagocytes, through extensive testing these adaptable cells have been revealed to play a crucial role in responding to any issues or problems that could arise in the body. Yet, it should be noted that microglia are dedicated

phagocytes. Not only are these cells small and highly specialized, but they also originate from early myeloid progenitors in the embryonic yolk sac, ultimately migrating into the CNS to fulfill their role as microglial cells. Their significance extends to brain development maintenance of neuronal networks and response to CNS trauma, positioning them as vital players in preserving the development and functionality of nerve networks within the brain[4].

Microglia play a pivotal role in brain development, tightly involved in synaptic pruning to organize neural connections. They actively participate in maintaining the neural landscape by selectively eliminating underperforming synapses, streamlining synaptic connectivity, and sculpting the brain's architecture. Moreover, these specialized cells diligently monitor the neural environment to respond to issues or abnormalities that may arise swiftly. For injury repair processes within the brain, microglia assume a crucial role by recognizing abnormalities, becoming activated, and initiating an elaborate response to start tissue repair and regeneration, fostering the restoration of homeostasis[5]. This multi-faceted involvement underscores the crucial role of microglia in orchestrating brain development, maintaining its health, and facilitating recovery after neural injury or damage.

Microglia are vital in the selective refinement of neural networks, playing a crucial part in ensuring the elimination of weak or excessive synapses to optimize network efficiency. These cells control neuroinflammatory responses, delicately maintaining the balance between inflammation and resolution, which is instrumental for sustaining a healthy nerve network[6]. Moreover, microglia orchestrate the intricate repair and recovery mechanisms that follow a neural injury or damage. By secreting anti-inflammatory factors, promoting the recruitment of other immune cells, and initiating tissue repair and regeneration, microglia contribute significantly to the resolution of inflammation and the restoration of homeostasis within the affected brain tissue.

Neuroinflammatory Disorders

Neuroinflammatory disorders involve the body causing itself harm in respect to the immune system causing damage to the nervous system. Neurodegenerative diseases are a group of disorders characterized by the gradual degeneration or death of neurons in the central nervous system (the brain and spinal cord). When damage to the nervous system occurs, there are quite a few symptoms that can arise such as cognitive decline, motor skill issues, and fatigue. In this article multiple sclerosis (MS), Alzheimer's disease (AD), meningitis, and mad cow disease will be discussed, the pathologies revolving around them, and their relationship with the microglia.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic neurological disease that affects the central nervous system (CNS). It is considered an autoimmune disease, meaning the immune system mistakenly attacks the body's tissues. In the case of MS, the immune system targets the protective myelin-insulating sheath that surrounds nerve fibers, leading to inflammation, damage, and scarring (sclerosis) in multiple areas of the CNS[7]. This demyelination disrupts the normal flow of electrical impulses along the nerves, resulting in a wide range of issues.

This disease also has multiple variations such as relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing. Relapsing-remitting (RRMS) is the most common form, which includes unpredictable times of heightened symptoms that break up times of remission where the patient experiences little to no symptoms. As far as research has gone in regards to MS, there has yet to be a certain answer as to what might cause MS. However, there are speculations that genetics play a role, as those who are related to someone with the condition are more likely to develop it[8]. Additionally, one's environment (low sunlight during childhood, high BMI, smoking) and immune system also correspond to the occurrence of this disease.

Treatments for MS are varied, as some modify the disease called dimethyltryptamine. There are specific treatments to target the symptoms of the disease. However, at the time of this article, there is no cure for MS, but there is certainly much that can be done to treat it. Often these medications are helpful for RRMS, as it is the most common, and thus there is more data available to find treatments for those suffering from the disease. Dimethyltryptamine (DMT) is designed to modify the course of the ideas by reducing the frequency and severity of the relapses, slowing down the progression, and decreasing the formation of brain lesions[9]. Some of the more effective treatments against the symptoms of MS are to reduce inflammation, manage muscle spasms, and pain, and use physical and occupational therapy.

Meningitis

Meningitis is a condition of the inflammation of the protective membranes covering the brain and spinal cord, also known as the meninges[10]. This disease has many causes, including bacterial, viral, and or fungal infections. The symptoms of meningitis can range from fever, headaches, neck stiffness, and a harsh sensitivity to light. On the severe side of the spectrum, some might experience seizures, confusion, and become comatose. If this disease is left untreated, meningitis can lead to severe complications, including brain damage, hearing loss, and eventually, death.

For individuals diagnosed with meningitis, several treatments are available depending on the cause of the infection. In the

case of bacterial meningitis, antibiotics are the primary treatment option [11]. These medications are designed to target and eliminate the specific bacteria responsible for the infection. For viral meningitis, antiviral medications may be prescribed to help manage the symptoms and shorten the duration of the illness. Antifungal medications, on the other hand, are utilized to treat fungal meningitis. These medications work to combat the fungal infection and restore the health of the affected individuals. Healthcare professionals must identify the specific cause of meningitis to provide appropriate and effective treatment.

Mad Cow Disease

Mad cow disease, also known as bovine spongiform encephalopathy (BSE), is caused by a prion infection in the brain and spinal cord. The infectious agent causing prion disease-PrPSc is a pathogenic misfolded and aggregated form of the cellular prion protein, PrPC [12]. The transmission of mad cow disease primarily occurs through consuming contaminated meat products from infected cattle. It is important to note that mad cow disease is a zoonotic disease, meaning it can be transmitted from animals to humans. The symptoms of mad cow disease can vary but often include some sort of neurological problems such as muscle stiffness, cognitive decline, and drastic behavioral changes.

As this disease was mainly prevalent many years ago; less research is currently being done to counteract the disease. As of now, there are no known cures for mad cow disease in humans, but supportive treatments are available to help relieve symptoms and manage complications [13]. These treatments focus on providing comfort and maintaining the overall well-being of affected individuals. Supportive care may involve physical therapy to manage muscle stiffness and improve mobility. Additionally, medications can be prescribed to alleviate specific symptoms such as pain, sleep disturbances, and mood changes.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that exacerbates symptoms and accelerates myelin loss. In addition to the buildup of amyloid plaques, it results in the death of the cells in the brain and commonly occurs in those 65 years or older [14].(See Figure 1) This disease can have various symptoms such as problems with cognitive function, short and long-term memory loss, and reasoning [14]. With these issues occurring in those who are elderly, the symptoms worsen as age progresses. Therefore, it is common for those in the later stages of the disease to be sent to assisted living facilities. As this is a progressive disease it can be classified into a few different classifications from preclinical to cognitive impairment, with around three stages in total. In general, it will take anywhere from four to eight years to completely progress through the disease accumulating more of the common symptoms and increased severity.

Treatments for AD exist, and more have been emerging in recent years with the most common treatments being cholinesterase enzyme inhibitors and antagonists to N-methyl d-aspartate [15] to help with memory. However, these treatments do not effectively cure AD. At the time of this paper's publishing, there is no cure, but the treatments do help with treating the symptoms of the disease. Much research is still being done to find treatments for the disease; it has the possibility of affecting over 10% of those ages 65 and older, with an emphasis placed on protein metabolism, inflammatory response, and other damage being done through the disease.

Microglial Involvement in Alzheimer's Disease

Inflammation is a core driver of neurodegeneration and diseases like Alzheimer's disease. The way the immune response will begin is following the start of the buildup of tau proteins and amyloid beta that get aggregated, forming a plaque within the brain that may lead to cell death. This plaque, as time progresses, may eventually spread across the brain into many different areas which will activate the microglia. With this, the neuroinflammatory response gets kick-started within the brain and will start its immune response.

Microglia, as the specialized immune cells within the brain [16], the immune response of microglia in a quiescent yet vigilant state until something happens to "wake them up", to solve some sort of pressing issue. The microglia are unique in that they constantly survey the areas around them to determine if there is some sort of foreign substance within the CNS to eliminate. Microglia are phagocytic cells that are an appropriate response to combat infectious diseases such as meningitis or other pathogens. Plaque buildup causes microglial activation that furthers the inflammatory response. The issue is that the microglia cells will stay activated for an extended period, and release an agent that in the proper amount is therapeutic, but in overabundance is toxic to the brain. This increases the overall damage done to the CNS, which is done in response to excess plaque, but doesn't, and eventually contributes to the overall problem.

To get a better picture of what inflammation looks like in the brain, also known as neuroinflammation, it must be determined whether it is a disruption of the blood-brain barrier, which normally separates blood from the brain tissue. This disruption can trigger a response from the immune system. Cytokines, chemokines, and reactive oxygen species are released, causing damage to neurons and other glia. Additionally, neuroinflammation is connected with Alzheimer's disease through the accumulation of beta-amyloid and tau proteins. These proteins trigger an immune response, leading to inflammation in the surrounding area [17].

Research continues to be funded and performed for Alzheimer's disease including its components that have relations to different plaques and proteins. The aforementioned research has revealed an aspect connecting inflammation back to the disease in an ever-continuing fashion. Amyloid beta plaques build in the brain, which start to initiate this immune response hosted by the microglia in their attempt to defend the brain. After this buildup occurs, there is damage done to the neurons in the brain to an extent where that area of the brain stops functioning and does not further interact with the brain. Further amounts of plaque are established, which is associated with more loss of cerebral function and a proceeding amount of inflammation to follow. This "loop" per se is a dangerous cycle of degeneration that has been established in the course of the disease and will continue throughout the cycle of the disease until certain parts of the brain that are essential to vital functioning are damaged. The body is no longer able to function.

The preceding information begs the question "If it is already known why this damage was being caused, then why aren't there already medications to combat this problem." The brain's inflammatory response may hold the answer to this question. According to [18], the anti-inflammatory mechanisms help to reduce inflammation and protect against tissue damage. It involves the release of anti-inflammatory molecules, such as cytokines and prostaglandins, which help to suppress the activity of pro-inflammatory molecules and promote healing.

Given this understanding of the anti-inflammatory mechanism, some commonly used medications that are used to combat inflammation in the body would be nonsteroidal anti-inflammatory drugs (NSAIDs), but it is a very difficult process to get NSAIDs into the brain due to the blood-brain barrier [19]. Due to the size and polarity of most anti-inflammatory drugs, they cannot penetrate this barrier [19]. This means that the human body's defense mechanisms block essential drugs that could potentially improve the quality of life for those with autoimmune and neurodegenerative disorders like AD. As such, a connection could be established between the necessity to combat the inflammatory aspect of AD to find a treatment that directly attacks the anti-inflammatory response of the disease to achieve better lives for the many who are suffering from this disease.

Methods

As this is a review-style paper, no physical research has been performed, but this is the fashion in which the literature review was. Initially, after finding the topic to explore, much research was performed via Google Scholar and PubMed. To find the specific articles concerning the topic at hand, filters were imputed into PubMed to search for articles published in the last 20 years to utilize the most relevant literature possible. Specific search terms were used such as "Alzheimer's Disease" or "Microglial immune response", as an understanding had to be made of the topic at hand before the author wrote about it. The selected information was then collected via Zotero to organize, to later be further organized into sections and sub-sections in the paper, so the information could build upon itself with the reader gaining the knowledge needed to understand every next sentence that should appear if they had little prior knowledge on the subject. Finally, each article was reviewed to verify the information corresponded to the article it cited.

Conclusion

A connection exists between the inflammatory response done by the microglia and Alzheimer's disease. Not only do the microglia, as the main defense in the central nervous system, participate in creating this inflammatory response, but as part of an excessive autoimmune response, they are also a significant cause of the degradation of the brain throughout the disease. More research exploring the inflammatory aspect of Alzheimer's disease could be done to better understand this aspect of the disease and more effective treatments for Alzheimer's disease.

Limitations & Future Directions

The limitation of this study is a review of literature that was limited to that which the search engines of Google and PubMed would provide me. Proprietary information spaces were not available for the present review, reducing the range of articles available for review. This research was conducted by an author who was a novice in this field. The present research is limited to a review of the literature without the benefit of follow-up experimentation to evaluate the hypotheses. A greater focus of resources on the inflammatory etiology of Alzheimer's Disease needs to be prioritized. Because of the 8-year course of the disease, in addition to lab research, resource prioritization is indicated for experimental treatments.

References

1 S. Khan, K. Barve and M. Kumar, *Current Neuropharmacology*, **18**, 1106–1125.

2 E. Solito and M. Sastre, *Frontiers in Pharmacology*, **3**, year.

3 D. Nayak, T. L. Roth and D. B. McGavern, *Annual Review of Immunology*, **32**, 367–402.

4 M. Colonna and O. Butovsky, *Annual Review of Immunology*, **35**, 441–68.

5 F. H. Brennan, Y. Li, C. Wang, A. Ma, Q. Guo, Y. Li and N. Pukos, *Nature Communications*, **13**, 4096.

6 C. Stadelmann, S. Timmler, A. Barrantes-Freer and M. Simons, *Physiological Reviews*, **99**, 1381–1431.

7 R. Murúa, M. F. Sofía and F. J. Quintana, *Annual Review of Pathology: Mechanisms of Disease*, **17**, 121–39.

8 M. Ward and M. D. Goldman, *CONTINUUM: Lifelong Learning in Neurology*, **28**, 988–1005.

9 M. P. McGinley, C. H. Goldschmidt and A. D. Rae-Grant, *JAMA*, **325**, 765.

10 K. Putz, K. Hayani and F. A. Zar, *Primary Care: Clinics in Office Practice 40*, 707–26.

11 R. Helbok, G. Broessner, B. Pfausler and E. Schmutzhard, *Journal of Neurology*, **256**, 168–75.

12 C. J. Sigurdson, J. C. Bartz and M. Glatzel, *Annual Review of Pathology: Mechanisms of Disease*, **14**, 497–516.

13 A. Aguzzi and C. J. Sigurdson, *Nature Reviews Immunology*, **4**, 725–36.

14 A. Porsteinsson, R. Isaacson, S. Knox, M. Sabbagh and I. Rubino, *The Journal Of Prevention of Alzheimer's Disease*, 1–16.

15 Z. Breijyeh and R. Karaman, *Molecules*, **25**, 5789.

16 K. Borst, A. Dumas and M. Prinz, *Immunity*, **54**, 2194–2208.

17 V. Calsolaro and P. Edison, *Alzheimer's amp; Dementia*, **12**, 719–32.

18 R. Liu, S. Qin and W. Li, *Biomedicine amp; Pharmacotherapy*, **153**, 113362.

19 N. Kubick, P. C. Flournoy, A.-M. Enciu, G. Manda and M.-E. Mickael, *Pharmaceutics*, **12**, 880.