International Journal of Frontiers in
Science and Technology Research
Journal homepage: https://frontiersrj.com/journals/ijfstr/
ISSN: 2783-0446 (Online)

(REVIEW ARTICLE)

Check for updates

Prevalence of viral infections in MS and ALS

AISWARYA LAKSHMI A G [1,*], ATHIRADHA SB [2], FIDHA AV [2], ANJU PAUL [2] and MAHSHU MOOSA AP [2]

[1] *Assistant Professor, Department of pharmacology, Kerala University of Health Sciences, College of pharmaceutical sciences, Government medical college Kannur, Kerala, India.*
[2] *VII semester B Pharm student, Kerala University of Health Sciences, College of pharmaceutical sciences, Government medical college Kannur, Kerala, India.*

International Journal of Frontiers in Science and Technology Research, 2024, 06(01), 019–033

Publication history: Received on 03 December 2023; revised on 02 February 2024; accepted on 05 February 2024

Article DOI: https://doi.org/10.53294/ijfstr.2024.6.1.0022

Abstract

Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are neurological diseases with complex etiologies, involving both genetic and environmental factors. Evidence suggests that viral infections may play a role in pathogenesis of these diseases. This review aims to summarize the current understanding of the prevalence of viral infections in MS and ALS. In MS, several viruses have been implicated, including Epstein-Barr virus, human herpesvirus 6, and varicella-zoster virus. Studies have reported elevated antibody titers against these viruses in MS patients compared to controls, suggesting a potential association between viral infections and MS risk. viral infections have been linked to MS relapses and disease progression, indicating a possible role in disease activation. In ALS, viral infections as enteroviruses and retroviruses have been investigated as potential triggers or contributors to disease pathogenesis. While the evidence linking viral infections to ALS is less robust than in MS, studies have reported associations between specific viral infections and ALS progression. Understanding the prevalence of viral infections in MS and ALS is crucial for unraveling the complex interplay between viruses and the immune system in these diseases. Further research is needed to elucidate the mechanisms by which viral infections may influence disease development and progression in MS and ALS, which could lead to the development of novel therapeutic strategies targeting viral pathways in these neurological disorders. This review briefly discusses the epidemiology and pathophysiology related alterations of Multiple sclerosis and Amyotrophic lateral sclerosis, and their immune responses highlighting the viral infections associated with these diseases.

Keywords: Multiple sclerosis; Amyotrophic lateral sclerosis; Neurodegeneration; Measles virus; Herpes virus; Retro virus

1. Introduction

The progressive decline in structural integrity or coordinated function of neurons leads to neurodegenerative diseases, wherein neuronal damage may eventually result in cell death, posing a significant global health challenge. Examples of neurodegenerative diseases encompass Amyotrophic lateral sclerosis, Multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, among others [1].

Multiple sclerosis (MS) is an autoimmune disorder impacting the central nervous system, causing inflammation and damage to the myelin sheath of nerve fibers. On the other hand, amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease primarily affecting motor neurons in the brain and spinal cord, leading to their gradual degeneration and eventual loss. Despite both being neurological disorders, MS and ALS exhibit notable differences. MS manifests with symptoms such as fatigue, numbness or tingling, muscle weakness, visual abnormalities, and a lack of coordination and balance [2]. In contrast, ALS is characterized by muscle weakness, stiffness, and eventual paralysis.

* Corresponding author: AISWARYA LAKSHMI A G

MS follows a relapsing-remitting course, where symptoms may flare up and then partially or completely improve, while ALS typically progresses relentlessly, resulting in a gradual loss of motor function. The exact cause of MS is unknown, but it is thought to involve a combination of genetic and environmental factors, including an autoimmune component. ALS may have a familial component in some cases. MS primarily affects young adults aged 20 to 40 [3,] whereas ALS does not show a specific age pattern but predominantly occurs sporadically without known genetic factors after the age of 40. Women are twice as likely as men to develop MS, while men have a higher risk of developing ALS compared to women.

Multiple sclerosis (MS) is an autoimmune-mediated condition affecting the central nervous system, encompassing the brain and spinal cord. It has the potential to result in significant physical or cognitive disability and is currently the most prevalent neurological disorder. On the other hand, Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a neurological ailment that damages motor neurons—the nerve cells responsible for voluntary muscle movement in the brain and spinal cord. Although the precise underlying cause of ALS remains unknown, researchers believe it may stem from a combination of genetic mutations and environmental factors. In MS, the immune system targets and damages the protective myelin sheath covering nerve fibers, leading to communication breakdown between the brain and other parts of the body. Consequently, the disease can cause irreversible deterioration of nerve fibers, with signs and symptoms varying widely among patients based on the location and severity of nerve fiber damage. Typical symptoms include numbness or weakness in one or more limbs, tingling, and electric-shock sensations triggered by certain neck movements, as well as a lack of coordination. Affected areas often include the optic nerve, brain (cerebrum), brain stem, cerebellum, and spinal cord [4].

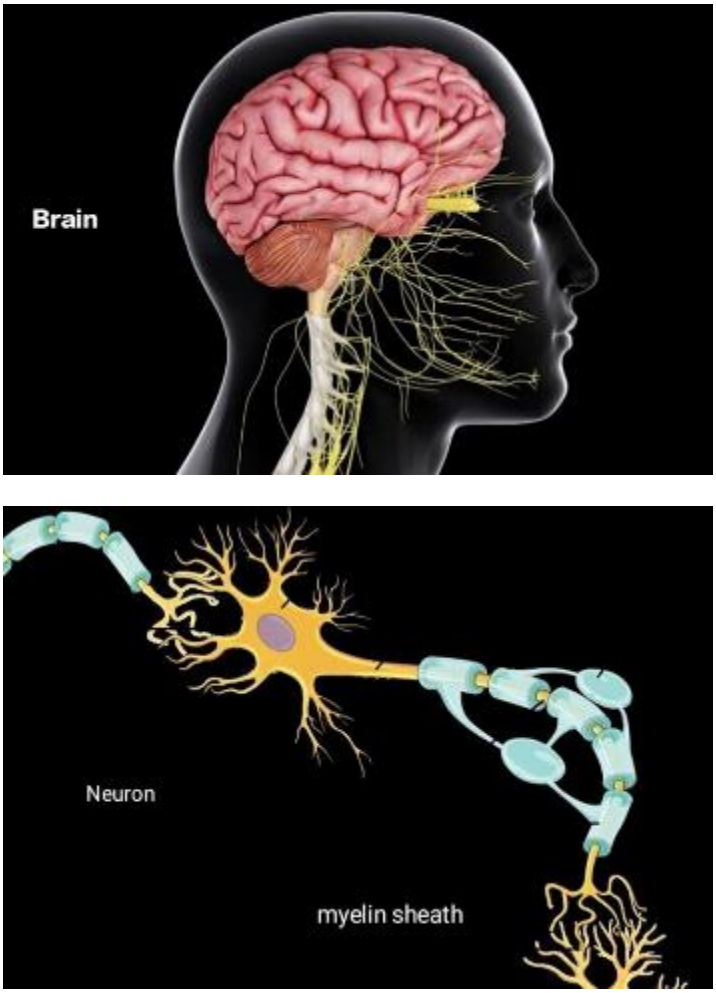

Figure 1 Areas of the CNS often affected by MS

The symptoms of ALS start as muscle twitches in the arm, leg, shoulder also tongue, muscle cramps, slurred and nasal speech. As the stage progress, muscle weakness and atrophy spread throughout body then worsen that he/she will not be able to, stand or walk, get in or out of bed by themself or even move their hands [5]. ALS usually associated with

dysphagia, dysarthria, dyspnea etc. [6] are **Mainly affecting parts** are upper motor neurons, lower motor neurons, corticospinal tract and bulbar neurons [3].

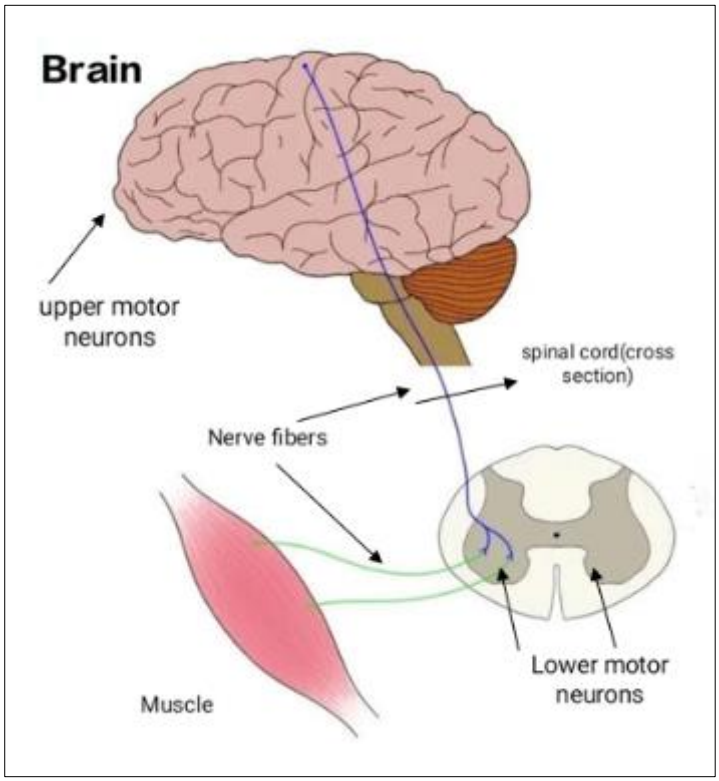

Figure 2 Areas of the CNS often affected by ALS

2. Epidemiology

Multiple sclerosis affects approximately 2.8 million people worldwide, with an estimated incidence of 35.9 cases per 100,000 population. Since 2013, there has been a noticeable increase in MS cases in India. Among those affected, female young adults are twice as likely to live with MS as males, and the average age of diagnosis is 32 years [7].

Amyotrophic lateral sclerosis (ALS) is categorized into two main types: sporadic and familial. The majority, 90 to 95%, of ALS cases are sporadic, while the remaining cases are familial. ALS has an estimated annual incidence of 1.75-3 cases per 100,000 persons and a prevalence of 10-12 cases per 100,000 in Europe, although significant geographical variations exist. ALS shows a higher prevalence among males than females, and the average age at onset of symptoms is 58-63 years for sporadic ALS and 40-60 years for familial ALS [6].

3. Pathophysiology of MS and ALS

The pathophysiology of multiple sclerosis (MS) primarily involves the central nervous system (CNS), where two fundamental processes contribute to the general pathological manifestations observed in MS patients [8]

- Focal Inflammation and Plaque Formation: - Focal inflammation leads to the development of macroscopic plaques, causing damage to the blood-brain barrier (BBB). These plaques, occurring in waves throughout the disease course, result from inflammation, demyelination, axonal injury, axonal loss, and edema. These lesions, known as plaques, are found in various CNS locations, including the brain, spinal cord, white matter around ventricles, optic nerves, tracts, corpus callosum, cerebellar peduncles, long tracts, and subpial regions of the spinal cord and brain stem, as well as in the grey matter.
- Neurodegeneration and Microscopic Injury:- Microscopic injury involves different axons, neurons, and synapses in the CNS, contributing to neurodegeneration.

The combined effects of focal inflammation and neurodegeneration result in both macroscopic and microscopic injuries.

Lesions, referred to as plaques, exhibit a wave-like occurrence throughout the course of the disease in both multiple sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS). These plaques result from focal inflammation and are characterized by a combination of inflammation, demyelination, axonal injury, axonal loss, and edema, all of which contribute to the pathology of the plaques.

In MS, these plaques are primarily located in the brain and spinal cord. They are found in the white matter around the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, subpial region of the spinal cord, and the brain stem. Importantly, plaques can also manifest in the grey matter [3].

However, despite some similarities in the manifestation of lesions, the pathophysiology of MS and ALS diverges significantly. ALS pathophysiology is characterized by damage to lower motor neurons, specifically in the bulbar motor nuclei and the spinal anterior horn. This distinction underscores that the pathological and physiological cascades involved in the development of MS and ALS are distinct and should not be viewed as a single entity. The unique features of each condition involve different regions of the nervous system and necessitate specific considerations in understanding their respective pathophysiological processes [9].

3.1 Motor neuron damage

In Amyotrophic Lateral Sclerosis (ALS), the disease initially targets the motor neurons, which are nerve cells responsible for controlling voluntary muscle movements. As ALS progresses, these motor neurons undergo a gradual degeneration that ultimately leads to their death. This degeneration results in a loss of the ability to control voluntary muscle movements [10].

Conversely, during a multiple sclerosis (MS) attack, the immune system becomes activated, leading to inflammation along the nerves. This inflammation then progresses to affect glial cells. The manifestation of MS commonly includes muscle weakness associated with visible wasting. The immune system's inflammatory response disrupts the normal functioning of nerves, leading to a range of symptoms, including muscle weakness and atrophy. Both ALS and MS involve complex processes that affect the nervous system but differ in their specific mechanisms and outcomes [11].

3.2 Glutamate excitotoxicity

In the context of Amyotrophic Lateral Sclerosis (ALS), one of the proposed mechanisms involves the heightened activity of the neurotransmitter glutamate [12]. The rate of glutamate release is found to be elevated, leading to the activation of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and voltage-gated calcium channels. This receptor activation, coupled with an excess of glutamate, can overstimulate nearby neurons, causing a lethal influx of extracellular calcium. This process is known as excitotoxicity and contributes to the damage and death of neurons in ALS [13].

In Multiple Sclerosis (MS), a similar mechanism involving excitotoxicity occurs. However, in MS, the AMPA/kainite type of glutamate receptors is activated, leading to an excess influx of calcium. This severe glutamate excitotoxicity not only damages neurons but also affects the myelin-producing cells of the central nervous system, specifically the oligodendrocytes. This dual impact on both neurons and oligodendrocytes contributes to the complex pathophysiology of MS, involving disruptions in both nerve cell function and myelin integrity [14].

3.3 Oxidative stress

In Amyotrophic Lateral Sclerosis (ALS), patients often experience a disturbance in the balance between the production of harmful reactive oxygen species (ROS) and the body's natural mechanisms to counteract them through the release of antioxidants. This imbalance results in oxidative stress, a condition that can contribute to neuronal damage in ALS [15].

Similarly, in Multiple Sclerosis (MS), there is evidence of excessive reactive oxygen species at the affected sites. Accumulating research suggests that oxidative stress plays a substantial role in the pathogenesis of MS. A random-effects meta-analysis has demonstrated that individuals with MS exhibit significantly increased concentrations of blood oxidative stress markers compared to healthy control subjects. Specifically, markers such as malondialdehyde (MDA) and lipid hydroperoxide by tert-butyl hydroperoxide-initiated chemiluminescence (CL-LOOH) are found at elevated levels in MS patients. Conversely, concentrations of albumin, an antioxidant, are significantly decreased in MS patients compared to healthy controls [16]. These findings highlight the involvement of oxidative stress in both ALS and MS, underscoring its potential as a contributing factor to the progression and pathology of these neurological disorders[15].

3.4 Protein misfolding

In Amyotrophic Lateral Sclerosis (ALS), various abnormal protein aggregates are commonly found in the neurons of affected individuals. The aggregation abnormality often involves misfolding, particularly in the protein TDP-43. These misfolded proteins can disrupt cellular functionalities and may even trigger inflammatory responses. The accumulation of misfolded proteins is a characteristic feature of ALS pathology, contributing to the neurodegenerative process [17].

Similarly, in Multiple Sclerosis (MS), a new study suggests that the disease appears to be a transmissible protein misfolding disorder, similar to Alzheimer's and Parkinson's diseases. The study proposes that MS may even be caused by prions, which are misfolded proteins with the ability to induce the misfolding of normal proteins. The pathogenic basis of many neurodegenerative diseases, including MS, involves the disruption of protein homeostasis (proteostasis) at various levels, leading to protein misfolding. Misfolded proteins tend to aggregate and accumulate, triggering neurotoxicity through cellular stress pathways and ultimately causing neurodegenerative diseases [18].

The unfolded protein response (UPR) is a cellular mechanism that responds to endoplasmic reticulum (ER) stress resulting from the accumulation of unfolded or misfolded proteins. In MS, the UPR is activated, and it comprises three signaling pathways that initially promote cytoprotective functions to correct ER stress. However, if ER stress cannot be resolved, the UPR may lead to apoptosis, or programmed cell death, in affected cells. The UPR is recognized as an important feature in various human diseases, including MS, highlighting the significance of protein homeostasis in the pathophysiology of these conditions.

3.5 Mitochondrial dysfunction

Mitochondria, the energy-producing organelles in cells, play a crucial role in maintaining cellular function, particularly in energy production through oxidative phosphorylation. Dysfunction in mitochondria can have significant consequences, leading to reduced energy production. In the context of neurological disorders like Multiple Sclerosis (MS), several independent investigations have indicated abnormalities in mitochondrial function. In MS, there is evidence of mitochondrial respiratory chain deficiency, suggesting impaired function within the electron transport chain responsible for energy production. Additionally, abnormalities in mitochondrial transport have been observed. Mitochondria rely on proper transport within the cell to reach areas with high energy demands. Any disruption in these processes creates an energy imbalance, contributing to progressive neurodegeneration and irreversible disability in individuals with MS.

The compromised mitochondrial function can result in a reduced capacity to generate adenosine triphosphate (ATP), the primary energy currency of cells. This energy deficit affects the ability of motor neurons to function and survive, exacerbating the neurodegenerative processes seen in MS. Understanding the role of mitochondria in MS pathology provides insights into potential therapeutic targets aimed at preserving mitochondrial function and mitigating the impact of energy imbalance in the context of the disease [19] .

Mitochondrial dysfunction has been implicated as playing a role in motor neuron death in ALS. Fragmentation of mitochondria and changes in mitochondrial morphology and expression of fusion/fission proteins are well described in ALS and have pronounced effects on normal mitochondrial function. Defective mitochondrial transport may be responsible for the accumulation of abnormal mitochondria in motor neuron axons seen in animal models of ALS and also in human patients [20].

3.6 Neuroinflammation

In the context of Amyotrophic Lateral Sclerosis (ALS), inflammation is a part of the body's response to injury. The immune system within the central nervous system (CNS) can become stimulated, along with the activation of glial cells, impacting the blood-brain barrier (BBB). This stimulation results in the release of various inflammatory mediators such as interleukin-2 (IL-2), gamma interferon, tumor necrosis factor, and others. The ongoing response can progress to chronic inflammation, leading to further neuronal damage in ALS [21] .

In the case of Multiple Sclerosis (MS), the disease disrupts the flow of information between the brain or spinal cord and the rest of the body. MS presents with individual variations in its development. Immune cells are continually at work within the brain, including resident immune cells performing routine maintenance, and immune cells from the periphery that cross the immune barrier to carry out "immune surveillance." In MS, both types of immune cells can become aggressive and malfunction. T-cells, antibody-producing B-cells, and other immune cells crossing the blood-brain barrier may launch attacks on the brain and spinal cord. Inside and outside the CNS, B-cells release substances known as cytokines that trigger inflammation, contributing to the pathology of MS. Understanding these immune-

mediated processes is crucial for comprehending the complexity of ALS and MS and developing targeted therapeutic approaches [22].

3.7 Genetic factor

Approximately 10% of Amyotrophic Lateral Sclerosis (ALS) cases have a familial (genetic) component. Over 40 genes have been identified in connection with ALS, and four of these—c9orf72, SOD1, TARDBP, and FUS—account for up to 70% of individuals with familial ALS. The most common genetic cause of familial ALS is a hexanucleotide repeat expansion in the c9orf72 gene, located on chromosome 9. In this mutation, a six-letter repeated segment (GGGGCC) within the gene is expanded. The healthy version of the gene typically has about six of these hexanucleotide repeat units, while the disease-causing mutation can involve hundreds to thousands of repeats. Another example is the SOD1 mutation, known as A4V, which changes the fourth amino acid in the protein from alanine to valine [23].

On the other hand, Multiple Sclerosis (MS) is not directly inherited, but individuals with a family history of the condition are more likely to develop it. The estimated chance of a sibling or child of someone with MS also developing the condition is around 2 to 3 in 100. The predisposition to MS is consistent with a polygenic model, where multiple genes contribute to disease susceptibility. Major histocompatibility complex (MHC) and T-cell receptor (TCR) gene associations with MS are relatively weak, and despite intensive research, no other definitive "MS genes" have been firmly established. The analysis of TCR rearrangements in brain lesions has helped identify a major target of the immune response in MS, contributing to our understanding of the immunogenetics of the disease [24].

3.8 Motor neuron death

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the selective death of motor neurons in the motor cortex, brainstem, and spinal cord. Excitotoxicity is considered to play a role in the selectivity of motor neuron death. Excitotoxicity is a phenomenon where the normal glutamate-mediated communication between neurons is disrupted, leading to abnormal activation of glutamate receptors and, ultimately, neuronal death [11].

In the case of Multiple Sclerosis (MS), both electrophysiological and morphological analyses indicate a significant loss of lower motor neurons. Dying spinal motor neurons are often observed to be surrounded by CD3+ (CD4+ as well as CD8+) T cells expressing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). This observation suggests an immune-mediated attack on motor neurons in MS. Interestingly, studies with different variants of experimental autoimmune encephalomyelitis (EAE), a widely used animal model for MS, have shown a similar degree of damage and immune attack. However, lower motor neurons were preserved in adoptive transfer EAE induced with TRAIL-deficient T-lymphocytes. This suggests a potential role of TRAIL in the immune-mediated attack on motor neurons in the context of MS [11].

4. Immune Responses in MS and ALS

In Multiple Sclerosis (MS) research, the murine Experimental Autoimmune Encephalomyelitis (EAE) model has made a significant contribution. This model has demonstrated myelin-reactive T cells, drawing considerable attention to cellular immunity in MS. Traditionally considered a Th1-driven disease, MS involves inflammatory Th1 cells that produce cytokines such as interleukin-2 (IL-2), gamma interferon, and tumor necrosis factor alpha. These cells also induce antibody switching from IgM to IgG2a and IgG3. On the other hand, Th2 cells, known for their anti-inflammatory role, secrete IL-4, IL-5, IL-10, and transforming growth factor beta1, playing a crucial role in stimulating antibody production. Most studies on the role of T cells in MS have focused on myelin-activated peripheral T cells restricted by major histocompatibility complex (MHC) class 2 molecules. Myelin basic protein (MBP) has been the primary and extensively studied myelin protein associated with MS. Other myelin proteins, including proteolipid protein (PLP), MOG, myelin-associated glycoprotein (MAG), and myelin-associated oligodendrocytic basic protein, have also been suggested as potential autoantigens in MS [25].

In Amyotrophic Lateral Sclerosis (ALS), increased levels of circulating chemokines and cytokines have been observed. Patients with a shorter diagnostic delay, indicating more severe rapidly progressing disease, exhibit higher levels of the chemokine MCP-1. The expression of the MCP-1 receptor (CCR2) is decreased on circulating monocytes in ALS. Elevated levels of IL-17 are found in the serum of subjects with ALS. Additionally, levels of IL-6 are increased in ALS, particularly in subjects with hypoxia, suggesting that the elevation is likely a response to hypoxia rather than a direct consequence of the disease itself. These observations contribute to our understanding of the inflammatory and immune components involved in the pathophysiology of ALS [26].

5. Viral infections associated with MS and ALS

A prolonged viral infection in both animal models and humans can lead to damage to the central nervous system (CNS) and the stripping away of myelin, either presenting as a persistently progressive condition or as a course marked by periods of relapse and remission after an extended incubation period. The manifestation of the disease is influenced by diverse mechanisms triggered by these viruses, acting in conjunction with an individual's unique genetic background. Consequently, various forms of the disorder may arise due to the interplay between viral factors and genetic predispositions in different individuals [25]. Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are considered complex and multifactorial diseases, involving a combination of genetic and environmental factors in their development. While the primary understanding revolves around genetic predispositions and environmental influences, it's acknowledged that viral infections may play a role in certain cases. The intricate interplay of these factors contributes to the complexity of both MS and ALS, and ongoing research aims to unravel the specific mechanisms and interactions that lead to the manifestation of these neurological disorders [27].

5.1 Measles virus

It is the ability of measles virus to induce post infectious encephalomyelitis (PIE) as well as chronic, progressive neurologic disease. circulating anti-measles virus antibodies may persist for decades after primary infection suggesting a continuous low grade viral persistence or a cross reactive immune response. CSF samples from MS patients were found to be have high anti-measles virus antibody induces, suggesting on intrathecal synthesis of measles virus specific antibodies.

5.2 Herpesviruses

5.2.1 Human herpes virus-6(HHV-6)

Various members of the Herpesviridae family are believed to potentially contribute to the pathogenesis of multiple sclerosis (MS). Herpesviruses, known for establishing persistent lifelong infections, exhibit a high affinity for the nervous system and have the capacity to dysregulate the immune response. The ability of these viruses to persist in the body and interact with the immune system may play a role in the complex processes underlying the development or exacerbation of MS. Ongoing research continues to explore the intricate relationships between herpesviruses and the pathogenesis of MS. [25]. There are two recognized variants of Human Herpesvirus 6 (HHV-6): HHV-6A and HHV-6B. HHV-6A exhibits a particular affinity for infecting neural cells and has been identified in lesions associated with multiple sclerosis (MS). This observation suggests a potential association between HHV-6A infection and the pathology of MS, emphasizing the complex interplay between viral infections and the neurological aspects of the disease. Ongoing research aims to elucidate the specific mechanisms and implications of HHV-6A in the context of MS development [27]. Human Herpesvirus 6 (HHV-6) has been reported to utilize CD46 as its receptor. CD46 is a glycoprotein belonging to a family described as regulators of complement activation. These glycoproteins are distributed on all nucleated cells and play a protective role by preventing the spontaneous activation of complement on the cell surface. This process appears to be crucial in preventing demyelination. Furthermore, HHV-6 has been observed to infect oligodendrocytes, which are cells responsible for producing myelin in the central nervous system. The virus is capable of active replication both in vivo (within the living organism) and in vitro (in laboratory cultures). This interaction between HHV-6 and oligodendrocytes, along with the utilization of CD46 as a receptor, underscores the potential involvement of HHV-6 in processes that could contribute to demyelination, as seen in conditions such as multiple sclerosis [25]. Indeed, there is evidence suggesting that Human Herpesvirus 6 (HHV-6) may play a role in triggering an autoimmune response in multiple sclerosis (MS). This is proposed to occur through mechanisms such as inducing the expression of pro-inflammatory cytokines and activating autoreactive T cells. HHV-6's potential contribution to MS pathogenesis extends to promoting neuroinflammation, disrupting the blood–brain barrier (BBB), and causing direct damage to oligodendrocytes, which are the cells responsible for producing myelin in the central nervous system. Moreover, some studies indicate that HHV-6 proteins might exhibit cross-reactivity with myelin basic protein, a crucial component of the myelin sheath. This cross-reactivity could potentially contribute to CD8+ T cell-mediated oligodendrocyte death. The intricate interplay between viral infection, immune response, and neural damage highlights the complexity of the relationship between HHV-6 and the development or exacerbation of multiple sclerosis. Ongoing research seeks to further elucidate these mechanisms [27].

Another study suggests that human herpes virus 6 (HHV-6), a newly described beta-herpes virus that shares homology with cytomegalovirus (CMV), has been reported to be present in active MS plaques. In order to extend these observations, they have demonstrated increased IgM serum antibody responses to HHV-6 early antigen (p41/38) in patients with relapsing-remitting MS (RRMS), compared with patients with chronic progressive MS (CPMS), patients with other neurologic disease (OND), patients with other autoimmune disease (OID), and normal controls. Given the

ubiquitous nature of this virus and the challenging precedent of correlating antiviral antibodies with disease association, these antibody studies have been supported by the detection of HHV-6 DNA from samples of MS serum as a marker of active viral infection [28].

Until now, research on HHV-6 infection has predominantly focused on inflammatory and autoimmune disorders of the central nervous system. In light of viral hypotheses regarding the etiology of amyotrophic lateral sclerosis (ALS) and considering the biological characteristics of HHV-6, an investigation was conducted to assess the presence of viral-specific sequences in the total DNA extracted from peripheral blood mononuclear cells (PBMCs) from 20 ALS patients and 20 blood donors using PCR. The findings indicated the absence of HHV-6 specific sequences in both the DNA of ALS patients and the control group. However, to draw definitive conclusions regarding the potential role of HHV-6 as a cofactor in ALS development, further examination of cell types beyond lymphocytes and an increased sample size are deemed necessary [29].

5.2.2 HHV-8

More recently, specific viral sequences associated with HHV-8 have been identified in postmortem brain samples from both multiple sclerosis patients and controls. This discovery implies that, much like HHV-6, this novel herpes virus exhibits a strong affinity for the nervous system. HHV-8 is atypical among herpes viruses in its capability to generate counterparts of several human gene products, leading to modifications in cell cycle regulation, apoptosis, and cell-mediated immune responses. To explore a potential connection between HHV-8 and the onset of amyotrophic lateral sclerosis (ALS), the presence of HHV-8 infection indicators was investigated in ALS patients using both nested polymerase chain reaction (nPCR) and indirect immunofluorescence analysis. However, findings from both PCR and serological assessments did not indicate a definitive role of this virus in the origin of ALS. Nevertheless, the evolving understanding of how viruses may interact with the host cell genome and the human immune system underscores the continued relevance of investigating the viral hypothesis of ALS [30].

5.2.3 Epstein–Barr virus (EBV)

The Epstein-Barr virus (EBV) is a widely distributed enveloped double-stranded virus belonging to the Herpesviridae family, and its transmission occurs through saliva.[27]. among the gamma herpes viruses, Epstein-Barr virus (EBV) has been thoroughly examined as a potential factor in the development of multiple sclerosis (MS) [25]. EBV infection may induce autoreactive T cells that cross-react with myelin antigens, leading to an autoimmune response and promoting the onset of diseases such as MS, and other autoimmune disorders[27].A study describe two patients with unusual and severe neurological complications in association with serological evidence of EBV-infection [31]. A distinctive oligoclonal cerebrospinal fluid (CSF) banding pattern specific to anti-EBV nuclear antigen EBNA-1 was identified in a subset of multiple sclerosis (MS) patients (5 out of 15), contrasting with the absence of such a pattern in control CSF samples (0 out of 12). The presence of anti-EBNA-1 antibodies in Oligoclonal bands (OCBs) could be attributed to cross-reactivity with host cell components—a phenomenon known as molecular mimicry. This is suggested by the shared pentapeptide sequences between EBNA-1 and myelin basic protein (MBP). Another possibility is the chronic release of EBNA-1 due to apoptosis of latently infected B cells infiltrating MS plaques. Throughout its various infection phases, EBV expresses up to 44 different viral microRNAs (miRNAs), some of which function as viral immunoevasins. These miRNAs have demonstrated the ability to counteract both innate and adaptive immune responses [32]. Interestingly, despite these findings, EBV has been rarely observed in MS lesions, and EBV mRNA has not been detected in plaques. Such contrasting findings might suggest that EBV infection, and possibly reactivation, could act as a peripheral trigger for the pathogenesis of MS. In a study, comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus [33]. EBV infection is associated with increased risk of relapse in people with MS and may also contribute to disease progression and disability [27].

Research has indicated that Epstein-Barr virus (EBV) has the capability to directly or indirectly infect neurons, potentially through infected B-lymphocytes. It can induce neuroinflammation and demyelination, as well as stimulate the proliferation, degeneration, and necrosis of glial cells. Furthermore, EBV has been associated with promoting proliferative disorders in both B- and T-lymphocytes. These various interactions contribute to the onset and progression of nervous system diseases, including but not limited to multiple sclerosis, Alzheimer's disease, Parkinson's disease, acute cerebellar ataxia, meningitis, acute disseminated encephalomyelitis, and brain tumours [34]. But there is no clear evidence for the development of ALS associated with EBV.

5.2.4 Herpes simplex virus-1(HSV-1)

Anti-Herpes simplex virus-1 (HSV type 1) antibodies, along with HSV-1 coupled immune complexes, have been identified in the cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients. This discovery suggests that a specific viral strain might be implicated in the disease. In a mouse model, HSV-1 was shown to induce a demyelination disease that shares some similarities with MS. The susceptibility of different mouse strains to multifocal demyelination induced by HSV-1 was demonstrated to vary. The same research group also found that an increased viral spread was associated with a lack of demyelination in immunosuppressed mice. This finding aligns with a demyelinating mechanism that depends on a combination of immunity- and genetics-related factors [25].

In a conducted study using a mouse model to explore HSV latency and its associated neuroinflammation in the spinal cord, the primary objective was to observe neuroinflammatory changes resulting from latent HSV infections and determine if these changes mirrored alterations seen in the spinal cords of amyotrophic lateral sclerosis (ALS) patients. The examination of infected spinal cords revealed a significant infiltration of leukocytes and pronounced alterations in microglia in close proximity to motor neurons. The study also analyzed proteins associated with ALS, revealing no changes in TDP-43 and Fus in neurons. However, notably, there were decreased protein levels of C9orf72, a gene critically implicated in microglia homeostasis and severely altered in certain familial forms of ALS.

The latent HSV infection in the spinal cord induced altered microglia and leukocyte infiltration, resembling the inflammatory features observed in the spinal cords of ALS patients. Despite the absence of changes mimicking ALS neuropathology, such as TDP-43 cytoplasmic inclusions, the study did identify a decrease in protein levels of C9orf72 in the infected spinal cords [35].

5.2.5 Varicella zoster virus (VZV)

Varicella-zoster virus is a highly contagious, ubiquitous alpha herpesvirus that causes two distinct clinical syndromes: varicella (chickenpox) and herpes zoster (shingles) [27]. The potential connection between multiple sclerosis (MS) and other alpha herpesviruses, specifically Varicella-Zoster Virus (VZV), has been explored through epidemiological studies revealing a similar geographical distribution of VZV infection and MS, manifesting as a north-south prevalence gradient. Additionally, VZV encephalitis is marked by focal white matter demyelination. Furthermore, the presence of intrathecal synthesis of anti-VZV antibodies in the cerebrospinal fluid (CSF) of individuals with MS has been documented [25]. VZV is transmitted through respiratory secretions or contact with skin lesions of an infected person. VZV establishes latency in the dorsal root or cranial nerve ganglia. VZV has been considered as a potential etiologic agent in MS. Thus, VZV may play a role in the CNS inflammation seen in MS. Previous studies have indicated that reactivation of latent VZV might correspond with relapse in MS patients. Sotelo et al. indicated a causal role for VZV in the pathogenesis of MS relapse [27]. In a study focusing on ultrastructural observations, electron microscopy was utilized to examine viral particles in cerebrospinal fluid (CSF) from 15 multiple sclerosis (MS) patients during relapse, 19 MS patients during remission, and 28 control subjects. The initial findings were confirmed in a subsequent cohort. Additionally, real-time polymerase chain reaction was employed to quantify Varicella-Zoster Virus (VZV) DNA in peripheral blood mononuclear cells (PBMCs) and CSF from a substantial number of MS patients (n = 78).

The study revealed the presence of abundant viral particles identical to VZV in CSF obtained from MS patients within the initial days of an acute relapse, as observed through electron microscopy. In contrast, viral particles were not observed in CSF samples from MS patients in remission or from neurological control subjects. Furthermore, DNA from VZV was detected in CSF and PBMCs during relapse, disappearing in most patients during remission. The mean viral load was found to be 542 times higher in CSF during relapse compared to CSF during remission and 328 times higher in CSF during relapse compared to PBMCs during relapse [36].

In a separate study, a 57-year-old female patient who had undergone cortisone treatment for 7 years due to myelophthisis developed amyotrophic lateral sclerosis (ALS) four months after experiencing a herpes zoster infection. The study noted the presence of cellular and humoral immunodeficiency in the patient. The investigation explored potential connections between herpes zoster infection and the subsequent development of ALS in the context of the observed immunodeficiency [37]. Herpes Zoster Virus (shingles) is produced by reactivation of Varicella Zoster Virus, a painful dermatomally distributed vesicular eruption. Zoster may be further complicated by postherpetic neuralgia, VZV vasculopathy, myelitis, and segmental motor weakness [38].

5.2.6 Cytomegalovirus (CMV)

Cytomegalovirus (CMV), a widespread herpesvirus, has attracted considerable attention as a potential factor in the development and progression of multiple sclerosis (MS). CMV is a prevalent virus that infects a significant portion of

the global population, and, akin to Epstein-Barr virus (EBV), it is transmitted through saliva. Given its widespread prevalence and capacity to establish lifelong latent infections, CMV has emerged as a candidate in the search for potential contributors to MS pathogenesis [39].

Two studies conducted on an Iranian cohort of MS patients revealed higher levels of CMV DNA compared to the control group. These findings were supported by evidence indicating CMV reactivation as a potential exacerbating factor in MS patients. CMV infection triggers a robust immune response involving both innate and adaptive immunity. In individuals with MS, immune response dysregulation is a key characteristic of the disease pathogenesis. Research has proposed that the immune response activated by CMV infection may play a role in the autoimmune processes that underlie the development of MS. However, a thorough understanding of the precise mechanisms involved in CMV-induced immune dysregulation in MS requires further investigation [27].

6. Enteroviruses and neurological disorders

The potential involvement of Enteroviruses (EVs), a family of single positive-stranded RNA viruses within the Picornaviridae family that includes poliovirus, coxsackievirus, echovirus, enterovirus-A71, and enterovirus-D68, in the development of Amyotrophic Lateral Sclerosis (ALS) has been suspected. This suspicion arises from their ability to target motor neurons, and there is an observed higher risk of motor neuron disease in individuals with a history of prior poliomyelitis. EVs exhibit a high tropism for the central nervous system, contributing to various neurological disorders. For decades, a potential role of EVs in ALS has been proposed, stemming from their ability to target motor neurons and the occurrence of ALS-like post-polio myelitis syndrome. In a study involving 17 patients with confirmed ALS and 29 control subjects without a history of motor neuron disease, Reverse Transcriptase-PCR (RT-PCR) and direct RT in situ PCR (RT-IS-PCR) were performed on formaldehyde-fixed spinal cord samples. When PCR products were obtained, subsequent sequencing revealed that EV nucleic acid sequences were detected in 15 (88.3%) of the 17 patients with ALS, compared to only 1 (3.4%) of the 29 control subjects. These findings suggest a potential association between Enteroviruses and the development of ALS [11].

While the majority of the EVs are transmitted through the fecal-oral route and replicate in the gastrointestinal tract. Available evidence suggests that EVs can invade the CNS from these primary infection sites through three main mechanisms: (i) retrograde axonal transport—both poliovirus and EV-A71 can infect the peripheral nerve and gain access into the CNS via retrograde axonal transport and trans-synaptic spread; (ii) blood-brain barrier (BBB) penetration—during viremia, poliovirus in the blood can directly cross the BBB through disrupted tight junctions that are likely induced by inflammation independently of viral receptor, and/or via transferrin receptor 1-mediated direct transmission; and (iii) “Trojan-horse” invasion—EVs, such as poliovirus , EV-A71 and coxsackievirus , can also invade the CNS through virus-infected immune cells, including macrophage/monocytes, dendritic cells, lymphocytes and nesting+ myeloid cells, which act as carriers to deliver virus into the CNS. EVs likely utilize one or multiple routes of entry into the CNS [10].

To explore the potential association between enterovirus (EV) infection and the development of multiple sclerosis (MS), a study utilized magnetic resonance imaging (MRI) to compare the neuroimaging findings in children experiencing their initial episode of clinical enterovirus 71-associated transverse myelitis (EV71-TM) with those in children with transverse myelitis in the context of multiple sclerosis (MS-TM). The study conducted a retrospective blinded radiological assessment, comparing the neuroimaging results of 11 children with their first episode of myelitis caused by EV71-TM and 13 children with MS-TM. In the EV71-TM group, lesions were observed throughout the spinal cord, and enhancement of nerve roots (both ventral and dorsal) was a common feature. On the other hand, the MS-TM group typically exhibited multiple short-segment lesions of the cord involving the cervicothoracic spine. Enteroviruses were considered potential candidates due to their neurotropic nature and ability to cause chronic infections. The study included testing serum and cerebrospinal fluid (CSF) using reverse transcription-polymerase chain reaction specific for enteroviruses in 17 MS twin pairs. However, no enteroviral RNA was detected in any serum samples (n = 34) or CSF samples (n = 12). The study did not find any evidence of enterovirus infection in twins with MS or their healthy siblings. This study is noteworthy as it is the first to assess the role of enterovirus infections in the risk of developing MS in twins [40].

7. Retroviruses

7.1 Human T-lymphotropic virus-1(HTLV-1)

Human T-lymphotropic Virus 1 (HTLV-1) was the first human retrovirus to be discovered and is prevalent in specific regions of the world, particularly in southwestern Japan, the Caribbean Islands, and parts of Africa and South America, where up to 10% or more of the population may be infected. HTLV-1 has been investigated as a potential etiological agent in multiple sclerosis (MS), primarily because of the observed similarities between HTLV-1-associated neurologic disease, termed HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and MS [25]. HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP), goes through an inflammatory phase followed by a degenerative phase quite reminiscent of MS [41]. Anti HTLV-1 Gag protein antibodies were detected in the serum and CSF of MS patient. The same study revealed HTLV-1 genomic sequences in cell cultures inoculated with CSF from one third of MS patients [25].

There is currently no clear evidence supporting a direct relationship between Human T-cell lymphotropic virus type I (HTLV-I) and amyotrophic lateral sclerosis (ALS). While the understanding of ALS is still evolving, it is generally considered a complex neurodegenerative disorder with multiple potential contributing factors. Research has primarily focused on genetic and environmental factors in ALS development. HTLV-1 is indeed associated with a distinct neurological disorder known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 is primarily transmitted through sexual contact, blood transfusion, and breastfeeding. However, the specific association between HTLV-1 and ALS remains uncertain, and further research is needed to establish any potential links between the virus and ALS. It's important to note that the scientific understanding of neurodegenerative diseases like ALS is continuously evolving, and new research may provide more insights into potential associations with viral infections [42]. The epidemiology of tropical spastic paraparesis/human T lymphotropic virus I (HTLV-I)-associated myelopathy (TSP/HAM) is frequently inconsistent and suggests environmental factors in the etiology of these syndromes [43]. In a case study report of Human T-lymphotropic virus type-I (HTLV-I)-associated myelopathy with bulbar palsy-type amyotrophic lateral sclerosis-like symptoms, a 52-year-old woman developed dyslalia at approximately 40 years of age, which slowly progressed. She presented with muscular atrophy and increased tendon reflexes of the extremities as well as bulbar palsy, from which motor neuron disease was suspected [43]. Studies of antibodies against HTVL-I virus are performed in serum and CSF; this marker is important to differentiate between patients with high viral load and ALS-like symptoms directly affected by the virus and patients who are asymptomatic carriers with low viral load [42].

7.2 Human endogenous retrovirus (HERV)

HERV are the remnants of ancient retroviruses integrated into the human genome and normally inactivate, but can be reactivated under physiological and pathological stress [25] Retroviruses have shown notable reactivity in cases of Amyotrophic Lateral Sclerosis (ALS), contributing to the exploration of human endogenous retroviruses (HERVs). HERVs are categorized into different families, with HERV-K and HERV-W being among the most studied. Research by Douville et al. has demonstrated increased expression of HERV-K in the brain tissue of ALS patients. Interestingly, the reactivity varied based on the specific brain region involved. Greater reactivity was observed in the prefrontal cortex and the sensory cortex, while less reactivity was noted in the motor cortex. These findings suggest a potential association between HERV-K expression and ALS pathology, highlighting the complexity of retroviral involvement in neurodegenerative diseases [42]. Several studies have reported the detection of enhanced gene expression of HERV-K and reverse transcriptase activity in the blood and brain tissues of ALS patients. More notably transgenic mice express in HERV-K in the neurons develop progressive motor neuron disfunction similar to human ALS phenotype, suggesting a potential viral etiology of ALS [25]. Similar to ALS patient tissues, the mouse neurons showed expression of env protein in the cytoplasm of the neuronal cell bodies and the apical dendrite. There was accompanying astrocytosis in regions surrounding the neurons where HERV-K env was expressed, but there was no difference in immune reactivity of microglial cells. Golgi staining showed decreased length, branching, and complexity of dendrites. The number of dendritic spines was also decrease and was associated with morphological changes showing loss of stalks resulting in an increase in stubby spines and a decrease in mushroom spines. There was also beading of the axons and dendrites [45].

Several studies suggest that specific HERVs that occur in few copies in the genome (e.g. ERV-3, HERV-R and HRES-1) may show polymorphic patterns in MS and might act as auto-, super- or neoantigens with the potential to enhance inflammatory responses or induce autoimmune reactions. RNA encoded by these HERVs has been detected by reverse transcriptase polymerase chain reaction (RT-PCR) with degenerate primers in sera/plasma and brain tissues from MS patients. Other methods employed for detecting evidence HERVs in MS and other diseases include electron microscopic identification of ‘virus-like’ particles, reverse transcriptase activity and autoantibodies in blood and CSF [46]. Multiple

Sclerosis Associated Retrovirus (MSRV) genetic sequences were found to share a close homology with the HERV-W endogenous family, and MSRV was subsequently regarded as the founder discovery of this endogenous virus family. The growing link between a HERV-W env gene and MS was highlighted when the Italian group – who had earlier confirmed a link between detection of MSRV in CSF on first presentation with eventual poorer prognosis – now showed that the measurable viral load of MSRV in the blood and cerebrospinal fluid of MS patients correlated closely with clinical activity score, stage and progression of MS [45].

7.3 Human immunodeficiency virus (HIV)

The AIDS virus has the potential to induce a form of ALS, which responds well to antiretroviral drugs. Researchers identified six HIV-infected patients exhibiting ALS symptoms, a rate 27 times higher than the general population. This syndrome progresses more rapidly than typical ALS, manifesting within weeks or months rather than the usual 2 to 5 years, and tends to affect individuals at a younger age. The HIV-associated ALS targets both upper and lower motor neurons, originating at the cervical level and differing from classical ALS in its clinical features [44].

The underlying causes of the ALS-like syndrome in HIV-positive patients are debated, with suggested mechanisms mirroring those proposed for classical ALS, involving neuronal excitation and free radical generation. Previously, only a few case reports detailed ALS-like presentations in HIV-infected patients, most being categorized as probable or possible ALS. Notably, these cases deviate from classical ALS by occurring in younger patients, progressing rapidly, and sometimes improving with antiretroviral therapy[47].

In a recent study, a middle-aged man with lower limb onset was found to be HIV-1 seropositive. A retrospective review of 1700 HIV-1-infected cases revealed six instances of a reversible ALS-like syndrome, presenting a 27-fold increased risk in that specific patient population. These cases, typically younger than typical ALS patients, exhibited a monomelic pattern of onset followed by rapid progression within weeks, involving both upper and lower motor neurons [48].

MacGowan et al. reported an ALS-like syndrome in a 32-year-old woman with HIV infection, showing motor deficit recovery with antiretroviral therapy. Interestingly, this patient's brain MRI revealed white matter abnormalities in the brain stem, resolving after therapy and clinical recovery [48].

Another case involved a previously healthy 28-year-old Brazilian woman, initially presenting with left arm paresthesia. A brain scan revealed a solitary lesion, and subsequent tests confirmed HIV infection. Despite positive anti-HIV antibodies, the patient had a negative test four months earlier. A brain biopsy diagnosed subacute demyelination consistent with multiple sclerosis (MS). Treatment with dexamethasone led to resolution, but optic neuritis manifested later, responding well to high-dose methylprednisolone [49].

In this patient, other causes for brain lesions were ruled out, and the biopsy indicated extensive demyelination, resembling an MS lesion. Few cases of HIV-positive patients with MS-like lesions have been reported, with some showing a temporal relationship between HIV seroconversion and neurological symptoms. The question of HIV's role in the pathogenesis of demyelinating diseases arises, with the possibility that HIV-1 might trigger such diseases, as no other pathogen was detected in this patient [50].

8. Conclusion

Higher levels of the chemokine MCP-1 in patients with findings such as expression of MCP-1 receptor (CCR2) decrease on circulating monocytes, IL 17 level elevation in serum denoted ALS. The myelin-reactive T cells, Th1- driven cytokines involved in T cell mediated immunity such as interleukin-2(IL-2), gamma interferon, and tumour necrosis factor alpha found crucial roles in MS. These induce antibody modified from IgM to IgG2a and IgG3. Th2 cells responsible for IL-4, IL-5, IL-10 and transforming growth factor beta1 and generation and imparts antibody production. The myelin-activated peripheral T cells restricted by major histocompatibility complex (MHC) class2 molecules, Myelin basic protein (MBP), proteolipid protein (PLP), MOG, myelin-associated glycoprotein (MAG), and myelin-associated oligodendrocytic basic protein were proved to exhibit autoimmune responses in various episodes of MS. EVs have a high affinity for the central nervous system and target motor neurons and the development of the ALS like post-polio myelitis syndrome

The viral infections leading to CNS damage and demyelination of varying severity operating through different mechanism in individual with dissimilar genetic background precipitating neurodegeneration pointing to ALS/ MS. The measles virus found to induce post infectious encephalomyelitis (PIE) along with progressive neurodegeneration. It was also noted that circulating anti-measles virus antibodies may persist for decades after primary infection led to long term

viral persistence more seriously a cross reactive immune response. It is evident that HHV-6A cooled persist extensively and cause viral reactivation in CNS. HHV-6 has been reported to use CD46 as its receptor and alter the receptor function of controlling demyelination. The molecular mimicry mechanises in EBV due to apoptosis of latently infected B-cells infiltrating neuronal plaques and possibly reactivation could act as a peripheral trigger to neuronal damage.

HSV-1 experimented mouse model possess anti HSV type 1 antibodies as well as HSV-1 coupled immune complexes and induced multifocal demyelination. Anti HTLV-1 Gag protein antibodies were detected in PBMCs and CSF T cells in serum and CSF of MS patients. The detection of extracellular virions with reverse transcriptase activity generated in leptomeningeal cells from MS affected subjects and the group named MS associated retroviruses. The occurrence of neurodegenerative diseases in viral infection exposed patients have derived in various studies whose mechanisms and correlations yet to be explored in detail. Upcoming researchers have a great scope in the micro molecular, genetic, metabolic, biochemical alterations in CNS associated with viral infection-based investigations to be performed so as to understand the underlying interlinks.

Compliance with ethical standard

Acknowledgement

Authors would like to express their gratitude to all those who contributed indirectly or directly in collecting and compiling the data's of the review.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Neurodegenerative disease. In: Wikipedia [Internet]. 2023 [cited 2023 Dec 8]. Available from:https://en.wikipedia.org/w/index.php?title=Neurodegenerative_disease&oldid=1188868421

[2] Mayo Clinic [Internet]. [cited 2023 Dec 14]. Multiple sclerosis - Symptoms and causes. Available from: https://www.mayoclinic.org/diseases-conditions/multiplesclerosis/symptoms-causes/syc-20350269

[3] Multiple Sclerosis | National Institute of Neurological Disorders and Stroke [Internet]. [cited 2023 Dec 14]. Available from: https://www.ninds.nih.gov/health-information/disorders/multiple-sclerosis

[4] Multiple sclerosis: MedlinePlus Medical Encyclopedia [Internet]. [cited 2023 Dec 14]. Available from: https://medlineplus.gov/ency/article/000737.htm

[5] Mayo Clinic [Internet]. [cited 2023 Dec 14]. Amyotrophic lateral sclerosis (ALS) - Symptoms and causes. Available from: https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022

[6] Brotman RG, Moreno-Escobar MC, Joseph J, Pawar G. Amyotrophic Lateral Sclerosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Dec 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK556151/

[7] Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler Houndmills Basingstoke Engl. 2020 Dec;26(14):1816–21.

[8] Multiple Sclerosis: Pathology [Internet]. [cited 2023 Dec 14]. Available from: https://library.med.utah.edu/kw/ms/path.html#:~:text=Plaques%20were%20demonstrated%20to%20occur,often%20correlate%20with%20clinical%20symptoms

[9] Grad LI, Rouleau GA, Ravits J, Cashman NR. Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS). Cold Spring Harb Perspect Med. 2017 Aug;7(8):a024117. doi: 10.1101/cshperspect.a024117. PMID: 28003278; PMCID: PMC5538408.**4.**

[10] Motor Neuron Diseases | National Institute of Neurological Disorders and Stroke [Internet]. [cited 2023 Dec 14]. Available from: https://www.ninds.nih.gov/health-information/disorders/motor-neuron-diseases

[11] Vogt J, Paul F, Aktas O, Müller-Wielsch K, Dörr J, Dörr S, et al. Lower motor neuron loss in multiple sclerosis and experimental autoimmune encephalomyelitis. Ann Neurol. 2009 Sep;66(3):310–22.

[12] Spalloni A, Nutini M, Longone P. Role of the N-methyl-d-aspartate receptors complex in amyotrophic lateral sclerosis. Biochim Biophys Acta BBA - Mol Basis Dis. 2013 Feb 1;1832(2):312–22.

[13] Van Den Bosch L, Van Damme P, Bogaert E, Robberecht W. The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis. Biochim Biophys Acta BBA - Mol Basis Dis. 2006 Nov 1;1762(11):1068–82.

[14] Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. Nat Med. 2000 Jan;6(1):67–70.

[15] Hemerková P, Vališ M. Role of Oxidative Stress in the Pathogenesis of Amyotrophic Lateral Sclerosis: Antioxidant Metalloenzymes and Therapeutic Strategies. Biomolecules. 2021 Mar 16;11(3):437.

[16] Zhang SY, Gui LN, Liu YY, Shi S, Cheng Y. Oxidative Stress Marker Aberrations in Multiple Sclerosis: A Meta-Analysis Study. Front Neurosci [Internet]. 2020 [cited 2023 Dec 15];14. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2020.00823

[17] McAlary L, Plotkin SS, Yerbury JJ, Cashman NR. Prion-Like Propagation of Protein Misfolding and Aggregation in Amyotrophic Lateral Sclerosis. Front Mol Neurosci. 2019 Nov 1;12:262.

[18] Stone S, Lin W. The unfolded protein response in multiple sclerosis. Front Neurosci. 2015 Jul 29;9:264.

[19] de Barcelos IP, Troxell RM, Graves JS. Mitochondrial Dysfunction and Multiple Sclerosis. Biology. 2019 May 11;8(2):37.

[20] Muyderman H, Chen T. Mitochondrial dysfunction in amyotrophic lateral sclerosis – a valid pharmacological target? Br J Pharmacol. 2014 Apr;171(8):2191–205.

[21] Liu E, Karpf L, Bohl D. Neuroinflammation in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia and the Interest of Induced Pluripotent Stem Cells to Study Immune Cells Interactions With Neurons. Front Mol Neurosci [Internet]. 2021 [cited 2023 Dec 15];14. Available from: https://www.frontiersin.org/articles/10.3389/fnmol.2021.767041

[22] Targeting Neuroinflammation in Multiple Sclerosi [Internet]. [cited 2023 Dec 15]. Available from: https://www.sanofi.com/en/magazine/our-science/how-multiple-sclerosis-affects-the-brain

[23] The ALS Association [Internet]. [cited 2023 Dec 14]. ALS Genes and Mutations. Available from: https://www.als.org/research/als-research-topics/genetics

[24] Multiple sclerosis - Causes - NHS [Internet]. [cited 2023 Dec 15]. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/causes/

[25] Donati D, Jacobson S. Viruses and Multiple Sclerosis. In: Polymicrobial Diseases [Internet]. ASM Press; 2002 [cited 2023 Dec 6]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2494/

[26] Increased levels of inflammatory chemokines in amyotrophic lateral sclerosis | Request PDF [Internet]. [cited 2023 Dec 15]. Available from: https://www.researchgate.net/publication/24034200_Increased_levels_of_inflammatory_chemokines_in_amyotrophic_lateral_sclerosis

[27] Landry RL, Embers ME. The Probable Infectious Origin of Multiple Sclerosis. *NeuroSci*. 2023; 4(3):211-234. https://doi.org/10.3390/neurosci4030019

[28] Landry RL, Embers ME. The Probable Infectious Origin of Multiple Sclerosis. NeuroSci. 2023 Sep;4(3):211–34.

[29] Soldan SS, Berti R, Salem N, Secchiero P, Flamand L, Calabresi PA, et al. Association of human herpes virus 6 (HHV-6) with multiple sclerosis: Increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA. Nat Med. 1997 Dec;3(12):1394–7.

[30] Human herpes virus 6 (HHV-6) in amyotrophic lateral sclerosis: a polymerase chain reaction (PCR) study - Sola - 1996 - European Journal of Neurology - Wiley Online Library [Internet]. [cited 2023 Dec 6]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1468-1331.1996.tb00223.x

[31] Sola P, Bedin R, Casoni F, Barozzi P, Mandrioli J, Merelli E. New Insights into the Viral Theory of Amyotrophic Lateral Sclerosis: Study on the Possible Role of Kaposi's Sarcoma-Associated Virus/Human Herpesvirus 8. Eur Neurol. 2002 Feb 15;47(2):108–12.

[32] Corssmit EP, Leverstein-van Hall MA, Portegies P, Bakker P. Severe neurological complications in association with Epstein-Barr virus infection. J Neurovirol. 1997 Dec;3(6):460–4.

[33] Albanese M, Tagawa T, Hammerschmidt W. Strategies of Epstein-Barr virus to evade innate antiviral immunity of its human host. Front Microbiol. 2022;13:955603.

[34] Bjornevik: Longitudinal analysis reveals high prevalence... - Google Scholar [Internet]. [cited 2023 Dec 6]. Available from: https://scholar.google.com/scholar_lookup?title=Longitudinal+analysis+reveals+high+prevalence+of+Epstein-Barr+virus+associated+with+multiple+sclerosis&author=Bjornevik,+K.&author=Cortese,+M.&author=Healy,+B.C.&author=Kuhle,+J.&author=Mina,+M.J.&author=Leng,+Y.&author=Elledge,+S.J.&author=Niebuhr,+D.W.&author=Scher,+A.I.&author=Munger,+K.L.&publication_year=2022&journal=Science&volume=375&pages=296%E2%80%93301&doi=10.1126/science.abj8222

[35] Frontiers | Epstein-Barr Virus and Neurological Diseases [Internet]. [cited 2023 Dec 6]. Available from: https://www.frontiersin.org/articles/10.3389/fmolb.2021.816098/full

[36] Cabrera JR, Rodríguez-Izquierdo I, Jiménez JL, Muñoz-Fernández MÁ. Analysis of ALS-related proteins during herpes simplex virus-2 latent infection. J Neuroinflammation. 2020 Dec 7;17(1):371.

[37] Sotelo J, Martínez-Palomo A, Ordoñez G, Pineda B. Varicella-zoster virus in cerebrospinal fluid at relapses of multiple sclerosis. Ann Neurol. 2008;63(3):303–11.

[38] Maida E, Kristoferitsch W. Amyotrophic Lateral Sclerosis following Herpes zoster Infection in a Patient with Immunodeficiency. Eur Neurol. 2008 Jan 29;20(4):330–3.

[39] Kennedy PGE. Issues in the Treatment of Neurological Conditions Caused by Reactivation of Varicella Zoster Virus (VZV). Neurother J Am Soc Exp Neurother. 2016 Jul;13(3):509–13.

[40] M Vanheusden Cytomegalovirus: a culprit or protector in multiple sclerosis? Trends Mol Med. 2015 Jan 1;21(1):16–23.

[41] Kuusisto H, Hyöty H, Kares S, Kinnunen E, Saarelainen M, Elovaara I. Enteroviruses and the risk of MS in the Finnish Twin Cohort. Eur J Neurol. 2005 Sep;12(9):707–9.

[42] Oger J. HTLV-1 infection and the viral etiology of multiple sclerosis. J Neurol Sci. 2007 Nov 15;262(1):100–4.

[43] Gonzalez Trujillo F, Parra Cortes K, Álvarez Pareja Y, Onate J. Human T-cell Lymphotropic Virus Type I Associated with Amyotrophic Lateral Sclerosis Syndrome: Immunopathological Aspects and Treatment Options. Cureus. 12(4):e7531.

[44] Zaninovic: Possible etiologies for tropical spastic... - Google Scholar [Internet]. [cited 2023 Dec 7]. Available from: https://scholar.google.com/scholar_lookup?journal=Braz+J+Med+Biol+Res&title=Possible+etiologies+for+tropical+spastic+paraparesis+and+human+T+lymphotropic+virus+I-associated+myelopathy&volume=37&publication_year=2004&pages=1-12&pmid=14689037&

[45] Ando: Human T-lymphotropic virus type-I (HTLV-I)-associat... - Google Scholar [Internet]. [cited 2023 Dec 7]. Available from: https://scholar.google.com/scholar_lookup?journal=Intern+Med&title=Human+T-lymphotropic+virus+type-I+(HTLV-I)-associated+myelopathy+with+bulbar+palsy-type+amyotrophic+lateral+sclerosis-like+symptoms&volume=54&publication_year=2015&pages=1105-1107&pmid=25948358&

[46] Human endogenous retrovirus-K contributes to motor neuron disease - PMC [Internet]. [cited 2023 Dec 7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6344353/

[47] Antony JM, DesLauriers AM, Bhat RK, Ellestad KK, Power C. Human endogenous retroviruses and multiple sclerosis: Innocent bystanders or disease determinants? Biochim Biophys Acta BBA - Mol Basis Dis. 2011 Feb 1;1812(2):162–76.

[48] Satin ZA, Bayat E. ALS-Like Disorder in Three HIV-Positive Patients: Case Series. Case Rep Neurol. 2021 Jan 28;13(1):59–64.

[49] PhD JC. Woman's ALS-like Symptoms Linked to Retrovirus in Case Report [Internet]. 2020 [cited 2023 Dec 15]. Available from: https://alsnewstoday.com/news/woman-als-like-symptoms-linked-to-retrovirus-in-case-report/

[50] Anand KS, Wadhwa A, Garg J, Mahajan RK. Amyotrophic Lateral Sclerosis-Like Presentation in a HIV-Positive Patient. J Int Assoc Provid AIDS Care JIAPAC. 2014 Nov 1;13(6):515–8.

[51] Graber P, Rosenmund A, Probst A, Zimmerli W. Multiple sclerosis-like illness in early HIV infection. AIDS. 2000 Oct 20;14(15):2411.