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Latent microbial infections leading to myelin and axonal damage in multiple sclerosis: A narrative review

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Keywords
Multiple Sclerosis; Therapeutics; Demyelinating Diseases; Axonal Damage; Latent Infections

Abstract

Background: Multiple sclerosis (MS) is a complex autoimmune disease characterized by chronic inflammation, demyelination, and axonal damage in the central nervous system (CNS). This review specifically aims to investigate the role of latent microbial infections-such as those caused by Epstein-Barr virus (EBV), Chlamydia pneumoniae, and others-in contributing to myelin and axon damage in MS.

Methods: We evaluated recent studies from PubMed, Google Scholar, and Scopus databases that focus on the relationship between latent microbial infections and MS pathogenesis.

Results: In MS, emerging evidence suggests that latent microbial infections play a significant role in triggering and perpetuating the inflammatory processes associated with the disease. The potential mechanisms by which these infections contribute to the pathogenesis of MS, highlighting the interplay between the immune system, microbial agents, and the CNS are evaluated. These include molecular mimicry, where similarities in sequence or structure between viral, bacterial, or self-peptides can activate autoreactive T or B cells through cross activation by pathogen-derived peptides, chronic inflammation triggered by persistent infection, leading to immune-mediated damage, and disruption of the blood-brain barrier, allowing microbial agents or immune cells to infiltrate the CNS.

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Conclusion: This review underscores the critical role of latent microbial infections in MS pathogenesis. By elucidating these mechanisms, we provide new insights that could inform the development of innovative therapeutic interventions and preventive strategies for MS.

Introduction

Background and significance of multiple sclerosis (MS)

MS is a chronic autoimmune disease characterized by inflammation, demyelination, and axonal damage within the central nervous system (CNS). It affects approximately 2.8 million people worldwide, with a higher prevalence in temperate regions, and it predominantly affects young adults.[1] The etiology of MS is multifactorial and remains incompletely understood. However, it is widely accepted that a complex interplay between genetic susceptibility and environmental factors contributes to the development and progression of the disease.[2]

The pathological hallmark of MS is the destruction of myelin, the protective sheath surrounding nerve fibers, leading to impaired nerve conduction and subsequent axonal degeneration. This process results in the characteristic neurological symptoms observed in MS patients, including weakness, sensory deficits, coordination difficulties, and cognitive impairments.[3] The impact of MS goes beyond the physical symptoms, as individuals with the disease often face significant challenges in their daily lives, including decreased quality of life (QOL), increased healthcare utilization, and socioeconomic burden.[4] Therefore, there is a pressing need to unravel the underlying mechanisms driving MS pathogenesis in order to develop targeted interventions that can halt disease progression, improve symptom management, and enhance overall patient cure.

Emerging evidence suggests that certain viral and bacterial infections may trigger or exacerbate the immune dysregulation observed in MS, leading to an inflammatory cascade that results in autoimmune destruction of myelin and subsequent axonal loss.[5,6] Understanding the association between latent microbial infections and MS pathogenesis is of utmost importance, as it not only provides insights into the disease mechanisms, but also offers potential therapeutic targets.

Recent breakthroughs in research have highlighted specific microbial agents linked to MS exacerbations, revealing unresolved questions about their roles in disease pathology. Additionally, controversies surrounding the effectiveness of current diagnostic and therapeutic approaches-particularly regarding their ability to target these latent infections-underscore the necessity for this review.

This narrative review aims to synthesize current findings, highlight gaps in knowledge, and propose directions for future research. By focusing on the relationship between latent microbial infections and MS, we hope to illuminate potential pathways for novel interventions and preventative measures. The information obtained to write this study was collected from reliable databases including Scopus, PubMed, and Google Scholar.

Overview of myelin and axonal damage in MS

Myelin, a fatty substance produced by specialized cells called oligodendrocytes, forms a protective sheath around nerve fibers in the CNS. It plays a vital role in facilitating rapid and efficient conduction of nerve impulses. In MS, myelin becomes the primary target of autoimmune attack, leading to its destruction and subsequent disruption of nerve signaling.[7] Activated immune cells, including T cells and macrophages, infiltrate the CNS and release pro-inflammatory cytokines and other mediators, leading to the breakdown of myelin. This process exposes nerve fibers and disrupts their normal functions.[8]

Axonal damage is another critical aspect of MS pathology. Axons, the long projections of nerve cells, transmit electrical signals between different regions of the nervous system. In MS, axonal injury can occur independently or as a consequence of demyelination. The loss of myelin, and the subsequent inflammation, disrupts the normal environment necessary for axonal survival, leading to degeneration and progressive loss of axons.[3]

Axonal damage in MS is multifactorial and involves various mechanisms. These include direct injury from inflammatory mediators, such as cytokines and free radicals, as well as indirect mechanisms resulting from the loss of trophic support from surrounding myelin. Additionally, immune-mediated mechanisms, such as antibody-mediated attacks on axonal proteins, contribute to axonal injury.[9] The extent of myelin and axonal damage in MS varies among individuals, leading to heterogeneous clinical presentations and disease courses. While early stages of MS may involve remyelination and partial recovery of neurological function, as the disease progresses, chronic

inflammation and cumulative damage to myelin and axons result in irreversible disability.[10]

Immune-mediated mechanisms of microbial-induced myelin and axonal damage

One of the primary immune-mediated mechanisms involved in microbial-induced myelin and axonal damage is the activation of autoreactive T cells.[11] Microbial antigens can activate T cells that recognize both the microbial antigens and self-antigens present in the CNS, including myelin proteins.[12] These activated T cells can infiltrate the CNS, release pro-inflammatory cytokines, and recruit other immune cells, leading to local inflammation and tissue damage.[11] Figure 1 illustrates the potential mechanisms by which viruses and bacteria can contribute to the development of MS or trigger exacerbations.

Another immune-mediated mechanism implicated in microbial-induced myelin and axonal damage is the production of autoantibodies. Following microbial infections, B cells can produce antibodies that recognize both microbial antigens and self-antigens present in the CNS. These autoantibodies can bind to myelin and axonal components, leading to complement activation, recruitment of immune cells, and subsequent tissue damage.[13] In addition to autoreactive T cells and autoantibodies, other immune cells, such as macrophages and microglia, play a crucial role in the clearance of microbial pathogens as well as in tissue damage. These immune cells can release pro-inflammatory molecules and cytotoxic factors that contribute to myelin and axonal damage. For example, activated macrophages and microglia can release reactive oxygen species, nitric oxide, and proteases, which can directly damage myelin and axons.[14] Moreover, the chronic activation of the immune system in response to persistent or recurrent microbial infections can lead to dysregulation of immune responses. This dysregulation can result in the loss of immune tolerance, leading to the activation of autoreactive immune cells that attack myelin and axonal components in a chronic and sustained manner.[15]

It is important to note that the specific mechanisms underlying microbial-induced myelin and axonal damage can vary depending on the type of pathogen and the host's genetic and immunological factors. Furthermore, the interplay between microbial infections and other environmental and genetic factors can further modulate the immune responses and contribute to the progression and severity of myelin and axonal damage in neuroinflammatory disorders.[16]

The potential mechanisms by which viruses and bacteria can contribute to the development of MS or trigger exacerbations are shown in figure 1.[17]

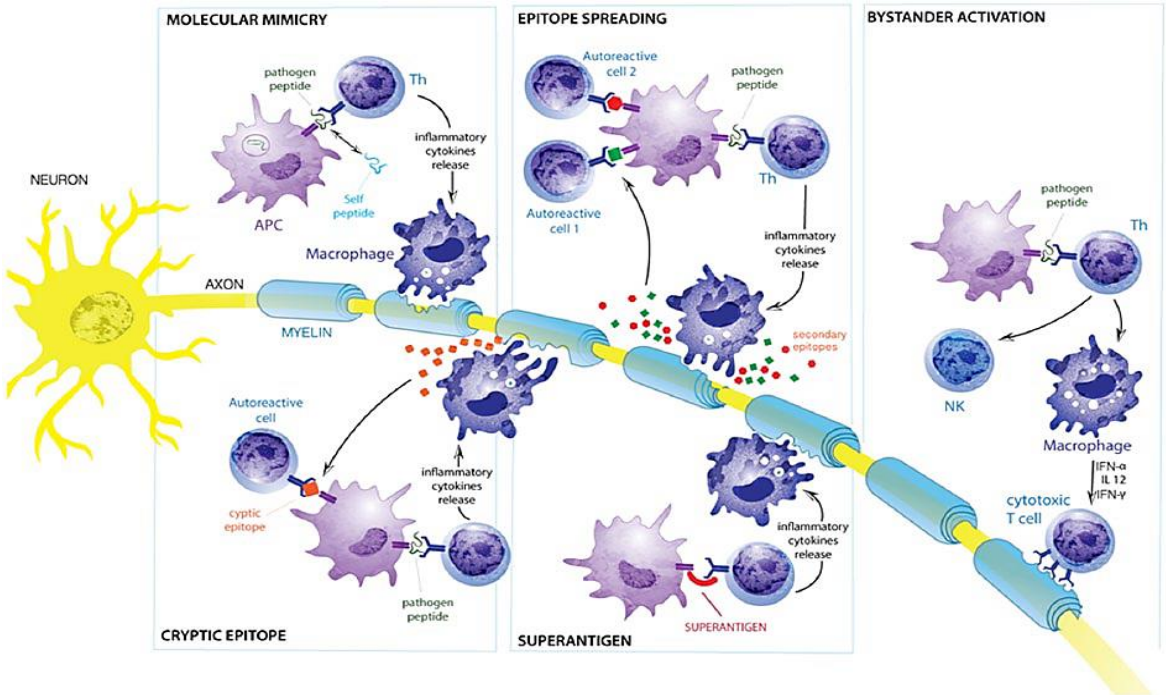

Figure 1. The potential mechanisms by which viruses and bacteria can contribute to the development of MS or trigger exacerbations

One mechanism is molecular mimicry, where similarities in sequence or structure between viral, bacterial, or self-peptides can activate autoreactive T or B cells through cross activation by pathogen-derived peptides. Epitope spreading refers to the process of diversifying the immune response from the initial dominant epitope of a protein to secondary epitopes on the same protein (intramolecular spreading) or other proteins (intermolecular spreading). Bystander activation occurs when unrelated infectious agents stimulate natural killer (NK) cells, NKT cells, and macrophages, leading to the production of pro-inflammatory cytokines. These cytokines can non-specifically activate previously primed T or B cells at the target tissue. Subdominant cryptic antigens, usually hidden from the immune system, may be released by antigen-presenting cells (APCs) due to increased protease production in the inflammatory environment caused by infections. Superantigens, which are bacterial, viral, or retroviral proteins, can activate a large proportion of T cells by binding to major histocompatibility complex class II molecules. Unlike classical peptide antigen recognition, superantigens do not require processing into small peptides and can stimulate polyclonal T cell activation and the release of large amounts of cytokines, particularly in T cells expressing specific receptor Vβ chains. For clarity, the figure does not include other cellular groups involved in the immune response during infections, such as CD8+ cytotoxic T cells, B cells, or microglial cells.

Molecular mimicry and cross-reactivity

Molecular mimicry refers to the structural similarity between microbial antigens and self-antigens, which can result in the activation of autoreactive immune cells that target both the microbial pathogens and components of the CNS.[18] When a microbial infection occurs, the immune system mounts a response to eliminate the invading pathogen. However, in some cases, the immune response can also target self-antigens due to the resemblance between microbial antigens and self-antigens. This occurs when the epitopes of the microbial antigens share molecular similarities, such as amino acid sequences or structural motifs, with self-antigens present in the CNS (Figure 1).[12]

The activation of autoreactive immune cells, particularly T cells, plays a central role in the process of molecular mimicry and cross-reactivity.[18] Autoreactive T cells can be activated by the microbial antigens presented by APCs, and subsequently, recognize self-antigens in the CNS that share similarity with the microbial antigens. This recognition leads to the activation and expansion of autoreactive T cells, which can infiltrate the CNS and initiate an immune response against myelin and axonal components.[19,20]

In the context of neuroinflammatory disorders like MS, molecular mimicry and cross-reactivity have been extensively studied. For example, in MS, myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) are major target antigens of autoreactive T cells. Several microbial agents, such as human herpesvirus-6 (HHV-6), Epstein-Barr virus (EBV), and certain strains of bacteria, have been implicated in molecular mimicry with MBP and MOG.[21,22]

Cross-reactivity between microbial antigens and self-antigens can also lead to the activation of autoreactive B cells. B cells can produce autoantibodies that recognize both microbial antigens and self-antigens, including myelin and axonal components. These autoantibodies can contribute to tissue damage by initiating complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity.[23] The mechanisms underlying molecular mimicry and cross-reactivity involve complex interactions between the immune system, microbial antigens, and self-antigens. Various factors, such as genetic susceptibility, exposure to specific microbial pathogens, and the host's immune response, can influence the development and progression of autoimmune reactions mediated by molecular mimicry.[24]

Dysregulation of immune responses and chronic inflammation

Dysregulation of immune responses and chronic inflammation play significant roles in the mechanisms underlying microbial-induced myelin and axonal damage in neuroinflammatory disorders. When the immune system fails to effectively control microbial infections or becomes chronically activated, it can lead to sustained inflammation and immune-mediated destruction of myelin and axonal components in the CNS by the continuous activation of immune cells, such as T cells and macrophages.[11,25] This chronic immune activation results in the release of pro-inflammatory cytokines, chemokines, and cytotoxic molecules that contribute to tissue damage. The chronic inflammation can lead to bystander damage of myelin and axons in the CNS, even in the absence of direct infection.[26]

The dysregulation of immune responses in

microbial-induced myelin and axonal damage involves various mechanisms. One such mechanism is the imbalance between pro-inflammatory and anti-inflammatory signaling pathways. Microbial infections can promote the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). These cytokines can activate immune cells and amplify the inflammatory response, leading to tissue damage. At the same time, the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-β), which normally help regulate inflammation, may be impaired.[27-29]

Furthermore, dysregulated immune responses can result from defects in immune cell function or regulation. For example, dysfunction of regulatory T cells (Tregs), which play a crucial role in maintaining immune tolerance, can contribute to the breakdown of self-tolerance and the activation of autoreactive immune cells.[30] Regulatory T cells help suppress the activation and proliferation of autoreactive T cells, preventing excessive immune responses against self-antigens. In the context of microbial-induced myelin and axonal damage, defects in Treg function can lead to the unchecked activation of autoreactive T cells, perpetuating the inflammatory response and causing tissue damage.[31]

Additionally, dysregulation of the immune response can arise from aberrant activation of complement, a system that plays a role in immune defense and tissue homeostasis.[32] In some cases, microbial infections can trigger complement activation, leading to the deposition of complement components on myelin and axonal structures. The activation of complement can initiate an immune response, recruit immune cells, and induce inflammation, which can ultimately contribute to myelin and axonal damage.[21]

The sustained activation of immune cells, such as macrophages and microglia, leads to the release of cytotoxic molecules, including reactive oxygen species, nitric oxide, and proteases. These molecules can directly damage myelin and axonal structures, exacerbating the inflammatory response and further promoting tissue destruction.[5,11] An important issue is that dysregulation of immune responses and chronic inflammation in the context of microbial-induced myelin and axonal damage can vary depending on the specific microbial pathogen, the host's genetic factors, and environmental influences. The interplay between these factors contributes to the heterogeneity and complexity of neuroinflammatory disorders.[18]

Impact of microbial infections on blood-brain barrier integrity

The integrity of the blood brain barrier (BBB) is crucial for maintaining the homeostasis of the CNS and protecting it from harmful substances.[33] Microbial infections can disrupt the BBB, leading to increased permeability and allowing the entry of pathogens, immune cells, and inflammatory mediators into the CNS. This disruption of BBB integrity plays a significant role in the mechanisms underlying microbial-induced myelin and axonal damage in neuroinflammatory disorders.[29] Microbial infections can directly affect the BBB through various mechanisms. One mechanism involves the direct invasion of pathogens into the CNS.[34] Certain microbial agents including bacteria, viruses, and fungi can breach the BBB by targeting and disrupting the endothelial cells that form the barrier. These pathogens can induce the production of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs) that compromise the tight junctions between endothelial cells, leading to increased BBB permeability.[35,36]

In addition to direct invasion, microbial infections can indirectly impact BBB integrity through the activation of immune cells and the release of inflammatory mediators.[37] Following an infection, immune cells, such as monocytes, macrophages, and neutrophils, are recruited to the site of infection. These immune cells can produce inflammatory cytokines, such as IL-1β and TNF-α, as well as reactive oxygen species and nitric oxide, which can disrupt the tight junctions and compromise BBB integrity.[38,39]

Furthermore, the activation of immune cells in response to microbial infections can lead to the release of MMPs, enzymes that degrade extracellular matrix components.[40] MMPs, particularly MMP-2 and MMP-9, can degrade the basement membrane proteins of the BBB, further compromising its integrity and increasing its permeability. This increased permeability allows immune cells and inflammatory mediators to enter the CNS, exacerbating the neuroinflammatory response and contributing to myelin and axonal damage.[41,42]

The breakdown of BBB integrity also facilitates the entry of microbial toxins into the CNS. Some pathogens produce toxins that directly affect the tight junction proteins and disrupt the BBB.[43] For example, certain strains of Escherichia coli produce

cytotoxic necrotizing factor (CNF), which can induce the internalization of tight junction proteins and weaken the integrity of the barrier.[44]

The entry of immune cells and inflammatory mediators into the CNS due to BBB disruption leads to the activation of neuroinflammatory processes.[45] Immune cells, such as T cells and macrophages, can directly target myelin and axonal components, resulting in immune-mediated tissue damage. Additionally, the release of pro-inflammatory cytokines and cytotoxic molecules by immune cells exacerbates the inflammatory response, leading to further myelin and axonal damage.[5]

Latent microbial infections: Unveiling the culprits

Latent microbial infections refer to the presence of microorganisms within the body that can persist in a dormant or inactive state for extended periods. These infections may not cause immediate symptoms or active disease, but can reactivate under certain conditions, leading to pathological consequences.[46,47] In the context of MS, emerging evidence suggests that latent microbial infections play a significant role in triggering and perpetuating the inflammatory processes associated with the disease.[17,48,49]

Viruses associated with MS

Latent viral infections have been extensively studied in relation to MS. Several viruses have been implicated, including members of the herpesvirus family. Herpesviruses, such as EBV, HHV-6 human endogenous retrovirus (HERV), varicella-zoster virus, Torque Teno virus (TTV), and cytomegalovirus, have been identified as potential triggers for MS due to their ability to establish lifelong latent infections in the human host.[17,48,50,51]

EBV is one of the most extensively studied viruses in relation to MS.[48,52] It is highly prevalent worldwide, with more than 90% of the adult population being infected.[53] EBV infection is associated with infectious mononucleosis, and individuals who experience symptomatic primary infection have an increased risk of developing MS later in life.[54-56] Furthermore, serological studies have consistently shown a higher prevalence of EBV antibodies in MS patients compared to healthy controls.[56-59]

The exact mechanisms by which EBV contributes to MS pathogenesis are not fully defined, but several hypotheses have been proposed. One hypothesis suggests that EBV, upon primary infection, may dysregulate the immune system, leading to a cascade of events that ultimately result in an autoimmune response against myelin in susceptible individuals.[60] EBV infection has the potential to induce host immune responses, including the production of pro-inflammatory cytokines such as IL-12, IL-1β, IL-6, IL-17, IL-15, GM-CSF, TNF-α, IFN-γ, lymphotoxin-α, and osteopontin through the stimulation of immune-related cell lines. These immune mediators can exacerbate inflammation reactions within MS lesions, leading to neuronal damage and disruption of cellular activity. Furthermore, it is believed that these inflammatory pathways may be activated by sensitization of brain neurons, which could be influenced by genetic alterations associated with MS.[17,22,48,61,62]

Another hypothesis involves molecular mimicry, where viral antigens resemble self-antigens, leading to cross-reactive immune responses that target both the virus and myelin.[57] Autoreactive antibodies in MS can cross-react with viral proteins, particularly EBV nuclear antigen 1 (EBNA1).[62] Both serum and cerebrospinal fluid (CSF) of MS patients often show elevated levels of antibodies against EBNA1. EBNA1 is consistently recognized as an EBV-specific antigen and stimulates CD4+ T-cell responses in individuals carrying the virus. MS patients exhibit a selective expansion of T cells specific to EBNA1. Additionally, a small subset of these T cells has been found to cross-react with myelin antigens, supporting the hypothesis that clonally expanded EBNA1-specific T cells may play an active role in the immunopathology of MS by promoting cross-recognition through molecular mimicry.[63] In addition, during the initial infection, EBV can disrupt the BBB, enabling activated immune cells to enter the CNS, which triggers a series of events that result in CNS inflammation. Moreover, there is evidence to suggest that persistent EBV infection may induce inflammation and immune dysregulation, potentially playing a role in the onset and progression of MS.[57] Over-activation of B-cells and T-cells during infectious mononucleosis can occur, leading to increased inflammatory reactions in MS.[17]

HHV-6 is another double-stranded DNA herpesvirus that has been implicated in MS. Like EBV, HHV-6 is highly prevalent and establishes lifelong latency after primary infection. Studies have reported an increased prevalence of HHV-6 DNA in the blood and CSF of MS patients compared to controls.[64] HHV-6 infection has been associated with increased disease activity and exacerbations in MS, suggesting a potential role in

disease pathogenesis.[65]

The mechanisms by which HHV-6 influences MS are not abundantly understood, but may involve direct viral-induced damage, activation of immune responses, or interactions with other viral or environmental factors.[66,67] HHV-6 has been shown to infect and replicate within astrocytes, microglia, and oligodendrocytes, leading to cellular damage and inflammation.[68] According to study findings, the continuous presence of active HHV-6 infection in glial cells within inflamed CNS tissue could potentially lead to virus-induced immune-pathologies in MS.[63]

It is worth noting that a remarkable similarity exists in the amino acid sequence of HHV-6 24-hour urine (U24) protein and MBP, which is considered a potential autoantigen associated with MS. Moreover, there is evidence of cross-reactivity between autoreactive T-cells and MBP, indicating the possibility of a molecular mimicry mechanism in HHV-6 infection.[69] HHV-6 infection may induce the production of pro-inflammatory cytokines and chemokines, contributing to the perpetuation of the inflammatory processes observed in MS.[65]

In the context of HHV-6 infection, virus-infected T lymphocytes exhibit an upregulation of proinflammatory genes, including IL-1, IL-2, IL-18, IFN, and TNF-α, while simultaneously downregulating anti-inflammatory cytokines such as IL-10 and IL-14. The elevated production of these inflammatory mediators by immune cells is responsible for triggering intense inflammatory reactions, leading to the development of demyelination and damage to nerve myelin and axons.[61] There is much evidence indicating a correlation between levels of inflammatory cytokines, including TNF-α, in the CSF and the degree of disability and progression rate observed in patients with MS.[66] The response of CD8+ T lymphocytes to HHV-6-infected CNS cells can lead to tissue injury and the release of sequestered antigens. This, in turn, activates self-reactive lymphocytes and enhances autoreactive immune reactions. Activation of the complement system can be improved through the utilization of CD46, which is used by HHV-6A as a cellular receptor.[52] Viruses involved in MS are presented in table 1 in terms of virus type, involvement with the disease, and relationship with MS.

Bacterial infections and their role in MS pathogenesis

Bacterial infections have also been implicated in the development and progression of MS. Chronic infections, such as those caused by Chlamydia pneumoniae, Mycoplasma pneumoniae, Helicobacter pylori, Borrelia burgdorferi, Mycobacterium tuberculosis (TB), and Mycobacterium avium have been shown to be associated with MS and have been detected in MS patients. These bacteria can persist within cells and tissues, evading the immune system and potentially contribute to chronic inflammation and tissue damage.[17,48,49,70-72]

The exact mechanisms by which bacterial infections contribute to MS pathogenesis are not fully understood. However, several hypotheses have been proposed. One hypothesis suggests that bacterial infections may trigger an immune response that leads to chronic inflammation. This chronic inflammation can subsequently damage myelin and contribute to the development of MS.[73] Another hypothesis involves molecular mimicry, where bacterial antigens resemble self-antigens, leading to cross-reactive immune responses that target both the bacteria and myelin.[74]

Chlamydia pneumoniae is an intracellular bacterium that can cause respiratory tract infections. This bacterium has been detected in the CNS of MS patients, suggesting its potential involvement in the disease.[17] Studies have shown an increased prevalence of C. pneumoniae antibodies in MS patients compared to healthy individuals.[48] Furthermore, experimental models have demonstrated that C. pneumoniae infection can induce a persistent infection in the brain, and consequently, induce immune responses and promote CNS inflammation, which may contribute to pathogenesis of chronic inflammatory diseases such as MS.[36,75]

Chlamydia pneumoniae has the ability to enhance the expression of MHC class II molecules CD40, CD80, and CD86 on bone marrow-derived dendritic cells (BMDDC). This, in turn, induces the production of proinflammatory cytokines by macrophages. The secretion of these cytokines can increment the frequency of T-lymphocytes, leading to the recognition of various antigens, including antigens that react with self-proteins. This process has the potential to trigger autoimmune disorders.[76]

Chlamydia pneumoniae has the ability to infect various types of cells, including macrophages, monocytes, endothelial cells, and smooth muscle cells in blood vessels. As a result, infected monocytes/macrophages, responding to an initial trigger such as an acute viral infection or autoimmune reaction, could transport this pathogen to inflamed CNS tissues.[77]

Table 1. Viruses implicated in MS: Virus, disease involvement, and association with multiple sclerosis (MS) (Adapted from Bar-Or et al.[60])

Virus	Disease involvement	Association with MS
EBV, HHV-4, lymphocryptovirus Double-stranded (ds) DNA virus, neurotropic Tropism: B cells, epithelial cells Cell latency: memory B cells	Infectious mononucleosis, Hodgkin and non-Hodgkin's lymphoma, Burkett's lymphoma, gastric and nasopharyngeal cancer, hairy cell leukemia, MS	Mononucleosis predisposes to MS, reduced activity of EBV-specific cytotoxic T cells (e.g., exhausted) in MS patients, EBV seropositive epidemiological studies, virus present in MS brain, EBV prolongs the lifespan of B cells
HHV-6, roseolovirus dsDNA, neurotropic Tropism: broad; hematopoietic and epithelial cells Cell latency: lymphocytes and monocytes	Exanthema subitum (roseola infantum) and pneumonitis, MS	Present in MS plaques, reactivation during relapses, high levels found in oligodendrocytes and areas of demyelination, elevated levels are found early in MS and during relapses/exacerbations, anti-HPV IgG and IgM titers are reported to predict relapses
CMV, betaherpesvirinae dsDNA, neurotropic Tropism: broad; hematopoietic cells, smooth muscle, monocytes, epithelial and endothelial cells, fibroblasts, connective tissue Cell latency: cells of the myeloid lineage	Retinitis, hepatitis, colitis, pneumonia, encephalitis, MS	Both detrimental and beneficial properties reported, large meta-analysis MS versus controls did not yield a conclusive link between CMV and MS
VZV, HHV-3 dsDNA, neurotropic Tropism: mononuclear cells Cell latency: sensory ganglia	Chickenpox, shingles, MS	Virus is present during relapses, recent studies failed to show an increased risk of MS associated with varicella or zoster infections
HERV-W Tropism: cells of the nervous system, syncytiotrophoblast layer of the placenta Cell latency: multiple	MS, diabetes, autoimmune arthritis, and schizophrenia In most cases the observed expression profiles of specific HERV-W sequences have not led to a definitive association with human disease pathology.	Present in infiltrating macrophages and activated MS lesions, MSRV Env protein is detected in blood of active MS patients, drives the expression of proinflammatory cytokines, reduces myelin protein, expression and kills oligodendrocyte precursors

MS: Multiple sclerosis; EBV: Epstein-Barr virus; VZV: Varicella zoster virus; HHV-3: Human herpesvirus-3; CMV: Cytomegalovirus; IgM: Immunoglobulin M; HPV: Human papillomavirus; HERV: Human endogenous retrovirus

Recent reports have shown that C. pneumoniae can infect glial cells and ependymal cells within the CNS of mice.[70] The bacterium was noted to cross the BBB and enter the CNS, disrupting its permeability by releasing toxic components from its cell wall.[49] This process leads to the increased production of inflammatory factors by activated microglia, which can have either neurotoxic or neuroprotective effects depending on the disease stage.[78] The presence of C. pneumoniae in the CNS can initiate an initial inflammatory response and also serve as a chronic stimulus, leading to a sustained state of immune activation. On the other hand, CNS infection by C. pneumoniae in patients with MS may simply be a secondary infection of already damaged CNS tissue.[77]

Mycoplasma pneumonia is a small microorganism that adheres to host cells by specific attachments and adhesin antigens that has been associated with MS.[49] This bacterium can cause respiratory tract infections and has been detected in the CNS of MS patients.[76,79] Studies have reported an increased prevalence of M. pneumoniae antibodies in MS patients compared to controls.[17] Mycoplasma infections have been shown to induce immune responses and promote inflammation, potentially contributing to the development or exacerbation of MS.[80]

The lipoproteins of M. pneumoniae play a significant role in infection and modulation of immunity through TLR1 and TLR2. The co-expression of TLR2 and TLR6 mediates the cellular response to lipopeptides from M. pneumoniae, which have been recognized in cerebral endothelial cells and microglia of MS patients.[49] Additionally, M. pneumoniae has

been found to invade the CNS and is known to induce demyelination, at least in the peripheral areas. It is considered a possible co-factor in the development of MS.[81]

Helicobacter pylori is a gram-negative bacterium that resides on the surface of gastric epithelial cells and is generally considered a non-invasive bacterium, but laboratory observations have shown that it can enter the epithelial and immune cells of the host.[82] While a number of studies have not found an association between H. pylori and susceptibility to MS, several reports have demonstrated a high incidence of acute H. pylori infection and significantly higher frequency of H. pylori immunoglobulin G (IgG) seropositivity in remitting-relapsing and secondary progressive MS patients during the stable phase, compared to healthy people.[49,83-85] Some studies indicate that H. pylori infection leads to a decrease in the levels of Th1 and Th17 cells in the CNS and spleen, in comparison to the control group. Consequently, these findings have prompted suggestions of a potential protective effect of H. pylori against MS.[17,86] Persistent bacterial infection can lead to a loss of self-tolerance due to the continuous release of bacterial antigens capable of motivating the release of pro-inflammatory cytokines from immune cells. H. pylori can apply these effects not only locally, but also directly on the CNS, modulating the brain-gut axis.[87]

Borrelia burgdorferi is the bacteria responsible for Lyme disease, a syndrome that shares similarities with MS. The bacterium activates macrophages through TLR2 and stimulates Th1-type T-lymphocytes immunity. During an infection, B. burgdorferi employs various mechanisms to manipulate the innate and adaptive immune systems, enabling its survival within mammalian host cells.[48,88,89] In some patients, Borrelia infection can trigger an autoimmune response and the release of inflammatory mediators, leading to the improvement of chronic neurological abnormalities similar to MS. This is according to the observation that both Lyme disease and MS are related to abnormal immune reactions, and some individuals with MS have stated a history of Lyme disease or exposure to disease vectors. Both disorders exhibit myelin damage and inflammation, which can make it challenging to differentiate between Lyme borreliosis and MS.[48] Several studies have indicated an increase in anti-Borrelial antibody levels in MS patients, suggesting a potential relationship between Lyme disease and MS.[48,90]

It is important to consider Lyme disease during the differential diagnosis of MS, as it mimics several neurological symptoms. However, the presence of antibodies against B. burgdorferi in MS patients does not confirm current or past infections, nor does it prove that the bacteria is the cause of the disease.[49]

Mycobacterium TB is an exceptionally successful pathogen that can persist in host tissues for years without triggering disease. This bacterium is responsible for TB, an infectious and contagious disease primarily affecting the lungs.[91] TB is categorized into two types: latent tuberculosis infection (LTBI) and active TB disease. LTBI refers to a persistent immune response to M. tuberculosis antigens lacking clinically manifested active TB disease.[92]

The connection between TB and MS can be understood in two aspects. Firstly, immunomodulation or immunosuppression treatments may lead to the reactivation of latent TB infection. Secondly, the intense inflammatory response of the body prior to bacillus infection can increase susceptibility to autoimmune diseases like MS. This occurs because there is a similarity observed between epitopes from the chaperone HSP60 of M. tuberculosis and fragments of HSP60 found in MS patients. Notably, a specific peptide of the bacillus binds strongly to multiple alleles, suggesting its contribution in the pathogenesis of MS by inducing a robust immune response.[71] Several studies have demonstrated an association between mycobacteria and MS. Components of mycobacteria have the ability to activate the innate immune system through toll-like receptors (TLRs). Stimulation of the host immune response via TLR2, TLR4 and TLR9 trigger cytokines production, leading to the differentiation of naive CD4+ T cells into Th1 and Th17 cells. Consequently, this results in the production of IL-17 and IFN-γ. These combined factors facilitate the migration of leukocytes across the BBB, contributing to the activation of inflammatory immune responses, tissue damage and neuronal dysfunction in MS disease.[93,94] Regarding their possible role in MS, several studies have shown a higher frequency of lymphocyte proliferative response against recombinant proteins HSP70 and HSP65 derived from M. tuberculosis in MS patients compared to those with other neurological disorders or healthy individuals.[93,95]

Mycobacterium avium subsp. Paratuberculosis (MAP), classified as an intracellular pathogen within the M. avium complex, is a non-tuberculous mycobacterium responsible for paratuberculosis in ruminants. Additionally, it has been suggested as the potential cause of Crohn's disease and other chronic inflammatory infections in humans.[96] Recent research indicates that MAP may have a causative role in MS pathology, particularly in genetically susceptible individuals, according to the theory of molecular mimicry. Currently, clinical trials are underway to investigate antimycobacterial therapy targeting MAP.[93] The involvement of mycobacteria in the development and progression of MS may be specific to certain populations and strongly influenced by various genetic and non-genetic factors. However, the potential of immune modulation as an approach to combat mycobacterial infection remains largely unexplored.[93]

Furthermore, MAP peptides have been found to elicit a T cell response in peripheral blood mononuclear cells (PBMCs) isolated from individuals with relapsing-remitting MS.[97] Additionally, MS patients have shown the presence of intrathecally synthesized IgG antibodies that react to specific MAP-derived peptides.[98] In the context of MAP infection or antigen exposure, autoreactive T-cells activated in the peripheral immune system through molecular mimicry may cross the BBB and become reactivated in the CNS by local APCs.[49]

Regarding the invasion of MAP, it primarily occurs through M cells located in the Peyer's patches. Subsequently, it invades intra-epithelial macrophages where it can proliferate. The recognition of MAP involves TLR2 and NOD2, which bind to mannosylated-lipoarabinomannan (Man-LAM) and peptidoglycans, respectively.[49,99] Moreover, MAP has the aptitude to inhibit MyD88 and TLR9 signaling and modulate the expression of IFN-γ receptors, permitting evasion of both innate and acquired immune responses in cattle.[49]

The specific roles of various TLRs and MyD88-mediated immune responses in MS, as well as the impact of MAP antigens on experimental autoimmune encephalomyelitis (EAE), are still subjects of investigation. One theory proposes that chronic MAP infection in the human gastrointestinal tract may induce the release of proinflammatory mediators, leading to neurons inflammation and polarization of the immune response toward a Th1/Th17 phenotype.[100]

It is important to note that while there is evidence supporting the association between bacterial infections and MS, causality has not been definitively established. The presence of bacterial DNA or antibodies in MS patients may reflect a response to infection or colonization rather than direct causation. Further research is needed to better understand the relationship between bacterial infections and MS.

Other potential microbial triggers: fungi and parasites

In addition to viruses and bacteria, other microbial agents, such as fungi and parasites, have been investigated for their potential involvement in MS pathogenesis. Although the evidence is limited, studies have reported associations between fungal infections, such as those caused by Candida species, Aspergillus and Cryptococcus neoformans.[101,102] Similarly, parasitic infections, such as those caused by helminths, have been investigated for their potential immunomodulatory effects and their influence on MS development and progression.[103,104]

Candida species are opportunistic pathogens that can cause superficial and systemic infections, while C. neoformans is a fungal pathogen associated with meningitis. Studies have shown an increased prevalence of fungal infections and elevated levels of anti-fungal antibodies in MS patients compared to healthy controls.[105] Antibodies against Candida designate a past fungal infection which can generate memory B-lymphocyte diagnosing epitopes of fungal infection. Memory B-cells which recognize both a fungal epitope and an epitope in the nerve cells might elucidate the association between Candida antibodies and MS disease.[106]

Parasitic infections have also been explored as potential triggers of immune dysregulation in MS. Parasites such as Toxoplasma gondii and Plasmodium spp. (the causative agents of toxoplasmosis and malaria, respectively) have been studied in relation to MS. Toxoplasma gondii infection has been associated with an increased risk of developing MS and exacerbation of disease activity, although the results of several studies suggest a negative relationship among Toxoplasma gondii infection and MS which can be considered as a likely protective feature of toxoplasmosis against the improvement of MS disease.[107-110] Plasmodium infection has been suggested to have a protective effect against MS development due to its ability to induce

immunomodulatory responses.[111,112] These findings highlight the complex interactions between parasites and the immune system in the context of MS. Therefore, some microorganisms, such as the mentioned parasites, can play a disease suppressor role against MS. More extensive studies are needed to achieve reliable results and confirm the association between these microbes and MS disease.

The mechanisms by which fungi and parasites may contribute to MS pathogenesis are still being investigated. It is hypothesized that these microorganisms can trigger immune responses that result in chronic inflammation and immune dysregulation. Additionally, molecular mimicry and cross-reactivity between microbial antigens and self-antigens may lead to autoimmune reactions targeting both the microorganism and myelin components.[113]

Diagnostic methods for identifying latent infections in MS

Serological and molecular techniques: Various serological and molecular techniques have been employed to investigate the presence and potential contribution of latent infections in MS. These diagnostic methods provide valuable insights into the association between infectious agents and the development or progression of MS.[114,115] Serological techniques involve the detection of specific antibodies in blood samples to determine exposure or immune response to particular infectious agents. In the context of latent infections in MS, serological testing can help identify the presence of antibodies against specific pathogens. For instance, the presence of antibodies against common viruses such as EBV or HHV-6 may indicate prior exposure or reactivation of these viruses in individuals with MS. Enzyme-linked immunosorbent assay (ELISA), immunofluorescence assays, and Western blotting are commonly used serological techniques to detect specific antibodies.[116,117]

Molecular techniques play a crucial role in identifying the presence of latent infections by detecting the genetic material or specific markers of infectious agents. Polymerase chain reaction (PCR) is a widely used molecular technique that amplifies and detects specific DNA or RNA sequences. In the context of MS and latent infections, PCR can be utilized to detect viral DNA or RNA in CSF or PBMCs. For example, PCR-based assays can detect the presence of viral genetic material, such as EBV or HHV-6 DNA, in biological samples from individuals with MS. Real-time PCR, nested PCR, and quantitative PCR (qPCR) are variations of PCR commonly employed in diagnostic settings.[115,118,119]

In addition to PCR, other molecular techniques such as next-generation sequencing (NGS) have emerged as powerful tools in the identification of latent infections. NGS allows for the comprehensive analysis of the entire microbial community within a sample, enabling the detection of known and potentially novel infectious agents. By sequencing the genetic material present in a sample, NGS can provide a more comprehensive view of the microbial landscape associated with MS. This technique has the potential to identify previously unrecognized infectious agents and elucidate their potential role in MS pathogenesis.[120]

It is important to note that the identification of latent infections in MS using serological and molecular techniques has its challenges and limitations. Serological assays may have limitations in terms of sensitivity and specificity, as the presence of antibodies does not necessarily indicate active infection or a causal relationship with MS. Molecular techniques, while highly sensitive, may also suffer from false positives and negatives, depending on factors such as the timing of sample collection, handling, and assay design. Additionally, the presence of viral genetic material alone does not establish causality, as viral reactivation or persistence may occur without direct involvement in MS pathology.

Imaging modalities for detecting CNS infections

In addition to serological and molecular techniques, imaging modalities play a crucial role in the identification and evaluation of latent infections in MS. These imaging techniques allow for the visualization of CNS structures and the detection of abnormalities associated with infectious processes. Magnetic resonance imaging (MRI) is the primary imaging modality used in the diagnosis and monitoring of MS. MRI can also provide valuable insights into CNS infections associated with MS. Various MRI sequences and contrast agents can be applied to detect specific imaging findings indicative of infectious processes. These findings may include the presence of parenchymal lesions, periventricular or juxtacortical white matter abnormalities, or enhancement patterns suggestive of active inflammation.[121] Contrast-enhanced MRI with gadolinium is particularly useful in detecting areas of BBB disruption and assessing the extent of

inflammatory processes.

In the context of latent infections in MS, MRI can help identify specific characteristics associated with CNS infections. For example, certain infectious agents, such as progressive multifocal leukoencephalopathy (PML) caused by JC virus, can exhibit characteristic imaging features on MRI. PML typically presents as asymmetrical white matter lesions with a predilection for the subcortical and periventricular regions.[122] These lesions often lack mass effect or significant enhancement, which can help differentiate them from other MS-related lesions.

In addition to conventional MRI, advanced imaging techniques can provide further insights into the pathophysiology of CNS infections. Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) can assess the microstructural integrity of brain tissue and detect changes associated with infectious processes. Quantitative measures derived from DWI and DTI, such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA), respectively, can provide valuable information about tissue damage and inflammation.[123] Functional MRI (fMRI) techniques can assess alterations in cerebral perfusion and neuronal activity, aiding in the characterization of infection-related changes in brain function.

Positron emission tomography (PET) is another imaging modality that can contribute to the evaluation of CNS infections in MS. PET scans, combined with specific radiopharmaceuticals, can detect metabolic changes associated with infectious processes. For instance, fluorodeoxyglucose (FDG) PET can assess glucose metabolism and identify areas of increased metabolic activity, which may be indicative of infectious or inflammatory foci.[124] Other specific radiotracers, such as [11C]-PK11195, can target microglial activation and provide insights into the inflammatory response associated with CNS infections.

It is important to note that while imaging modalities can provide valuable information about CNS infections in MS, they are not definitive diagnostic tools on their own. The interpretation of imaging findings should be considered in conjunction with clinical history, serological and molecular test results, and other diagnostic data. Furthermore, imaging findings may not always be specific to a particular infectious agent and can overlap with MS-related abnormalities.

Therapeutic approaches targeting latent infections in MS

Antiviral therapies: Antiviral medications aim to suppress viral replication and reduce viral-induced inflammation. For example, ganciclovir and valganciclovir have been explored for the treatment of HHV-6-associated MS, while antiviral drugs like acyclovir and valacyclovir have been investigated for their potential benefits in EBV-associated MS. These medications may help control viral activity and potentially modify disease course. Immunomodulatory therapies, such as IFN-beta (IFN-β) and glatiramer acetate, which are commonly used in MS treatment, have been suggested to have antiviral effects. These medications may exert their therapeutic effects by modulating the immune response against viral infections and suppressing viral replication. By reducing viral-induced inflammation, these immunomodulatory therapies may indirectly impact the progression of MS. A combination of antiviral medications targeting HHV-6 with immunomodulatory therapies such as IFN-β has been investigated in clinical trials to assess their efficacy in controlling viral infections and modifying the course of MS.[125,126]

Another important aspect of therapeutic approaches targeting latent infections in MS is personalized medicine. As MS is a heterogeneous disease with variations in viral associations, disease progression, and treatment response, individualized treatment strategies may be necessary. By identifying specific viral infections and their impact on an individual's disease, personalized therapy can be tailored to target existing specific latent infection(s). This may involve selecting the most appropriate antiviral medication or combination therapy based on the viral profile and disease characteristics of each patient.[127]

Antibiotics and immunomodulators

In addition to antiviral therapies, other therapeutic approaches have been explored to target latent infections in MS. These approaches involve the use of antibiotics and immunomodulators, which aim to modulate the immune response, reduce inflammation, and potentially alleviate MS symptoms.[128,129] Tetracyclines, such as minocycline and doxycycline, have been investigated for their potential therapeutic effects in MS. These antibiotics have both antimicrobial and immunomodulatory properties. They can suppress bacterial infections associated with MS, such as C. pneumoniae, and also modulate the immune response and reduce inflammation. Tetracyclines

have been shown to inhibit immune cell activation and migration, reduce the production of pro-inflammatory cytokines, and promote anti-inflammatory responses. Clinical trials assessing the efficacy of tetracyclines in MS are ongoing.[130]

Macrolide antibiotics, including azithromycin and clarithromycin, have also been studied in the context of MS. Like tetracyclines, macrolides possess antimicrobial and immunomodulatory properties. They can target bacterial infections associated with MS, such as M. pneumoniae and C. pneumoniae and modulate the immune response. Macrolides have been shown to inhibit the production of pro-inflammatory cytokines, reduce immune cell activation, and promote regulatory T-cell responses. Clinical trials investigating the use of macrolides in MS are currently underway.[131]

IFN-β is a widely used immunomodulatory therapy in MS. It can reduce inflammation, modulate the immune response, and potentially impact latent infections. IFN-β has been shown to have antiviral properties by inhibiting viral replication and promoting an antiviral state within cells. Additionally, it can modulate the immune response against viral infections. Clinical studies have suggested that IFN-β treatment may reduce viral activity and potentially modify the course of MS in individuals with latent infections.[132]

Immune checkpoint inhibitors, such as natalizumab and fingolimod, are immunomodulatory therapies that target specific molecules involved in immune cell migration and activation. These medications have been investigated for their potential effects on latent infections in MS. By modulating immune cell trafficking and reducing immune cell infiltration into the CNS, these therapies may indirectly impact viral replication and inflammation associated with latent infections. However, caution must be exercised when using immune checkpoint inhibitors, as they can increase the risk of certain viral infections.[133]

Combination therapies and future directions

Combination therapies and future directions in the treatment of latent infections in MS have gained attention as potential strategies to target the underlying viral involvement and modify the disease course. By combining different therapeutic approaches, such as antiviral therapies, immunomodulators, and other emerging treatments, it is hoped that a synergistic effect can be achieved to control viral replication, modulate the immune response, and potentially alleviate MS symptoms.[134]

Personalized medicine holds great promise in the treatment of MS and latent infections. By identifying specific viral infections and their impact on an individual's disease, tailored treatment strategies can be developed. This may involve selecting the most appropriate combination therapy based on the viral profile, disease characteristics, and treatment response of each patient. Personalized medicine can optimize treatment efficacy and minimize any potential adverse effects.[135]

Another future direction is the investigation of immune tolerance induction strategies. These approaches aim to reprogram the immune system to tolerate viral infections and reduce the inflammatory response in MS. Techniques such as antigen-specific immunotherapy, regulatory T-cell induction, and immune modulation through microbiota may potentially be effective in promoting immune tolerance and mitigate viral-associated inflammation in MS.[136]

Conclusion

In this narrative review, we highlight the growing evidence supporting the involvement of latent microbial infections in the pathogenesis of MS, specifically focusing on myelin and axonal damage observed in this disease. By elucidating the underlying mechanisms and exploring potential diagnostic methods and therapeutic interventions, we aimed to contribute to a better understanding of MS and pave the way for improved management strategies that target latent infections. Further research is warranted to unravel the complex interactions between microbial agents and the immune system in MS, ultimately, leading to improved patient outcomes and the development of novel treatment approaches.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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