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Neurological complications caused by SARS-CoV-2

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SUMMARY SARS-CoV-2 can not only cause respiratory symptoms but also lead to neurological complications. Research has shown that more than 30% of SARS-CoV-2 patients present neurologic symptoms during COVID-19 (A. Pezzini and A. Padovani, Nat Rev Neurol 16:636–644, 2020, https://doi.org/10.1038/s41582-020-0398-3). Increasing evidence suggests that SARS-CoV-2 can invade both the central nervous system (CNS)

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(M.S. Xydakis, M.W. Albers, E.H. Holbrook, et al. Lancet Neurol 20: 753–761, 2021 https://doi.org/10.1016/S1474-4422(21)00182-4) and the peripheral nervous system (PNS) (M.N. Soares, M. Eggelbusch, E. Naddaf, et al. J Cachexia Sarcopenia Muscle 13:11–22, 2022, https://doi.org/10.1002/jcsm.12896), resulting in a variety of neurological disorders. This review summarized the CNS complications caused by SARS-CoV-2 infection, including encephalopathy, neurodegenerative diseases, and delirium. Additionally, some PNS disorders such as skeletal muscle damage and inflammation, anosmia, smell or taste impairment, myasthenia gravis, Guillain-Barré syndrome, ICU-acquired weakness, and post-acute sequelae of COVID-19 were described. Furthermore, the mechanisms underlying SARS-CoV-2-induced neurological disorders were also discussed, including entering the brain through retrograde neuronal or hematogenous routes, disrupting the normal function of the CNS through cytokine storms, inducing cerebral ischemia or hypoxia, thus leading to neurological complications. Moreover, an overview of long-COVID-19 symptoms is provided, along with some recommendations for care and therapeutic approaches of COVID-19 patients experiencing neurological complications.

KEYWORDS SARS-CoV-2, COVID-19, neurological disorders, long-COVID-19, central nervous system, peripheral nervous system

INTRODUCTION

The central nervous system (CNS) and the peripheral nervous system (PNS) make up the human nervous system (1). And the CNS consists of the brain and spinal cord, which integrates and coordinates information and transmits it from neural tissues to various parts of the body. While the PNS consists of the somatic nervous system, autonomic nervous system, enteric nervous system, and other neural tissues outside the CNS (1).

Since the outbreak of the COVID-19 pandemic, increasing clinical and experimental evidence indicates that *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) infection can trigger neurological complications (2, 3). Neurological manifestations associated with SARS-CoV-2 have increased to more than 30% (4). The autopsy results confirmed the presence of SARS-CoV-2 nucleic acids in the cerebrospinal fluid and brain tissue of COVID-19 patients (5, 6), thus validating the possibility that COVID-19 may complicate with neurological symptoms (7).

Encephalopathy and neurodegenerative diseases (8) are the most frequently reported CNS symptoms, while olfactory deficits (9) and skeletal muscle symptoms, such as muscle weakness and damage, are prevalent in the PNS (10). Additionally, patients who experience long-COVID-19 commonly exhibit symptoms such as fatigue, muscle weakness, headache, cognitive impairment, and brain fog (11, 12).

This manuscript provides a comprehensive overview of the CNS and PNS symptoms observed in COVID-19 patients, as well as an analysis of the pathophysiological mechanisms underlying the neurological manifestations associated with SARS-CoV-2 infection. According to existing evidence, there are multiple potential explanations for neurological manifestations in COVID-19 patients, including the potential invasion of SARS-CoV-2 into the brain through retrograde neuronal (13, 14) or hematogenous pathways (13), the disruption of CNS function by cytokine storm induced by SARS-CoV-2 (15), the cerebral ischemia (16), or hypoxia (17) induced by SARS-CoV-2, and neuronal fusion caused by SARS-CoV-2 (18).

Additionally, this manuscript discusses neurological symptoms in long-COVID-19 patients, along with recommendations for the care and therapeutic approaches of COVID-19 patients with neurological complications during the pandemic.

CENTRAL NERVOUS SYSTEM DISORDERS ASSOCIATED WITH SARS-CoV-2

The available evidence indicated that SARS-CoV-2 is associated with a variety of CNS complications, such as headache, encephalitis, and cerebrovascular disorders (19),

leading to significant mortality in some cases (20). Even COVID-19 patients with asymptomatic or mild symptoms may exhibit neurological symptoms (21). To effectively cope with the diverse range of CNS symptoms, it is recommended to include an electroencephalogram examination in the evaluation of COVID-19 patients (22). This article provides a comprehensive review of the prevalent CNS disorders caused by SARS-CoV-2 infection (Table 1).

Encephalopathy

SARS-CoV-2 has been implicated in the development of various encephalopathy, including acute cerebrovascular disease (23, 24), meningitis, encephalitis (25), acute necrotizing encephalopathy (26), headache (27, 28), and dizziness (29, 30), which can be detected through brain imaging tests. These encephalopathy are supposed to be associated with acute respiratory distress syndrome caused by SARS-CoV-2 infection (2, 48, 49). Some COVID-19 patients have presented disseminated encephalitis and autoimmune encephalitis according to clinical manifestations although encephalitis is not universally recognized as a typical symptom of COVID-19 (50–52). Acute necrotizing encephalopathy is a CNS complication induced by SARS-CoV-2 infection, with magnetic resonance imaging revealing abnormalities in affected areas that may be linked to an intracranial cytokine triggered by SARS-CoV-2 (53, 54).

TABLE 1 Description and distribution of central nervous system symptoms in COVID-19 patients

Central nervous system clinical conditions associated with COVID-19		Symptoms description of central nervous system involvement	Prevalence
Encephalopathy	Acute cerebrovascular disease	Autonomic disturbances (23)	2.3% (24)
	Meningitis/encephalitis	Consciousness, altered mental state, seizures, headaches, and weakness (25)	0.215% and 6.7% (in severely ill patients) (25)
	Acute necrotizing encephalitis/acute hemorrhagic necrotizing encephalitis	Impairment of consciousness and orientation (26)	6.59% (12/182) (26)
	Headache	Pain is insidious onset, is bilateral, is of a moderate to strong intensity, and presents a pressing or tightening quality (27)	47.1% (27) and 15% for long-COVID-19 (28)
	Dizziness	/[a]	0.03%–20% (29), 3% for long-COVID-19 (30)
Stroke	Ischemic stroke	Hemiparesis, hemianaesthesia (numbness on one side of the body), aphasia, homonymous hemianopia, and hemispatial inattention (31)	1%–6% (32–34) [mortality: 38% (35)]
	Hemorrhagic stroke		2.4% (36), 21.7%–25.7% of stroke (37) [mortality: 12%–15% for subdural hematoma and 35%–59% for intraparenchymal hemorrhage (38)]
Neurodegenerative diseases	Parkinson's disease	Bradykinesia, increased muscle tone, tremors, and altered gait and postural reflexes (39)	The pooled prevalence of COVID-19 patients among Parkinson's disease patients is 5% (40)
	Multiple sclerosis	The clinical symptoms and signs are result from the involvement of sensory, motor, visual, and brainstem pathways (41)	The pooled prevalence of suspected COVID-19 in MS patients was 4% (42)
	Dementia and Alzheimer's disease	Delirium is specifically characterized by clinical presentation among SARS-CoV-2 infection dementia patients (43)	The access rate in emergency rooms, hospitalization, and mortality from infection with COVID-19 is higher in patients with AD than in healthy elderly people (44, 45)
Delirium		Symptoms include attention deficit, impaired short-term working memory, orientation, comprehension, vigilance, visuospatial ability, and executive dysfunction (46)	In hospitalized older adults is estimated at 23%, in critical care settings, 31% in all patients, 50% in mechanically ventilated patients, and 34% in critically ill children (46)
Brain fog		Confusion, short-term memory loss, dizziness, distraction, and decreased mental acuity experienced by patients infected with SARS-CoV-2 (47)	32% for long-COVID-19 (28)

[a]/, no specific symptom.

Stroke

Stroke, characterized by necrosis of brain tissue and focal neuronal dysfunction due to intravascular thrombosis (55), is a cerebrovascular disease that can be induced by SARS-CoV-2 (56). The data indicate that 46.4% of COVID-19 patients exhibit a notable increase in D-dimer levels (57), a recognized indicator of venous thromboembolism (58). The mortality rate of COVID-19-associated stroke exceeds the global average for stroke mortality (59–61). Common symptoms of stroke include hemiparesis, hemianaesthesia, aphasia, homonymous hemianopia, and hemispatial inattention (31). Stroke is typically classified as ischemic or hemorrhagic stroke.

Ischemic stroke is mainly manifested as cerebral, spinal cord, or retinal infarction (31), and the causes of ischemic stroke include cerebral vascular arteriosclerosis plaque rupture, arteriosclerosis plaque rupture, cardiogenic cerebral infarction, lacunar infarction of small vessel lesions, and vasculitis (55). Ischemic stroke has been recognized as a clinical manifestation of COVID-19, as evidenced by various brain imaging findings (48, 62, 63), with the prevalence ranging from 1% to 6% (32–34) and a mortality rate of 38% (35). After SARS-CoV-2 infection, there is an increased susceptibility to thromboembolic events, leading to a higher incidence of stroke and more severe symptoms among COVID-19 patients (64, 65). While there is a suggested association between SARS-CoV-2 infection and an increased risk of ischemic stroke, specifically cryptogenic stroke, further studies are needed to confirm this hypothesis (66, 67).

Hemorrhagic stroke has many manifestations, such as primary intraparenchymal hematoma, intraventricular hemorrhage, and subarachnoid hemorrhage. Cerebral venous thrombosis, CNS vasculopathy, vasculitis, and other factors can lead to hemorrhagic stroke (68). Hemorrhagic stroke, although less common than ischemic stroke, has been notably linked to SARS-CoV-2 infection, with a prevalence of 2.4% (36), accounting for 21.7% to 25.7% of all stroke cases in a study (37). The mortality rate for hemorrhagic stroke increases with its duration, possibly due to the SARS-CoV-2-induced degradation of angiotensin-converting enzyme 2 (ACE2) (69, 70). ACE2 exhibits pro-inflammatory and vasoconstrictive properties (71), and its depletion can potentially result in hypertension and hemorrhagic stroke (69).

Currently, based on global reports of coagulation in COVID-19 patients, it is suggested that SARS-CoV-2 infection can initiate a coagulation cascade (72), but it cannot exclude the effect of use of vaccination during COVID-19 (73–75). The etiology of coagulation abnormalities in SARS-CoV-2 patients includes an increase in cytokine storm and heparanase activity (76). SARS-CoV-2 infection can stimulate the production of IL-6, IL-1, TGF-β, and TNF-α, which are known to influence blood coagulation (77). Among them, IL-6 and IL-1β can overactivate platelets and eventually lead to hypercoagulability of whole blood (78, 79). Furthermore, one study has revealed that the heparanase activity significantly increased in the COVID-19 patients' plasma, and heparanase activity is an important factor involved in the promotion of coagulation cascades (76) (Fig. 1).

Neurodegenerative diseases

The olfactory dysfunction serves as an initial indicator of neurodegenerative diseases (80), which can predict a heightened susceptibility to neurodegenerative diseases in COVID-19 patients. Clinical manifestations of neurodegenerative diseases often involve elevated levels of biomarkers, including neurofilaments, total Tau, and phosphorylated Tau (8, 81, 82). Previous research has demonstrated a correlation between SARS-CoV-2 infection and an elevated risk of neurodegenerative diseases, including Parkinson's disease (PD), multiple sclerosis (MS), and Alzheimer's disease (AD).

Parkinson's disease

PD is a disease defined by symptoms including bradykinesia, increased muscle tone, tremors, and changes in gait and postural reflexes (39). Research suggests that infection caused by H1N1, SARS-CoV, MERS-CoV, and SARS-CoV-2 may trigger the development of

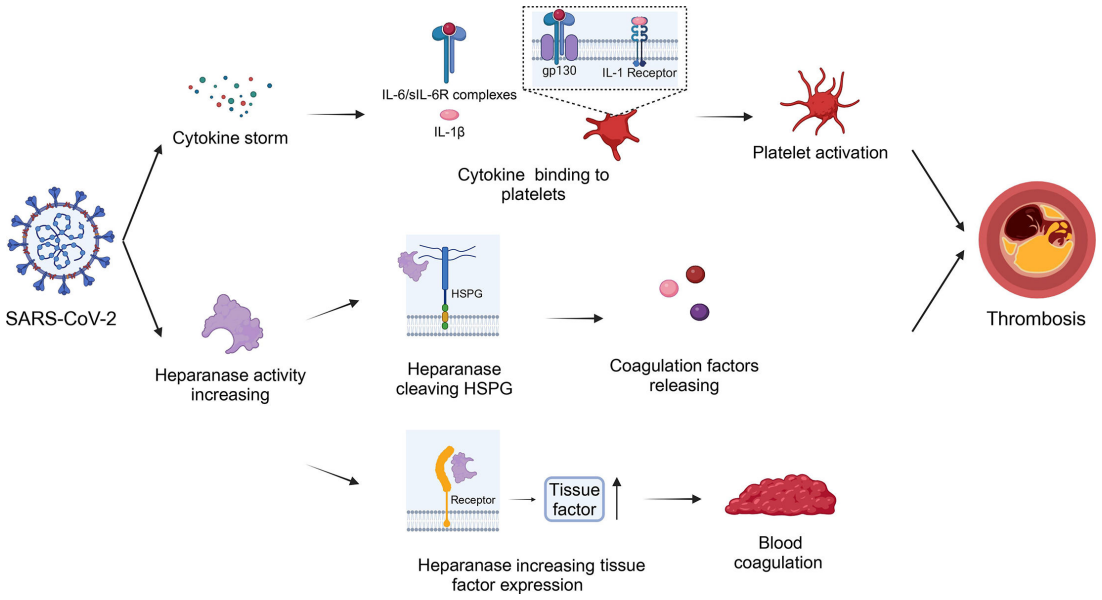

FIG 1 The mechanisms of SARS-CoV-2 initiate coagulation cascades. SARS-CoV-2 can induce a cytokine storm, among them, IL-6 with the IL-6 receptor complexes, and IL-1β can bind to platelets and over-activate platelets. SARS-CoV-2 can increase heparanase activity. Also, heparanase can cleave the heparan sulfate proteoglycan, thus releasing the coagulation factor. Heparanase induces the expression of tissue factors which initiates blood coagulation.

neurodegenerative diseases such as PD (83–85). There are clinical cases that individuals lacking a familial history of PD have developed PD after SARS-CoV-2 infection (86), with a pooled prevalence of COVID-19 patients among PD patients estimated at 5% (40). It has been proposed that the pathogenesis of PD induced by SARS-CoV-2 may be due to hypoxic ischemia (87), as well as potential mechanisms including mitochondrial dysfunction, autophagy impairment, and α-synuclein aggregation, meanwhile, SARS-CoV-2 could enhance endoplasmic reticulum stress, exacerbating neuroinflammatory activity, thus to mediate dopaminergic neurodegeneration (88).

Indeed, various symptoms induced by COVID-19 are associated with the risk of PD (89). Specifically, smell impairment is a prevalent sequela of COVID-19 and a common nonmotor characteristic of PD (90). Additionally, accelerated tissue aging may emerge as a possible long-term complication of SARS-CoV-2 infection, serving as a significant risk factor for PD (84). Moreover, SARS-CoV-2 has the ability to invade the brain and trigger cellular neurodegenerative pathologies, which can exacerbate or complicate PD in COVID-19 patients (91).

Multiple sclerosis

Multiple sclerosis (MS) is a persistent CNS condition characterized by chronic neuroinflammation, focal demyelination, and a high incidence of neurodegeneration (92, 93), resulting in irreversible clinical disability over time (94). There was a 4% prevalence of suspected SARS-CoV-2 infection in MS patients (42). Clinical manifestations of MS are variable and can affect the sensory, motor, visual, and brainstem pathways (41). After infection with SARS-CoV-2, the virus can breach the blood-brain barrier, potentially leading to acute or delayed demyelination of CNS (95). Previous studies have shown that viral infections can lead to demyelination in mice, and the administration of anti-inflammatory or pro-regressive factors, such as regulatory T cells or interleukins-10, has been shown to mitigate host tissue damage (96).

Factors such as obesity, disability, age, ethnicity, and a more severe course of COVID-19 have been associated with the severity of MS (97, 98). In MS patients, long-term and systematic treatment with individual immunomodulatory therapy, immunosuppressants, or corticosteroids can modify the immune response and affect the severity of MS symptoms after SARS-CoV-2 infection (99). MS is the predominant involvement of

$CD4^+$ T cells, with additional contributions from adaptive and innate immune cells in its pathogenesis (93).

While immunomodulatory and immunosuppressive therapies for MS are generally considered safe, the potential impact of SARS-CoV-2 on patients' immune responses necessitates a personalized treatment, considering the individual immune function and the situation of vaccination during the infection (100).

Dementia and Alzheimer's disease

Alzheimer's disease (AD) is a prevalent etiology of dementia, affecting the gradual cognitive decline in daily functioning (101). Growing evidence supports the association between SARS-CoV-2 infection and cognitive impairment, as well as an increased risk of AD and other forms of dementia among elderly patients (102). SARS-CoV-2 spike induces toll-like receptor 4 signaling in the brain, resulting in subsequent microglial activation and cognitive dysfunction (103). Specifically, SARS-CoV-2 infection has been shown to result in the atrophy of the cerebral cortex, cerebellar Purkinje layer, and hippocampus, impairing memory function and contributing to the development of dementia (55). Evidence has indicated a correlation between SASR-CoV-2 infection and higher mortality rates in dementia patients and AD patients. However, further investigation is required to elucidate the underlying causal mechanisms. Notably, there is currently insufficient evidence to support a link between mild cognitive impairment and increased mortality (104–108).

Delirium

Delirium is a prominent neurological sequela of COVID-19 (43), with different statistical results indicating that 25%–42% of COVID-19 patients suffer from delirium, particularly among critically ill patients and the elderly. Therefore, it is imperative to provide meticulous follow-up care and treatment for post-COVID-19 delirium (109–111), as research indicates that delirium is associated with a heightened risk of dementia in the future and significantly elevated mortality rates, particularly when diagnosis and treatment are delayed (109, 112, 113). Recent researches indicate that the elevated incidence of delirium among critically ill patients may be attributed to microvascular disease and inflammatory pathways, with benzodiazepine use and limited family visitation recognized as potentially modifiable risk factors for delirium (114, 115).

Other central nervous system disorders caused by SARS-CoV-2 infection

Several CNS diseases are related to SARS-CoV-2 infection, including sleep behavior disorders and neurodegenerative diseases (116). Additionally, COVID-19 patients may develop myalgic encephalomyelitis/chronic fatigue syndrome after infection, necessitating extended monitoring for up to 6 months.

The significant impact of vascular and inflammatory processes on the CNS represents a notable sequela of COVID-19 (117, 118). Furthermore, research indicates that COVID-19 patients may exhibit isolated bulbar palsy, potentially stemming from motor neuropathy in the medullary nucleus or lower cranial polyneuropathy (119).

The term "brain fog" encompasses a variety of cognitive impairments experienced by COVID-19 patients, including confusion, short-term memory loss, dizziness, distraction, and reduced mental acuity (47, 120). SARS-CoV-2 can enter the brain via the olfactory system, triggering the activation of cerebral mast cells and microglia in the hypothalamus, resulting in the secretion of pro-inflammatory molecules, brain inflammation, and brain fog (121). The manifestations of brain fog symptoms are associated with various factors including cognitive decline, disrupted sleep patterns, and nutritional and mental health deficiencies (47).

PERIPHERAL NERVOUS SYSTEM SYMPTOMS ASSOCIATED WITH COVID-19

Recent findings indicate that SARS-CoV-2 is associated with a variety of PNS symptoms, including skeletal muscle damage and inflammation (122), myasthenia gravis (123), and ICU-acquired myasthenia gravis (124). And this review aims to explore the diverse PNS symptoms induced by COVID-19 (Table 2).

Skeletal muscle damage and inflammation

Exposure to SARS-CoV-2 has the potential to trigger the onset of various musculoskeletal autoimmune diseases (137), with fatigue, myositis, myalgia, joint pain, fibromyalgia (125), and musculoskeletal inflammation (126) being prevalent complications in COVID-19 patients (122). Recent research has demonstrated the association between SARS-CoV-2 and skeletal muscle injury.

Tom et al. (138) proposed that SARS-CoV-2 could be associated with immune myopathies, noting that a significant proportion of patients with severe COVID-19 exhibited symptoms of skeletal muscle inflammation, with varying degrees of severity that were influenced by the duration of COVID-19. Additionally, the study found that around two-thirds of patients reported persistent fatigue or muscle weakness 6 months after recovery.

Smell or taste impairment

Altered senses of smell and taste are frequently observed sequelae in COVID-19 patients. Studies indicate that patients are three times more likely to experience olfactory loss compared to taste loss, with more than half of COVID-19 patients reporting changes in their sense of smell. This suggests that olfactory loss is more common than taste loss in COVID-19 patients (139, 140). Evidence has concluded that olfactory loss may serve as a potential indicator of SARS-CoV-2 infection, as a higher percentage of patients present with this symptom compared to fever. Specifically, 64.6% of patients exhibit olfactory loss and only 42.7% present with fever, with a significant portion (34.7%) of patients without fever also reporting olfactory loss, indicating that olfactory loss may be a more reliable indicator of SARS-CoV-2 infection than fever (9).

It has been suggested that olfactory dysfunction could be considered a diagnosis indicator of COVID-19 to improve detection capabilities. However, up to 80% of people over 75 years of age experience hyposmia after infection with SARS-CoV-2. Therefore, it is imperative to establish precise testing criteria, and monitoring self-reported olfactory dysfunction in real-time may serve as a predictive tool to identify SARS-CoV-2 infection (141, 142).

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder that can impact the neuromuscular junction and potentially result in respiratory muscle weakness, eventually leading to respiratory insufficiency (myasthenic crisis) (128); further research is needed to explore its possible association with SARS-CoV-2. Acetylcholine receptor (AChR) antibodies are the potential biomarker in MG patients, and there are three COVID-19 patients with AChR antibody positivity (143), suggesting that they developed MG complication. Restivo et al. (123) analyzed that SARS-CoV-2 may interact with molecules on the postsynaptic membrane and provoke cross-reactivity with AChR subunits, potentially inducing myasthenia gravis symptoms in COVID-19 patients.

Hübers et al. (144) identified mild and non-worsening symptoms of MG in four patients during SARS-CoV-2 infection, suggesting the necessity for additional research to validate the impact of COVID-19 on MG patients.

Based on the analysis of clinical symptoms and treatment outcomes in five clinical cases, Saied et al. proposed that long-term immunosuppressive immunotherapy may be beneficial for patients with MG and recommended the use of azithromycin for the treatment of COVID-19 patients with MG (145).

TABLE 2 Description and distribution of peripheral nervous system symptoms in COVID-19 patients

Peripheral nervous system clinical conditions associated with COVID-19		Symptoms description of peripheral nervous system involvement	Prevalence
Skeletal muscle damage and inflammation	Myalgia	/[a]	28% for long-COVID-19 (28)
	Joint pain	/	2%–65% (125), 19% for long-COVID-19 (30)
	Fibromyalgia	/	40% (125)
	Musculoskeletal Inflammatory	/	Case report (126)
Smell/taste impairment	Anosmia and ageusia	/	33.73% (477/1414) (36) and ageusia (23%) and anosmia (21%) for long-COVID-19 (127)
	Anosmia/hyposmia		9.05% (128/1414) (36)
	Ageusia/dysgeusia		9.97% (141/1414) (36)
Myasthenia gravis		Respiratory muscle weakness and respiratory insufficiency (myasthenic crisis) (128)	10%–15% exacerbation during COVID-19 (128)
ICU-acquired weakness		Critical illness polyneuropathy: symmetric, distal sensory-motor axonal polyneuropathy that affects limb muscles, respiratory muscles, and sensory and autonomic nerves. Critical illness myopathy: symmetric, proximal >distal myopathy that affects limb muscles, and respiratory muscles. Critical illness neuromyopathy: the presence of both critical illness myopathy and critical illness polyneuropathy (129)	Critical illness polyneuropathy: patients with COVID-19 (50%) vs patients with non-COVID-19 ICU control (0%). Critical illness myopathy: patients with COVID-19 (29%) vs patients with the non-COVID-19 ICU control (70%) (129)
Post-acute sequelae of COVID-19		Fatigue, breathlessness, post-exertional malaise, brain fog, headaches, nausea, vomiting, anxiety, depression, skin rash, joint pain, and palpitations (130)	50% of patients may show at least one symptom up to 12 months after infection (131)
Guillain-Barré syndrome		Limb weakness, refractive errors, sensory deficits, facial palsy, and autonomic dysfunction (132, 133)	16% (133)
Multisystem inflammatory syndrome in children		Fever, gastrointestinal symptoms, mucocutaneous symptoms, respiratory symptoms (134)	66% (135), 383 (64%) in the Alpha era, 111 (19%) in the Delta era, and 104 (17%) in the Omicron era (136)

[a]/, no specific symptom.

ICU-acquired weakness

COVID-19 patients may experience acute respiratory distress syndrome and require invasive mechanical ventilation (146), resulting in the development of ICU-acquired weakness (ICU-AW). It is a common complication among critically ill COVID-19 patients, which is encompassing critical illness polyneuropathy, critical illness myopathy and critical illness neuromyopathy (124, 129).

Van et al. (124) evaluated the incidence of ICU-AW in critically ill patients with COVID-19 and found that the prevalence of ICU-AW was 72%, 52%, and 27% in awake, ICU, and discharged, respectively. Additionally, Dodig et al. (147) proposed a correlation between critical illness myopathy and COVID-19, indicating that direct muscle infection by SARS-CoV-2 can cause critical illness myopathy in critically ill patients. The presence of ICU-AW has been associated with adverse outcomes, such as prolonged hospitalization and increased mortality rates. While it cannot be definitively concluded that sedatives directly cause ICU-AW (148), prolonged administration of sedatives may increase the likelihood of ICU-AW in critically ill COVID-19 patients (124).

Peripheral nervous system involvement

Researchers have presented varying conclusions about the potential for SARS-CoV-2 to induce PNS involvement. Li et al. (149) found extensive vascular and inflammatory involvement of the CNS and PNS in COVID-19 patients, leading them to assert that SARS-CoV-2 can, indeed, prompt PNS involvement. The predominant manifestation of PNS involvement is Guillain Barré syndrome (GBS) (150).

Among COVID-19 patients with GBS, limb weakness, refractive errors, sensory deficits, facial palsy, and autonomic dysfunction are commonly reported clinical symptoms (132). Since the first report of a COVID-19 patient exhibiting acute GBS, there has been ongoing debate on the potential correlation between GBS and COVID-19 (151). Research indicates a notable increase in the occurrence of GBS among COVID-19 patients, with more than half of GBS cases in COVID-19 patients either detected positive for SARS-CoV-2 nucleic acid or had symptoms associated with COVID-19. Furthermore, another study revealed that the prevalence of GBS in COVID-19 patients was five times higher compared to non-COVID-19 people (152–155). However, statistical analyses have illustrated the lack of correlation between COVID-19 and GBS, with only 16% of GBS patients testing positive for SARS-CoV-2. Additionally, some studies have reported a decrease in the incidence of GBS during the COVID-19 pandemic (133, 156, 157), potentially attributed to a heightened emphasis on hand hygiene and reduced social interactions, which may also contribute to a decline in other infectious diseases (158).

Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children, a rare delayed hyperinflammatory response to SARS-CoV-2 infection (134), with a prevalence of 66% (135), exhibits varying incidence rates in different eras of SARS-CoV-2, 64% in the Alpha era, 19% in the Delta era, and 17% in the Omicron era (136). Clinical manifestations in children can include encephalopathy, peripheral neurological involvement, behavioral changes, and hallucinations (159). Treatment options such as intravenous immunoglobulins and steroids can be administered to mitigate the inflammatory response (160).

Al Maskari et al. presented a case series consisting of six clinical cases, detailing the symptoms of multisystemic inflammatory syndrome in children. These symptoms included fever in the six cases, abdominal pain in four cases, diarrhea in two cases, conjunctivitis or rash in four cases, lymphadenopathy in three cases, extremity edema in four cases, hepatosplenomegaly in two cases, altered mental status in two cases, shock in three cases, and respiratory symptoms in two cases (161).

MECHANISMS OF SARS-CoV-2 CAUSED NEUROLOGICAL DISEASES

The ACE2 receptor on the cell surface serves as a key factor for SARS-CoV-2 entry (162) and is prominently present in various organs and tissues throughout the body, including the upper respiratory tract, oral cavity, lungs, blood, intestines, and brain (163). In particular, ACE2 is highly expressed in constituents of the blood-brain barrier (BBB) such as vascular endothelial cells and astrocytes. Invasion of SARS-CoV-2 into the brain has the potential to activate these cells, triggering neuroinflammation and potentially leading to significant impairment of CNS function (164). Subsequently, we will elucidate the potential mechanisms underlying the neurological effects induced by SARS-CoV-2.

Invading the brain via the retrograde neuronal pathway

The neuronal retrograde pathway involves viruses entering the CNS through trans-synaptic neuronal retrograde transmission after peripheral neuron infection (165). Examples of viruses known to utilize this pathway include rabies virus (166). HCoV-OC43, porcine hemagglutinating encephalomyelitis virus (167), and avian bronchiolitis virus have also been reported to enter the CNS by retrograde axonal transport and trans-synaptic transport (165, 168). These viruses are able to spread to other neurons within the central nervous system through synaptic and medullary neurons (168).

SARS-CoV-2 has been reported to infect peripheral neurons, specifically olfactory epithelial nerves (169) and the gastrointestinal tract (170), which gives credence to the hypothesis that the virus enters the CNS through a retrograde pathway and leads to the development of central neurological disorders.

Retrograde olfactory epithelial nerves

The olfactory system is composed of two parts, the peripheral and central systems. The peripheral olfactory system encompasses the olfactory epithelium and nerve bundles, while the central olfactory system comprises the olfactory bulb and its central connections (171). SARS-CoV-2 has been observed to potentially facilitate brain infection through olfactory nerves that travers the cribriform plate (13, 172–174). This neurological invasion may result in anosmia. Additionally, SARS-CoV-2 infection induces a significant release of inflammatory mediators, disrupting BBB dysfunction and initiating neuroinflammation and neuronal apoptosis (175) (Fig. 2A).

Despite the absence of ACE2 and TMPSSR expression in olfactory sensory neurons (176, 177), SARS-CoV-2 can infect the olfactory epithelium, a non-neuronal cell type that does express ACE2 (178). This infection leads to non-cell-autonomous effects that alter nuclear architecture and down-regulate the expression of olfactory receptors and their signaling components in olfactory sensory neurons, altering the transcriptome and indirectly impacting the function of these neurons (179). These effects exacerbate olfactory nerve dysfunction and may contribute to the development of neurological diseases.

MERS-CoV and SARS-CoV have been shown to potentially invade and infect the brain through olfactory nerves (180), while HCoV-OC43 (181) and hemagglutinating encephalomyelitis virus (182) have been observed to target the olfactory bulb or medullary neurons for infection and gain access to the brain through the retrograde neural pathway facilitated by synaptic transmission (13), these findings suggest that the olfactory bulb serves as a gateway for SARS-CoV-2 to invade the central nervous system.

Furthermore, SARS-CoV-2 can enter the nervous system through the neuromucosal interface in the olfactory mucosa, in addition to the olfactory bulb, and subsequently traverse the olfactory tract of the CNS, accessing specific neuroanatomical regions, including the major respiratory and cardiovascular control centers in the medulla oblongata before ultimately reaching the CNS (180).

Retrograde brain-gut axis nerves

The brain-gut axis serves as a bidirectional communication pathway connecting the CNS with the enteric nervous system, facilitating communication between the gastrointestinal tract and the brain (183).

The identification of infectious SARS-CoV-2 in the intestine and feces (184), along with the presence of ACE2 expression in the intestine and the prevalence of gastrointestinal symptoms in COVID-19 patients (14), implies the potential for intestinal infection by SARS-CoV-2 (185) (Fig. 2B) and its potential impact on the CNS through the brain-gut axis (186).

Specifically, SARS-CoV-2 can enter the CNS through the vagus nerve after infecting the gastrointestinal tract (14). Simultaneously, the gut microbiota can impact the CNS by producing metabolites such as short-chain fatty acids, bile acids, choline metabolites, lactic acids, and vitamins, which can modulate levels of various neurotransmitters (185). Consequently, SARS-CoV-2 infection of the intestinal tract can induce or exacerbate symptoms of neurodegenerative diseases and other CNS diseases (e.g., confusion and delirium) by disrupting the equilibrium and composition of intestinal microorganisms (14, 185, 186).

Enters the brain via the hematogenous route

Current research suggests that SARS-CoV-2 can enter the brain through three potential mechanisms: indirect crossing of the BBB through infected immune cells, direct crossing

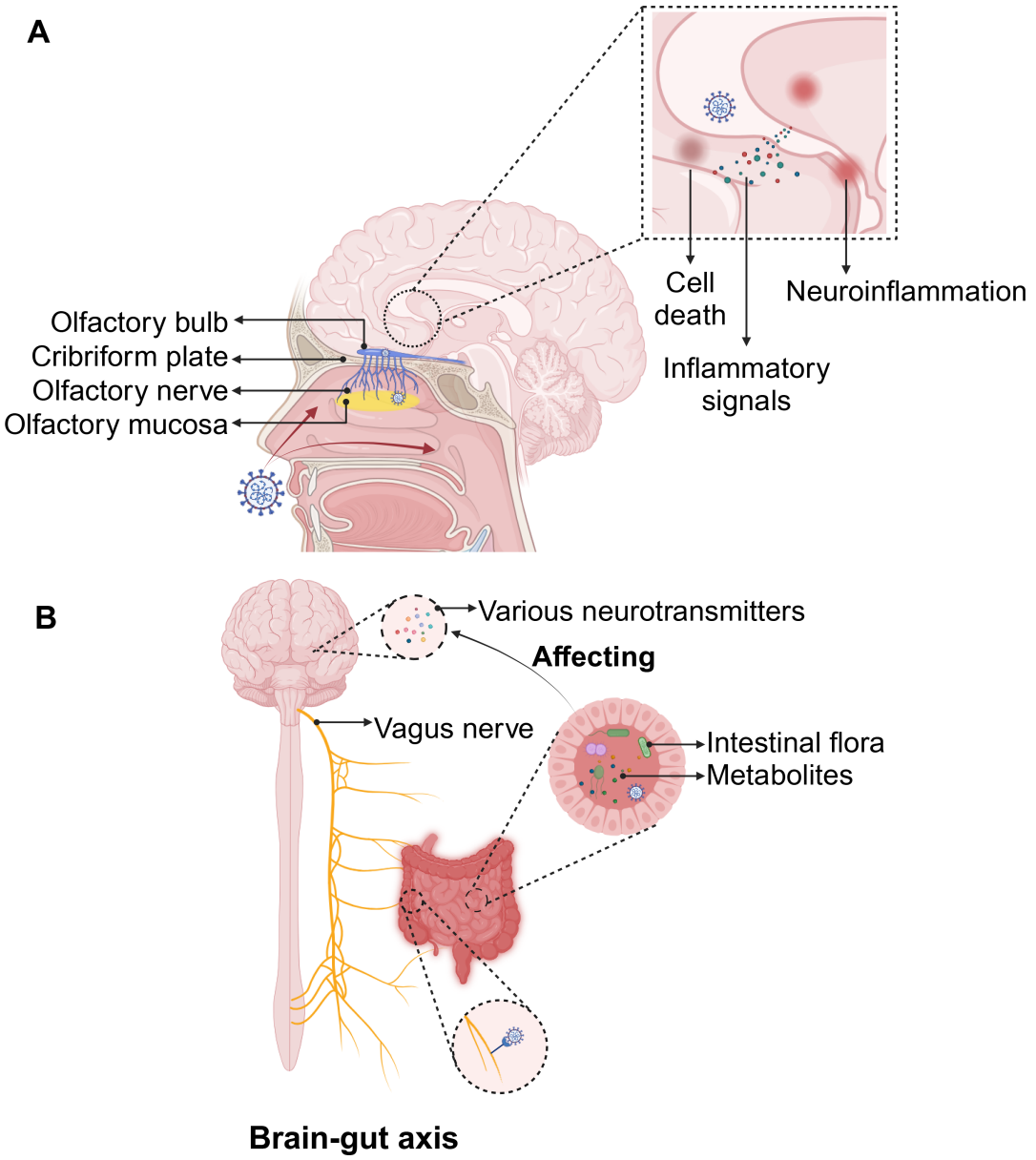

FIG 2 SARS-CoV-2 invades the brain via the retrograde neuronal pathway. (A) SARS-CoV-2 infects the brain by infecting the olfactory bulb through the olfactory nerve passing through the cribriform plate. At the same time, it can trigger a significant release of inflammatory signals to promote neuroinflammation and brain cell death. (B) After SARS-CoV-2 infects the gastrointestinal tract, the virus can gain access to the central nervous system through the vagus nerve. Concurrently, the gut microbiota can impact the central nervous system by the synthesis of metabolites that affect neurotransmitter levels.

of the BBB, and through circumventricular organs (CVOs) (13, 187). The BBB is made up of endothelial cells, pericytes, astrocytes, microglia, and neurons (188, 189). The BBB separates the CNS from the peripheral circulation and regulates the exchange of cells and molecules between the blood vessels and brain parenchyma (189). BBB dysfunction is associated with various neurological disorders like AD, PD, amyotrophic lateral sclerosis, MS, and stroke (189). We will discuss three ways of SARS-CoV-2 entering the brain through the hematogenous route.

Trojan horse mechanism

HIV can enter the brain through a Trojan house mechanism (190), and SARS-CoV-2 may have a similar mechanism (174, 191). Lam et al. demonstrated that high-density

lipoprotein (HDL) and exosomes can cross the BBB (191, 192) and act as Trojan horses for SARS-CoV-2 to enter the brain (191). HDL binds to the SARS-CoV-2 spike protein, facilitating the binding of SARS-CoV-2 to ACE2 and infection of host cells (193), potentially allowing SARS-CoV-2 to cross the BBB through the bloodstream (Fig. 3A).

The virus directly infects the blood-brain barrier

The high expression of ACE2 in BBB cells, such as vascular endothelial cells, pericytes, and astrocytes (13, 164), may allow SARS-CoV-2 to infect brain endothelial cells, leading to dysfunction and damage (166). Concurrent blood flow provides an opportunity for SARS-CoV-2 to interact with ACE2 on the surface of brain endothelial cells, this interaction may also promote viral invasion of the brain (13) and infect other BBB cells and astrocytes (168).

SARS-CoV-2 can also disrupt the integrity of the BBB by affecting tight junction proteins and the actin cytoskeleton (168), allowing it to enter the CNS (Fig. 3B).

Access to the brain through the circumventricular organs of the brain

Circumventricular organs (CVOs) are highly vascularized anatomical structures located proximal to the third and fourth ventricles, characterized by highly permeable capillaries (13, 194). These CVOs include vascular organs, subfornical organ, area postrema, pineal gland, subcommissural organ, median eminence, and neurohypophysis (13, 195). ACE2 is highly expressed in CVOs and nuclei that are connected to the CVOs (195), and CVOs lacking of a BBB may serve as a potential pathway for SARS-CoV-2 to enter the brain (195, 196). Furthermore, CVOs have been implicated in the pathogenesis of certain parasitic and viral infections (13). Previous research has demonstrated elevated levels of SARS-CoV and MERS-CoV in this region of the brain, providing potential evidence for SARS-CoV-2 infection in this region (197).

Cytokine storm

Cytokines, such as interleukins (IL), interferons, chemokines, tumor necrosis factors (TNF), and lymphotoxins, along with other mediators (198, 199), play a crucial role in coordinating antibacterial effector cells and regulating immune responses (199).

Some exogenous pathogens can induce excessive activation of immune cells after invading the human body, resulting in the release of a significant quantity of cytokines. This phenomenon is commonly named cytokine release syndrome, and severe cases are classified as cytokine storm (198). Extensive cytokine release leads to uncontrolled systemic hyperinflammation and eventually precipitates multiple organ failure or mortality (200). Additionally, increased cytokine release can lead to peripheral inflammation. Peripheral inflammation can disrupt the BBB through various mechanisms, including alteration of tight junctions, damage to endothelial cells, activation of astrocytes and microglia, and other pathways. This disruption can contribute to the development or exacerbation of neurodegenerative diseases and CNS disorders such as stroke (189) (Fig. 4A).

Cytokines may enter the bloodstream and be transported to other organs. Some cytokines can cross the BBB through specialized transport systems that utilize transmembrane diffusion (166). Given the increased permeability of the BBB (56), it is assumed that the elevated systemic cytokine levels induced by SARS-CoV-2 can cross the BBB and reach the CNS, thus instigating neuroinflammation (168) and aggravating neurodegenerative diseases (201, 202).

Research has shown that SARS-CoV-2 infection can promote the degradation of ACE2 in brain tissue (70) and enhance the activity of TMPRSS2 and cathepsin L, resulting in increased expression of pro-inflammatory mediators and reactants (such as cytokines IL-6, IL-1, IL-17; chemokines CCL2, CCL3, CCL5; and TNF-α, granulocyte concentration stimulating factors, monocyte chemoattractant protein-1, transforming growth factors, interferons, C-reactive protein and D-dimer) (164, 189, 203, 204), thus initiating a

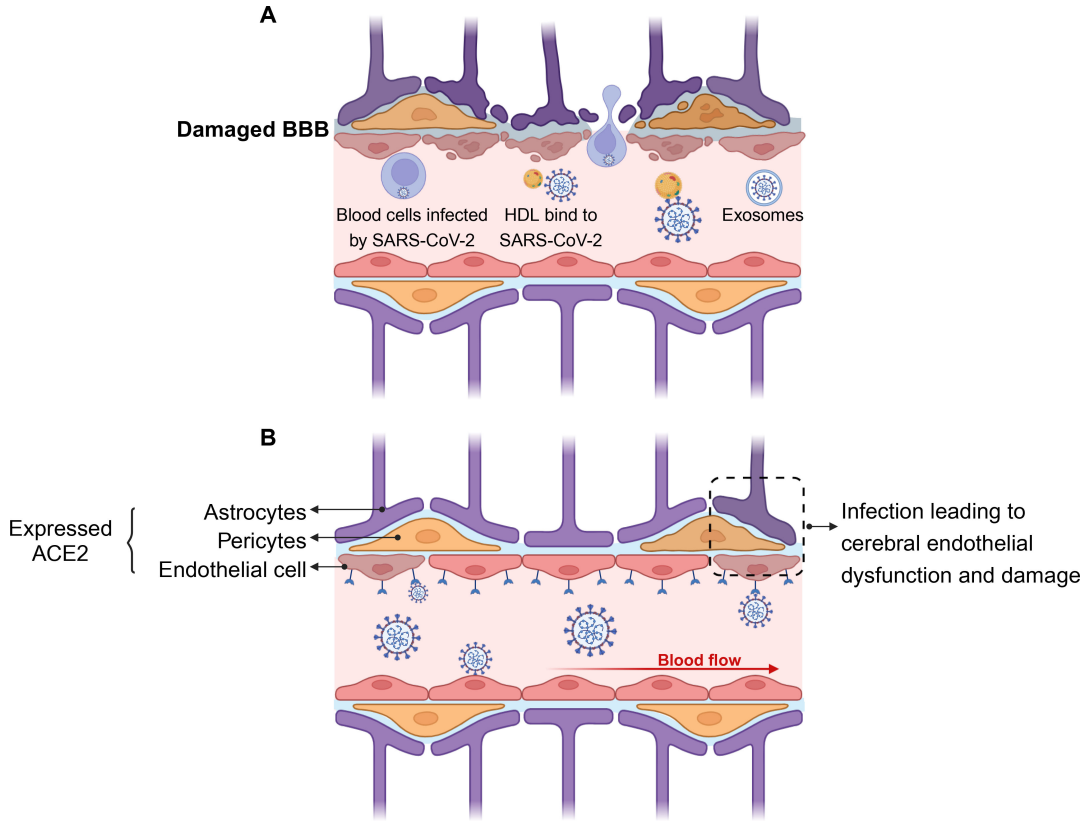

FIG 3 SARS-CoV-2 enters the brain via the hematogenous route. (A) After SARS-CoV-2 infects blood cells, these cells can traverse the BBB utilizing a Trojan horse mechanism. Additionally, high-density lipoprotein (HDL) can bind to the SARS-CoV-2 spike protein and cross the BBB through blood circulation. Exosomes also have the potential to act as Trojan horses to facilitate the entry of SARS-CoV-2 into the BBB. (B) Increased expression of ACE2 on various components of BBB cells, including endothelial cells, pericytes, and astrocytes, suggests that SARS-CoV-2 can infect brain endothelial cells, ultimately resulting in dysfunction and damage to the brain endothelium. Blood flow promotes the interaction between SARS-CoV-2 and ACE2, which helps the entry of virus into the brain. BBB, blood-brain barrier; HDL, high-density lipoprotein.

neuroinflammatory response and disrupting the BBB (164), and leads to the presence of brain injury markers such as tTau, GFAP, NfL, and UCH-L1 in the patient's blood for an extended period after infection (205). Type I interferon triggered by SARS-CoV-2 has been reported to cause neurological injury in mice (206).

In human primary endothelial cells with high ACE2 expression, infection with SARS-CoV-2 led to a greater expression of coagulation factors and pro-inflammatory cytokines, ultimately culminating in the development of multinucleated syncytia and endothelial cell lysis (166). In an *in vitro* model of the human BBB, the SARS-CoV-2 S protein was found to induce a pro-inflammatory response, resulting in compromised BBB integrity (207).

In the K18-hACE2 transgenic mouse model, SARS-CoV-2 induces damage to endothelial cells, resulting in increased expression of pro-inflammatory cytokines, aggravating the disruption of the BBB, and leading to perivascular inflammation (208). These results suggest that SARS-CoV-2 infection promotes the expression of pro-inflammatory mediators, aggravated endothelial cell damage, and BBB breakdown.

The current hypothesis posits that the unrestrained release of cytokines after SARS-CoV-2 infection is attributed to viral replication-induced pyroptosis, which then triggers the release of pro-inflammatory factors (203).

Moreover, the cytokine storm induced by SARS-CoV-2 is related to the angiotensin 2 (Ang II) pathway. SARS-CoV-2 infection degrades ACE2 (70), leading to an increase in Ang II levels and activation of NF-κB (209). The activation of the type I Ang II

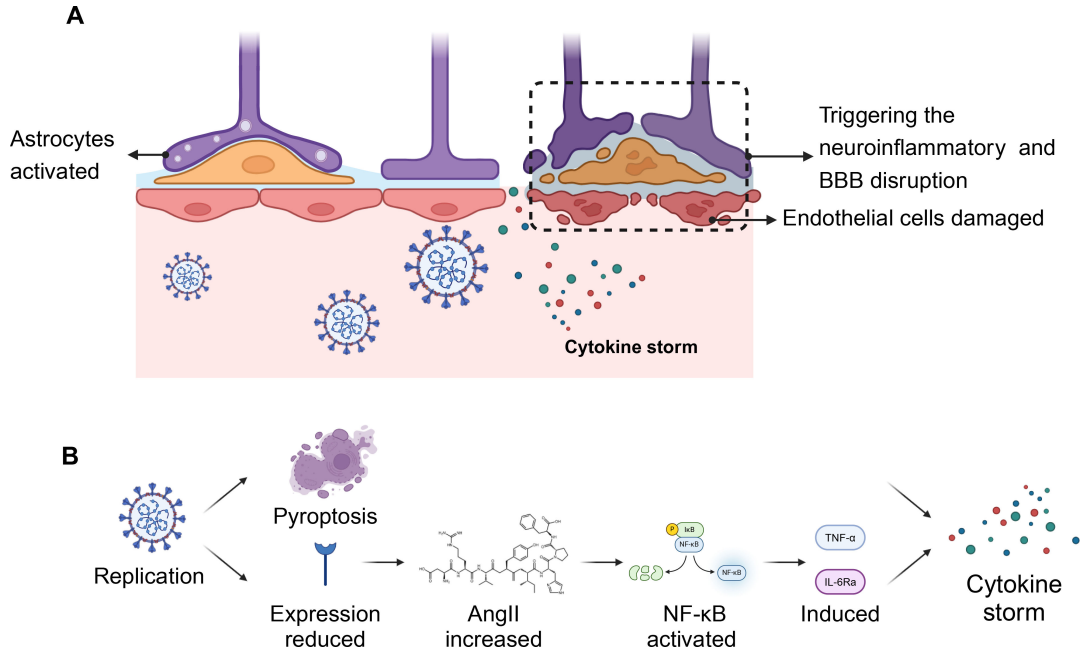

FIG 4 Cytokine storm induced by SARS-CoV-2 infection. (A) SARS-CoV-2 infection induces the cytokine storm, resulting in endothelial cell damage, astrocyte activation, and exacerbation of blood-brain barrier dysfunction. (B) Viral replication can trigger cell pyroptosis, resulting in the release of pro-inflammatory factors. In addition, SARS-CoV-2 infection downregulates ACE2 expression, increases AngII levels, and activates of NF- κB signaling pathways. This cascade induces the expression of the TNF-α and IL-6 receptor alpha, the production of various pro-inflammatory cytokines and chemokines.

angiotensin receptor axis can also trigger the production of TNF-α and the soluble form of IL-6 receptor alpha, ultimately resulting in the induction of various pro-inflammatory cytokines and chemokines through the IL-6 amplifier (210, 211) (Fig. 4B).

Other mechanisms

SARS-CoV-2 causes an insufficient blood supply to the brain

The results of animal experiments indicate that SARS-CoV-2 can infect pericytes located in capillaries of the body, including the brain. This infection hinders the functionality of pericyte receptors, resulting in the contraction of capillaries in tissues. Consequently, this constriction leads to decreased blood flow to the brain, impacting the blood supply to the brain and causing impairment in neuronal function (16, 212) (Fig. 5A).

SARS-CoV-2 causes brain hypoxia

After respiratory distress and lung injury caused by SARS-CoV-2 infection (17), patients may experience a reduction in blood oxygen level, while patients without respiratory distress may also experience a significant decrease in blood oxygen levels (166), ultimately resulting in brain hypoxia (17). Hypoxia can trigger mitochondrial anaerobic metabolism in nerve cells, resulting in excessive lactate production, decreased intracellular pH, causing cerebral vasodilation (17), and eventually destroying the integrity of the BBB (17, 166), which consequently leads to CNS disease (Fig. 5B).

SARS-CoV-2 compromises neuronal activity

Some virus infections have the potential to induce cell fusion, as evidenced by the formation of syncytia in HIV-infected T cells and subsequent infection of other lymphocytes through transient contact (213). Experimental data indicate that SARS-CoV-2 infection can induce fusion between neuronal cells or between neuronal cells and glial cells in murine hippocampal and human-derived brain organoids, leading to

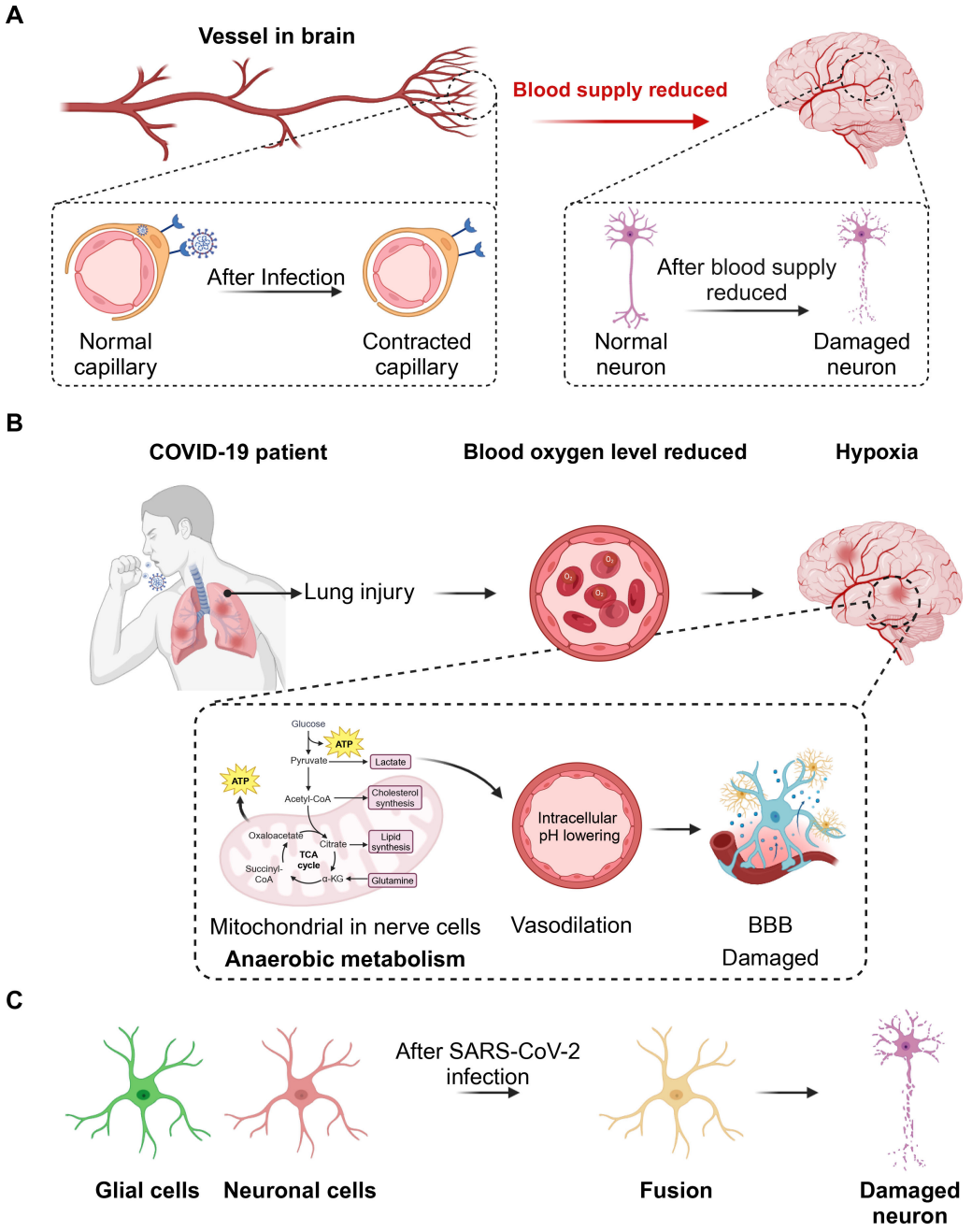

FIG 5 Other mechanisms of SARS-CoV-2 cause neurological complications. (A) SARS-CoV-2 infects pericytes located on brain capillaries, causing capillary constriction and ultimately reducing blood flow to the brain, thereby impacting cerebral blood supply and impairing neuronal function. (B) Patients diagnosed with COVID-19 exhibit reduced blood oxygen levels, leading to cerebral hypoxia. This hypoxia will trigger mitochondrial anaerobic metabolism in neuronal cells, heighten lactate production, reduce intracellular pH, and lead to cerebral vasodilation, eventually destroying the integrity of the blood-brain barrier. (C) SARS-CoV-2 infection can induce fusion between neuronal cells or between neuronal cells and glial cells, leading to neuronal damage.

compromised neuronal function and potential alterations in nervous system function (18) (Fig. 5C).

LONG-COVID-19

Most COVID-19 patients can recover completely, but a subset of patients have symptoms that persist for a long time (214), such as dyspnea, fatigue, palpitation, and muscle weakness, with female patients being more prone to these symptoms (130, 215). This phenomenon is called long-COVID-19 or post-acute sequelae of SARS-CoV-2 infection, denoting long-term sequelae of SARS-CoV-2 infection (216). The prevalence of long-COVID-19 among non-hospitalized patients ranges from 10% to 30%, while among hospitalized patients, it ranges from 50% to 70% (217). This phenomenon has gained increasing attention, with smell or taste impairment emerging as the predominant symptom of long-COVID-19 (127). Two-thirds of infected people exhibit smell and taste problems whose duration ranges from 1 to 9 months, as evidenced by an experiment involving direct exposure to the virus (218, 219). Additionally, some patients have reported enduring neurological complications, ranging from mild symptoms such as headache, anosmia, vision impairment, and fatigue to more severe manifestations such as sleep disturbances, pain, cognitive impairment, Guillain-Barre syndrome (216), and Parkinson's symptoms (220).

In 2021, a study conducted by Bjørn Blomberg involved long-term follow-up on 312 COVID-19 patients and revealed that 61% of them experienced persistent symptoms independent of the initial disease severity, convalescent antibody titers, and pre-existing lung conditions. Furthermore, mild patients with COVID-19 who self-isolated at home were found to be at risk of long-term dyspnea and cognitive impairment (221). Some patients exhibit cough symptoms that are different from typical fever or cold symptoms. In the cases of long-COVID-19, chronic cough is usually accompanied by additional symptoms such as fever and loss of smell and taste, indicating a potential multifactorial pathogenesis or co-mechanism. Research suggests that SARS-CoV-2 can infect the sensory nerves involved in the cough reflex, resulting in neuroinflammation and neuroimmune interactions, ultimately triggering hypersensitivity of cough pathways (222).

A study reported that 85% of patients experiencing long-COVID-19 still exhibit symptoms 1 year after the onset of the disease, similar to the findings of a single-center study conducted in Germany, which indicated that 77.1% of patients had at least one symptom (symptoms that include reduced exercise capacity, fatigue, dyspnea, problems with concentration and sleep disturbance, etc.) at 12 months (223, 224). The progression of symptoms exhibited three discernible patterns over time. First, there was a decrease in the prevalence of symptoms such as anosmia, dysgeusia, cough, or diarrhea. Conversely, the prevalence of other symptoms such as alopecia increases over time (225). Lastly, symptoms that displayed no change of prevalence over time can be attributed to mechanisms that do not change rapidly over time, such as post-traumatic stress disorder (224).

In fact, SARS-CoV-2 has been shown to induce lasting detrimental effects in patients with neurological diseases, including PD. In addition to general symptoms such as fatigue, patients may experience a myriad of specific symptoms, including worsened motor and non-motor symptoms, and increased mortality rates (220). A study involving 102 patients with cerebellar ataxia, a degenerative neurological disorder, revealed that two patients exhibited short-term memory loss and confusion (226). Therefore, it should pay more attention and care to these patients in the future.

Research indicates that children are not the most severely impacted during the COVID-19 pandemic (227), yet there is a growing concern regarding the phenomenon of long-COVID-19 in this population (228). Despite they typically present with mild initial symptoms, children may have lingering symptoms, such as headaches, fatigue, and sleep disturbance, suggesting a potential risk of developing long-COVID-19 (229, 230). Danilo Buonsenso et al. found that 25.3% of children experienced persistent symptoms after infection, with 94.9% reporting at least four symptoms (231). Jakob Armann, a pediatrician in Germany, believed that the prevalence of long-COVID-19 in children may be relatively low (232, 233). In addition, it has been suggested that the virus may cause

widespread inflammation and organ complications in a minority of cases, potentially due to hyperactivation of certain immune systems (234).

Researchers have sought to elucidate the underlying mechanisms of long-COVID-19, with findings indicating that persistent dysfunction of the blood-cerebrospinal fluid barrier and heightened cytokine levels could contribute to the development of long-COVID-19 (235).

RECOMMENDATIONS FOR CARE AND THERAPEUTIC APPROACHES FOR PATIENTS WITH NEUROLOGICAL DISORDERS INDUCED BY SARS-CoV-2

Care

The increasing evidence underscores the importance of prompt medical intervention in neurological disorders induced by SARS-CoV-2 to mitigate the potential development of chronic conditions in affected patients (236). Research suggests that symptoms and complications associated with certain neurological diseases may stem from an exaggerated or aberrant immune response after exposure to coronavirus, so intravenous immunoglobulin suppresses detrimental autoantibodies (212). A research investigating the impact of immunosuppressive and immunomodulatory regimens on the severity of COVID-19 patients with MS revealed that these treatments with various effects are generally safe for the majority of individuals although caution should be exercised in older populations (237).

For patients with anosmia, olfactory training is the most effective rehabilitation method (238). Some people believe in the efficacy of vitamin A drops for improving the olfactory function in COVID-19 patients (239). However, the effectiveness of oral steroids, including topical corticosteroids, remains unconfirmed (139). In cases where patients are suspected of acute COVID-19 patients, it is advisable to refrain from administering oral steroids such as prednisolone to minimize the risk of adverse effects (139, 239).

Therapeutic approaches

IL-6, a key component in cytokine storms caused by SARS-CoV-2 infection, has been associated with neurological disorders (240). Tocilizumab, a treatment for neuroendothelial dysfunction, works by inhibiting IL-6 signaling by competitively blocking the IL-6 receptor-binding site (188), thus reducing inflammation-induced endothelial activation. Concurrently, decreasing convalescent plasma levels in recovered COVID-19 patients can aid in the restoration of olfaction (241).

Researchers have been suggested to address other inflammatory responses, such as targeting the NLRP3 inflammasome, which has been implicated in the development of neurodegenerative diseases, including AD and PD (166). Glibenclamide can also mitigate the neuroinflammatory response induced by SARS-CoV-2 by inhibiting the NLRP3 inflammasome, microglia activation, and oxidative stress (242). Beta-blockers exhibit anti-inflammatory effects by suppressing the release of pro-inflammatory cytokines, helping to ease cytokine storms and sympathetic nervous system hyperactivity, and preventing the development of neuro-cytokine loops after SARS-CoV-2 infection (243). On the other hand, histone deacetylase inhibitors inhibit proinflammatory cytokines (IL-6 and TNF-α), thereby reducing neurotoxicity (244). Additionally, histone deacetylase inhibitors can also reduce virus replication by downregulating the viral receptors, resulting in a direct antiviral effect (245, 246). Simultaneously, remdesivir can inhibit the rapid replication of SARS-CoV-2, reducing recovery time in adults hospitalized patients with COVID-19 (188). A study found that COVID-19 patients administered dexamethasone, remdesivir, or a combination of both exhibited a decreased incidence of neurological complications, suggesting that administration with these medications can reduce neurological complications in patients (247).

In addition, researchers have demonstrated that some antimalarial medications, chloroquine and hydroxychloroquine, possess special anti-inflammatory properties, enhanced lipophilicity that facilitates BBB penetration, and have been used in

clinical trials for malaria elimination (NCT02698748) and school-based malaria control (NCT05980156). Beyond their potential as anti-SARS-CoV-2 agents, chloroquine and hydroxychloroquine have shown efficacy in treating neurovascular conditions such as stroke and vascular dementia (248).

Adamantanes have been demonstrated to provide significant therapeutic advantages in the management of neurodegenerative diseases and relief from fatigue in patients with MS (249). Furthermore, adamantanes may exert their antiviral effects on the viroporin E of coronaviruses (250), thus potentially inhibiting the replication of SARS-CoV-2 within the cell (251). Additionally, adamantanes have shown efficacy in promoting recovery of COVID-19 patients (252). Therefore, adamantanes possess the potential to address neurological symptoms of degenerative disorders and comorbidities associated with severe SARS-CoV-2 infection (249).

Various treatment options, including anti-inflammatory therapy, mitochondrial therapy, detoxification, hormonal correction vasoactivity therapy, and symptomatic therapy, have been proposed and tested in clinical trials. It is hoped that further research will lead to the development of more effective treatment options (253).

CONCLUSIONS AND PERSPECTIVES

In conclusion, current experimental and clinical evidence have suggested that SARS-CoV-2 infection can cause CNS diseases, such as encephalitis, and delirium, (19). Furthermore, SARS-CoV-2 has the potential to trigger or exacerbate symptoms associated with neurodegeneration such as PD, AD, and MS (23). Additionally, skeletal muscles express ACE2 receptors, making them susceptible to SARS-CoV-2 infection. Research has also demonstrated that SARS-CoV-2 can cause PNS diseases such as skeletal muscle damage and myasthenia gravis (122).

The pathogenesis of neurological disorders caused by SARS-CoV-2 involves several mechanisms. First, SARS-CoV-2 could enter the brain through retrograde transmission (13, 14) and hematogenous routes (13), and disrupt brain function and structure, thus causing or exacerbating neurological disorders. Additionally, cytokine storm induced by SARS-CoV-2 infection exacerbates neuroinflammation and neurological disorders (15), potentially contributing to inadequate blood (16) and oxygen supply (17) to the brain. Lastly, cerebral ischemia and hypoxemia caused by SARS-CoV-2 are also possible mechanisms to trigger the development of COVID-19-associated neurological diseases.

Depending on the mechanism and manifestation of SARS-CoV-2-induced neurological disorders, corticosteroids (254), glibenclamide (242), antimalarials (248), vitamin B12 (255), and probiotics (256) may be used to alleviate symptoms.

With the global spread of SARS-CoV-2 since 2020, olfactory dysfunction has become a common sequela (139, 140), raising the concern about virus-induced neurological sequelae. This review concentrates on the CNS and PNS disorders resulting from SARS-CoV-2 infection and outlines the mechanisms underlying neurological complications associated with SARS-CoV-2. Furthermore, it addresses long-term symptoms, care strategies, and therapeutic approaches for COVID-19 patients, with an optimistic outlook toward the development of improved treatment strategies for neurologic sequelae in the future.

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