Archives of Virology (2021) 166:733–753
https://doi.org/10.1007/s00705-021-04959-6

REVIEW

Viral infections and their relationship to neurological disorders

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Received: 31 August 2020 / Accepted: 27 November 2020 / Published online: 27 January 2021

Abstract

The chronic dysfunction of neuronal cells, both central and peripheral, a characteristic of neurological disorders, may be caused by irreversible damage and cell death. In 2016, more than 276 million cases of neurological disorders were reported worldwide. Moreover, neurological disorders are the second leading cause of death. Generally, the etiology of neurological diseases is not fully understood. Recent studies have related the onset of neurological disorders to viral infections, which may cause neurological symptoms or lead to immune responses that trigger these pathological signs. Currently, this relationship is mostly based on epidemiological data on infections and seroprevalence of patients who present with neurological disorders. The number of studies aiming to elucidate the mechanism of action by which viral infections may directly or indirectly contribute to the development of neurological disorders has been increasing over the years but these studies are still scarce. Comprehending the pathogenesis of these diseases and exploring novel theories may favor the development of new strategies for diagnosis and therapy in the future. Therefore, the objective of the present study was to review the main pieces of evidence for the relationship between viral infection and neurological disorders such as Alzheimer's disease, Parkinson's disease, Guillain-Barré syndrome, multiple sclerosis, and epilepsy. Viruses belonging to the families *Herpesviridae, Orthomyxoviridae, Flaviviridae,* and *Retroviridae* have been reported to be involved in one or more of these conditions. Also, neurological symptoms and the future impact of infection with SARS-CoV-2, a member of the family *Coronaviridae* that is responsible for the COVID-19 pandemic that started in late 2019, are reported and discussed.

Introduction

Neurological disorders (NDs) are among the most significant public health challenges in today's society, and they are mainly associated with the aging of the population [1]. NDs are the leading cause of disability-adjusted life years (DALYs), with approximately 276 million cases [2]. The continuous dysfunction provoked by NDs triggers degeneration and consequent cell death in the nervous system [3]. Although neurological disorders have a multifactorial etiology, most of them have a strong genetic and environmental association [4]. Recently, some studies have also associated NDs such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), Guillain Barré syndrome (GBS), and epilepsy with viral infections [5–9]. Viral diseases are widely distributed, easily transmitted, and challenging to control. Thus, the hypothesis of viral agents as possible triggers of NDs makes them more impactful [10].

The viral etiology of some neuroinfections is well described in the literature, especially those related to neurotropic viruses such as poliovirus, coxsackievirus, and enterovirus 71 (EV71). However, our understanding of the relationship between other viral infections and the development of neurological diseases is still limited. In addition, current ND challenges include the lack of reliable biomarkers for early diagnosis and effective preventive strategies and treatments [11]. In this context, this work relates NDs, such as AD, PD, GBS, MS, and epilepsy, to viral infections. Moreover, we discuss the possible neurological impact of SARS-CoV-2 infection, which is caused by the new coronavirus responsible for the current COVID-19 pandemic.

Handling Editor: Zhongjie Shi.

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The relationship between neurological disorders and infectious etiology

The first report of a central nervous system (CNS) infection with a consequent ND was by Bowery et al. in 1992 [12]. Subsequently, enterovirus (EV) and human herpesvirus (HHV) infections were found to be associated with ALS [13], Japanese encephalitis (JE) virus and Influenza virus with PD [14], herpes simplex virus type 1 (HSV-1) and *Chlamydia pneumoniae* with AD [15], and Epstein-Barr virus (EBV), varicella-zoster virus (VZV), cytomegalovirus (CMV), HHV-6, and HHV-7 with MS [16]. Although studies have shown that MDs begin in the CNS, the brain-periphery relationship may influence the development and progression of these disorders [17].

These disorders may be caused directly by infection of the CNS by specific pathogens or indirectly, through the host response to the infection. In case of the direct damage, some pathogens can cross the intact blood-brain barrier (BBB), causing severe encephalitis or acute infections that can be fatal or progress to chronic diseases [18]. Also, aging can make the CNS more vulnerable to infectious agents due to changes in the BBB, increased oxidative stress, and less energy production [19]. In the indirect-damage mechanism, various factors may be involved, such as the accumulation of protein aggregates, high levels of oxidative stress, alterations in autophagic mechanisms, synaptopathy, and neuronal destruction [16]. Fig. 1 illustrates the cascade of immune responses produced by the body against infections of the CNS and their deleterious effects.

In addition to the direct infection of CNS via blood and the BBB, other possible pathways involve monocyte-macrophage/microglia cells that can cross the BBB or inter- and trans-neuronal transfer in peripheral neurons (Fig. 2A). Human immunodeficiency virus (HIV), for example, crosses the BBB by infecting blood leukocytes and, subsequently, microglia [20]. Although HIV is not capable of attacking

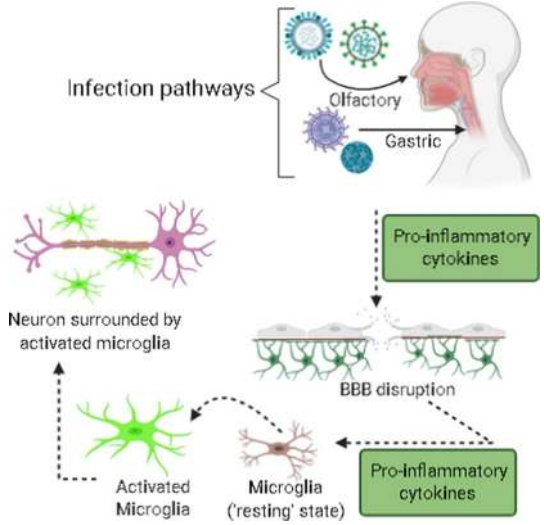

Fig. 1 Pathological agents may infect the organism by different pathways, such as olfactory and gastric. These pathogens trigger a cascade of inflammatory responses (increased levels of cytokines, for example) that disrupt the BBB, activate microglia, and lead to a subsequent clustering around neuronal cells, resulting in neuronal damage. **Source:** adapted from Limphaibool et al. (2019) [71]

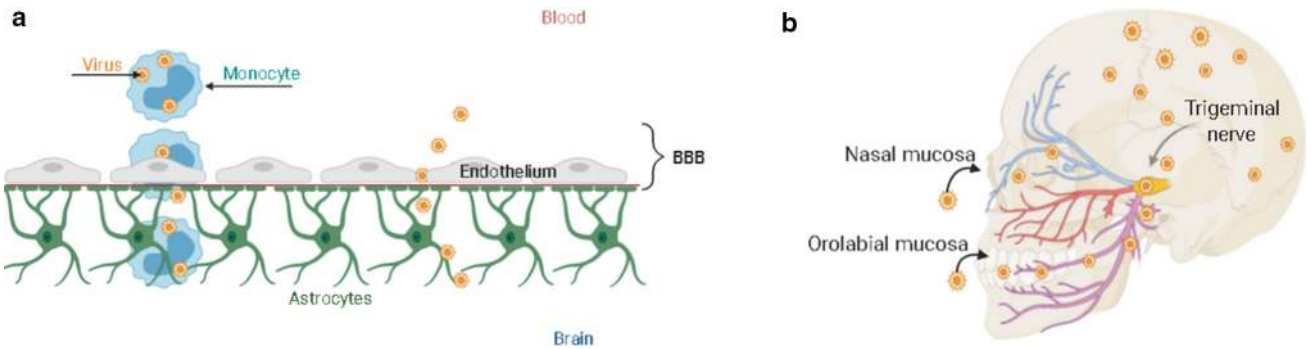

Fig. 2 Mechanisms used by pathological agents to cross the BBB. (a) A direct crossing may be possible when cells of monocyte-macrophage/microglia lineage are infected by the pathogens and carry them through the BBB, reaching the CNS. This mechanism is also called "Trojan horse" because the microorganism eludes the immune system defense by using these cells to move from the bloodstream to the brain. The transport of pathogens to CNS is favored by inflammation, which is typically observed in neurological disorders. During the inflammation process, inflammatory molecules are released, triggering the activation of infected leukocytes. The postcapillary venule is attacked by the infected leukocytes, which encircle the endothelial and parenchyma basement membranes. Next, these cells enter the CNS by crossing the BBB. Another mechanism used by pathological agents is to impair the BBB and reach the CNS directly, using the porous capillaries of the choroid plexus. In various neurological diseases, the BBB is damaged, which favors the entry of pathogens into the brain through the bloodstream. (b) Neurotropic viruses may enter the CNS through retrograde axonal transport. These pathogens infect the peripheral nerve that creates a link from the skin and the mucosa to the sensory, motor, and olfactory neurons. In neuronal cells, viruses can replicate and infect adjacent cells. **Source:** adapted from De Chiara et al. (2012) [16]

neurons directly, this infection provokes an increase in inflammatory cytokines and viral proteins that indirectly harm these cells [16].

The neurotropism of some viruses is established through the nerves rooted in mucosa and skin. Infection is dependent on the recognition of receptors in sensory, motor, and olfactory neurons and retrograde axonal transport through axonal microtubules [21]. Certain viruses reach the brain through the olfactory system, which connects peripheral areas and with the CNS. Triplets and vagus nerves may also be an entry point for some viruses in intranasal infections [22]. After entering the CNS, viruses spread from cell to cell by being released in the synaptic cleft or by merging with neighboring neurons. The reinfection of peripheral tissue is possible for some viruses, which travel through anterograde transport and are released into the synaptic cleft [23]. The spread of neurotropic viruses in the CNS is illustrated in Fig. 2B. Several viruses have been associated with NDs, as described below. The effects of viral infections on the pathophysiology of NDs are summarized in Table 1.

Neurological disorders and viral infections

Alzheimer's disease (AD)

AD, described for the first time in 1906, is the most common type of dementia, and in approximately 95% of the cases, it occurs after 60 years of age. In young individuals, 13% of cases show an autosomal dominant pattern of inheritance. An increased amount of beta-amyloid (Aβ) is found in the brains of AD patients. This overproduction may be related to the mutation of the genes encoding presenilins I and II (PSEN1 and PSNE2) and amyloid precursor protein (APP). In addition to these mutations, early-onset AD may also be related to mutations in apolipoprotein E (apoE) and tau protein genes [24]. The etiology of late-onset AD is often associated with a complex synergy of factors, such as the susceptibility to multiple genes (the E4 allele of the *apoE* gene, for example) and environmental factors [25]. ApoE is essential for repairing damage to neurons by redistributing lipids to axons and regenerating Schwann cells, restoring synaptic-dendritic connections [26].

One of the main characteristics of AD is the accumulation of Aβ peptide in the brain. Multiple forms of this peptide are derived from cleavage of the APP, the expression of which increases during cell stress [27]. The homeostasis of the CNS depend on the levels of Aβ in the brain, which assist in vital processes such as synapsis, calcium homeostasis, neurogenesis, the antioxidant system, and metal ion capture [28]. An altered level of Aβ peptide leads to the formation of amyloid fibrils. In a cascade of events, amyloid fibrils trigger amyloid plaques and formation of neurofibrillary tangles (NFTs), causing a loss of synapses and neuronal death [29].

Another factor associated with AD is the tau protein, which contributes to the assembly and stabilization of microtubules [30] and is important in the regulation of plasticity and synaptic function [31]. Under physiological conditions, phosphorylation of tau proteins for binding to microtubules occurs in a balanced way. However, when they are hyperphosphorylated, tau proteins undergo conformational changes leading to the formation of NFTs, destabilization of associated microtubules, synaptic damage, and neurodegeneration [29]. In addition to amyloid plaques and NFTs, the presence of extensive oxidative stress and dysregulation of calcium homeostasis are also characteristic of an AD patient's brain [32]. Aβ can promote cellular calcium overload, inducing associated oxidative stress and formation of pores in the cell membrane [33]. Oxidative stress can increase Aβ production and tau hyperphosphorylation, promoting the onset and progression of AD [34]. Other events may influence the pathogenesis of AD, such as defective autophagy [35], mitochondrial dysfunction [36], synaptic dysfunction [37], and neuroinflammation [38]. AD causes several types of tissue damage, including brain atrophy, loss of neurons, and amyloid angiopathy [39].

Tests for the presence of microorganisms in the nervous system of patients with AD manifestations have yielded positive results for fungi [40, 41], bacteria [15], and viruses such as CMV, HSV-1, HHV-6, and hepatitis C virus (HCV). Unlike the brains of young patients, postmortem examination of the brains of elderly people with AD has shown them to be positive for HSV-1 DNA [42]. Seropositivity for HSV has already been associated with the development of AD in other studies [43–45]. Reactivation of HSV-1 in the CNS has been suggested to be the main connection between HSV-1 infection and AD development. This reactivation triggers an inflammatory process, causing damage to the cells, along with formation of amyloid plaques and NFTs [7]. The HSV-1 glycoprotein B (gB) is 67% identical to the Aβ peptide. In an *in vitro* study, gB promoted the development of Aβ fibrils in primary cortical neurons, causing cytotoxicity [46]. Decreased Aβ clearance and the accumulation of amyloid plaques in AD can impair cell autophagy [47]. Neuroblastoma cells infected with HSV-1 also produce hyperphosphorylated tau protein [48]. ApoE seems to have a strong correlation with HSV-1 lip infection in the peripheral nervous system, with the E4 allele being present in 60% of those infected [42]. In mice infected with HSV-1, viral DNA concentrations in the brain were 13.7 times higher in apoE +/+ wild-type mice than in apoE -/- knockout mice. Also, HSV-1 infection induces the expression of cytokines and proinflammatory molecules that can cause oxidative damage [49]. In human neuroblastoma cells infected with HSV-1, experimentally induced oxidative stress has been shown

Table 1 Viruses and their neurological impact

Viruses			Neurological impact		References
Classification		Primary infection/ latency			
Herpesviridae	Herpes simplex virus 1 (HSV-1) Subfamily *Alphaherpesvirinae*	Epithelial cells of the oral and genital mucosa/ sensory ganglion neurons	AD	Periodic reactivations of the virus in the CNS – direct cytotoxicity and inflammatory damage in the CNS Formation of amyloid plaques and NFTs ApoE4 factor Oxidative stress	[7, 42, 49, 50]
			PD	Molecular mimicry with α-synuclein promoting its aggregation and consequent neuronal degeneration Increased TNF-α secretion inducing the death of dopaminergic neurons	[77, 78]
			Epilepsy	The encephalitis caused by the infection can lead to epilepsy. Inflammatory processes – increased neuronal excitability, contributing to epileptogenesis Neurotropism – damage to brain tissue and neurological sequelae	[111–113]
			GBS	Inflammatory nerve injury caused by cross-reactive antibodies against HSV-1 (anti-GQ1b antibodies) Alteration of ganglioside composition on the cell surface of neuronal and glial cells	[165–168]

Table 1 (continued)

Viruses			Neurological impact		References
Classification		Primary infection/ latency			
	Cytomegalovirus (CMV) *Human herpesvirus 5* (HHV-5) Subfamily *Betaherpesvirinae*	Mucosal epithelial cells and leukocytes/ peripheral blood $CD14^+$ monocytes and bone marrow $CD34^+$ cells	AD	Increase of pro-inflammatory cytokine IFN-γ in the CNS and peripheral tissue and association with the formation of NFTs	[55, 56]
			PD	Immunological reactivation Secretion of pro-inflammatory cytokines by dendritic cells Autoimmune response to neuromelanin	[80, 81]
			Epilepsy	The inflammatory process generated by the activation of microglia triggers the release of cytotoxic substances that lead to cell damage and induce necrosis.	[117]
			GBS	Expression of an immunogenic GM2-like epitope Autoantibodies against moesin production	[170, 171]
	Human herpesvirus 6 (HHV-6) Subfamily *Betaherpesvirinae*	B lymphocytes/ monocytes and macrophages, salivary glands, brain and kidneys	AD	The infection causes a cascade of events, such as decreased autophagy and the stress activation of the endoplasmic reticulum, which may trigger the generation of Aβ, causing tau protein hyperphosphorylation	[59]
			PD	Parainfectious cytotoxic changes, immunologically mediated mechanisms, or direct CNS invasion	[79]
			Epilepsy	Tropism for glial cells	[110]
			GBS	Important antigen-antibody reaction Polyclonal B cell activation Reactivation of a latent infection	[155, 156, 162, 172]
			MS	The latency established by HHV-6A in oligodendrocytes may contribute to, or even trigger an autoimmune reaction that leads to myelin impairment. Affecting the repairing process of myelin in the brain by infecting OPCs	

Table 1 (continued)

Viruses			Neurological impact		References
Classification		Primary infection/ latency			
	Epstein-Barr Virus (EBV) Subfamily *Gammaherpesvirinae*	Mucous epithelial cells/ B lymphocytes	PD	Molecular mimicry with α-synuclein promotes its aggregation and consequent neuronal degeneration.	[77]
			GBS	Polyclonal B cell activation Vascular damage: direct invasion of endothelial cells or immune-complex-mediated	[162, 175]
			MS	Stimulates the expression of HERVs that contribute to the development of MS EBV replication in CNS chronically activates the immune system, recruiting microglia and astrocytes, which become destructive and neurotoxic. EBV-infected B-cells are not able to protect proteolysis-sensitive immunodominant MOG from the cytotoxic effects of T cells, leading to impaired myelination of CNS nerves and damage to the structural integrity of the myelin sheath. Primary EBV infection induces an increase in BBB permeability.	[143–146, 148–150]
Orthomyxoviridae	Influenza A virus subtype *H5N1* (H5N1)	Respiratory tract Infects the CNS (mice)	PD	The direct or indirect inflammatory response in the CNS with degeneration of dopaminergic neurons Neuronal loss in SNpc	[8, 71]
			GBS	Anti-glycolipid antibody production (infection) Autoimmune responses (vaccine) Increases the permeability of BBB by endotoxin Formation of sialic acid-HA complexes that mimic GM-1	[176]

Table 1 (continued)

Viruses			Neurological impact		References
Classification		Primary infection/ latency			
Flaviviridae	Hepatitis C virus (HCV)	Peripheral blood lymphocytes and monocytes	AD	Direct damage to the CNS by activation of neurotoxic cytokines (TNF-α, IL-6) Indirect damage by chronic systemic inflammation that may affect the CNS	[60, 61]
			PD	Positive regulation of chemokines with dopaminergic neurotoxicity	[83]
			GBS	Reactivation of the virus or its enhanced replication Immune complex deposition along the vascular endothelium Anti- MAG antibody production	[162, 179, 181]
	Dengue virus (DENV)	Dendritic cells, monocytes, and macrophages	Epilepsy	DENV infection may lead to meningitis, encephalitis, and encephalomyelitis.	[119]
			GBS	Pro-inflammatory cytokine production Cross-reactivation of antibodies with endothelial cells (anti-NS1) and platelets	[182–184]

Table 1 (continued)

Viruses			Neurological impact		References
Classification		Primary infection/ latency			
Retroviridae	Human immunodeficiency virus (HIV)	Dendritic cells, followed by T-helper cell ($CD4^+$ T)/ memory T cells	PD	Accumulation of α-synuclein in SNpc, presence of HIV in inflammatory infiltrates, glial cells and in the substantia nigra Deregulation of protein levels associated with PD (DJ1 and LRRK2)	[87, 88]
			Epilepsy	Secondary infections of the CNS and metabolic disorders Formation of autoantibodies, causing neuronal death, with increased exocytosis of glutamate and decreased recapture, which leads to the activation of calcium channels and consequent neuronal hyperexcitability	[125–128]
			GBS	Direct action on the nerves by neurotropic strains or autoimmune mechanisms Alteration of BBB integrity by Tat, gp120, and Nef Increase of TNFα	[185, 188, 189]
Coronaviridae	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Cells in the respiratory tract, most likely type II pneumocytes in the lungs, goblet secretory cells in the nasal passages, and the absorptive enterocytes in the intestines Suggested neurotropism to brain cells (due to high expression of ACE2 receptors in this organ)	*SARS-CoV-2 infection may trigger encephalitis, seizure (or focal status epilepticus), meningitis, acute cerebrovascular diseases, impaired consciousness, skeletal muscle symptoms, agitation, confusion, and signs of corticospinal tract dysfunction *This infection may trigger immune-mediated processes, which may lead to GBS. *SARS-CoV-2 infection is likely to trigger demyelination similar to MS. *SARS-CoV-2 causes a cytokine storm, which may trigger acute necrotizing hemorrhagic encephalopathy and BBB disruption.		[195-203, 205, 211-213]

AD, Alzheimer's disease; PD, Parkinson's disease; GBS, Guillain-Barré Syndrome; MS, multiple sclerosis; HERVs, human endogenous retrovirus; MOG, myelin oligodendrocyte glycoprotein; OPCs, oligodendrocyte progenitor cells; BBB, blood-brain barrier; CNS, central nervous system; NFTs, neurofibrillary tangles; apoE4, apolipoprotein E4; TNFα, tumor necrosis factor alpha; IFN-γ, interferon gamma; GM-1, gangliosidosis 1; IL-6, interleukin 6; anti-MAG, anti-myelin-associated glycoprotein; SNpc, substantia nigra pars compacta; Tat, transativator of transcription; Nef, negative regulatory factor

*All neurological effects of SARS-CoV-2 infection described in the table are based on isolated cases or studies based on a small group of patients infected. Further investigation must be conducted to clarify the neurological effects of SARS-CoV-2 infection. Also, long-term monitoring of patients is necessary to verify its impact on neuronal function and its possible impact on the development of neurological diseases.

Source: authors

to significantly increase the accumulation of intracellular Aβ, inhibit Aβ secretion, and potentiate the accumulation of autophagic compartments within the cell [50].

Another HHV related to AD is CMV. Studies have demonstrated that individuals with higher levels of CMV IgG have more significant cognitive decline and a higher risk of developing AD [51–53]. Also, 93% of brains with vascular dementia that were examined postmortem were positive for CMV [54]. CMV-specific $CD8^+$ T cells produce increased amounts of proinflammatory IFN-γ and decreased levels of the anti-inflammatory cytokines IL-2 and IL-4, with a potential shift to a proinflammatory cytokine profile in elderly people [55]. Serum levels of CMV-specific IgG have been shown to be significantly associated with NFTs. An increase in IFN-γ was also detected in the cerebrospinal fluid (CSF) of more than 80% of subjects who were positive for CMV [56].

HHV-6 rarely causes serious CNS complications; however, its ability to establish latency in the brain with possible reactivation under conditions of immunosuppression may relate this virus to AD development [57]. HHV-6 has been found in the brain [58] and leukocytes of AD patients, being significantly associated with the development of the disease and the cognitive decline of these individuals [52]. It has been suggested that HHV-6 deregulates autophagy and activates a stress response in the endoplasmic reticulum in various types of cells, particularly in astrocytes. The reduction of autophagy increases the production of Aβ and activates the stress response in the endoplasmic reticulum, promoting hyperphosphorylation of the tau protein [59].

Studies have also suggested a relationship between HCV and AD. It has been proposed that this occurs thorough direct viral infection in the brain or through cerebral or systemic inflammation [60]. In the first hypothesis, HCV can infect monocytes/macrophages, cross the BBB, and provoke the secretion of large amounts of cytokines (TNF-α, IL-6), causing cytotoxicity in the brain tissue. In the second hypothesis, HCV activates the immune system, triggering excessive systemic or local inflammation [61].

Parkinson's disease (PD)

PD is a neurodegenerative motor disease, initially described by James Parkinson as "paralysis agitans" [62]. Approximately 10 million people are living with PD worldwide. Four percent of PD patients are under the age of 50, and the incidence of this disease increases with age [63]. An epidemiological study based on a North American population has suggested that, by 2030, over 1.2 million people will be living with PD [64]. This disease is characterized by motor changes, cognitive impairment, and autonomic dysfunction [65]. The damage caused by PD is related to dopaminergic neuron degeneration that occurs in the nigrostriatal pathway. The reduction of striatal dopamine modulation is also responsible for disease signs [66]. These alterations happen not only in the substantia nigra (SN) but also in the dorsal motor nucleus of the vagus and peripheral neurons [67].

Lewy bodies are formed mainly by α-synuclein, neurofilament proteins, and ubiquitin. It is suspected that presynaptic α-synuclein is the main protein involved in the formation of these bodies. Genetic or epigenetic factors may be responsible for their appearance in neurons. The PD development is related to the protein aggregates formed inside the nerve cells and their location in the brain. That is, if Lewy bodies are located in the nigrostriatal pathway, they would be related to extrapyramidal manifestations; in autonomic ganglia, postural hypotension; in the limbic cortex, psychosis; and, in the neocortex, cognitive decline [68, 69].

A D620N mutation in vacuolar sorting protein 35 (VPS35) causes subcellular retromer complex dysfunction; therefore, it is believed that it may affect the pathogenesis of PD. An alteration in retromer cargo molecule trafficking, a reduction of cell survival, and alteration of α-synuclein processing were observed when the D620N mutation was present. The retromer complex is also used by viral and bacterial pathogens to aid in their assembly, replication, and movement within the cell and as a mechanism to avoid the destruction that may be triggered by the cell defense machinery [70].

After the H1N1 pandemic in 1918, the number of cases of post-encephalitic parkinsonism and lethargic encephalitis increased. Based on this fact, a "dual-hit hypothesis" was suggested regarding PD pathogenesis. It was proposed that microorganisms may enter the host via the intestinal mucosa and attack the nervous system. These neurotropic agents may infect the substantia nigra pars compacta (SNpc) and trigger neurodegenerative events [71].

Although rare, experimental evidence has shown that some influenza A viruses are neurotropic, moving into the nervous system following systemic infection [72–74]. H5N1 influenza virus was used to infect the CNS of mice. A continuing inflammatory response in the animals' brains was demonstrated after the viral infection, which may have induced degeneration of dopaminergic neurons [8]. The H1N1 influenza virus does not appear to be neurotropic in mice, suggesting that the peripheral immune response activated after an infection is probably responsible for the secondary inflammation observed in the CNS [75].

HHV infection is also associated with PD development. Elevated serological test values and the presence of serum inflammatory cytokines and α-synuclein support this theory. Moreover, studies suggest a relationship between viral load and the severity of PD symptoms [76]. Scientists have proposed a role of molecular mimicry between HSV-1 (region *Ul4222-36*) and α-synuclein (*αsyn100-114*). In the membrane of SNpc dopaminergic neurons, this phenomenon may

trigger aggregation of α-synuclein and subsequent neuronal degeneration. A similar mechanism is observed for EBV, with molecular mimicry between a repeat region in latent membrane protein 1 (LMP1) encoded by EBV and the C-terminal region of α-synuclein, inducing its oligomerization [77]. HSV-1 infection may be associated with secretion of TNF-α, which is known to be involved in PD pathogenesis. It has been reported that dopaminergic neurons are very susceptible to TNF-α, which may affect the cells' plasticity, and that neuronal death can occur in response to TNF-α binding to its receptors [78].

Parkinsonism symptoms were described in a patient who demonstrated HHV-6 infection reactivation after transplantation. Brain injuries may indicate parainfectious cytotoxic changes, direct CNS invasion, or immunologically mediated mechanisms [79]. Immunological reactivation may also be related to the development of PD in CMV infection. Dendritic cells, which preferentially secrete proinflammatory cytokines, are in higher numbers in patients with CMV and PD than in patients with CMV without PD [80]. In addition, the possible immunogens presented by these cells may be derived from dopaminergic neurons, triggering an autoimmune response to neuromelanin [81].

Studies suggest that patients who have previously been infected with HCV are more likely to develop PD. HCV may replicate in the CNS, triggering a higher prevalence of mental illness in chronic HCV patients than in the general population [82]. Dopaminergic neurotoxicity after HCV infection has been observed in co-cultured neuron-glial cells from rats. Also, it has been suggested that HCV infection induces positive regulation of ICAM-1 (intercellular adhesion molecule 1) and RANTES (regulated on activation, normal T expressed, and secreted) chemokines [83]. Tissue inhibitor of metalloproteinases 1 (TIMP-1), which is responsible for neuronal survival, is downregulated by HCV [71]. The entry and replication of this virus in the CNS may be facilitated by the high level of expression of HCV receptors in the brain microvascular endothelium [84]. Despite this fact, no correlation was found between HCV infection and PD development when more than one million patients were studied in the USA [85]. The discrepancy in the results was suggested by the substantial difference in the geographic areas of the studies, considering the prevalence of the infection, pathogenic profile of the genotype, variability of extrahepatic manifestation, and association with comorbidities.

Patients infected with HIV may develop parkinsonian features. This movement disorder may be triggered by a cascade of events caused by the infection, such as basal ganglia dysfunction, BBB alteration, chronic neuroinflammation, and neurodegeneration [86]. Post-mortem autopsies demonstrated signs of HIV in the brain, mostly in inflammatory infiltrates and glial cells, and a higher prevalence of α-synuclein in SNpc [87]. DJ1 regulates the production of reactive oxygen species (ROS) and dopamine transmission in neurons, whereas leucine-rich repeat kinase 2 (LRRK2) mediates neuroinflammation and neuronal damage. Studies suggest that HIV infection may influence DJ1 and LRRK2 levels [88].

Epilepsy

Epilepsy is an ND characterized by the rapid occurrence of epileptic seizures due to abnormal or excessive brain/neuronal activity [89]. An individual can also be diagnosed with epilepsy if he or she experiences an unprovoked or reflexive seizure and has at least a 60% chance of developing another seizure in the next 10 years [90]. Approximately 20% of all epilepsy cases are caused by acute CNS insults, 11% by cerebrovascular accident, 6% by traumatic brain injury, and 4% by infections [91]. Changes associated with post-traumatic epilepsy (PTE) include hemosiderin deposition with an incompletely formed wall of gliosis [92] and persistent BBB disruption. A correlation is also found between late-poststroke seizures and BBB disruption [93]. Post-injury epilepsy develops most commonly in the temporal and frontal lobes [94]. PTE and some infections cause an initial lesion, and if it is outside of the temporal lobes, it may result in seizures due to mesial temporal sclerosis (MTS) [94, 95]. After an injury, the latency time for the development of seizures may vary, suggesting possible variability in mechanisms of epileptogenesis [91]. Surgical specimens from patients with epilepsy show common pathological features that may be relevant to the epileptogenic process, such as astrocytes activated at the BBB, inflammatory cellular infiltrates, extravasation of blood, severe injury, disruption of the BBB with encephalitis, and involvement of frontal or temporal lobes. The majority of these features are associated with inflammatory responses [91, 94].

Inflammation in the CNS may participate in the progression of epileptogenesis as well as in the induction of seizures [96]. The progression of seizures depends on several factors. This cascade of events includes exacerbated generation of inflammatory factors, such as prostaglandin E2 (PGE2), IL-1β, IL-6, and TNF-α, and activation of inflammatory mediators, cyclooxygenase (COX)-2, and nuclear factor kappa B (NF-κB), for example [97]. Depending on its receptor, TNF-α may act as a pro-convulsant via TNF receptor 1 (TNFR1) or an anti-convulsant through TNF receptor 2 (TNFR2) [98]. Similar to other proinflammatory cytokines, such as IL-1β and TNF-α, IL-6 signaling may activate NF-κB transcriptional signaling and induce the synthesis of PGE2 by COX-2. These physiological changes assist in regulating immune and inflammatory responses [99]. The overexpression of TNF-α or IL-6 in mice leads to chronic inflammation in the brain, predisposing to seizures [100].

A great diversity of viruses has been associated with epilepsy [13, 101, 102]. One hypothesis suggests that common childhood viral infections can generate acute and chronic inflammatory processes in the CNS, which increases BBB permeability and neuronal excitability [103]. Acute seizures and epilepsy have been linked to HHV-6 infections, especially in children [104]. The number of HHV-6 infections associated with mesial temporal or temporal lobe epilepsy range from 9.1% to 55.6% [5, 105]. However, many HHV-6 infections are not associated with epilepsy, and the association of this virus with ND is controversial [106–109]. HHV-6 has a tropism for glial cells, and as the nasal cavity is constituted of oligodendrocyte progenitor cells (OPCs), the virus can replicate and cause a significant increase in the production of IL-6, chemokine ligand 1 (CCL-1), and CCL-5 [110].

HVS-1 is the leading agent of viral encephalitis, with an incidence of 2 or 3 cases per million people, per year [111]. Studies suggest that encephalitis caused by HSV-1 replication increases the likelihood of spontaneous seizures and epilepsy by approximately 20%. This fact is due to the involvement of the frontotemporal cortex, including the hippocampus, elevated CSF opening pressure, and signs of cerebral hernia [112, 113]. When viral replication is activated during latency, HSV-1 can ascend through the trigeminal and olfactory nerves to the frontal and temporal lobes, spreading to other regions of the brain [114]. HSV-1 infections trigger an inflammatory response, recruiting activated leukocytes, which, when repeated continuously, may cause brain tissue damage and neurological sequelae [111].

Less commonly, CMV and EBV may also cause nonparaneoplastic autoimmune encephalitis, which has been related to late-onset epilepsy. Antineuronal autoantibodies were detected in 48 of 113 patients with epilepsy and suspected autoimmune encephalitis [115]. The relationship between epilepsy and congenital CMV infection indicates that the 37% of the patients developed epilepsy at approximately 20 months of age [116]. CMV infection may affect the fetus directly via virally encoded gene products that may impair vital cellular processes, such as the cell cycle, cellular proliferation, and apoptosis, or induce inflammatory responses, trigger vascular injury, and promote evasion of host immune responses [117]. Increased expression of late CMV genes has been reported in individuals with intractable epilepsy, in addition to higher levels of CMV-IgG and CMV-IgM, highly sensitive C-reactive protein (Hs-CRP) and IL-6, suggesting increased viral replication and inflammatory responses in these patients [118].

It is known that several arboviruses can cause meningitis, encephalitis, and encephalomyelitis [119]. Verma and Varathanaj [120] reported a case of *epilepsia partialis continua* associated with dengue virus (DENV) encephalitis. Although seizures occur in approximately 47% of encephalitis cases caused by DENV, it is not possible to establish a causal relationship between encephalitis and the epileptic condition. According to Guabiraba et al. [121], there is currently no specific *in vivo* model that can demonstrate the relationship of epileptic manifestations and the pathogenesis of DENV infection. Trials were conducted in AG129 mice, which are deficient in interferon (IFN) types I and II and are highly susceptible to DENV infection [122]. When these animals were infected intraperitoneally with a neurotropic strain of DENV-2, 100% paralysis and lethality was demonstrated [123].

The prevalence and incidence of epilepsy and seizures among HIV patients are higher than in the general population. About 5 to 10% of HIV-positive patients in developed countries present with seizures or epilepsy [124]. It is known that HIV can invade neural tissue; however, there is still no proof of the relationship between the damage caused by the virus and seizures. Factors that may be associated with seizures and epilepsy in HIV-positive patients include the course of the disease and the establishment of acquired immunodeficiency syndrome (AIDS), opportunistic infections, and metabolic disorders [125]. Also, HIV infection can induce the formation of autoantibodies, causing neuronal death, with increased glutamate exocytosis and decreased recapture. Glutamate depletion is associated with the activation of calcium channels stimulated by phosphorylation of N-methyl-D-aspartate receptors by kinases arising from the activation of IL-1 receptors, causing neuronal hyperexcitability, with a consequent decrease in the seizure threshold [126–128].

Multiple sclerosis (MS)

MS is an immune-mediated disease in which the myelin sheath of CNS neurons is injured and the communication between the muscles and the brain is progressively interrupted [129]. The International Advisory Committee on Clinical Trials of MS classifies four basic courses for this disease: clinically isolated syndrome, relapsing-remitting, secondary progressive, and primary progressive. The most frequent kind of MS is relapsing-remitting MS (RRMS) [130]. Patients may exhibit cognitive deficits, such as difficulties in processing information and impairment of working memory and attention, as well as balance, locomotion, and fine motor control [131, 132]. Spasticity is a common symptom in MS patients. This condition is characterized by hyperreflexia, spasms, poor muscle tone, and pain, causing severe functional disability, which compromise the quality of life of these patients [133]. The prevalence of MS varies worldwide, reaching 12.8 out of every 100,000 inhabitants in Asia [134], 290 in Canada, 203 in the United Kingdom, 189 in Sweden, and 3.2 in Ecuador [135].

Although the etiology of MS is still uncertain, immunological, genetic, and environmental risk factors have been proposed. Immunological factors that trigger MS are related to T cells and antibodies, which are autoreactive in these patients. Inhibitory molecules, which generally regulate adaptive system activation, are impaired and are not able to suppress uncontrolled immune responses in MS patients. As a consequence, the chronic inflammation process leads to further damage [136]. Family clustering and specific genetic characteristics are being examined as risk factors for MS. While the general population shows a 0.1% risk of recurrence, first-degree relatives of MS index cases have up to a 50-fold greater risk of developing the disease. Moreover, smoking, body mass index, and vitamin D are among the environmental factors that may influence the onset of this disease [137, 138]. Although the etiology of MS is multifactorial, viral infections are mentioned as one of the disease's environmental risk factors.

When analyzing the relationship between HHV-6 and EBV infections and MS, higher titers of antibodies against these viruses and a higher seroprevalence were found in patients with the disease when compared to healthy paired-control subjects [139]. The first evidence correlating EBV infection and MS was the fact that MS patients' B lymphocytes carry and transport EBV antigens [140]. Subsequently, other evidence was suggested, such as genetic susceptibility and EBV infection, as a higher risk of MS was found in individuals with infectious mononucleosis (IM) [141, 142]. The indirect effect of EBV on MS onset may be related to the activation of silent human endogenous retrovirus W (HERV-W) [143]. *In vitro* and *in vivo* studies demonstrated that the envelope protein (Env) of HERV-W may trigger inflammatory responses and cause cytotoxicity, as well as cell death [144, 145]. Another hypothesis suggested a cascade of events evolving EBV, B cells, T cells, and inflammation processes. In healthy seropositive individuals, the immune system manages to regulate the memory B cells against the latent virus, so there are no further complications. However, in individuals who are genetically predisposed to MS, memory B cells can cross the BBB and trigger an inflammatory response in the CNS and, consequently, germinal-center-like structures. T cells may be activated at this point, and the infected cells, although latent and with limited viral gene expression, may act as antigen-presenting cells. After differentiation, some infected memory B cells can trigger the EBV replicative cycle and the production of virions. In diseases such as MS, microglia and astrocytes are chronically activated, causing neurotoxicity [146].

Myelin oligodendrocyte glycoprotein (MOG) is an essential glycoprotein involved in the myelination process in CNS nerves. MOG is also responsible for ensuring the structural integrity of the myelin sheath [147]. Changes in MOG have been experimentally associated with B cells infected with EBV, which convert the destructive processing of MOG into productive processing. This conversion facilitates the cross-presentation of the pathogenic MOG epitope (residues 40-48) to autoaggressive cytotoxic T cells [148]. Additionally, studies have shown that during primary EBV infection, this virus may induce an increase in BBB permeability, which allows pre-existing polyclonal antibody-producing B cells to penetrate the CNS. This event could explain the lower levels of EBV-specific IgG antibodies in the CNS compared to IgG produced against other viruses [149, 150].

When relating HHV-6A and HHV-6B with MS, HHV-6A was more prevalent in serum and urine samples of patients with MS than HHV-6B [151, 152]. The first murine model of HHV-6-induced brain infection was developed by Reynaud et al. [153]. First, these researchers studied different transgenic mouse lines and their ability to express the receptor for HHV-6, CD46. Further results showed that HHV-6A, but not HHV-6B, triggered the expression of viral transcripts in primary brain glial cultures from CD46-expressing mice. HHV-6B DNA did not persist in the brain, decreasing rapidly after the infection, while HHV-6A DNA levels remained high for up to 9 months. Immunohistological analysis showed the infiltration of lymphocytes in the periventricular region of mice infected with HHV-6A. Moreover, this virus triggered production of proinflammatory chemokines such as CC-chemokine ligand 2 (CCL2), CC-chemokine ligand 5 (CCL5), and C-X-C motif chemokine ligand 10 (CXCL10). A recent study measured IgG reactivity against HHV-6A and HHV-6B immediate-early protein 1 (IE1A and IE1B) and showed a positive association between IgG response against IE1A and an increased risk of developing MS in the future. In contrast, a negative association between the IgG response against IE1B and MS was demonstrated. Therefore, this study supports the role of HHV-6A in the etiology of MS by showing an increase in serological response against the immediate-early protein of this virus [154]. Oligodendrocytes are myelin-producing cells that are targeted by the immune system of patients with MS. The latency established by HHV-6A in oligodendrocytes may contribute, or even trigger, this unwanted autoimmune reaction, which leads to myelin impairment [155]. In patients with MS, in addition to the ongoing destruction of myelin, impairment in myelin repair by differentiating OPC is observed [156].

Guillain-Barré syndrome (GBS)

GBS is characterized by a dysfunction in the peripheral nerve, which suggests that immune and inflammatory mechanisms are involved [157]. Its main clinical manifestations are the absence of reflexes, paresthesia with sensory loss, and motor weakness [158]. Classification of GBS into subtypes depends on the underlying pathology, clinical presentation, and neurophysiological features. The most

common subtypes include the following: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute axonal motor neuropathy (AMAN), acute motor-sensory axonal polyneuropathy (AMSAN), and Miller-Fisher syndrome (MFS) [159].

In GBS, antibodies and inflammatory cells produced in response to infections cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage [160]. Macrophages initiate damage to the peripheral nervous system (PNS) by producing and secreting matrix metalloproteinases and nitric oxide. As a consequence, activated T cells release proinflammatory cytokines such as TNF-α [161]. The humoral response is initiated through activation of B cells, and antigen-antibody interactions can activate the complement system, resulting in membrane attack complex (MAC) formation and leading to nerve cell membrane damage and destruction [162]. Multiple antecedents and potentially triggering events have been reported. The association with infections has been established for *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae,* and the viruses CMV, EBV, influenza A virus, and Zika virus [163]. Some genetic and environmental factors that affect the susceptibility of individuals to the disease have also been described [164].

Cases of patients with a combination of HSV-1 and GBS are suggested by the occurrence of molecular mimicry and high serum anti-GQ1b IgG antibody titers, causing inflammatory nerve damage [165–167]. Infection with HSV-1 could cause a change in the ganglioside composition of neuronal and glial cell surfaces, followed by the activation of autoantibodies in patients with antiganglioside antibodies [168]. Molecular mimicry is also proposed between CMV and GBS, which is the most frequent infectious etiology of GB, described for the first time by Klemola et al. [169]. Patients with CMV who develop GBS have high levels of anti-GM2 antibodies in their CSF and serum. In these people, carbohydrate structures similar to the GM2 ganglioside may induce antiganglioside antibodies [170]. Also, autoantibodies against moesin, which is crucial for myelination, have been demonstrated in 83% of patients with CMV-GBS. This may be due to six consecutive amino acids that are identical in moesin and CMV phosphoprotein 85 [171].

Although studies have associated HHV-6 infection with GBS development, this theory is generally based on minimal observations such as significantly higher antibody titers to HHV-6 in GBS patients compared to control groups [172]. This persistence of HHV-6 antibodies in the serum can be due to a stronger antigen-antibody reaction or to polyclonal B cell activation. Reactivation of latent HHV-6 infection has also been considered, but the influence of HHV-6 in GBS etiology is still inconclusive due to the lack of experimental studies [162]. The neurological involvement of EBV is also unusual, but it should be treated as a post-infection disease due to the abnormal immunological response observed [173]. Grose and Feorino [174] described five cases of GBS with high levels of antibodies to EBV, even in the absence of IM. Multivariate analysis showed that of 154 GBS patients, 10% had serologic evidence of recent EBV infection [6]. It has been suggested that the virus has a predilection for B lymphocytes and that it activates polyclonal B cells with increased production of immunoglobulins [175]. Other studies have suggested that EBV may infect endothelial cells and trigger vascular damage or cause vessel inflammation mediated by the immune complex, which could trigger the development of GBS [162].

The envelope of the influenza A virus consists of a lipid bilayer containing several glycoproteins, such as neuraminidase (NA) and haemagglutinin (HA). Therefore, anti-glycolipid antibodies may be produced during influenza virus infection because of possible molecular mimicry between glycoproteins of influenza viruses and glycolipids localized in human peripheral nerves [176].

Infectious hepatitis has been associated with GBS etiology. The case of a patient with manifested distal paresis of both legs and arms with areflexia and paresthesia was studied by De Klippel and collaborators [177]. Scientists believe the disease onset occurred during the pre-convalescent phase of an acute HCV infection, when the level of liver enzymes was consistently and rapidly normalized and signs of fibrosis were found in this organ. GBS may also occur in patients with chronic HCV infection, albeit rarely [178]. The reactivation of the virus or its intense replication may trigger the development of GBS [179]. A case of severe GBS was related to chronic active HCV infection and mixed cryoglobulinemia (MC) [180]. Other findings, such as immune complex accumulation in the vascular endothelium and vasculitis over the nerve, may explain the relationship between the infection and GBS onset [162]. A few cases of peripheral neuropathy secondary to chronic HCV infection have been described. These cases were often associated with cryoglobulinemia or with anti-myelin-associated-glycoprotein (MAG) antibodies [181].

Scientific studies were performed on the relationship between DENV infection and GBS. The infection may directly influence the disease or trigger postinfectious autoimmune responses that might lead to GBS [171]. Several studies on DENV infection have demonstrated abnormal immune responses, including cytokine and chemokine production, complement activation, and immune cell activation. Shah [182] suggested that proinflammatory cytokines that participate in the immune response in dengue fever might play a causal role in the etiopathogenesis of GBS. This infection may cause the generation of a complex immune response, with high levels of TNFα, IL-2, and IFNγ, as well as an inversion of the CD4:CD8 ratio [183]. Also, autoimmune responses may be involved, mainly in the

pathogenesis of the severe phase of dengue. Patients with dengue can produce antibodies that cross-react with platelets and endothelial cells. After DENV infection, antibodies against nonstructural protein 1 (anti-NS1) are generated. Studies suggest these antibodies may influence the cross-reactivity of endothelial cells, which play a crucial role in the development of neurological disease [184].

One of the proposed mechanisms for GBS in HIV-1-infected patients includes a direct action of an HIV-1 neurotropic strain on the nerves. Another theory is based on an autoimmune response, in which abnormal immunoregulation is followed by the formation of antibodies against myelin [185]. HIV can cause direct and indirect neurotoxic effects on the CNS and PNS. The relationship between GBS and the stage of HIV infection is also unclear. The authors characterized the GBS as an indication of early HIV infection or seroconversion [186]. However, GBS has been reported in chronic HIV-1 infection cases or as a complication of immune reconstitution inflammatory syndrome in severely immunocompromised patients [187]. The HIV-1 infection may alter the integrity of the BBB through the action of the viral proteins Tat, gp120, and Nef [188]. In a study using a murine model, exposure to HIV-1 envelope protein gp120 caused swelling and increased TNFα levels in the sciatic nerve trunk. These findings suggest that HIV infection may cause nerve damage [189].

SARS-CoV-2, the virus responsible for COVID-19 pandemic, and its neurological impact

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is the virus responsible for the disease COVID-19 [190], a global pandemic that started in late 2019 and in a few months has affected 250 countries around the world [191]. Coronaviruses (CoVs) typically cause respiratory disease in humans; however, some studies suggest an association with neurological symptoms. Two different coronaviruses that caused epidemic infections in the past, SARS-CoV, and Middle East respiratory syndrome-associated coronavirus (MERS-CoV), have triggered neurological harm in isolated cases [192]. Patients infected by these viruses have developed neurologic symptoms, such as neuropathy, myopathy, Bickerstaff brainstem encephalitis (BBE), and GBS, two to three weeks after the appearance of typical symptoms [193, 194]. The causality cannot be proven, since these findings were reported in isolated cases and with a small number of patients. On the other hand, some scientists have suggested that the neurological manifestations of MERS might have been neglected and underdiagnosed [193].

In Wuhan, China, a study was performed during the COVID-19 outbreak with 214 patients. The results showed that 36.4% of the patients with severe disease exhibited neurologic manifestations, such as acute cerebrovascular disease, impairment of consciousness, and skeletal muscle symptoms [195]. A study performed in Strasbourg, France, demonstrated that 84% of COVID-19 patients in intensive care units (ICU) who had respiratory difficulties also showed neurological symptoms such as agitation, confusion, and signs of corticospinal tract dysfunction [196]. It has been suggested that these signs of neurological damage might be caused by severe hypoxemia and hypoxia, an inflammatory process triggered by SARS-CoV-2 infection, or by virus infiltration and spread in the brain [197]. The SARS-CoV-2 infection begins with the spike protein S1 binding to the host receptor ACE2 (angiotensin-converting enzyme 2). The human brain expresses ACE2 at a high level, which may allow the virus to invade the CNS [198]. Xiang et al. [199] reported the first confirmed case of encephalitis caused by SARS-CoV-2. The presence of this virus in the CSF of this patient was confirmed by genome sequencing. The first case of meningitis associated with COVID-19 was reported by Moriguchi et al. [200]. Although nasopharyngeal swabs obtained from this patient were negative, the infection was confirmed by viral RNA detection in the spinal fluid.

COVID-19 triggers increased production of inflammatory cells, and along with them, high levels of inflammatory cytokines, which induce immune-mediated processes [201], and this is one of the proposed explanations for GBS symptoms [202]. Sedaghat and Karimi [203] reported the development of GBS in a 65-year-old male COVID-19 patient two weeks after developing cough and fever. In another case study, the first GBS symptoms overlapped with the period of SARS-CoV-2 infection, making investigators unsure about the causal connection between the two [204].

A patient with well-controlled post-encephalitic epilepsy was infected with SARS-CoV-2 and presented with focal status epilepticus in the early stage of the disease. The 78-year-old patient was seizure-free for more than two years, and based on a historical correlation of symptoms, it was suggested that SARS-CoV-2 might have triggered the seizures [205]. The relationship between COVID-19 and epilepsy is still unknown, and conclusions will depend on new reports and updates from clinicians [206].

A study of 90 brain autopsy samples from patients with NDs (mostly MS) and healthy controls showed that 48% of the samples contained human coronavirus RNA [207]. However, further studies should be performed to determine if the presence of virus in human brains is opportunistic or disease-associated. It has been suggested that SARS-CoV-2 infection is likely to trigger demyelination similar to MS. Based on this fact, periodic neurological assessments, such as auditory brainstem responses and neuroimaging, should

be carried out on recovered COVID-19 patients to follow up any signs of dysfunction [199]. When comparing COVID-19 with past viral pandemics, a concern about neuropsychiatric sequelae emerges. Previous outbreaks of virus infection have triggered long-term neurodegenerative effects such as encephalopathy, psychosis, demyelinating processes, and neuromuscular dysfunction, weeks, or even months after the patient's recovery [208]. Therefore, Troyer et al. [209] have also emphasized the need for long-term monitoring of patients who were once infected with SARS-CoV-2. Several neurodegenerative diseases, such as AD, PD, and MS, are related to high levels of cytokines/chemokines and other chronic neuroinflammation effects [210]. In this way, the cytokine storm triggered by COVID-19 and BBB disruption could affect the CNS and cause the onset of these diseases [211, 212]. However, further studies should be conducted to investigate the involvement of SARS-CoV-2 infection in neurodegenerative diseases [211].

Conclusion

In this review, we have discussed a number of studies that relate viral infections to the development of neurological disorders. It is important to consider that viruses are responsible for various epidemics and even pandemics, and some of them can cause irreversible damage to the nervous system. This work demonstrates that considerable attention should be given to the relationship between viral infections and NDs. The inclusion of viruses in the etiology and diagnosis of diseases of the nervous system would have a positive impact on the management and treatment of disabling and potentially lethal complications. New studies that investigate the mechanism of action of the viruses in these pathologies should be encouraged, aiming mainly at the development of novel control and intervention therapies.

Acknowledgements The authors are grateful to Coordination for the Improvement of Higher Education Personnel (CAPES—Proc. Nos. 88881.362216/2019-01; 88882.448082/2019-01; 88882.448103/2019-01) and National Council for Scientific and Technological Development (CNPq), Brazil, for post-graduate scholarships.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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