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Underestimated virus impaired cognition-more evidence and more work to do

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Neurodegenerative disorders (NDs) are chronic neurological diseases that can be of idiopathic, genetic, or potentially infectious origin. Although the exact cause of neurodegeneration is unknown, it might be result of a confluence of age, genetic susceptibility factors, and environmental stresses. The blood-brain barrier shields the brain from the majority of viral infections, however neurotropic viruses are able to breach this barrier and infect central nervous system. Growing research points to a possible connection between viruses and neurodegenerative diseases, indicating that virus-induced neuroinflammation and disruption of neuronal protein quality control may play a role in the initial stages of disease progression. The diagnosis and treatment of NDs are urgent and challenging. Even though there is limited clinical evidence to support the use of antiviral medications and their dose regimens within the central nervous system (CNS), with the exception of acyclovir, they are currently utilized to treat various viral CNS infections. Understanding the neuropathogenesis of viral CNS infection may help with targeted diagnosis and treatment plans by focusing on the molecular mechanisms of the CNS. It may also be helpful in the search for new antiviral drugs, which are crucial for better managing these neurotropic viral infections. This review focuses on new findings linking viral infection to NDs and explores how viral modifications of cellular functions can impact the development of neurodegeneration and will also explore the therapeutic potential of antiviral drugs in NDs.

KEYWORDS

neurodegeneration, virus, antiviral drugs, impaired cognition, dementia

Introduction

Neurodegenerative diseases (NDs) are chronic degenerative disorders of the central nervous system (CNS) that are characterized by the chronic and progressive loss of the structure and function of neurons (1). Millions of people worldwide are impacted by them, making them the fourth most common cause of mortality in developed nations.

Furthermore, their influence is growing in developing countries. With an increasing lifespan, it is expected that the incidence rate will rise. Even with extensive investigation, most NDs' basic root causes are still poorly understood (1, 2). Numerous intracellular mechanisms, such as apoptosis, inefficient axonal transport, mitochondrial malfunction, and protein degradation, are linked to neurodegenerative diseases (3). The etiology of numerous neurodegenerative illnesses has also been linked to long-term viral infections, malnutrition, exposure to heavy metals in the environment, autoimmune reactions, vascular disorders, head trauma, brain fluid buildup, and alterations in neurotransmitter concentrations (2, 4, 5). Viral infections can infiltrate the immune system and other organ systems, resulting in a variety of symptoms (6).

The majority of NDs have a pathogenic connection to the accumulation and aggregation of cellular proteins (7, 8). Notably, dementia with Lewy bodies, multiple systems atrophy (MSA), and Parkinson's disease (PD) have all been associated with α-synuclein (α-syn) aggregates (9). Alzheimer's disease (AD) patients also have extracellular amyloid-β (Aβ) plaques and intraneuronal tangles of hyperphosphorylated tau in their brains (10). Like prions, these pathogenic proteins can aggregate and form pathogenic plaques, which leads to the eventual development of NDs (11, 12). A significant contributing component to these processes is an imbalance in the cellular mechanisms that control the creation of misfolded proteins and their breakdown, or protein homeostasis (13). The potential for viral infections to significantly disrupt protein homeostasis makes cells more vulnerable to protein misfolding (14). Moreover, maintaining protein homeostasis may benefit from the release of pro-inflammatory cytokines and chemokines in response to a virus (15). Up-regulation of pro-inflammatory cytokines plays a dual role in neurodegeneration and neuroprotection. Activated microglia can cause harm by releasing pro-inflammatory cytokines such IL-1β, IL-6, and TNF-α, which affect surrounding brain tissue.

Therefore, it is believed that viruses, particularly neurotropic viruses, play a part in the genesis of various NDs. Table 1 lists the several viruses that are believed to be involved in NDs.

Viruses in neurodegeneration

It is likely that aging, genetic vulnerability, and environmental stressors all play a part in this process, even if the precise etiological reasons of NDs are still not entirely understood. There is mounting evidence that suggests viral infections, especially neurotropic viruses, may play a factor in the onset and progression of depressions that are not diagnosed. The progressive loss of cognitive, motor, and behavioral abilities is a hallmark of neurodegenerative illnesses like AD, PD, and amyotrophic lateral sclerosis (ALS) (53). Despite early assumptions that neuroinflammation results from neurodegeneration, further studies have demonstrated that neuroinflammation can both cause and accelerate the development of NDs. The hypothesis that neuroinflammation causes neurodegeneration was reinforced

by genome-wide association studies (GWAS) that identified immune-related genes, including as CD33 and TREM2, as risk factors for AD (54). Additionally, it has been suggested that neuroinflammatory processes are largely influenced by the ε4 allele of the apolipoprotein E gene (APOE ε4), which is the most powerful genetic risk factor for AD and accounts for around 10–20% of the risk of late-onset illness (55). These genetic factors increase the risk of NDs, but they are not sufficient to cause the condition on their own. There is increasing evidence that viruses and neurodegenerative illnesses are associated (56–59). Virus-induced neuroinflammation and disruption of neuronal protein quality control may also be involved in the early phases of illness development (60). Viruses can begin and/or aggravate degenerative processes because they have the capacity to take over the host cell's internal machinery and induce inflammation. Viral infections can stimulate astrocytes and microglia or allow peripheral immune cells to invade the central nervous system, which can result in neuroinflammation (61). Certain viruses can disrupt neuronal activities, cause neuronal death, or trigger lytic egress from infected neurons, all of which can lead to neurodegeneration. Numerous negative outcomes are brought on by CNS viral infections, such as elevated morbidity and mortality as well as mild to severe neurological aftereffects, shown in Figure 1. Viral infections have a wide range of impact on neuronal dysfunction, including promoting chronic inflammation, inducing cellular oxidative stress, impairing mitophagy, interfering with mitochondrial dynamics, enhancing metabolic rewiring, altering neurotransmitter systems, and inducing misfolded and aggregated pathological proteins linked to neurodegenerative diseases. These pathogenetic processes cause a multifaceted brain injury that results in neuronal and brain dysfunctions. By interfering with the immune system, it can either directly or indirectly induce encephalitis (62). Neurotropic viral infections have an impact on a multitude of factors related to neuronal dysfunction. These include the induction of misfolded and aggregated pathological proteins linked to neurodegenerative diseases, the promotion of chronic inflammation, the induction of cellular oxidative stress, the impairment of mitophagy, the interaction with mitochondrial dynamics, the enhancement of metabolic rewiring, the modification of neurotransmitter systems (63). A complex brain injury brought on by these pathogenetic mechanisms gives rise to specific brain and neuronal dysfunction (64). Understanding the molecular mechanisms behind the neurophathogenesis associated with viral infection-induced neurodegeneration could lead to the development of efficient prophylactic, therapeutic, and preventive measures against CNS virus infections.

Molecular mechanisms associated with viral infection-related neurodegeneration

Viruses can directly cause neuronal dysfunction through their cytolytic effects, and they can also indirectly cause neuronal degeneration through a variety of mechanisms, including the

TABLE 1 Viruses in Neurodegeneration.

Neurodegenerative disorders (NDs)	Virus	References
Parkinson's disease (PD)	Coxsackievirus B3 (CVB3)	(16, 17)
	Human Immunodeficiency Virus (HIV)	(18)
	Influenza A virus (IAV)	(19, 20)
	West Nile Virus (WNV)	(21, 22)
	Western equine virus (WEV)	(23, 24)
	Hepatitis C virus (HCV)	(25–28)
	Hepatitis B virus (HBV)	(28, 29)
	Japanese encephalitis virus (JEV)	(30, 31)
	Herpes simplex virus (HSV)	(32)
	Varicella-Zoster Virus (VZV)	(33)
	Epstein-Barr virus (EBV)	(34, 35)
Alzheimer's disease (AD)	Herpes simplex virus (HSV)	(36, 37)
	Human immunodeficiency virus (HIV)	(18, 38, 39)
	Human Herpesvirus (HHV)	(40)
	Hepatitis B virus (HBV)	(41, 42)
	Hepatitis C virus (HCV)	(41–44)
	Epstein-Barr virus (EBV)	(35, 45)
	Varicella Zoster Virus (VZV)	(46, 47)
Amyotrophic lateral sclerosis (ALS)	Enteroviruses (EVs)	(48)
	Herpes simplex virus (HSV)	(49)
(Multiple sclerosis) MS	Epstein-Barr virus (EBV)	(50)
	HSV	(51)
Vascular dementia	VZV	(52)

expression of viral genes that disrupt the host's immune system and cellular functions, bystander inflammatory responses, or apoptosis (65). Herpes simplex virus (HSV; family Herpesviridae) and human immunodeficiency virus (HIV; family Retroviridae) are two examples of viruses that exhibit oxidative stress and cause latent or delayed infections. Microglia and brain cells were found to produce intracellular ROS in response to HSV-1 infection. In cultured mouse neural cells, HSV-1 infection results in oxidative stress and triggers the production of bioactive lipid peroxidation byproducts, MDA/hydroxyalkenals (HAEs), which are essential for viral replication (66). A number of HIV-1 component proteins, through various processes, increase the formation of ROS in neural cells, including neurons, microglial cells, and astrocytes. ROS generation and substantial DNA damage are induced by the HIV-

1 transactivator of transcription (Tat) protein (67). Nitroxidative stress marker proteins, including cytochrome P450-2E1 (CYP2E1), iNOS, and NADPH oxidase, are found to be elevated in the brains of HIV-1 transgenic rats. Neuronal cell death in HIV-1 transgenic rats was linked to markedly increased hippocampal levels of activated caspase-3 and BCL2 associated X (BAX) in the HIV-1 model. In conjunction with the activation of MAPK pathways mediated by ERK and JNK and the reduction of B-cell lymphoma 2 (BCL-2) expression, HIV-1 gp120 protein causes death in neurons and microglial cells (68). In neurons and glial cells, JEV (family Flaviviridae) infection raises the concentrations of superoxide anions ($O_2.-$), nitric oxide (NO), and peroxynitrite (OONO-) (69). Neuronal cells infected with other members of the Flaviviridae family, such as West Nile virus (WNV) (70) and dengue virus type 2 (DENV-2), also showed excessive $O_2.-$ production during viral infection (71, 72), which resulted in host cell apoptosis.

The coronavirus is the largest kind of RNA virus, human proteins that interact with SARS-CoV-2 proteins have also been implicated in a number of biological processes linked to aging and neurodegenerative diseases, including lipid metabolism, responses to oxidative stress, and problems with protein homeostasis and mitochondrial function (73). Due to immune-response dysregulation and the effect of COVID-19-related discomfort on cognitive performance, people with AD seem to be at a higher risk of experiencing severe COVID-19 outcomes. COVID-19-induced systemic inflammation may be a factor in neurodegeneration and cognitive impairment.PD patients have a higher case fatality rate during COVID-19 infections, but the underlying mechanisms remain unclear. Additional research is required to determine whether the diseases share any pathophysiological pathways or risk factors. Akinetic-rigid parkinsonism that develops after severe COVID-19 instances begs the question of how the virus affects dopamine pathways. Due to respiratory muscle involvement and heightened vulnerability to respiratory problems during the pandemic, ALS patients face challenges. In COVID-19 cases, some genetic variants associated with familial ALS, like C9orf72 repeat expansions, may affect the severity of the disease (74). A study revealed that Intranasal infection of C57BL/6J mice with the SARS-CoV-2 Beta strain causes Ly6Chi monocyte infiltration of the central nervous system and activation of microglia. SARS-CoV-2, but not H1N1 influenza virus, raises brain IL-1β levels and causes IL-1R1-mediated loss of hippocampus neurogenesis, resulting in post-acute cognitive impairments. Vaccination with a low dosage of adenoviral-vectored spike protein suppresses hippocampus synthesis of IL-1β during breakthrough SARS-CoV-2 infection, resulting in neurogenesis loss and memory impairments (75, 76).

Influenza virus, belonging to Orthomyxoviridae family, which are negative sense, single-stranded, segmented RNA viruses. Influenza A virus was found to be present in substantia nigra pars compacta (SNpc) from postmortem PD brain sections. Neuroinflammation and the influenza A virus's function in PD pathogenesis were convincingly demonstrated by the colocalization of influenza A and immune cells with caspase-cleaved Beclin-1 within the SNpc. It has been shown that the H5N1 influenza virus
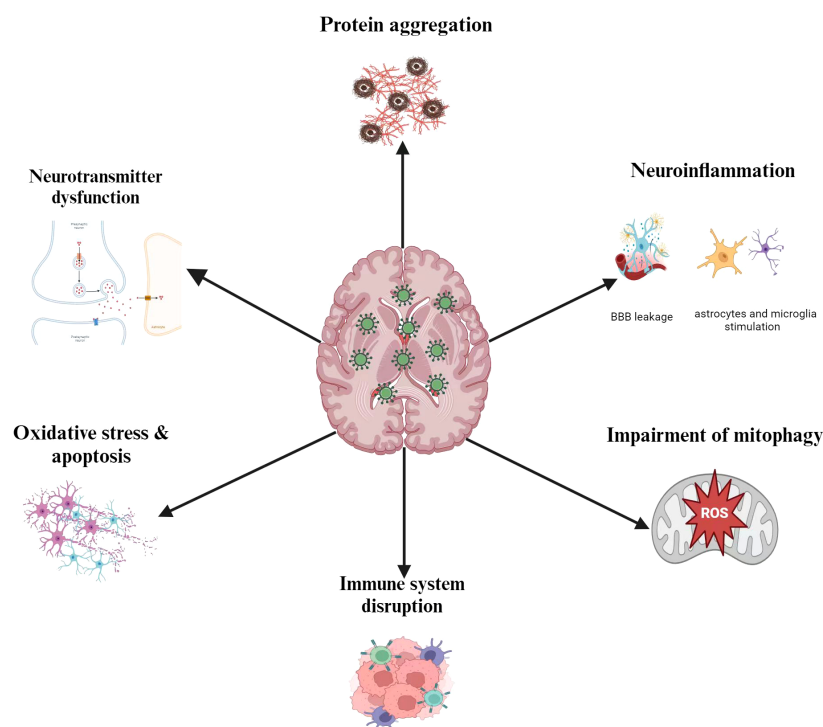
FIGURE 1
Molecular mechanisms adapted by viruses in causing Nds.

enhances α-synuclein phosphorylation and aggregation as it moves from the peripheral nervous system into the central nervous system (77).

Emerging RNA viruses that target the CNS cause cognitive consequences in survivors. Studies in people and animals infected with WNV, a re-emerging RNA virus linked to learning and memory disorders, demonstrated microglial-mediated synapse destruction in the hippocampus. Furthermore, CNS-resident memory T (TRM) cells activate microglia, which limits synapse regeneration and causes spatial learning deficits in WNV-recovered animals (78). Innate immune responses to emerging RNA viruses are becoming recognized as having substantial implications to neurologic sequelae, including memory impairments. Using a recovery model of WNV encephalitis it was found that, while macrophages deliver the antiviral and anti-neurogenic cytokine IL-1β during acute infection; viral recovery is associated with continued astrocyte inflammasome-mediated production of inflammatory levels of IL-1β, which is maintained by hippocampal astrogenesis via IL-1R1 signaling in neural stem cells (NSC). As a result, the absence of IL-1 signaling in NSC prevents abnormal astrogenesis, implying that only freshly produced astrocytes cause neurotoxicity by blocking synapse repair and enhancing spatial learning deficits (79, 80). In mice recovering from WNV or ZIKV infection, T cell-derived interferon-γ (IFN-γ) signaling in microglia causes spatial-learning defects through virus-target-specific mechanisms. Recovery from WNV infection resulted in presynaptic termini elimination with no repair,

while recovery from ZIKV resulted in extensive neuronal apoptosis with loss of postsynaptic termini (81, 82).

Viral hepatitis B and C neurological impairment

Systemic parenteral hepatitis is characterized by a wide range of neurological issues and symptoms caused by several immune illnesses (6). Pathological processes are caused by viral agents replicating within and outside of brain. Depending on the degree, neurological problems brought on by acute or chronic viral hepatitis may arise from the brain, spinal cord, or peripheral nervous system. From subclinical alterations to neurocritical situations, these symptoms can occur (83, 84). Viral particles' direct neurotoxic effects on brain cells as well as the indirect effects of viruses' influence on the immune system or from the use of antiviral medication are the causes of these disorders (85). Identifying the key neurological symptoms of individuals with viral hepatitis is critical for neurologists who treat these patients on a regular basis. This will make it easier to guarantee the quick implementation of diagnostic and treatment plans (83, 84).

Nevertheless, in the last few years, a growing body of research has investigated the relationship between the Hepatitis C virus and dementia (41, 86, 87). The mechanism underlying the emergence of dementia in viral hepatitis C patients is still unclear (41). Hepatitis viruses may be able to directly infect endothelial cells and get

through the blood-brain barrier to reach the central nervous system The component molecules that viruses release during replication are known as pathogen-associated molecular patterns (PAMP). When the central nervous system is damaged in inflammatory infections, inflammatory mediators such TNF-α, IFN-γ, IL-1β, IL-6, IL-18, and chemokines are produced that promote neuronal death (88).

Parkinson's disease pathogenesis in viral hepatitis is associated with the ability of hepatitis viruses to replicate in brain macrophages and microglial cells as well as their capability to pass the blood-brain barrier. Pro-inflammatory cytokines and chemokines are released more frequently as a result, which damages neurons and eventually results in their death (89, 90). Moreover, recent studies on rats have shown that the hepatitis virus depletes dopaminergic neurons in rodents' brains (90, 91). Numerous studies have demonstrated that individuals with chronic viral hepatitis are more likely to develop PD (27, 29). Thus, a major population-based study conducted in Taiwan with 49,967 individuals who had viral hepatitis C revealed that this patient group is more prone to Parkinson's disease than those who had no history of viral hepatitis (92). Previous studies have found similar results showing a considerable increased risk of Parkinson's disease in individuals with viral hepatitis; nevertheless, to obtain more reliable data, the authors recommend doing further large-scale studies (28, 29, 93). Dementia, particularly Alzheimer's disease, has been linked to HCV infection (94). According to a recent study, treating HCV infection with direct-acting antivirals (e.g., ledipasvir/sofosbuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir) dramatically lowers the risk of death in individuals with dementia associated with AD (95). Furthermore, viruses play a significant role in the development of AD through promoting the accumulation of amyloid-β (Aβ) peptides in the brain (96). Previous research has shown that the blood-brain barrier permeability, which controls HCV infection and activity in the central nervous system, is influenced by the ApoE level, which is also strongly linked to the neuropsychiatric symptoms experienced by HCV-infected individuals (96, 97). Although evidence suggests that HCV infection is linked to CNS impairment, it is unclear if any HCV infection promotes AD etiology. Observational studies can be difficult to understand as the results may have been impacted by reverse causality and confounding factors.

Human immunodeficiency virus type 1

In elderly HIV-1-positive patients receiving highly active antiretroviral therapy, age-related AD-like illness may be more likely to occur due to neurocognitive impairments associated with Aβ deposition and hyperphosphorylated Tau (98). HIV multiplies and contributes to neurodegeneration by affecting brain energetics at the cellular level, causing changes in overall brain metabolic homeostasis. Even though immunological dysfunction and dysregulation are typically attributed to the underlying pathophysiology of HIV infection, cognitive impairments

associated with the virus have long been recognized. The spectrum of progressive neurological effects of infection includes asymptomatic neurocognitive impairments (ANI), moderate neurocognitive disorders (MND), and the more severe HIV-associated dementia (HAD) (99). According to estimates, 20–50% of HIV-positive individuals suffer from certain cognitive dysfunctions; these conditions are collectively known as HIV-associated neurological disorders (HAND). Functional status assessments and neuropsychological tests are used in the diagnosis of several disorders (100). HIV infection in the CNS is associated with activation of microglia and astrocytes, as well as the production of inflammatory and neurotoxic insults, all of which contribute to the neurodegeneration and cognitive impairment characteristic of HAND disease. Macrophages and microglia can release pro-inflammatory cytokines such as TNFα, IFNα, IL6, IL8, and IL1β, as well as chemokines such as CCL2, CCL5, and MIP-1β. These indications point to the presence of cellular reservoirs in the CNS established within 3 to 5 days of HIV-1 infection, which include three types of long-lived infected cells: astrocytes, monocyte lineage cells, and microglial cells (101). HIV enters the brain through infected CD4+ macrophages and lymphocytes, which permits the virus to transmigrate to the CNS's perivascular spaces without being noticed by the immune system (102). The molecular and cellular mechanisms underpinning HIV-associated cognitive dysfunctions (HAND) are poorly understood, despite the prevalence of these disorders. These pathways are thought to combine the neurotoxic effects of HIV-associated proteins, indirect host factor involvement, and direct viral infection of CNS cells (103). Notably, it has been shown that the HIV viral proteins Tat and gp120 both increase viral entry into the central nervous system and modify the integrity of the blood-brain barrier. HIV transactivator of transcription, or Tat, is a viral regulatory protein that initiates viral transcription and is among the first HIV proteins to be generated upon infection (104).

Moreover, HIV-RNA in the cerebrospinal fluid (CSF) and viral replication in the CNS can occur in non-viremic people receiving combined antiretroviral therapy, a condition that can cause neurological harm like cognitive decline (105, 106). Despite a decrease in the occurrence of these disorders throughout the era of combined antiretroviral medication, the frequency of minor to severe HAND remains high, even in those who get sufficient treatment (100, 107). Neopterin levels in the CSF in HIV patients with viral suppression can actually be high (108). Neopterin is associated with both cognitive decline and phagocyte activity, suggesting a potential role for CNS phagocytes in neuronal damage and degeneration. CNS phagocytes express neurodegeneration associated molecules and are located topographically in inflammatory foci rich in reactive astrocytes. Neurodegenerative phagocytes appose neurons and consume synaptic material. Aberrant phagocyte activation may be responsible for the cognitive abnormalities seen in HAND. A notable histological characteristic of HAND is synaptic degeneration (109, 110). While persistent chronic inflammation is thought to contribute to cognitive decline, the molecular basis of CNS immune activation in the context of HAND remains little known. Because the population of HIV-positive people is aging, it is imperative to understand the

processes behind these synaptic alterations in HIV in order to find new therapy targets to stop cognitive decline in HAND and other disorders (111).

Influenza virus

Flu and neuropsychiatric disorders include encephalopathy, delirium, convulsions, and confusion are well-establishedly linked (112). Influenza infections during pregnancy have also been linked to a higher chance of schizophrenia or bipolar illness in the child (113). Numerous studies suggest that the neurological effects of influenza are caused by neuroinflammatory insult, which is primarily immune-mediated rather than the result of direct viral invasion of the CNS (114). Studies on animals have raised the possibility of a link between influenza and AD. In particular, these investigations have revealed increased microglial activity in the mouse hippocampal region, a place critical for the formation of new memories and an early stage in the pathophysiology of AD due to loss of neuronal cells (115). A follow-up study on mice was able to demonstrate a connection between influenza-induced hippocampus neuroinflammation and cognitive impairment (114).

There has been speculation of an infectious etiology, and some research has linked certain diseases to PD (116, 117). Whether influenza and Parkinson's disease or parkinsonism are related has been debated for decades (118, 119). Influenza has been implicated in an outbreak of postencephalitic parkinsonism that happened from 1916 and 1930, right before and after the 1918 influenza pandemic (120, 121). The connection between influenza and Parkinson's disease and parkinsonism has been extensively studied, and some of the results suggest that infections may be the root cause of some cases (91, 122). Neurotropic influenza-A virus-infected mice exhibit activation of microglia, inflammatory responses, and inclusions of α-Synuclein in dopaminergic neurons in an experimental setting (19). The primary protein component of Lewy bodies and Lewy neurites, α-syn, was in fact produced by dopaminergic cells expressing the H1N1 influenza virus, but not tau or Transactive response DNA binding protein 43 kDa (TDP-43) (123).

SARS-CoV-2

Multiple sclerosis (MS), AD, and PD are neurodegenerative illnesses that are increasingly thought to be comorbidities in SARS-CoV-2-infected patients (124). Age dependence and co-morbidities like obesity, diabetes, and cardiovascular problems are among the many parallels between COVID-19 and PD. Furthermore, it is possible that COVID-19 will influence PD patient treatment practices and vice versa (125). Other common COVID-19 traits, such as fever, tension, and anxiety, may also negatively impact tremor, gait, and dyskinesias in PD, in addition to impairing the efficiency of L-Dopa (124). The functional relationship between AD and COVID-19 is becoming more and more evident. Like other neurodegenerative diseases, AD is considered a co-morbidity with COVID-19, meaning that having one condition usually makes the

other worse (126). Neurodegeneration and neurocognitive impairment are associated with both situations with the buildup of amyloid precursor protein (APP) and activation of N-methyl-D-aspartate (NMDA)receptors. Furthermore, because these disorders share proinflammatory signaling cascades, neuronal cell death and dysfunction in both circumstances have been linked to microglial-mediated responses (127).

One of the largest RNA viruses is the SARS-CoV-2 virus. With the help of a complex array of accessory and nonstructural proteins, the virus is able to elude the innate immune system and replicate, translate, and exocytose as a fully functional virion. The single-stranded RNA that encodes 29 proteins includes the spike protein, which has the essential domains needed for binding to Angiotensin-converting enzyme 2 (ACE2). Furthermore, the possibility that these proteins have a role in the metabolic and molecular pathways of neurodegeneration is starting to gain more attention. Viruses or necessary protein components can be transported by extracellular vesicles to neurons in the substantia nigra, human cortical astrocytes, and microglia in addition to being directly absorbed by brain endothelium. This facilitates the faster formation of pathogenic fibrils (128). Liquid condensate can be produced by the intrinsically disordered SARS-CoV-2 nucleocapsid protein, which can even create harmful heteropolymers with RNA-binding proteins associated with neurodegenerative disease, such as TDP-43, fused-in sarcoma (FUS), and heterogeneous nuclear ribonucleoprotein A1 (hnRNP1A). More transmissible but less severe than the initial strain, the SARS-CoV-2 virus is continually evolving in response to the immune pressure imposed by very efficient vaccinations. Its potential long-term impacts on the brain system may therefore be a legacy of a global health crisis far more grave than acute disease (129). More severe SARS-CoV-2 and IAV infections are significantly correlated with aging-related proteostasis degradation in older people. A growing body of research indicates that the SARS-CoV-2 infection affects cognitive function over the long term and may eventually result in neurodegenerative diseases like AD (129–131). A number of pathways have been suggested, which are not mutually exclusive, while research to identify the exact mechanism(s) by which SARS-CoV-2 attacks the neurological system, both acutely and chronically, is underway (132, 133).

Herpes simplex virus-1

Lifelong latent infections in sensory neurons are brought on by neurotropic herpesviruses. HSV-1 is a periodically reactivating virus that can enter the brain and cause encephalitis or create CNS latency. Many studies link AD and HSV-1. In fact, HSV-1 seropositivity appears to increase the risk of AD (134), and HSV-1 DNA can be detected in Aβ plaques (135). In animals and cellular models, reactivation of repeated HSV-1 infections results in the accumulation of hyperphosphorylated Tau and the AD biomarkers Aβ over time (136).

The ε4 genotype of APOE is a known risk factor for AD. In animal models, apoE ε4 appears to allow HSV1 latency in the brain

much more and is more effective than apoE ε3 in promoting viral colonization of the brain following acute HSV1 infection (137). It was demonstrated that apoE ε4 was more common in the brains of AD patients who were HSV1-positive than HSV1-negative, and in those who had recurrent cold sores than in those who did not (138). These findings suggest that individuals with the apoE ε4 allele may be more susceptible to HSV's effects on the brain.

Human herpesvirus 6

HHV6 belongs to the β herpesvirus subfamily, which consists of two distinct species. It damages nerve cells and has been connected to a number of neurological disorders. The olfactory route allows HHV6 to enter the brain (139). In addition to AD, HHV6 is frequently seen in older, healthy brains. The HHV6 IgG antibodies reactivity of AD patients were significantly lower than that of normal controls. Although HHV6 might be linked to the genesis of AD, these findings might potentially point to a causal relationship or an opportunistic participant in neurodegeneration (140). A multiscale network analysis that includes late-onset AD-associated viromes and integrated genomic, transcriptomic, proteomic, and histological data from four distinct brain regions in human post-mortem tissue was used to demonstrate that AD patients had greater levels of HHV6A and human herpesvirus 7 than controls (141). There are regulatory relationships between viral abundance and APP metabolism modulators, including HHV-6A's activation of APBB2, APPBP2, BIN1, BACE1, CLU, PICALM, and PSEN1. This suggests that specific virus species can cause neuropathology and Alzheimer's disease (142).

Other viruses involved in neurodegeneration

Recent research has unequivocally shown that a history of Epstein-Barr virus (EBV) infection is associated with a higher risk of developing multiple sclerosis (MS) (143). A motor neuron disease called ALS damages brain and spinal cord nerves. A build-up of RNA-binding proteins such as FUS or TDP-43, along with cytoplasmic mislocalization, are indicative of both frontotemporal dementia and ALS. An underlying viral infection that is ordinarily epigenetically repressed and incapable of replication is up-regulated in individuals with ALS (144). Enteroviruses in the brains and cerebrospinal fluid of individuals with ALS are a topic of discussion (48). However, mice infected with two enteroviruses developed an accumulation of TDP-43 and persistent inflammation (145). Mice infected with Theiler's murine encephalitis virus (TMEV) developed an ALS-like phenotype with TDP-43 and FUS inclusions in their cytoplasm, which affected their motor neurons and glial cells (146). The Japanese encephalitis virus (JEV) can infect humans and cause Japanese encephalitis, which has a high death rate in severe cases and leaves 30 to 50 percent of survivors with severe, permanent neurological or mental repercussions (147). Increased production of

reactive oxygen species (ROS) from JEV infection intensifies the death of neurons brought on by both mature and replication-incompetent viruses (148). Increased ROS production and decreased membrane fluidity in JEV-infected neuronal cells lead to serious cytopathic effects, which ultimately cause neuronal cell death (149). Neuronal cells infected with other members of the Flaviviridae family, such as West Nile virus (WNV) (70) and dengue virus type 2 (DENV-2) (150), also showed excessive O_2^- production during viral infection, which resulted in host cell apoptosis. Different viruses adapt different routes to enter the CNS and causes neurodegeneration explained in Figure 2.

The Venezuelan equine encephalitis virus (VEEV) causes serious neurological abnormalities in 4–14% of patients, and fatal encephalitis in 1% of cases (151). Upon infection with VEEV, astrocytoma U87MG cells exhibit an abrupt rise in ROS levels (152). Deadly rabies virus (RABV) attacks the central nervous system (CNS), leading to encephalitis and ultimately mammalian death. Research has shown that RABV infection results in increased ROS production in mouse neuroblastoma cells (153). Inducing oxidative stress is a crucial role of the RABV viral component (154). Infection with the deadly RABV causes changes in cellular gene expression. RABV, like other neurodegenerative diseases, may be involved in neuronal death due to an imbalance in Ca2+ homeostasis. Due to the role of calcium homeostasis in dysregulation in neurodegenerative diseases and other pathophysiology, there is reason to assume that neurons that contain certain intracellular calcium-binding proteins have a greater capacity to buffer calcium, and therefore would be more resistant to degeneration (155). Oxidative stress is a major factor in the pathogenesis of neurodegeneration in viral infections of the central nervous system, as evidenced by elevated levels of free radicals and lipid peroxidation caused by neurotrophic viruses. Table 2 lists the numerous population-based investigations that were carried out to determine the role of viruses in neurodegenerative diseases.

Possible mechanism of viral pathogenesis, inflammation and neurodegeneration

Neurotropic viruses are a type of newly and re-emerging infections that specifically target and damage the integrity of the CNS (159, 160). There are several distinctive ways in which they can enter the CNS, leading to a range of neurological symptoms (161). Viruses have a particular method in which they first enter the peripheral nervous system before migrating into the CNS via axon fibers (162). Neurotropic viruses employ a variety of techniques in addition to exploiting the peripheral nervous system to bypass host barrier defenses and directly infiltrate the central nervous system. For instance, immune cells like macrophages, monocytes, and dendritic cells can become infected by the Zika virus (ZIKV), human cytomegalovirus (HCMV), and human immunodeficiency virus (HIV), which then function as carriers to move the virus into the CNS (161, 163, 164). Moreover, it has been shown that viral

FIGURE 2
Entry routes of different viruses to infiltrate the CNS and induces neurodegeneration.
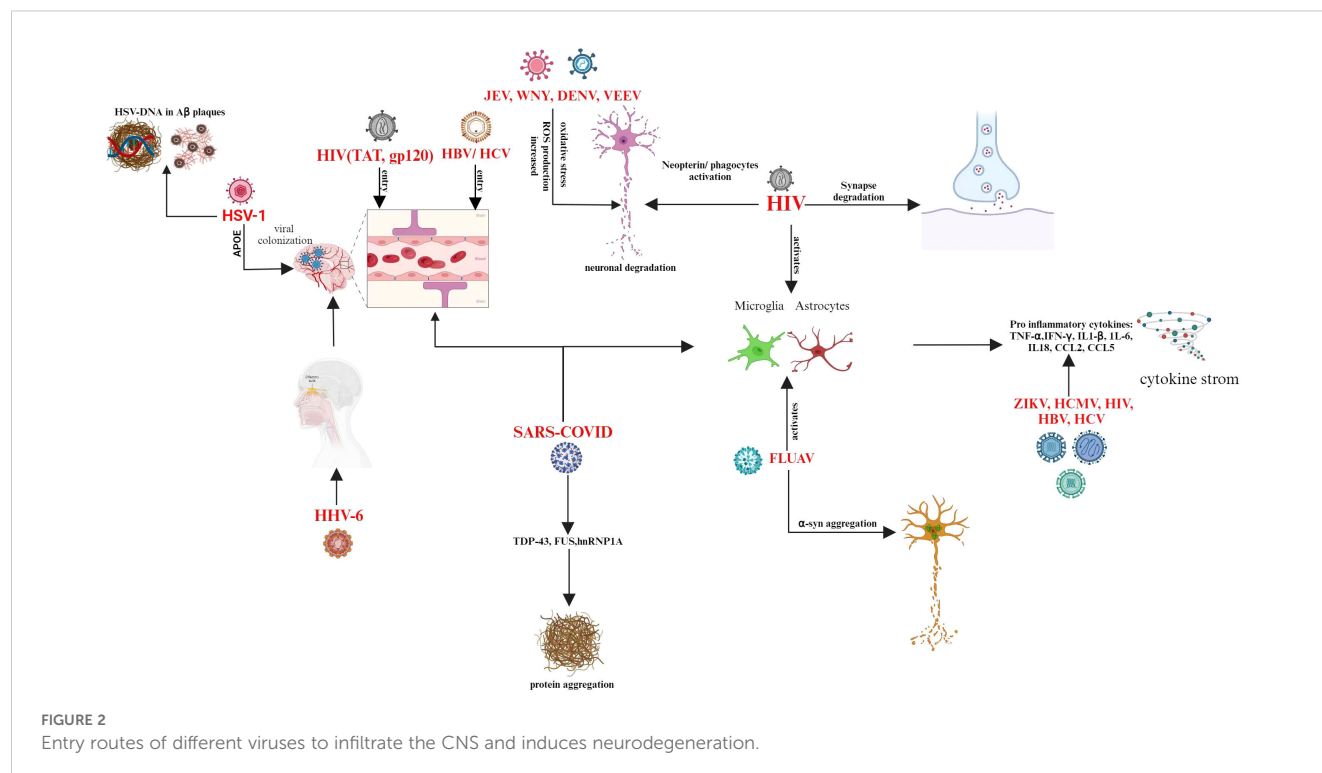
infections stimulate the production of chemokines and pro-inflammatory chemicals like TNF-α, CCL2, CCL5, IL-6, and IL-8, which can trigger a cytokine storm. The systemic pro-inflammatory state impairs the blood-brain barrier, allowing more pro-inflammatory cytokines and viruses to enter the CNS. The cytokine storm at the nervous system level can cause neuronal death, activation of microglia, synaptic plasticity impairment, and neurotransmission dysfunction (161, 165). Viruses have the ability to activate astrocytes and microglia (166, 167), cause neuroinflammation (167), oxidative stress (168), immunological responses (159), protein aggregation (169), and upset the balance of microbes in the gut (170) after they have entered the central nervous system. Accumulating data has revealed a bidirectional relationship between the gut microbiome and CNS, known as the "microbiota-gut-brain axis." Early microbiome changes were observed in preclinical Alzheimer's disease (AD) and prodromal Parkinson's disease (PD) patients (171, 172). These processes have the capacity to both initiate and exacerbate NDs.

Risk factors were recently analyzed with publicly available datasets from two large-scale population-based studies, UK Biobank and FinnGen. The UK Biobank contained twenty-two of the forty-five significant correlations between viral infections and NDs that were discovered in FinnGen. It's interesting to see that the strongest hazard ratio was associated with viral encephalitis and AD (57). Additionally, utilizing virome analysis, nine viruses were shown to be present in various CNS brain tissues in patients with PD, with PD patients showing greater positive frequencies of viruses than patients in the control group (173). Remarkably, evidence from recent studies provide credence to the hypothesis that persons with viral illnesses may be less likely to develop NDs if they receive immunizations or antiviral drugs (123, 174). When considered

collectively, these results provide credibility to the theory that viral infections raise the chances of NDs.

Viruses have evolved unique defense methods to evade host defense reactions. These mechanisms include autophagy disruption and additional interference with host antiviral signaling triggered by viral infection (175). In Table 3 various mechanisms are summarized through which viruses cause neurodegeneration in AD and PD. Although some illnesses interfere with specific signaling pathways to prevent autophagosomes from fusing with lysosomes or lysosomal breakdown, autophagosomes can also serve as reproduction sites for viruses as they infect a host (202–204). Activation of autophagy by various viruses, including flaviviruses and enteroviruses, can promote virus spread by assembling and releasing infectious particles through autophagic vacuoles. In certain viral infection cases, such as poliovirus and coronavirus infection, autophagy induction by infected cells promotes the generation of double-membrane vesicles to enhance viral replication (205).

Antiviral therapies in ND's

Antivirals could be interesting alternative drug options for treating NDs. In cell culture, antivirals were able to decrease HSV-1-induced production of Aβ and phosphorylated Tau (206) Acyclovir, penciclovir, and foscarnet are anti-HSV1 antiviral medications that decreased Aβ and P-tau accumulation along with HSV1. The antiviral-induced decrease in Aβ is attributable to the reduced number of new viruses, and hence the reduction in viral spread. Since antiviral agents reduce greatly Aβ and P-tau accumulation in HSV1-infected cells, they would be suitable for

TABLE 2 Prospective cohort studies for involvement of viruses in NDs.

Virus	ND	Source	Year	References
HCV	PD	Taiwan National Health Insurance Research Database	2016	(92)
HCV/HBV	PD	Community-based integrated screening program in Taiwan	2015	(156)
Cytomegalovirus	PD	UK Biobank	2024	(157)
HBV/HCV	Dementia	Korean National Health Insurance Service	2021	(41)
HSV	AD/Dementia	Vasculature in Uppsala Seniors (PIVUS) cohort	2024	(37)
HSV/VZV	Dementia	Korean National Health Insurance Service	2017	(47)
HCV	Multiple sclerosis (MS)	Neurology department at Ain Shams University Hospital, Egypt	2023	(158)

TABLE 3 Mechanisms adopted by viruses causing neurodegeneration in PD and AD.

Neurodegenerative disorder	Virus	Pathogenesis	Markers	References
PD	CVB3	cause neurons to develop α-syn-associated inclusion bodies, which may serve as a PD trigger	Elevated α-syn expression α-syn fibrils in damaged mitochondria	(16)
	HBV/HCV	Invade the central nervous system Dopaminergic neuron death	Elevated levels of TNF-a, IL-6, and IL-1b, IL-8, IL-29, IL-22	(176, 177)
	IAV	Increased mRNA levels of CD36, CD68, C1QA, and C3, together with a changed expression pattern of major histocompatibility complex classes I and II, CD80, and F4/80, indicating evolving synaptic pruning	Increased levels of IL-6 and IFN-γ, TNF	(114)
	West Nile virus (WNV)	Abnormalities in the basal ganglia, thalamus, and pons, mostly bilaterally, evident in T2 and DWI sequences	Damage to the substantia nigra Secretion of α-syn	(178–180)
	HIV	Dopaminergic basal ganglia damage Neuroinvasion	Tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β production	(181, 182)
	JEV	Profound gliosis in the substantia nigra pars compacta (SNpc), similar to that seen in PD lower dopamine and norepinephrine levels in JEV-infected rats Dopaminergic and norepinephrinergic system impairment	Lower CSF concentrations of dopamine, norepinephrine and homovanillic acid	(30, 183, 184)
	IAV H5N1	Blocking protein degradation pathways Blocking of autophagosome formation and inhibition of autophagic flux	α-syn phosphorylation and aggregation	(19, 123)
AD	HHV-6A HHV-6B	Dysregulation of autophagy in neurons astrocytoma cells Neuroinflammation	Aβ deposition Increasing beta-amyloid and tau	(14, 134, 185–188)
	HIV,	Synaptic deficits Trojan horse mechanism	Aβ1–42 dysregulated Amyloid plaques in the CSF and blood	(189, 190)
	HCMV	Neuroinvasion	Aβ production Astrocyte reactivity	(191, 192)
	HHV-6/7	Neuroinflammation	Elevated tau, ApoE, and Aβ1–42 protein expression	(186, 193, 194)
	HSV-1	Accelerated Aβ deposition Gliosis Cognitive dysfunction	triggers the phosphorylation of Tau by activating protein kinase A (PKA) and glycogen synthase kinase 3β (GSK3β)	(195–197)

(Continued)

TABLE 3 Continued

Neurodegenerative disorder	Virus	Pathogenesis	Markers	References
			Initiate the translation of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and the buildup of Aβ by activating RNA-activated protein kinase (PKR).	
	Hepatitis viruses (HBV, HCV)	Infect endothelial cells directly and enter the central nervous system across the blood-brain barrier	Elevated levels of TNF-α, IFN-., IL-1ß, IL-6, IL-18, IL-10, IL-12 Elevated tau and amyloid beta-peptide levels	(41, 88)
	HHV-6A HHV-6B	Dysregulation of autophagy in neurons astrocytoma cells Neuroinflammation	Aβ deposition Increasing beta-amyloid and tau	(14, 185, 186)
PD/AD	SARS-CoV-2	Viral invasion Immune-mediated inflammation Endothelial dysfunction	Aggregation of Aß, α-syn, tau, and TDP-43	(198–201)

treating AD with great advantage unlike current AD therapies, only the virus, not the host cell, would be targeted (206). Ribavirin is a low-molecular-weight nucleoside analogue and inhibitor of inosine monophosphate dehydrogenase that functions as a broad-spectrum antiviral drug against a variety of DNA and RNA viruses. Ribavirin is approved in the United States for the treatment of RSV infections and, when combined with interferon, for hepatitis C virus infections (207). However, studies have shown that, as compared to a placebo, oral ribavirin formulations do not improve virologic response or the treatment of chronic hepatitis C. As a result, ribavirin is not permitted for use as a monotherapy for hepatitis C (208). Moreover, despite divergent opinions in the literature, ribavirin has been shown to be efficient against HSV both on its own and in combination with acyclovir, where it has been shown to augment the effects of acyclovir (209). Activity of ribavirin against EV has been demonstrated *in vitro* (210). Hepatitis C, RSV, and HSV are among the infectious diseases that ribavirin effectively treats; AD has been connected to several of these infections (87, 209). In a clinical trial, the Apovir group's CSF biomarker levels showed a decrease in Aβ42 over the duration of treatment (86).

The main antiviral drug used to treat HSV1 infections is called acyclovir (ACV); as expected, ACV dramatically reduces the number of HSV1 and the levels of Aβ and P-tau in HSV1-infected cells in culture (206). P-tau production is reliant on HSV1 replication and eventually drops to zero. Antibody formation is significantly decreased, but it depends, at least partially, on a previous phase of the cycle. Lower viral DNA replication is probably the cause of this decrease in viral dissemination. These results suggest that ACV might be helpful in the management of AD (211). Individuals who test positive for HSV have a higher likelihood of cognitive impairment, and antiviral drugs have a potent anti-HSV infection impact. Recent studies employing databases incorporating electronic health information have shown that HSV infections increase the risk of dementia, but antiviral medication treatment lowers this risk. In a trial including schizophrenia, the generic antiviral drug valacyclovir showed better memory improvement than a placebo (212). It has also been shown

that acyclovir administration prevents HSV-1-induced neuronal death (213). When dexamethasone and acyclovir were given together, the impairments in spatial cognition were lessened. Together with microglia activation, this combination also decreased the levels of neuroinflammation markers as TNF-α and IL-6 (214). However, these effects happen only when acyclovir and dexamethasone are administered simultaneously.

Antiviral medication significantly reduces the risk of Parkinson's disease in patients with viral hepatitis (25, 215). *In vitro* models showed that the anti-influenza drug oseltamivir phosphate inhibited the aggregation of α-synuclein caused by H1N1 (123). Antiviral medication has demonstrated promise in reducing the likelihood of HCV infection, which is a risk factor for PD. In patients, the incidence of PD with persistent HCV infection appeared to be lower when treated with interferon-based antiviral therapy (216). Anti-HIV drug maraviroc specifically inhibited CCR5, ameliorating tauopathies and Huntington's disease (HD) in model mice (217).

Ever since the initial appearance of the acute respiratory coronavirus SARS-CoV-2, scientists have been searching for novel antiviral medications and repurposing those that have demonstrated efficacy against other coronaviruses. antiviral medication that could be applied in case of COVID-19 outbreak. PD, AD, and fatigue associated with multiple sclerosis have been shown to benefit from amantanes such as amantadine, rimantadine, and memantine. These conditions are all known comorbidities associated with COVID-19. Additionally, basic pharmacological studies conducted *in vitro* and *in vivo* have shown that amantadine can inhibit SARS-CoV-2 by down-regulating host-cell proteases, which impairs the release of the viral genome into the host cell, and by acting as an NMDA receptor antagonist, which prevents the acute lung injury and respiratory distress that are hallmarks of COVID-19 (124). Antiviral drugs like oseltamivir, which are frequently prescribed to treat influenza, have been demonstrated to significantly enhance parkinsonism and increase dyskinesia (218).

Antiviral drugs are now being tested for the treatment of ALS. Combination antiretroviral therapy lowers transcript levels of the

HERV-K subtype HML-2, that has been demonstrated to be elevated in ALS (219). A Phase IIa clinical trial including ALS patients found that antiretroviral medication (effective against HERV-K HML-2) indicates a trend toward delayed disease progression in patients with virological response to the treatment (220). Even though the results were encouraging, more randomized controlled trials (RCTs) are now required to assess any potential advantages for NDs.

Additionally, the potential antiviral properties of bioflavonoids produced from Ginkgo biloba leaves, such as ginkgetin, isoginkgetin, and ginkgolic acid, were investigated. These substances have a well-established antiviral profile from earlier research (221). Ginkgetin has been shown to effectively block the synthesis of viral proteins and impede the replication of HSV-1, HSV-2, and the human cytomegalovirus (222). The important significance that traditional Chinese medicine plays in treating COVID-19 aftereffects has been acknowledged. Research has demonstrated that chalcones and flavonoids can prevent neurodegeneration, prolonged COVID-19 illness, and SARS-CoV-2 infection (223). The bioactive constituents of Ginkgo biloba extract, ginkgolides and bilobalide (BB), have demonstrated neuroprotective effects in AD via pathways including anti-excitotoxicity, anti-inflammatory, and anti-oxidative properties. Furthermore, by blocking the major protease of SARS-CoV-2, ginkgolides and BB may also have antiviral effects against COVID-19. But whether pure ginkgolides or BB are given over an extended period of time at potentially therapeutic doses is actually beneficial or harmful for treating COVID-19 and AD is still up for debate (223).

Different medications have demonstrated promise in alleviating the long-term clinical symptoms of COVID-19 and neurodegenerative disorders, despite the fact that there is presently no standardized treatment for COVID-19. One way to lessen the harmful impact on nerve cells is to either preserve internal Ca2+ homeostasis or prevent the long-term inflow of Ca2+ ions. By inhibiting the extrasynaptic N-methyl-D-aspartate receptors, N-methyl-D-aspartate antagonists such as amantadine and memantine can do this by reducing the long-term Ca2+ ion influx that contributes to neuronal excitotoxicity. Amantadine is an antiviral medication that has been demonstrated to help patients with PD with their altered motor behavior. It may also help with persistent fatigue. However, memantine might aid in the improvement of cognitive deficiencies. Overlooking these issues may result in neuronal death and the associated functional deficits (224). To ascertain the effectiveness and comprehend the molecular underpinnings of these drugs' anti-coronavirus activity or inhibitory potential, more *in vitro* and *in vivo* research are required. Different antiviral drugs are in trials for neurodegenerative disorders explained in Table 4.

AAV gene therapy

In recent years, adeno-associated virus (AAV) has become the main vector for CNS gene therapy. AAV has already shown promising results in the clinic for a range of CNS ailments, including neuromuscular diseases, lysosomal storage disorders, and illnesses that are intractable with medicine. Gene therapy uses DNA or RNA as a pharmacological agent to produce gene products that permanently mute, repair, or modify endogenous genes. One "one-and-done" treatment method that can cross the blood-brain barrier is gene therapy (227) help prevent the long-term progression of neurological diseases (6). In recent years, gene therapies—like AAV-based therapy—have progressed from being the exclusive focus of preclinical research to being an effective form of treatment (228). AAV has the advantages of immunological privilege, high delivery efficiency, and specialized tissue or cell tropism in the CNS.

Regarding AAV-based gene therapy, the most clinically studied CNS condition is PD. PD is currently being studied using three different methods: glutamate decarboxylase (GAD)-inhibited glutamine synthesis as a neurotransmitter; aromatic amino acid decarboxylase, AADC-induced dopamine production; and glial cell line-derived neurotrophic factor (GDNF) in the substantia nigra to protect nigral neurons. However, the majority of AAV-based treatments are unable to treat pathologically complex diseases (229). To treat PD, AAV-based gene therapy vectors can increase dopamine levels in target cells (230). In PD primate model, intrastriatal infusion of an AAV vector containing the human aromatic l-amino acid decarboxylase (hAADC) gene results in robust gene expression (231). Alternatively, an AAV-based α-synuclein expression vector (AAV-PHP.B-GBA1) can be injected intravenously (IV) into the target neural parenchyma as an alternative to the more common injection of the mouse forebrain in PD gene therapy. Because of this, the vector was able to enter the brain parenchyma and propagate throughout it. This allowed the vector to target the central and peripheral nervous systems globally and restored animal behavior by reducing synucleinopathy (232).

More than one hundred clinical trials have involved Alzheimer's patients. Other than immunotherapy, there is currently no medication that can impede the progression of Alzheimer's disease in those with cognitive impairments. However, AAV-based gene therapy continues to be ineffective. The only experiment that was successfully completed used AAV2-driven nerve growth factor to reverse basal cholinergic neuronal dysfunction. Ten patients with mild-to-moderate AD were treated in a Phase I clinical trial with bilateral stereotactic injections of AAV2-nerve growth factor into the Meynert nucleus basalis without the use of immunosuppressive drugs (233). This medicine worked effectively, was safe, and was well tolerated. No side effects were reported. Another trial, a Phase II trial, used a higher dose, although the treatment and placebo groups' outcomes in terms of brain metabolic or cognitive performance did not vary statistically (234). The autopsy results of the three cases showed that stereotactically injected AAV2 did not reach the nucleus basalis of Meynert due to restricted AAV2 diffusion; hence, no reliable conclusions could be drawn (235). Three other therapeutic modalities are the subject of clinical investigation, the results of which have not yet been made public: Intravenous or intrathecal telomerase (hTERT) delivery to lengthen telomeres; brain-derived

TABLE 4   Clinical trials of antiviral drugs against NDs.

ND	Virus	Anti-viral Drugs	Clinical trial	References
AD	Pleconaril (active on enteroviruses) ribavirin (active on several viruses)	Apovir	Phase IIa	(86)
AD	HSV	Valacyclovir	Phase II	https://clinicaltrials.gov/study/NCT03282916
PD	Influenza	Amantadine	completed	https://clinicaltrials.gov/study/NCT00632762
AD	HSV-1	Penciclovir		(206)
PD	HCV	Interferon-α		(216)
PD	HCV	Interferon-free direct-acting antiviral (DAA) therapy with ledipasvir (LDV) plus sofosbuvir (SOF)		(225)
ALS	HIV/AIDS	Combination Antiretroviral Therapy (Triumeq)	Phase IIa	https://clinicaltrials.gov/study/NCT02868580
Schizophrenia	HSV-1	Valaciclovir (pro-drug of acyclovir)	Phase II	(226), https://clinicaltrials.gov/study/NCT02008773
AD	HSV-1	Acyclovir		(214)
AD	HBV/HIV	Lamivudine/3TC	Phase I Phase II	https://clinicaltrials.gov/study/NCT04552795
Mild Cognitive Impairment	HBV/HIV	Lamivudine/3TC	Phase II	https://clinicaltrials.gov/study/NCT06519357
Amyotrophic Lateral Sclerosis (ALS)	HIV	Antiretroviral regimen approved to treat HIV	Phase I	https://clinicaltrials.gov/study/NCT02437110
Multiple Seclerosis (MS)	Epstein-Barr virus (EBV)	Famciclovir	Phase II	https://clinicaltrials.gov/study/NCT05283551
PD	HBV/HIV	Tenofovir Disoproxil Fumarate	Phase I	https://clinicaltrials.gov/study/NCT06356662

neurotrophic factor administered via parenchymal delivery to minimize neuronal loss and promote synaptic reconstruction; and intra-CSF delivery of apolipoprotein E2 to restore protein expression in patients homozygous for apolipoprotein E4 (235).

Numerous novel issues highlight the need for further research, especially in the areas of safe delivery methods, well-understood immunological systems, cost-effective production procedures, targeted vectors, and further immune system suppression strategies. To extend AAV-based gene therapy from monogenic disorders to other diseases, we need to understand the whole phenotypic range of each disease and find objective biomarkers to capture the essential features of the condition. Ongoing research on the imaging of viral vectors is necessary to monitor the pharmacokinetics of viruses.

Conclusion

CNS infection diagnosis and therapy are difficult but essential. There are either none or very few antiviral medications on the market now for treating viral infections of the central nervous system. A viral infection causes an imbalance between free radicals and antioxidants, which increases oxidative stress within cells and causes neuronal cells to undergo programmed death through apoptosis. In order to interfere with mitophagy and mitochondrial dynamics in their hosts, viruses work with the recycling machinery of the cell.

Viral disturbance of mitochondrial homeostasis alters neuronal metabolism and consequently affects brain function. When neurotropic viruses enter the brain, specific brain functions are harmed, neurotransmitter systems are changed, and pathological

signs of NDs appear. An understanding of the neuropathogenesis of viral CNS infection may help in the creation of more efficient diagnosis and treatment plans by focusing on the molecular mechanisms underlying CNS infection. It might also be helpful in the search for new antiviral drugs, which are necessary to treat these neurotropic viral infections in an efficient manner.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AAV	Adeno-Associated Virus	HHV6	Human Herpesvirus 6
ACE2	Angiotensin-Converting Enzyme 2	HIV	Human Immunodeficiency Virus
ACV	Acyclovir	HSV	Herpes simplex virus
AD	Alzheimer's disease	HSV-1	Herpes Simplex Virus-1
ALS	Amyotrophic Lateral Sclerosis	IAV	Influenza A virus
ALS	Amyotrophic Lateral Sclerosis	IV	Intravenously
ANI	Asymptomatic Neurocognitive Impairments	JEV	Japanese encephalitis virus
ApoE	Apolipoprotein E	JEV	Japanese Encephalitis Virus'
APOE ε4	Apolipoprotein E ε4 allele	LDV	Ledipasvir
APP	Amyloid Precursor Protein	MND	Moderate Neurocognitive Disorders
Aβ	Amyloid-β	MS	Multiple sclerosis
BACE1	β-Site Amyloid Precursor Protein Cleaving Enzyme 1	MSA	Multiple Systems Atrophy
CNS	Central Nervous System	NDs	Neurodegenerative diseases
CSF	Cerebrospinal Fluid	NMDA	N-methyl-D-aspartate
CVB3	Coxsackievirus B3	PD	Parkinson's disease
DAA	Direct-Acting Antiviral	PKA	Protein Kinase A
DENV-2	Dengue Virus Type 2	PKR	RNA-Activated Protein Kinase
EBV	Epstein-Barr virus	RABV	Rabies Virus
EBV	Epstein-Barr Virus	ROS	Reactive Oxygen Species
EVs	Enteroviruses	SNpc	Substantia Nigra Pars Compacta
GAD	Glutamate Decarboxylase	SOF	Sofosbuvir
GDNF	Glial Cell Line-Derived Neurotrophic Factor	TMEV	Theiler's Murine Encephalitis Virus
GSK3β	Glycogen Synthase Kinase 3β	VEEV	Venezuelan Equine Encephalitis Virus
GWAS	Genome-Wide Association Studies	VZV	Varicella-Zoster Virus
HAD	HIV-Associated Dementia	WEV	Western equine virus
HAND	HIV-Associated Neurological Disorders	WNV	West Nile Virus
HBV	Hepatitis B virus	WNV	West Nile virus
HCMV	Human Cytomegalovirus	ZIKV	Zika virus
HCV	Hepatitis C virus	α-syn	α-synuclein.
HHV	Human Herpesvirus		