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A Review on the Role of Neuro-Inflammation in Multiple Sclerosis: Mechanisms, Pathogenesis, and Therapeutic Implications

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Abstract

Neuroinflammation is a prominent cause of multiple sclerosis pathogenesis. As a result, a greater understanding of the role played by neuroinflammation in these devastating conditions development should be deemed necessary for the design of effective new therapies. This review article investigates the pathways that contribute to neuroinflammation including: immune cells, cytokines, and the blood-brain barrier, as well as examines existing and emerging treatments that can be employed to systematically manage neuroinflammation. Developing a more sophisticated level of neuroinflammation awareness may prove to be the most effective means of permitting more precise therapy in multiple sclerosis patients.

Introduction

Multiple Sclerosis (MS) is a complex autoimmune disease characterized by inflammation, demyelination, and neurodegeneration in the Central Nervous System (CNS) [1]. Neuroinflammation is a key pathological feature of MS, contributing to disease progression and clinical disability. This review provides a comprehensive analysis of the mechanisms underlying neuroinflammation in MS, highlighting the involvement of immune cells, glial cells, and the Blood-Brain Barrier (BBB) [2]. Furthermore, it discusses the role of neuroinflammation in the pathogenesis of MS, focusing on immune dysregulation, myelin damage, and neurodegeneration. Finally, therapeutic strategies targeting neuroinflammatory pathways are explored, including immunomodulatory agents, anti-inflammatory drugs, remyelination-promoting therapies, and neuroprotective interventions. Multiple Sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, and

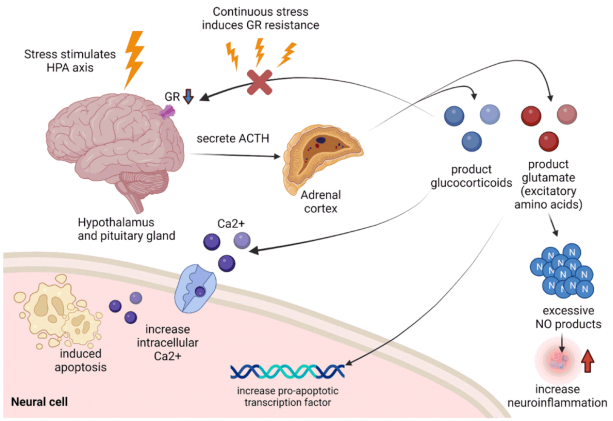

Figure 1: (79) Neuroinflammation occurs when Glucocorticoids contribute apoptosis by Intracellular calcium excess. The black arrow indicates it contributes to the following response. The Red arrow indicates increased neuroinflammation.

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axonal damage within the CNS. Neuroinflammation, driven by immune dysregulation and glial cell activation, plays a central role in the pathogenesis of MS [3,4]. This review aims to provide a comprehensive understanding of the mechanisms underlying neuroinflammation in MS and its implications for therapeutic interventions [5,6].

MS-Causes, Risk Factors and Types

Causes

A combination of genetic and environmental factors are thought to play a role in the development of Multiple Sclerosis (MS), a complex disease for which the precise cause is unknown. These are a few of the main theories regarding the causes of multiple sclerosis [7-9].

Immune System Dysfunction: The immune system of the body unintentionally targets its own tissues in Multiple Sclerosis (MS), an autoimmune disease. The myelin sheath that protects nerve fibres in the central nervous system-the brain and spinal cord-is attacked by the immune system in Multiple Sclerosis (MS). This results in damage to nerve fibres, inflammation, and demyelination (loss of myelin) [10,11].

Genetic Factors: Genetic factors may be involved in MS even though the disease is not directly inherited. Individuals with a family history of multiple sclerosis are marginally more likely to get the illness. It is believed that certain genes linked to immune response regulation and immune function increase susceptibility [12,13].

Environmental Factors: For those who are genetically predisposed, specific environmental stimuli may cause MS. Among these are:

Viral Infections: A higher chance of developing Multiple Sclerosis (MS) has been associated with certain viruses, including Epstein-Barr virus (EBV). In instance, EBV infection is prevalent in MS patients [14].

Vitamin D: Low vitamin D levels have been linked to an increased risk of MS, according to available research. It is thought that vitamin D regulates the immune system.

Smoking: There is a link between cigarette smoking and a higher risk of MS as well as a higher risk of disability and disease progression.

Other Factors: A person's risk of developing MS may also be influenced by other factors, including geography (MS is more common in higher latitudes), certain childhood infections, and possibly dietary factors.

Gender and Age: MS typically strikes women between the ages of 20 and 40, with a higher incidence rate in females than males. There could be a hormonal component to this gender disparity.

Other Potential Causes: The blood-brain barrier anomalies, which control the flow of substances from the bloodstream to the brain, and possibly other immune system abnormalities, are among the other causes and triggers of multiple sclerosis that researchers are still investigating. [15,16].

Risk Factors

Multiple Sclerosis (MS) is influenced by various risk factors that can increase a person's likelihood of developing the disease. Here are the key risk factors associated with MS:

Gender: MS is more common in women than in men. The female-to-male ratio is approximately 3:1. This gender difference suggests that hormonal factors may play a role in the development of MS [18].

Age: Although MS can strike anyone at any age, it usually starts in the 20s to 40s. On rare occasions, it can also affect elderly people and small children. [19,20].

Genetics: Being related to someone with MS raises an individual's risk even though MS is not inherited directly, particularly if it is a first-degree relative such as a parent or sibling. Families with multiple affected members are more at risk [21].

Ethnicity and Geography: Compared to Asian, African, and Native American populations, populations with European ancestry are more likely to have MS. Furthermore, MS is more common in latitudes higher than the equator, indicating a possible influence of environmental factors like sunshine and vitamin D levels.

Viral Infections: There is a connection between certain viral infections, specifically Epstein-Barr virus (EBV), and a higher chance of developing multiple sclerosis. Although EBV is almost universal in the population, those who have previously experienced infectious mononucleosis (caused by EBV) may be at an increased risk.

Smoking: In addition to raising the risk of MS disease progression and disability in people who have already been diagnosed with the condition, cigarette smoking is linked to an increased risk of developing MS [22.23].

Low Vitamin D Levels: There is proof that having low vitamin D levels may make MS more likely to develop. This could help to explain why MS is more common in areas with less exposure to sunlight and how it is distributed geographically.

Other Autoimmune Diseases: An autoimmune disease such as thyroid disease or type 1 diabetes may marginally raise the chance of developing multiple sclerosis.

Obesity: According to certain research, obesity in adolescence may raise the chance of acquiring Multiple Sclerosis (MS) in later life [11,24].

It's crucial to remember that a person does not automatically develop MS just because they have one or more of these risk factors. The precise cause of MS is still unknown, and many individuals who have the disease do not have any known risk factors. The goal of ongoing research is to learn more about how immune system, environment, and genetic factors interact to cause Multiple Sclerosis (MS).

Types

There are numerous clinical patterns or types of multiple sclerosis (MS), and these can change over time. The primary varieties of multiple sclerosis comprise There are numerous clinical patterns or types of multiple sclerosis (MS), and these can change over time. The primary varieties of multiple sclerosis comprise:

Relapsing-Remitting Multiple Sclerosis (RRMS):

Description: The most prevalent type of MS is typified by erratic relapses, sometimes known as exacerbations, attacks, or flare-ups, interspersed with intervals of either full or partial recovery, or remissions.

Symptoms: Relapses can cause old symptoms to get worse or cause new ones to emerge. Remissions are times when symptoms get better or go away entirely.

Progression: There may be minimal or no disease progression in between relapses.

Treatment: The frequency and severity of relapses are frequently decreased with the use of Disease-Modifying Therapies (DMTs) [24,25].

Secondary Progressive Multiple Sclerosis (SPMS)

Description: A large number of RRMS patients eventually switch to SPMS. With SPMS, neurological function gradually deteriorates over time, sometimes accompanied by relapses and remissions.

Progression: The progression could happen gradually or in quick spurts, or relapses. Generally speaking, disability increases more gradually than in RRMS.

Treatment: Even though some DMTs used for RRMS may still work for SPMS, treatment plans might put more of an emphasis on symptom management and enhancing quality of life [26,32].

Primary Progressive Multiple Sclerosis (PPMS):

Description: Without noticeable relapses or remissions, the neurological symptoms of PPMS develop gradually from the time the illness first manifests.

Progression: Compared to RRMS or SPMS, disability increases more gradually and frequently results in significant disability over time.

Treatment: Compared to RRMS, there are fewer approved treatment options specifically for PPMS. Rehabilitation and symptom management are crucial aspects of care [24.27].

Progressive-Relapsing Multiple Sclerosis (PRMS)

Description: A less common type of MS known as PRMS is characterized by gradual disease progression from the start and sporadic relapses that may or may not have recovery intervals.

Symptoms: In PRMS, there is a persistent worsening of symptoms with superimposed relapses, in contrast to RRMS, where relapses are followed by remissions.

Treatment: Treatment plans frequently incorporate methods for both relapsing and progressive forms of multiple sclerosis [30].

Clinically Isolated Syndrome (CIS)

Description: The term "CIS" describes a single bout of neurological symptoms brought on by demyelination or inflammation in the central nervous system. It might be an initial MS episode or a related illness.

Progression: Not every CIS patient will go on to acquire MS. While some people may not experience any more symptoms, others may develop MS that is clinically certain.

Diagnosis and treatment: In order to ascertain the risk of future MS development, CIS needs to be closely monitored and evaluated. Decisions about treatment are based on risk evaluations and individual characteristics [24,31,32].

Treatment plans are often personalized based on the type of MS, the severity of symptoms, and other factors like age, overall health, and personal preferences. Regular monitoring and adjustments to treatment are common to manage the disease effectively. Each individual's experience with MS can vary greatly, and the progression and symptoms can change over time.

Pathogenesis and pathophysiology

A variety of features, such as changed BBB permeability, genetic changes that increase susceptibility to immune responses, myelin sheath destruction, axonal damage, and CNS scarring, are part of the core pathophysiology of Multiple Sclerosis (MS) [9,13].

MS Pathogenesis

Autoimmune Response and Inflammation

Immune System Activation: The autoimmune response that characterizes Multiple Sclerosis (MS) occurs when the body's immune system unintentionally targets the Central Nervous System (CNS), specifically focusing on the myelin sheath that surrounds nerve fibres. T cells play a major role in mediating this attack; they activate and enter the central nervous system.

Antigen Presentation: T cells in the Central Nervous System (CNS) are presented with myelin antigens by Antigen-Presenting Cells (APCs), which include dendritic cells and macrophages. Due to this interaction, myelin is attacked by the immune system, resulting in tissue damage and inflammation.

Th1 and Th17 Cells: Pro-inflammatory T helper 1 (Th1) and T helper 17 (Th17) cells are overrepresented in MS patients. These cells release cytokines (IL-17, IFN-gamma, etc.) that attract additional immune cells to the central nervous system and stimulate inflammation.

B Cells and Antibodies: By generating antibodies against myelin components, which can worsen the autoimmune response and cause tissue damage, B cells also contribute to the pathophysiology of MS [10].

Genetic Factors

HLA Genes: The HLA genes, specifically HLA-DRB1*15:01, have a strong correlation with the likelihood of developing multiple sclerosis. The proteins that these genes encode are essential for presenting antigens to T cells, which in turn affects immune responses and the risk of developing autoimmune diseases such as multiple sclerosis.

Non-HLA Genes: Numerous genetic variants that are not HLA-related have also been found to contribute to MS susceptibility, in addition to HLA genes. Numerous of these variations are connected to inflammatory processes, immune regulation, and myelin maintenance [13,14].

Environmental Triggers

Viral Infections: One of the most well-established environmental risk factors for multiple sclerosis is infection with the Epstein-Barr virus (EBV). EBV infects B cells and, in genetically susceptible people, may cause aberrant immune responses against myelin.

Low Vitamin D Levels: Research indicates that a vitamin D deficiency, which can happen from less time spent in the sun, raises the chance of developing multiple sclerosis. Important for immune regulation, vitamin D may also influence the autoimmune response in multiple sclerosis [35,36].

Demyelination and Axonal Injury

Demyelination: Demyelination, or the breakdown of the myelin sheath surrounding nerve fibers in the central nervous system, is the main pathological feature of multiple sclerosis. This causes neurological symptoms by interfering with the transmission of nerve signals.

Axonal Injury: Apart from demyelination, MS also causes axonal loss and injury. Long projections of nerve cells called axons, which carry electrical impulses, can sustain damage directly from inflammatory processes or indirectly from demyelination [36,38,39].

Blood-Brain Barrier (BBB) Dysfunction

BBB Permeability: In MS, the BBB's integrity is weakened, which typically prevents immune cells and molecules from entering the central nervous system. This exacerbates inflammation and tissue damage by making it easier for immune cells, cytokines, and antibodies to enter the central nervous system.

Gliosis and Scar Formation

Gliosis: Microglia, which are CNS glial cells, and astrocytes are activated in response to inflammation and injury. They play a part in gliosis, a condition in which areas of demyelination develop scar tissue, or sclerosis. Gliosis can worsen brain dysfunction and increase the likelihood of disability in MS patients.

Lesion Formation and Clinical Manifestations

MS Lesions: MRI scans of MS lesions reveal patches of demyelination, inflammation, and gliosis dispersed throughout the central nervous system. Over time, lesions can change in size, location, and activity, which can lead to a variety of clinical manifestations of multiple sclerosis.

Clinical Manifestations: The location and degree of CNS damage can have a significant impact on the symptoms of Multiple Sclerosis. Sensory abnormalities, motor impairments, visual disturbances, exhaustion, cognitive alterations, and mood disorders are typical symptoms [41,43].

Oligodendrocyte Dysfunction and Myelin Repair

Oligodendrocytes: Myelin, the fatty substance that envelops nerve fibers to insulate and promote effective nerve signal transmission in the central nervous system, is made by oligodendrocytes. Damage or impairment of oligodendrocytes in MS can result in insufficient production and repair of myelin.

Remyelination: Even though MS is associated with progressive demyelination, the central nervous system (CNS) can remyelinate, in which case oligodendrocytes try to restore damaged myelin. But in MS, this process is frequently lacking or ineffective, which adds to the disease's ongoing neurological deficits.

Factors Influencing Remyelination: The mechanisms promoting or impeding remyelination in multiple sclerosis are still being investigated. Enhanced remyelination processes are the goal of potential treatment approaches in order to maintain neurological function and possibly reverse damage [15,44,33].

Neurodegeneration and Brain Atrophy

Axonal Degeneration: Axonal degeneration and loss can result from neurodegenerative processes and chronic inflammation in multiple sclerosis (MS), in addition to demyelination. In MS patients, axonal damage plays a major role in contributing to long-term disability.

Brain Atrophy: Progressive brain atrophy, which is typified by a loss of gray matter and white matter tissue as well as a reduction in brain volume, can occur in MS patients over time. In MS, brain atrophy is correlated with the development of disabilities and cognitive impairment.

Mechanisms of Neurodegeneration: Multiple factors contribute to the multifactorial neurodegeneration associated with Multiple Sclerosis (MS), including direct damage from inflammation, mitochondrial dysfunction, excitotoxicity (excessive nerve cell activation), and reduced neurotrophic support (factors that promote neuron survival and function) [40,37].

Microglial activation and neuroinflammation

Microglia: Immune cells in the central nervous system called microglia are essential for immune response and surveillance. Through the release of pro-inflammatory cytokines, phagocytosis of myelin debris, and interactions with other immune cells, activated microglia in Multiple Sclerosis (MS) contribute to neuroinflammation.

Chronic inflammation: In MS, persistent neuroinflammation exacerbates demyelination, axonal injury, and neurodegeneration by continuing immune cell activation and tissue damage. One of the main therapeutic objectives for MS management is reducing chronic inflammation [50,51].

Heterogeneity and disease course

Clinical Heterogeneity: Because MS is a heterogeneous disease, each person's clinical presentation, course of the illness, and response to treatment will differ greatly from person to person. Genetic background, environmental exposures, and the particular immune mechanisms causing disease activity are some of the factors that contribute to heterogeneity.

Disease course evolution: Over time, the initial presentation of multiple sclerosis (MS) may change, alternating between distinct disease stages and patterns, such as relapsing-remitting, primary progressive, or clinically isolated syndrome. The dynamic nature of MS and the significance of individualized treatment approaches are highlighted by this evolution [53,54].

Emerging therapeutic approaches

Disease-Modifying Therapies (DMTs): The goals of DMTs for MS are immune response modulation, inflammation reduction, and possible promotion of neuroprotection and remyelination. More focused treatment approaches include B cell depletion, immune cell trafficking modulation, and improved remyelination processes.

Symptomatic and Supportive Care: Comprehensive MS care entails not only DMTs but also symptomatic therapies to address particular symptoms (such as fatigue, spasticity, and cognitive decline) and supportive care to enhance quality of life and functional results [55,56].

The Experimental Autoimmune Encephalomyelitis (EAE) Model of MS

Animal models are essential for comprehending the triggering events and pathogenetic mechanisms underlying Multiple Sclerosis (MS) in order to develop therapeutic strategies that may halt disease progression and eventually promote the development of treatments for the human condition, even though

there isn't a single model that can perfectly mimic all aspects of the disease. The rodent model of EAE is the most extensively researched and widely used of the various MS models currently in use [57]. Differential recruitment of immune cell types in the acute and chronic phases of EAE is one of the features that has demonstrated the validity of the EAE model in simulating the human condition. The kind of cells that are attracted to the site of injury or lesion appear to be, at least partially, correlated with the corresponding rise in IL-1β levels [42]. In other words, as EAE worsens, there are proportionately more cells that can produce higher levels of IL-1β (see Table 1 below).

Nevertheless, there is some evidence that IL-1β plays a role in remyelination in addition to its pro-inflammatory effect. Researchers are beginning to believe that these advantageous functions may be attributed to the stimulatory activity of IL-1β on the production and local release of trophic factors, such as insulin-like growth factor (IGF), by cells that participate in the demyelination process in the first place. The cytokine appears to be crucial for the aggregation, proliferation, and activation of oligodendrocyte progenitors around the areas of demyelination [65]. The temporal pattern of cytokine release and the cell types involved appear to be determinants of the apparent bipartite roles of IL-1β in immune cell recruitment and remyelination. It seems that during the acute phases of CNS inflammation, the first release of IL-1β encourages T and B cell recruitment; in the second stage, IL-1β appears to promote CNS repair [65,66]. (Please see Table 2 for more information on the major interleukins' roles in the pathophysiology of MS).

Table 1: Association between cell type, MS (multiple sclerosis) phase and cytokine production.

Cell Type	MS Phase	Cytokines Produced	Role/Function	References
T helper cells (Th1)	Relapsing-remitting (RRMS)	IFN-γ, IL-2	Pro-inflammatory; promote immune response	[40,41]
T helper cells (Th2)	Remission (RRMS)	IL-4, IL-5, IL-10	Anti-inflammatory; suppress immune response	[42,43]
T helper cells (Th17)	Active/Progressive	IL-17, IL-21, IL-22	Pro-inflammatory; involved in autoimmunity	[43,44,45]
Regulatory T cells (Tregs)	Remission	IL-10, TGF-β	Immunosuppressive; regulate immune response	[46]
B cells	Various	IL-6, IL-10, TNF-α	Produce antibodies; can be pro- or anti-inflammatory	[70,71]
Macrophages	Active/Inflammatory	IL-1β, IL-6, TNF-α, IL-10	Phagocytosis; cytokine production varies by phenotype	[44,45]
Microglia	Active/Inflammatory	IL-1β, TNF-α, IL-6	CNS-specific immune response; can be neurotoxic	[80,81]
Dendritic cells	Various	IL-12, IL-23	Antigen presentation; activate T cells	[48,80]

Table 2: Role of interleukins in MS Pathogenesis

Interleukin	Source	Role in MS Pathogenesis	References
IL-1β	Macrophages, microglia	Pro-inflammatory; promotes T cell activation and infiltration into the CNS, contributes to neuroinflammation.	50,51,52 53,54
IL-2	T cells	Promotes T cell proliferation and survival; involved in the activation of autoreactive T cells.	
IL-4	Th2 cells	Anti-inflammatory; promotes differentiation of Th2 cells and B cell antibody class switching.	
IL-6	Macrophages, microglia, T cells	Pro-inflammatory; promotes differentiation of Th17 cells, contributes to B cell activation and chronic inflammation.	
IL-10	Regulatory T cells (Tregs), B cells	Anti-inflammatory; inhibits pro-inflammatory cytokine production, promotes immune tolerance.	
IL-12	Dendritic cells, macrophages	Promotes differentiation of Th1 cells; enhances production of IFN-γ, contributing to pro-inflammatory responses.	
IL-17	Th17 cells	Pro-inflammatory; promotes recruitment of neutrophils and other immune cells to the CNS, linked to autoimmune responses.	
IL-21	Th17 cells, T follicular helper (Tfh) cells	Promotes differentiation and proliferation of Th17 cells and B cells, enhances autoantibody production.	
IL-22	Th17 cells	Pro-inflammatory; involved in tissue inflammation and autoimmune pathology, affects blood-brain barrier integrity.	
IL-23	Dendritic cells, macrophages	Promotes differentiation and maintenance of Th17 cells, enhances inflammatory responses in the CNS.	
IL-27	Dendritic cells, macrophages	Can have dual roles; may limit Th17 response but also promote anti-inflammatory Treg responses.	
IL-33	Endothelial cells, epithelial cells	Can promote Th2 immune responses and act as an alarmin, potentially involved in early immune activation.	

Role of Regulatory Adaptive Immune Cells in MS

Tregs

Tregs are a subset of T cells that help prevent autoimmune diseases by controlling the immune system and preserving tolerance to self-antigens. Tregs suppress the immune system by preventing effector T cell induction and proliferation. The groundbreaking description of Tregs in the mouse cerebrum by Xie et al. demonstrated the essential function of these cells in immune surveillance within the central nervous system and in regulating the inflammatory response. According to the study, Tregs suppressed LPS-induced neuroinflammation caused by macroglia and macrophages by releasing IL-10 and controlled and hampered the recruitment of CD4+ T cells in EAE mice [61]. The authors also proposed a potential link between the quantity of Treg cells and astrocytes' production of IL-2. The possible

function of Treg cells in controlling the activation and differentiation of oligodendrocytes from the pool of oligodendrocyte progenitor cells (OPCs) was examined in a recent review [72]. This was a follow-up to a study by Dombrowski's group that showed Treg deficient mice had a significantly lower rate of activated/differentiated OPCs and the remyelination process than wild or Treg depleted mice. The researchers came to the conclusion that Treg cells' primary purpose is to interact with oligodendrocytes in order to trigger remyelination. The process is thought to be connected to Tregs' synthesis of the growth regulatory protein (CCN3), which causes oligodendrocytes to differentiate into myelinating phenotypes.

B Regulatory Cells

In the pursuit of finding a solution to the autoimmune conundrum, a great deal of research has been done on the function of T cells, as these cells have long been recognized as the primary players in the adaptive immune system response. However, in recent times, there has been an increasing interest in a less well-known class of immune modulatory cells, known as B regulatory cells (Bregs). Research has shown that Bregs, particularly those that produce high levels of the cytokine IL-35, do play a crucial role in regulating the aberrant immune activation that occurs in multiple sclerosis [48,49,73]. Breg cell subtypes are typically identified based on the particular set of cytokines they are able to release, as there are currently no specific surface markers to accurately distinguish them. This class of Bregs is often referred to as B10 cells because the most researched cytokine released by Breg cells is IL-10, which is crucial for immune modulation in both human and experimental models [48]. Shen et al. proposed that decreased production of these two subtypes of B cells could play a direct role in modulating the functions of T cells in EAE as well as the activation of plasma cells during the disease's active phase. Bregs is known to secrete both IL-10 and IL-35. (B10 or B35, for example) may be linked to less favourable results [64]. Wang et al. observed a decrease in Bregs and an increase in the severity of autoimmune uveitis in mice after pharmacological or genetic blockade of IL-35 [63]. These findings were consistent with previous research.

Mechanisms of Neuroinflammation in MS

Immune Cell Activation: Pro-inflammatory cytokines and chemokines are released into the Central Nervous System (CNS) as a result of the infiltration of T cells, B cells, and antigen-presenting cells that are activated dysregulated [1]. Important participants are Th1 and Th17 cells, which contribute to tissue damage and neurodegeneration by producing cytokines like interferon-gamma (IFN-γ) and interleukin-17 (IL-17) [2].

Microglial Reactivity: In response to inflammatory stimuli, resident immune cells in the Central Nervous System (CNS) called microglia become activated and release pro-inflammatory cytokines, chemokines, and Reactive Oxygen Species (ROS) [3]. By phagocytosing myelin debris and presenting antigens, activated microglia contribute to tissue damage and neuroinflammation [4].

Astrocyte Dysfunction: Astrocytes contribute to neuroinflammation as well as neuroprotection in multiple sclerosis (5). Reactive astrocytes exacerbate neuroinflammation and BBB dysfunction by releasing inflammatory mediators like IL-1β and Tumour Necrosis Factor-alpha (TNF-α) [6].

Blood-Brain Barrier Dysfunction: Immune cells and inflammatory mediators can enter the central nervous system more easily when the blood-brain barrier is disrupted, which increases tissue damage and neuroinflammation [7]. Early in the course of MS, increased blood-brain barrier permeability is seen, and it is correlated with both disease activity and advancement [8].

Oligodendrocyte Injury and Demyelination: In MS, the immune system specifically targets oligodendrocytes, which are in charge of myelin synthesis [9]. Demyelination causes axonal dysfunction and adds to MS patients' neurological impairments.

Neurodegeneration: In multiple sclerosis, neurodegeneration characterized by axonal loss, synaptic dysfunction, and neuronal death is the result of chronic neuroinflammation [10]. With progressive forms of MS, neurodegeneration plays a role in irreversible neurological disability.

Therapeutic Implications

Immunomodulatory Therapies: MS patients' immune responses are intended to be modulated and relapse rates to be decreased by disease-modifying treatments such as glatiramer acetate and interferon-beta [11].

Anti-Inflammatory Drugs: Inhibiting particular inflammatory pathways implicated in the pathophysiology of multiple sclerosis, targeted therapies like natalizumab and fingolimod lessen the severity of the disease and its progression [12].

Remyelination-Promoting Therapies: New treatments for Multiple Sclerosis (MS) patients include clemastine and anti-LINGO-1 antibodies, which are intended to improve remyelination and encourage neural repair [13].

Neuroprotective Interventions: Antioxidants and neurotrophic factors are examples of neuroprotective tactics that target neuronal survival pathways and lessen neurodegeneration in multiple sclerosis [14].

Discussion

The main goal of this review was to present some of the most recent findings regarding the involvement of neuroinflammation in the onset and course of multiple sclerosis. Our goal was to perform a meta-analysis of the body of recent research in this area, focusing particularly on studies that examined the function that inflammation plays in the various stages of multiple sclerosis. Our research indicates that a significant portion of current research is devoted to elucidating the precise roles played by various cell populations and the cytokines secreted at various stages of the illness in the pathogenic cascades that sustain the immune response.

While most studies examining the role of various T cell subpopulations have focused primarily on T helper subclasses, we have recently turned our attention to cytotoxic T cells, or CD8+ T cells, and tried to understand why and how these cell types target the myelin sheath in the central nervous system during the stages of the disease that are worsening. This is especially true in the secondary progressive form of the disease, where CD8+ T cells are concentrated in higher densities around areas of demyelination, a factor that is typically linked to a poor prognosis [17,33,75,76]. Regarding B cells, we discovered that these immune cells appear to play a supporting role in the pathogenesis of MS. It is evident that there is still some degree of ambiguity surrounding the precise role that these cells play in the development of MS. Based on current knowledge, B cells function as professional Antigen-Presenting Cells (APCs) to prime cytotoxic T cells within the immune system. They are also highly

valuable for diagnostic purposes, as the detection of oligoclonal immunoglobulin bands in patients' CSF after lumbar punctures is considered the gold standard for diagnosing the condition. Furthermore, a severe prognosis is frequently predicted by high levels of oligoclonal bands in the early stages of MS [49,73].

Currently available MS medications work by modulating the immune system to suppress the neuroinflammatory response and avert tissue damage. These MS medications lessen relapses, but they are not very effective in postponing the long-term negative consequences of the illness. Finding more targeted treatments is therefore desperately needed. Targeting autoreactive immune cells and their byproducts has been the focus of new developments in recent years, demonstrating improved efficacy and selectivity while lowering the possibility of adverse effects from widespread immunosuppression. The creation of vaccines or cytokine- or antigen-specific antibodies seems to be a promising immunopharmacological target that is being investigated for MS [78]. Nonetheless, more research is necessary to fully comprehend these novel and intriguing roles, as doing so may advance our understanding of immune cell-to-cell communication in MS and during neuroinflammation.

Conclusion

MS is characterized by inflammatory demyelination of the central nervous system. Researchers are now being forced to reevaluate the future of the anti-inflammatory drugs currently used to treat afflicted patients due to their growing understanding of the complex relationship between cells and the cytokines released during the different stages of MS, including acute inflammation, endogenous immune modulatory responses, de- and re-myelination, and recovery in MS patients. Once believed to be the cause of the pathological condition, T cells and cytokines are now recognized as key participants in the healing process. Based on these results, it is suggested that researchers begin to take into account the possibility that anti-inflammatory medications and T cell inhibitors may impede myelin regeneration while addressing the ongoing inflammation. It is possible that treatment plans should be implemented following the proper staging of the illness. This would entail starting with medications that suppress inflammation at its peak and switching to Treg/Bregs stimulators to support regeneration later on or during remission.

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Author contributions

Conceptualization-S.A., M.K, Data curation-Z.D.T., A.F, Project Administration-M.K., U.K,

Supervision-M. K, S.A., Visualization-A. F, Z.D, Writing - original draft-M.K., A.F, Writing

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