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REVIEW ARTICLE

The Microbiome-Neurodegeneration Nexus in Multiple Sclerosis

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ABSTRACT

A significant amount of the health care burden in contemporary society is attributed to neurodegenerative diseases (NDs). Because of longer lifespans and changes in the world's population, the prevalence of these diseases will rise even more in the future decades. The primary cause of NDs is the progressive degeneration of neurones, which leads to dementia, motor impairments, and other associated functional impairments. Numerous illnesses, including Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and Amyotrophic Lateral Sclerosis (ALS), are brought on by these alterations. Neurone death, dendritic loss, and demyelination are general pathophysiological indicators. Furthermore, a number of molecular processes have been postulated to explain the pathophysiology of these disorders, while the precise reason is still unknown. Neuroinflammation and oxidative stress are the most prevalent. With regard to neuroinflammation, we attempt to draw attention to a neglected factor in the aetiology of multiple sclerosis in this review. Protein domains found in a number of bacteria imitate the cellular proteins found in the nervous system. As a result, even when the viruses are removed from the body, the immune system never stops functioning. Native proteins are nonetheless regarded as alien proteins, and the cells die as a result of subsequent immune cell activation and communication. As a result, we have compiled the research supporting this theory to link it to other chemical pathways in NDs.

Keywords: Immune system; Autoimmunity; Multiple Sclerosis; Molecular Mimicry; Neurodegenerative Diseases (NDs)

INTRODUCTION

The term "neurodegeneration" has been used to describe the loss of nerves, frequently due to unidentified causes, that leads to a number of nervous system disorders. A high mortality rate that increases significantly with age is attributed to neurodegenerative diseases, which include Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). These conditions are considered to be major global health concerns. A World Health Organization (WHO) report states that among neurodegenerative disorders, AD and PD are the most prevalent neurological conditions[1].

For instance, decades of research have shown the epidemiological occurrence of bacterial infections in NDs. Lipopolysaccharide (LPS) generated from the microbiota can activate microglia, which can lead to increased AD propagation[2,3]. Viruses are another risk factor for many neurological diseases; herpes simplex virus 1 (HSV-1) has been found in patients with AD and PD[4,5]. Furthermore, AD patients have been observed to have fungal infections in multiple brain regions[6].

Once microbes and their metabolites penetrate the central nervous system, the central immunity responds with neuroinflammation, which can lead to dementia and neurone death. Our protective response to microbial infections, traumatic brain injury, or toxic aggregates is usually neuroinflammation, which is the process of getting rid of waste products that create cytokines[7].

The neuroinflammatory processes in NDs are mostly caused by microglia and astrocytes, the two immune cells that are most common in the brain. Both undergo struc-

tural changes and promote the synthesis of inflammatory mediators during microbial infections; this phenomenon could be called infectious neuroinflammation. Although their neuroinflammation often has a protective function, certain infections result in detrimental proinflammation that can cause synapse degradation, neurogenesis entanglement, and cell death[8].

The idea of infectious neuroinflammation-driven neurodegeneration in NDs through multiorgan interconnections is presented in this paper. We examine the most recent findings in this area and provide an overview of the data pertaining to the ND infection theory.

More than 2 million people worldwide—at least 400,000 in the US—are afflicted with multiple sclerosis, the most crippling chronic inflammatory disease of the central nervous system (CNS), which is now incurable. It is interspersed by periods of neurologic impairment that are either totally or partially reversible and typically last a few days or weeks. Among the common syndromes upon presentation are ataxia from a cerebellar lesion, double vision from brain-stem dysfunction, limb weakness or sensory loss from transverse myelitis, and monocular visual loss from optic neuritis. About 15% of patients have a progressive course from onset; many people with the condition acquire a progressive clinical course after 10 to 20 years, which ultimately results in diminished mobility and cognition[9].

The condition typically manifests as a relapsing and remitting clinical course, beginning in the third decade of life. Most individuals see a steady progression of the disease after 10 to 15 years, which is known as secondary progressive MS. The disease begins with a progressive course in a portion of people, especially those who are older when it first manifests[10].

From relapsing to remitting, in which patients have periods of remission, to progressive types, the disease's clinical course varies widely. Relapsing–remitting MS (RRMS), progressive relapsing MS (PRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) are the four clinical variants of MS. They are all distinguished by periods of active disease with fresh pathology evidence interspersed with periods of inactivity. individuals with PPMS exhibit a reduced female predominance, whereas individuals with RRMS and SPMS have a male to female ratio of 1:3[11].

PATHOLOGY

Autoimmune-mediated destruction to the central nerves' myelin sheaths is believed to represent the fundamental disease. Multiple sclerosis is distinguished from other central nervous system disorders by a number of pathological characteristics. On the backdrop of a persistent inflammatory process, localized lesions with primary demyelination and astrocytic scarring are the most specific pathological alterations. These lesions are not limited to the white matter; they are also prevalent in the spinal cord, deep brain stem nuclei, and cortex's grey matter. Axons are at least partially retained during primary demyelination, but myelin sheaths and the oligodendrocytes that sustain them are destroyed[12].

Multiple sclerosis is a long-term inflammatory condition that affects the central nervous system. Perivascular T and B-lymphocytes and their dispersion into the parenchyma are indicators of inflammation, which is most noticeable in patients who have passed away soon after the commencement of the disease and diminishes with patient age and disease duration[13].

Similar to other chronic inflammatory illnesses of the human central nervous system, MHC Class I restricted CD8+ T-cells make up the majority of inflammatory cells from the adaptive immune system, but MHC Class II restricted CD4+ T-cells are either nonexistent or very uncommon. Within active lesions, these T-cells exhibit focally restricted activation and exhibit the characteristics of resident memory cells[2].

Nowadays, it is widely acknowledged that Th17 and Th1 lymphocytes play a key role in the pathophysiology of MS brain plaques. The brains of experimental autoimmune encephalomyelitis (EAE) mice, an animal model of multiple sclerosis, frequently contain large numbers of Th1 cells that express IL-12 and IFN-gamma. Additionally, active brain lesions in MS patients have been shown to include higher concentrations of CD8+ and CD4+ cells that produce IL-17. Th17 cells can readily cross the BBB, as they produce cytokines, chemokines and express receptors that compromise tissue barrier permeability[3].

ETIOLOGY

A multifactorial hypothesis is generally recognized, despite the fact that the exact origin of multiple sclerosis is still unknown: in genetically predisposed individuals, a variety of "environmental" variables may set off the immune response and accelerate the course of the disease. MS is more common in women, which is probably related to genetic factors. Its occurrence is highest after puberty and might be attributed to either environmental or genetic factors, or both. These elements are thought to interact to differing degrees, adding to MS's variability[5]. There is currently no agreement on the genesis of multiple sclerosis (MS), with ideas ranging from chronic viral infections to molecular mimicry to idiopathic loss of self-tolerance. Geographic latitude (with a higher prevalence in more temperate climates) is one of the main environmental risk factors. Seasonal variations in sunshine exposure may affect vitamin D levels or diseases that are common in these areas, while genetics may also play a role. An increased risk of multiple sclerosis is also linked to obesity, mononucleosis, and tobacco use. In the postpubertal population, Epstein-Barr virus infection causes mononucleosis, and only a small percentage of individuals with a history of mononucleosis (and a very small percentage

of all those infected with the almost universal Epstein-Barr virus) go on to develop multiple sclerosis. Although none have been conclusively proven, viruses other than Epstein-Barr virus have been proposed as possible causes of multiple sclerosis or of disease activity associated with multiple sclerosis[4].

The human leukocyte antigen (HLA) gene cluster corresponds to the main genetic risk factor, and HLA-DRB1 in the class II area confers the highest risk. Since MHC class II proteins primarily serve to deliver peptide ligands to CD4+ [64TD$DIF] lymphocytes, it is thought that these T cells play a significant pathogenic role in multiple sclerosis. Nonetheless, polymorphism areas linked to protection against multiple sclerosis can be found in the MHC class I cluster, which controls cytotoxic lymphocyte responses[14].

Major Histocompatibility Class II (MHC II) alleles are one of the genetic variables that influence the development of multiple sclerosis (MS). Some of these alleles enhance susceptibility, such as human leukocyte antigen (HLA) DRB1*15:01, while others decrease susceptibility. Similarly, some MHC I alleles (such HLA A*02.01) seem to be protective, whereas others make people more susceptible. The majority of the more than 100 genes that have been linked to the development of multiple sclerosis are involved in immune system function, including lymphocyte and antibody activity[15].

Bacteria like *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, enterotoxins produced by *Staphylococcus aureus* that act as superantigens, viruses of the herpes virus (Epstein-Barr virus and human herpesvirus 6) and human endogenous retrovirus (HERV) families, and the protozoa *Acanthamoeba castellanii* are among the pathogens linked to the onset or aggravation of multiple sclerosis. This evidence has led to the proposal of a potential viral etiology for MS, which is still causing a great deal of research in the area (Tables 1 and 2)[16].

The Viral Pathophysiology of Multiple Sclerosis

The importance of viral infections in the etiology of multiple sclerosis is supported by strong experimental and clinical evidence. It is conceivable that the neuronal and inflammatory processes associated with multiple sclerosis begin years before the realization of radiological and clinical symptoms. Since viral agents can trigger the dysimmune process through a variety of mechanisms, including molecular mimicry, bystander activation, epitope spreading, autoreactive immune cell survival and immortalization, and regulome modifications, they are good candidates to uncover the disease in this context.

It has long been believed that virus infections contribute to the development of multiple sclerosis (MS)[17]. The most plausible candidate for a causal virus, EBV, has been the subject of the majority of study; however, as will be detailed below, other viruses may possibly be involved. Although a clear cause-and-effect link has not been established, the presence of viral nucleic acid, protein, or antiviral antibodies in blood, cerebrospinal fluid, or brain tissue has raised the possibility that viral agents may be involved. A number of viruses have also been directly linked to multiple sclerosis. Virus infections may cause multiple sclerosis (MS) in a variety of ways and combinations[18].

Viral infection and multiple sclerosis have a complicated relationship. Despite coming from distinct families, these viruses are all capable of altering host gene expression, which may result in inflammation, myelin damage, and immunological dysregulation. All of these viruses have a DNA phase or DNA viruses, which are able to penetrate the blood-brain barrier (BBB) and cause chronic infections that last a lifetime.

HUMAN VIRUSES AND MULTIPLE SCLEROSIS

A huge body of evidence suggests that viral infections promote MS; however, no single causal virus has been identified due to the complexity and heterogeneity of MS it is possible that more than one viral agent is involved (Table 3)[19].

1. Epstein–Barr virus (EBV): Approximately 95% of people worldwide are seropositive with EBV, but nearly all MS patients are seropositive[20]. Additionally, the incidence of MS is greatly increased by a history of infectious mononucleosis, and CSF-restricted EBV-specific oligoclonal bands (OCB) have been seen in a subgroup of MS patients, however the specificity of these results is still up for question[21]. Accordingly, it has been proposed that EBV would save ”forbidden” memory B cells that are targeted at a central nervous system epitope. The idea that EBV memory B cells would maintain the identification of the ”forbidden” epitope but lose the episomic EBV DNA upon replication, potentially triggering a molecular mimicry mechanism, has been proposed as an explanation for the inconsistent detection of EBV in MS lesions[22]. To further explain the link between EBV infection and multiple sclerosis, a ”two hit hypothesis” has been developed. According to this theory, after the initial infection, EBV would interfere with BBB permeability, allowing activated immune cells to enter the central nervous system and causing a series of events that would ultimately result in CNS inflammation.

2. Human herpesvirus 6 (HHV-6): Since 1993, there have been numerous research that have focused on the possible link between HHV-6 and MS. There are two types of HHV-6 that share 95% homology: HHV-6 A and HHV-6 B[23]. Exanthema subitum and the majority of other symptomatic infections in infancy are caused by HHV-6B, which can thereafter develop latency. Although other researchers did not corroborate this association, a significant number of studies, as compiled by Virtanen and Jacobson in 2020, have shown a connection between HHV-6 and

MS, either by direct DNA detection in MS lesions or by elevated antiviral antibody titres in MS patients. A molecular mimicry mechanism may be involved, as evidenced by the cross-reactivity of autoreactive T-cells with MBP and the sequence homology between HHV-6 protein U24 and myelin basic protein.

Numerous investigations have linked clinically active multiple sclerosis to peripheral detection of HHV-6 or an immune response to HHV-6; associations between HHV-6 antibodies and the probability of an MS relapse or the progression of the disease have been documented across a range of geographic populations. According to other research, demyelinated plaques in MS brains exhibit larger quantities of viral DNA and mRNA, indicating increased HHV-6 expression in comparison to controls[24].

3. Human endogenous retroviruses (HERVs): According to de la Hera and Urcelay (2016)[25], MS has been linked to the presence and/or activation of three HERVs (HERV H, HERV K, and HERV W), which were integrated into the human genome millions of years ago. The results would imply that HERV activation could cause a demyelination process, which would aid in the progression of MS. Although viruses like VZV, HSV-1, EBV, and HHV-6 are among the triggers that can activate HERVs, the most extensively researched relationship is with EBV. Given the high prevalence of EBV positivity in MS and the fact that the HERV W MS-associated retrovirus (MSRV) is activated during infectious mononucleosis, it is plausible that MSRV activation may function as an effector in MS, induced by latent EBV infection.

4. Measles, Rubella and Varicella Zoster (VZ) viruses: Measles, Rubella, and VZ viruses (MRV) have been shown to be the most common component of the intrathecal polyspecific humoral response of MS patients, which can be helpful in diagnosing MS[19]. Additionally, a VZV infection is linked to an increased risk of MS. Despite various attempts to examine VZV neurotropism, there are currently no suitable animal models for the study of a function in MS.

It has also been proposed that other viruses, such as RuV, MuV, MeV, CMV, HHV6, VZV, John Cunningham Virus (JCV), and Human Endogenous Retrovirus W (HERV-W), either alone or in conjunction with EBV infection, contribute to MS[26]. A more active involvement for the viruses may be reflected in this, or it may simply reflect a viral Ag-induced reactivation and stimulation of EBV-infected B cells with specificity for the virus(es) in question.

5. SARS-CoV-2: Other coronaviruses that have also been often isolated in the brains and cerebrospinal fluid (CSF) of MS patients have also been shown to have the neuroinvasive capability of SARS-CoV-2[27]. Pericytes and astrocytes in the blood-brain barrier could be SARS-CoV-2 entrance sites. The neuroinflammatory processes for neurological involvement are being identified through omics investigations on brain samples from COVID-19 patients. Interactions with long-studied MS-associated pathogens, such as the Human Endogenous Retroviruses (HERVs) and the Herpesviridae members Epstein Barr Virus and Human Herpes Virus 6 (HHV-6), may support indirect pathways through which SARS-CoV-2 infection may disrupt the course of MS.

The novel coronavirus SARS-CoV-2 has recently complicated the association between chronic viral infection and multiple sclerosis (MS), as its severity of infection is largely dependent on the host's reaction to infection, which mirrors some characteristics of MS pathobiology[28]. Bellucci et al. examine the neuroinflammatory and demyelinating mechanisms linked to COVID-19, review the pathophysiological crosstalk between MS and SARSCoV-2 infection, and look into SARS-CoV-2 vaccination in relation to MS. They do this by closely examining an 18-month period of the SARS-CoV-2 pandemic through the lens of multiple sclerosis.

Table 1: Summary of reported associations between Pathogens and MS

S. No.	Type of pathogen	Pathogen	Reference
1	Bacteria	*Mycoplasma pneumoniae, Streptococcus pneumoniae, Chlamydia pneumoniae Staphylococcus aureus, Mycobacterium avium*, subspecies paratuberculosis (MAP)	Jessica Frau, et al (2021)[29]
2	Virus	Herpes viruses Epstein–Barr virus human herpesvirus 6 (HHV 6) human endogenous retroviruses (HERV), Measles, Rubella and Varicella Zoster (VZ) viruses Cytomegalovirus (CMV), John Cunningham virus (JCV) Rubella virus (RuV), Mumps virus (MuV), Measles virus (MeV)	Donatella Donati (2020)[19], Rachael et al (2020)[30]
3.	Protozoa	*Acanthamoeba castellanii*	Libbey et al, 2014[31]

GUT-BRAIN AXIS AND MS

The gut microbiota, comprising over 100 trillion microbes, can impact the central nervous system (CNS) through bidirectional communication between gut and brain. Gut metabolites, end products of the microbiota's metabolism, can affect CNS pathways and regulatory functions, playing a role in neuroinflammatory, neuropsychiatric, and neurodegenerative disorders like Parkinson's, ASD, AD, and MS. Dysbiosis refers to changes in gut microbiota balance, resulting in pathogenic bacteria over beneficial ones, pro-inflammatory effects, compromised gut barrier, systemic inflammation, and association with MS[32].

Table 2: Mechanisms of microbe mediated MS

S. No.	Mechanism of viral infections in MS	Description
1.	**Direct toxicity**	Despite clinical and experimental evidence supporting an autoimmune pathogenetic mechanism for the development of multiple sclerosis, the detection of cellular damage unrelated to inflammation or autoimmunity does not rule out the possibility of a direct viral toxic mechanism on actively infected neural cells.
2.	**Molecular mimicry**	Molecular mimicry is the process by which homologous viral sequences or structurally similar peptides can trigger an immune cross-reaction against myelin components by presenting them to autoreactive CD4 + T cells via major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs). It has been shown that some viruses cause MS, at least partially, via this method.
3.	**Dual T cell receptor (TCR)**	Contrary to earlier theories, it has been shown that T cells can carry multiple TCRs. This means that some T cells may carry two distinct TCR combinations, one for each of the viral and myelin antigens, and that when activated, they would react against both antigens.
4.	**Bystander activation**	Bystander activation suggests that a viral infection may cause tissue damage, which may lead to the release and presentation of hidden autoantigens by APCs as well as the generation of new autoreactive T cells and plasma cells, so triggering an overreactive inflammatory response.
5.	**Epitope spreading**	When myelin-producing cells are damaged by the methods shown above, myelin fragments are released into the inflammatory environment, which leads to a self-sustaining breakdown of myelin and the identification of further epitopes. Lehman et al. initially described this mechanism, which has been examined in TMEV-IDD and is referred to as epitope spreading.

Table 3: Subtypes of herpes virus

S. No	Type of herpes virus known to be human pathogens	Examples
1.	Alpha	Varicella-zoster virus (VZV),
2.	Beta	Cytomegalovirus (CMV), Human herpesvirus (HHV-6)
3.	Gamma	Epstein-Barr virus (EBV)

Gut microbiota produces three main metabolites associated with CNS health: short-chain fatty acids (SCFAs), aromatic amino acids (AAA), and trimethylamine N-oxide (TMAO).

SCFAs, produced from non-digestible carbohydrates like starch, can alter brain functions by inhibiting neuroinflammation and reducing pro-inflammatory cytokines. They also act as ligands for immune cells, modulating pro-inflammatory cytokine secretion[33].

AAA, consisting of tryptophan, phenylalanine, and tyrosine, is crucial for the microbiome gut-brain axis and precursors to neurotransmitters, impacting brain health, such as serotonin, vitamin B3, indole, and redox co-factors such as $NAD(P)^+$[34] [34] and dopamine, epinephrine, and norepinephrine[35].

TMAO, a gut metabolite, can cause dementia due to CD68 expression induction, neuronal aging, oxidative stress, and mitochondrial dysfunction[36]. Consumption of L-choline-rich foods can increase astrocyte activation and pro-inflammatory cytokines[37].

MECHANISM OF GUT MICROBIOME INDUCED MS PATHOGENESIS

In a healthy gut, intestinal epithelial cells barrier (IECs) hides gut microbiome from host immune response. However, several external agents such as antibiotics and other dietary habits cause changes in gut microbiome- dysbiosis. Dysbiosis can lead to breakage of intestinal epithelial cells barrier, which cause release of harmful toxins and pathogenic bacteria enrichment in the peripheral circulation. Recognition of this metabolites, pathogen-associated molecular patterns, contribute to systemic inflammation[38].

Proteobacteria, such as *Proteobacterium*, produce pro-inflammatory cytokines like LPS, which interact with CD14 and TLR4/MD-2, activating the immune cells to releasing cytokines. Gut bacteria, particularly *Bacteroides vulgatus*, induce pro-inflammatory endotoxin tolerance by binding to the MD-2/TLR4 receptor complex. Gut dysbiosis can alter microorganism makeup, impacting the immunological effects of LPS and potentially causing MS[39].

Leaky gut

Gut dysbiosis alters gut microbiota, leading to increased harmful metabolites and pro-inflammatory cytokines, breaking the intestinal epithelial barrier, and reducing anti-inflammatory factors. Increased intestinal permeability activates immune cells, transferring toxic compounds into the bloodstream. Leaky gut is predisposing to neurological conditions like schizophrenia and Crohn's and is correlated with elevated gut permeability and high pro-inflammatory cytokines[40]. MS patients exhibit elevated gut permeability and high levels of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, which are linked to leaky gut[41].

Microbiome triggered Pro-inflammatory T cells

MS is believed to be caused by self-reactive CD4+ T helper cells, with Th17 cells being the most implicated lineage. Gut microbiota, including *Acinetobacter calcoaceticus* and *Akkermansia muciniphila*, can stimulate Th17 induction and pro-inflammatory activities, leading to the development or progression of MS[42].

Pro-inflammatory B cells activation by Microbiota

Over 90% of MS patients have positive IgG oligoclonal bands in their cerebrospinal fluid, indicating abnormalities in immunoglobulins due to B cell infiltration. The gut microbiota's impact on pathogenic B cell responses is controversial, but B cells' anti-inflammatory function in multiple sclerosis has been clarified. IgA+ plasma cells exhibit selectivity for MS-associated immunostimulatory bacterial strains and can pass the blood-brain barrier during active multiple sclerosis[43].

Treg cells activity Modulation by Microbiome

Research on germ free (GF) mice has shown a link between the immune system and gut microbiota in immune disease development. GF mice show weakened MS, decreased pro-inflammatory cytokines, and increased regulatory T cells. Early antibiotic administration disrupts gut microbiota, leading to stronger immune response[44].

When compared to healthy controls, the gut microbiota of MS patients exhibits considerable changes in some microbial taxa, indicating the importance of the gut microbiota in the development of MS. When comparing the microbiota of MS patients in the relapse phase to that of healthy subjects or MS patients in remission, the 16S ribosomal RNA sequencing revealed a decrease in phylum Bacteroidetes, including Bacteroides and Parabacteroides species, and an increase in phylum Firmicutes, including *Dorea* and *Blautia* species[42].

Additionally, compared to controls, MS patients had higher levels of *Streptococcus mitis* (*S. mitis*) and *Streptococcus oralis* (*S. oralis*), both of which promote the differentiation of Th17 cells, and lower levels of *Prevotella*, a member of the Bacteroidetes phylum, which generates the anti-inflammatory propionate. Both *Prevotella* and *Clostridium*, which is associated with Th17 cell proliferation and increases the production of IL-10 (the anti-inflammatory cytokine) and Treg cells in peripheral compartments, were less common in Relapsing-remitting multiple sclerosis (RRMS) patients[45].

The symbiont *Bacteroides fragilis* (SBF), a short filamentous bacterium that is part of the gut microbiota, promotes neurological inflammation by activating macrophages and producing metabolites that aid in the synthesis of IL 23. Additionally, SBFs function as APCs that cause T cells to differentiate into Th17 cells[46]. Collectively, these studies show that the gut microbiota directly influences the pathogenic process of multiple sclerosis by regulating Th17 proliferation at the intestinal level (Figure 1)[47].

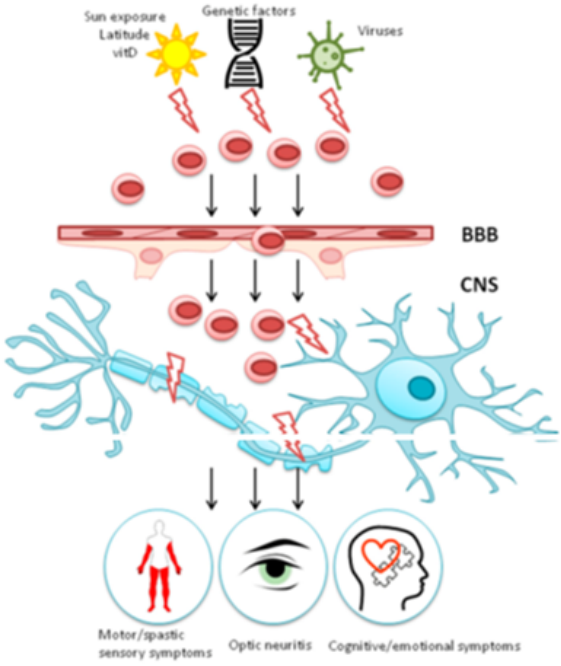

Fig. 1: Pathogenesis of MS. [Copyright Rachael Eugenie Tarlinton 2019]

THERAPEUTIC APPROACHES

The "disease modifying therapies" (DMTs) have expanded the therapeutic arsenal. These include cytokine therapies (like the interferons Anovex and Betaferon), small molecules (like teriflunomide, dimethyl fumarate, and fingolimod), and certain monoclonal antibodies (like alemtuzumab, anti-CD52; daclizumab, anti-CD25; natalizumab, anti-α4-integrin) that are immunomodulatory in RR-MS instead of

being etiologically driven[48].

Targeted treatments that modulate the composition of the gut microbiota to make it "healthier" remain a viable therapeutic option. Many methods are used to modify gut microbiota and show promise in MS, including faecal microbiome transplantation (FMT), probiotics, synbiotics, and diet. It has been shown that adding *Prevotella histicola* to food reduces inflammation and demyelination in the brain just as well as COPAXONE®[46].

CONCLUSION

Recent literature links microbial infections to neurodegenerative diseases like Alzheimer's, Parkinson's, and Alzheimer's Disease. However, the molecular and cellular mechanisms behind these associations remain unclear. Patients with neurodegenerative diseases may be at increased risk of infection with neurotropic agents due to compromised immune systems or leaky BBB. Further research using *in vitro* and *in vivo* models will help understand post-infectious neurologic and cognitive dysfunction.

Conflict of Interest

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