REVIEW

COVID-19-Related Brain Injury: The Potential Role of Ferroptosis

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Abstract: The COVID-19 pandemic has caused devastating loss of life and a healthcare crisis worldwide. SARS-CoV-2 is the causative pathogen of COVID-19 and is transmitted mainly through the respiratory tract, where the virus infects host cells by binding to the ACE2 receptor. SARS-CoV-2 infection is associated with acute pneumonia, but neuropsychiatric symptoms and different brain injuries are also present. The possible routes by which SARS-CoV-2 invades the brain are unclear, as are the mechanisms underlying brain injuries with the resultant neuropsychiatric symptoms in patients with COVID-19. Ferroptosis is a unique iron-dependent form of non-apoptotic cell death, characterized by lipid peroxidation with high levels of glutathione consumption. Ferroptosis plays a primary role in various acute and chronic brain diseases, but to date, ferroptosis in COVID-19-related brain injuries has not been explored. This review discusses the mechanisms of ferroptosis and recent evidence suggesting a potential pathogenic role for ferroptosis in COVID-19-related brain injury. Furthermore, the possible routes through which SARS-CoV-2 could invade the brain are also discussed. Discoveries in these areas will open possibilities for treatment strategies to prevent or reduce brain-related complications of COVID-19.

Keywords: brain injuries, cell death, COVID-19, ferroptosis, iron, neuropsychiatric symptoms

Introduction

Coronavirus disease 2019 (COVID-19), triggered by the coronavirus-2 virus of the severe acute respiratory syndrome (SARS-CoV-2), is a critical health concern worldwide.[1] By January 2022, over 349 million cases of COVID-19 and over 5.5 million people have died worldwide.[2] Central nervous system (CNS) involvement is one possible cause of death among patients with COVID-19.[3] Analysis of clinical data for 214 patients with COVID-19 indicated that 36% had CNS manifestations, including acute cerebrovascular disease with disturbances in consciousness.[4] Furthermore, SARS-CoV-2 infection has been shown to affect the CNS and cause a series of neuropsychiatric symptoms (eg, anosmia, headache, cognitive and attention deficits, disturbances in consciousness, anxiety, depression, delirium, and suicidal behavior) and diseases (eg, acute necrotizing encephalopathy, encephalitis, hypoxic brain injury, strokes, myelitis, tonic epilepsy, neurogenic respiratory failure, generalized myoclonus, and Kawasaki syndrome).[5–10] This wide range of symptoms and diseases suggests that various underlying mechanisms cause and promote brain injury in patients with COVID-19. Therefore, exploring possible underlying mechanisms can help guide the development of treatment for brain injuries with subsequent neuropsychiatric symptoms in patients with COVID-19.

Among these mechanisms, ferroptosis may contribute to the pathogenesis of COVID-19-related brain injuries. First described in 2012, Dixon et al[11] explained that ferroptosis is an iron-dependent programmed nonapoptotic cell death with unique biological processes and pathophysiologic characteristics. The pathogenic processes of ferroptosis involve an excessive iron metabolism that produces iron-dependent oxidative stress and causes damage to nucleic acids, proteins, and lipids that eventually induce cell death.[12,13] Ferroptosis has recently gained considerable attention in brain research

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and has significant implications for several neurologic diseases, such as ischemic stroke, intracerebral hemorrhage (ICH), Alzheimer's disease, and Parkinson's disease.[12–16] In addition, emerging evidence indicates that ferroptosis is a nexus between metabolism, redox biology, and human diseases such as COVID-19.[17] However, the specific underlying mechanisms of ferroptosis remain unclear. Exploring the role of ferroptosis in COVID-19 infection and COVID-19-related brain injury, in particular, could be valuable for identifying therapeutic targets to prevent or lessen brain complications of COVID-19 and improve prognosis. In this regard, brain-permeable ferroptosis inhibitors or iron-chelating agents could be tested to assess whether they affect neuropsychiatric symptoms caused by COVID-19-related brain injuries.[17]

Brain Injuries Caused by COVID-19
Neuropsychiatric Symptoms and Brain Injuries in Some Patients with COVID-19

COVID-19, mainly described as acute pneumonia, is increasingly recognized as a disease involving multiple organ dysfunction, including brain microbleeds.[18] All the results of different groups indicated the presence of neuropsychiatric symptoms in some patients infected with SARS-CoV-2 (Table 1). Two studies conducted in Germany and the United Kingdom showed that post-COVID neuropsychiatric symptoms were observed in 20% to 70% of patients, respectively. These symptoms lasted months after the resolution of respiratory symptoms.[8] A systematic review concluded that the average prevalence of headaches among COVID-19 patients was 8%.[19] An analysis of the clinical characteristics of 138 hospitalized patients with COVID-19 showed that the incidence of dizziness was between 7% and 9.4%.[20] A study of 31 patients with COVID-19 showed that 45% experienced anosmia, 29% had hyposmia, and 6% had dysosmia,[21] indicating that COVID-19 can damage the olfactory bulb. A review of the neurologic manifestations of COVID-19 showed that an average of 25% of the patients had CNS dysfunction, 7.5% had disturbances in consciousness, 3% had acute cerebro-vascular disease, and 0.5% had ataxia.[22]

Furthermore, COVID-19 may cause cognitive impairment, such as confusion, inattention, anxiety, and disorientation.[23,24] Neuropsychological evaluation of 57 patients with COVID-19 who had recovered showed that 81% of the cases had cognitive impairment ranging from mild to severe.[25] In addition, there have been case reports of seizures in some patients with COVID-19. The severity of the disease was affected by systemic inflammation, which differs from 'common seizures' that have specific cortical, thalamic, or posterior fossa involvement.[26] Together, these neuropsychiatric symptoms may be related to COVID-19-related brain damage to particular regions of the brain.

Brain injuries (eg, cerebral vascular pathology, arteriosclerosis, ischemic strokes, and ICH have been discovered in COVID-19. A magnetic resonance imaging study of 13 patients with COVID-19 showed that 11 (85%) had bilateral frontotemporal hypoperfusion, 3 (23%) had acute or subacute strokes, and 8 (62%) had enlargement of the papillary space.[24] Another study with high-resolution magnetic resonance imaging of 13 patients who died of COVID-19 showed abnormalities in the brains of 10 patients (76.9%).[27] The incidence of brain injury in critically ill and dead patients is higher than in noncritically ill patients.[22] A systematic review of patients with COVID-19 indicated that 35.6% had inflammation and activation of astrocytes and microglia in the brain, and 28.1% had hypoxic-ischemic injury.[28] Of these patients, 29.5% had arteriosclerosis, 12.4% had ICH, and 2.7% had infarcts in the cerebral cortex and subcortex.[28] COVID-19 is now an independent risk factor for acute stroke.[29] As an important but under-recognized complication of COVID-19,[30] acute stroke affects approximately 1–3% of hospitalized patients and 6% of ICU patients; male patients with COVID-19 have a higher incidence of strokes (62%) compared to female patients.[31] In a retrospective study of 219 hospitalized COVID-19 patients in China, 11 patients (5%) had an acute stroke (10 cases of ischemic stroke, 1 case of hemorrhagic stroke).[32] All of the above data indicate the presence of different brain injuries among COVID-19 patients.

SARS-CoV-2 Invasion with Subsequent Brain Injuries

Like SARS-CoV and the Middle East Respiratory Syndrome Coronavirus,[33] SARS-CoV-2 can also invade and spread throughout the brain.[34,35] Increasing numbers of studies provide direct evidence for the neuroinvasiveness of SARS-CoV-2 (Table 2). However, the mechanism by which the virus infects the specific regions of the brain has not been fully elucidated. In this review, we speculated and concluded that SARS-CoV-2 infection could cause brain damage through three routes

Table 1 Studies Reporting Neuropsychiatric Diseases and Symptoms Related to COVID-19

References	Country	Study Design	Sample Size	Age	Male (%)	Female (%)	Symptoms or Diseases
Helms et al[24]	France	Case series	58	63 years (median)	NR	NR	Symptoms: Agitation (69%); confusion (65%); dysexecutive syndrome (36%)
Varatharaj et al[159]	UK	Case report	125	NR	NR	NR	Diseases: Ischemic stroke (46%); intracerebral hemorrhage (7%); encephalopathy (7%); encephalitis (6%)
Paterson et al[160]	UK	Case report	43	NR	24 (56%)	19 (44%)	Symptoms: Delirium (23%); confusion (23%); disorientation (23%); psychosis (2%); seizures (2%) Diseases: Encephalopathy (23%)
Hao et al[161]	China	Case-control study	10	37.4±12.6 years	6 (60%)	4 (40%)	Symptoms: Impulsivity (50%); insomnia (50%); depression (40%); anxiety (30%) Diseases: Dysosmia (20%); dysgeusia (10%); posttraumatic stress disorder (50%)
Li et al[32]	China	Retrospective study	219	53.3±15.9 years	130 (59.4%)	89 (40.6%)	Diseases: Ischemic stroke (4.6%); intracerebral hemorrhage (0.5%)
Zhang et al[162]	China	Cross-sectional study	57	46.9±15.37 years	29 (50.9%)	28 (49.1%)	Symptoms: Depression (29%); anxiety (21%); depression comorbid with anxiety (21%)
Giacomelli et al[163]	Italy	Cross-sectional study	59	60 years (median)	40 (67.8%)	19 (32.2%)	Disease: Olfactory and taste disorders (33.9%)
Nalleballe et al[164]	USA	Cohort study	40469	18–50 years (48.7%) 51–80 years (41.8%)	22063 (55%)	18364 (45%)	Symptoms: Headache (3.7%); sleep disorder (3.4%) Diseases: Encephalopathy (2.3%); Olfactory and taste disorders (1.2%); stroke and transient ischemic attack (1.0%); dizziness (0.9%); extrapyramidal and movement disorder (0.7%); seizures (0.6%); polyneuropathy (0.6%); nerve root and plexus disorder (0.4%)

Abbreviation: NR, not reported.

(Figure 1). The SARS-CoV-2 viral particles can invade the brain through the vascular pathway once the blood-brain barrier (BBB) is broken,[36] or through peripheral nerves such as the vagus nerve and reverse transneuronal transport of axonal transport,[34,37] or through the cerebral spinal flow (CSF) pathway.[34]

SARS-CoV-2 can infect the brain through compromised vasculature. Cytokine storms can severely damage the BBB, allowing viral particles from SARS-CoV-2 to circulate in the bloodstream to enter the brain.[34] The serum level of S100B, an astrocyte marker, increased when symptoms of the CNS appeared[36] and reflected destruction of the BBB,[38] which is conducive to invasion by SARS-CoV-2 and opens a vasculature path for the virus with inflammatory cytokines.

Table 2 Evidence Supporting the Invasion of SARS-CoV-2 into the Central Nervous System

Researchers	Study Design	Main Findings	References
Moriguchi et al	Case report	The first case of COVID-19-related meningitis was reported, and SARS-CoV-2 RNA was detected in cerebrospinal fluid.	[165]
Dinkin et al	Case report	On MRI, two patients who developed cranial neuropathy associated with SARS-CoV-2 infection and had perineural or cranial nerve abnormalities were reported.	[166]
Kadono et al	Case report	Reported a COVID-19 patient with anosmia and transient cerebral edema, suggesting a neurological invasion of SARS-CoV-2.	[39]
Chiu et al	Case report	A case of COVID-19-related anosmia with definite atrophy of the olfactory bulb, indicating a possible neurological marker of coronavirus infection.	[44]
Jiang et al	Original research	SARS-CoV-2 RNA was isolated from lung and brain tissue from the mouse model transgenic for SARS-CoV-2 hACE2.	[167]
Chen et al	Original research	ACE2 is relatively highly expressed in certain locations in the brain, such as the choroid plexus and the paraventricular nucleus of the thalamus.	[168]
Qi et al	Original research	The substantia nigra and cortex are predicted to be high-risk tissues for SARS-CoV-2 infection.	[169]
Buzhdygan et al	Original research	The SARS-CoV-2 spike protein altered the barrier function in 2D static and 3D microfluidic in vitro models of the human blood-brain barrier.	[170]
Song et al	Original research	Using mice overexpressing human ACE2, the neuroinvasion of SARS-CoV-2 in vivo was demonstrated.	[171]
Paniz-Mondolfi et al	Autopsy research	The ultrastructure of the SARS-CoV-2 viral particles was found in the neural and capillary endothelial cells.	[172]
Puelles et al	Autopsy research	The genetic material SARS-CoV-2 was quantitatively detectable in brain tissue samples from 8 (36%) of 22 patients who died from COVID-19.	[173]
Meinhardt et al	Autopsy research	Demonstrated the presence of SARS-CoV-2 RNA and protein in the nasopharynx and brain of patients who died from COVID-19.	[42]
Martin et al	Autopsy research	Pathological features confirmed signs of hypoxia and SARS-CoV-2 brain invasion.	[174]

Abbreviations: COVID-19, coronavirus disease 2019; hACE2, human angiotensin-converting enzyme-2; MRI, magnetic resonance imaging; SARS-CoV-2, coronavirus-2 virus of the severe acute respiratory syndrome.

Neuroinvasion of the virus can cause severe brain edema and seizures due to a cerebrovascular event resulting from the hypercoagulable state of blood in COVID-19 patients.[39] Cerebral endothelial cells damaged by the SARS-CoV-2 virus produce thrombin, a key coagulation factor that leads to the formation of microthrombi within blood vessels.[40] Changes in blood components, such as increased thrombin and D-dimer levels and thrombocytopenia caused by COVID-19, can promote mini-strokes or microbleeds.[41] Neuropsychiatric symptoms of COVID-19 may develop due to damage to brain tissue caused by these mini-strokes or microbleeds.[41]

SARS-CoV-2 can enter the brain by crossing the neural-mucosal interface in the olfactory mucosa, conjunctiva, or taste buds and invades the brain by retrograde axonal transport.[42] The invasion of SARS-CoV-2 through peripheral nerve terminals (eg, olfactory nerve, trigeminal nerve, glossopharyngeal nerve, or vagus nerve) could be a reasonable route to brain infection,[34,35] leading to hyposmia, hypoplasia, and hypogeusia in patients with COVID-19.[43] Anosmia is a unique symptom of COVID-19[21] and may represent a neural invasion of the virus through the olfactory bulb during the early or chronic stages.[43,44] SARS-CoV-2 may directly infect olfactory sensory neurons through the nerve-mucosal interface in the olfactory epithelium and then enter the CNS through the olfactory nerve.[42] The SARS-CoV-2 virus spreads primarily
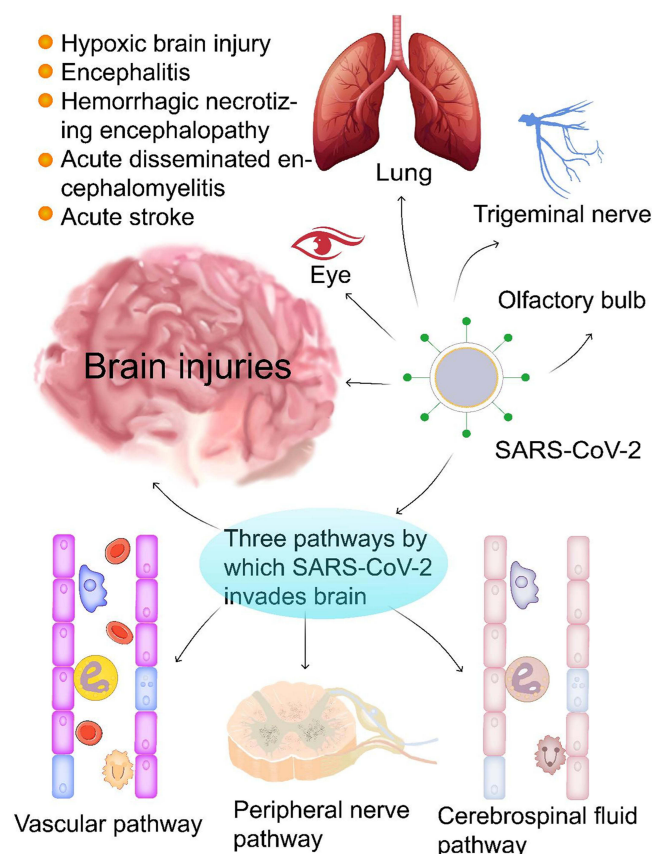
Figure 1 SARS-CoV-2 infection can cause brain damage through three possible routes. COVID-19 infection causes various brain injuries and diseases (eg, hypoxic brain injury, encephalitis, hemorrhagic necrotizing encephalopathy, acute disseminated encephalomyelitis, and acute stroke). SARS-CoV-2 invades the brain likely through three routes: (1) the vascular pathway where SARS-CoV-2 damages the blood-brain barrier to invade the brain via blood or lymphatic circulation; (2) the peripheral nerve pathway in which SARS-CoV-2 infects the olfactory bulb, the trigeminal nerve, the vagus nerve, and finally the brain through trans-neuronal or retrograde axonal transport; and (3) the cerebrospinal fluid pathway, SARS-CoV-2 can enter the brain through circulating cerebrospinal fluid to trigger a series of proinflammatory and immune responses that eventually result in various brain injuries with neuropsychiatric symptoms.

through respiratory droplets that enter the respiratory tract. However, a small fraction of viruses remain in the nose, conjunctiva, and oral cavity, rich in angiotensin-converting enzyme-2 (ACE2).[34,45] One report indicated the presence of SARS-CoV-2 RNA in conjunctival swabs and tear samples from some patients with COVID-19.[45] Conjunctival contact with droplets containing SARS-CoV-2 can result in the retrograde neuronal transmission of the virus to infect the brain and impair vision.[46] In addition, SARS-CoV-2 can enter the brain through the glossopharyngeal nerve or the vagus nerve that connects the nucleus of the solitary tract through the sensory neurons of the tongue.[46] Once the peripheral nerve, the nucleus of the solitary tract, the thalamus, or other pathways related to taste conduction are invaded and damaged by SARS-CoV-2, hypogeusia occurs in patients.[43] Furthermore, the solitary tract nucleus is located in the brainstem, close to the respiratory and cardiovascular control centers.[42] After SARS-CoV-2 infects the solitary nucleus along the nerve, it can infect this nucleus, resulting in refractory dyspnea.[47]

Although the frequency of SARS-CoV-2 RNA in the CSF of COVID-19 patients is low (~1.3%),[3] it cannot exclude the CSF as a potential route for the invasion of SARS-CoV-2 into the brain.[48] The brain has its lymphatic drainage system, in which the CSF plays a primary role. A new study showed that SARS-CoV-2 could invade peripheral lymphatic vessels connected to the brain's lymphatic system.[49] SARS-CoV-2 can invade the CSF and damage the brain through this anatomical connection. Furthermore, when the BBB is damaged, SARS-CoV-2 overflows from blood vessels and invades brain tissue and the CSF, resulting in brain edema and dysfunction.[34] SARS-CoV-2 antibodies have been detected in the CSF of patients with COVID-19 encephalopathy.[50] These antibodies may stimulate glial cells leading to neuroinflammation and other cytokine storm and oxidative stress that cause immune-mediated neurological damage.[51]

Furthermore, infiltration of the SARS-CoV-2 virus into the brain stem or limbic system can result in dysfunction of the autonomic nervous system and emotional dysfunction, respectively, in some patients with COVID-19.[8] In short, the COVID-19 virus can invade the brain via the routes above, resulting in brain damage with neuropsychiatric symptoms. These specific neuropsychiatric symptoms can vary in patients according to the location these pathologic events occur in the brain.

After invasion into the brain, SARS-CoV-2 invades brain cells through the ACE2 receptor, which is an identified receptor for SARS-CoV-2 invasion.[52] ACE2 is present mainly in mucosal epithelial cells of the lung and arteries but is also highly expressed in brain cells such as neurons, oligodendrocytes, and astrocytes.[53] The serine 4 transmembrane protease protein, which facilitates the fusion of SARS-CoV-2 and cellular membranes, is detectable in the cerebral cortex, caudate nucleus, and hippocampus and determines virus tropism.[37] Animal studies showed that SARS-CoV-2 damages the cerebral vascular endothelium and infects the brain parenchyma; ACE2 was a key mediator of neuronal damage.[54] Furthermore, the SARS-CoV-2 virus spike binds to ACE2 receptors to generate excessive cytokines and promote the formation of blood clots,[55] leading to cell apoptosis, necrosis, ferroptosis, and eventually brain tissue damage.[56]

Infection with SARS-CoV-2 can cause cytokine storms,[57] and large amounts of inflammatory factors produced during a cytokine storm can damage brain tissues.[36] High levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) induce a neuroinflammatory response in the brain.[58,59] Besides, COVID-19 infection activates various inflammatory pathways, such as that for tryptophan-kynurenine metabolism, which is an immunoregulatory pathway.[60] 2,3-dioxygenase-1 (IDO1) is located in the critical branch of kynurenine metabolism and is activated by inflammatory factors such as TNF-α and IL-6.[61] Activating IDO1 in COVID-19 can convert tryptophan to kynurenine and deprive T lymphocytes of tryptophan to inhibit T lymphocyte activation, thus limiting the host immune response.[62] Furthermore, the IDO1-kynurenine-aryl hydrocarbon receptor pathway is activated, leading to the lethal consequences of SARS-CoV-2 infection and immune evasion.[63] IDO1 activation increases kynurenine metabolism in COVID-19, and kynurenine produces large amounts of chemokines and neurotoxic substances that cause neuronal damage and long-term brain impairment.[61] In addition, enhanced inflammation decreases the synthesis of monoamines and trophic factors, thus inhibiting neurotransmitters and neuronal growth.[64] Therefore, cerebral inflammation and hypoxic brain injury result in short- and long-term neuropsychiatric symptoms.

Ferroptosis and Its Underlying Mechanism

Ferroptosis is a programmed non-apoptotic cell death associated with an increase in the liable ferrous iron pool (LIP) caused by iron overload. The accumulation of lethal levels of iron-dependent lipid peroxides and reactive oxygen species (ROS) due to the inactivation of glutathione peroxidase 4 (GPX4) and the depletion of glutathione (GSH) are the core mechanisms of ferroptosis.[65–67] At the molecular level, ferroptosis is characterized by changes in GSH, GPX4, and ROS levels and the expression of genes that regulate iron homeostasis and lipid peroxidation.[68] Changes in intracellular organelle microstructure are also a feature of ferroptosis. For example, during ferroptosis, mitochondria condense and become small, and the lipid bilayer membrane thickens and contracts with the outer membrane rupture. These features can be visualized by deep staining. Additionally, decreased or absent mitochondrial cristae are accompanied by a reduction in cell size and cell connections that lead to cell separation, although the nuclear and cell membranes remain intact.[69] F4-hydroxynonenal, cytotoxic malondialdehyde, and other products of lipid peroxide degradation are the primary biomarkers of ferroptosis.[70]

Ferroptosis is closely related to several pathologic processes, including inflammation, T-cell immunity, acute renal failure, blood disorders, ischemia/reperfusion injury, and CNS diseases.[65,71,72] Key regulatory targets of ferroptosis include system Xc- activity, intracellular LIP, GPX4 activity, GSH production, lipid ROS production, and phosphatidy-lethanolamine (PE) biosynthesis, detailed below.

(1) System Xc- activity regulation: The cell membrane system Xc-, a cystine/glutamate antitransporter comprising heterodimers SLC3A2 and SLC7A11, is involved in GSH synthesis to protect cells from oxidative damage. Beclin 1 regulates antioxidant capacity by directly blocking the activity of the Xc-system by binding to its core component SLC7A11 to promote ferroptosis.[73] Furthermore, inhibition of Beclin 1 expression decreases lipid peroxidation, thus mitigating brain

edema and neurologic deficits after subarachnoid hemorrhage, probably due to increased system Xc- activity.[74] Therefore, the system Xc- could be a therapeutic target for treating COVID-19-related brain injury.

(2) GPX4-GSH regulation: As a central regulator of ferroptosis, GPX4 inhibits the formation of toxic lipid ROS by converting lipid hydroperoxides to non-toxic lipid alcohols.[75,76] The availability of NADPH, a cell reducing agent, is critical since it transforms GSH from an oxidized state to a reduced form. If GPX4 cannot effectively degrade ROS, phospholipid hydroperoxides accumulate that can induce ferroptosis in the presence of iron.[77] Importantly, GPX4 overexpression can protect cells against ferroptosis.[78] Furthermore, selenium (Se) is a critical modulator of GPX4 activity,[79] and pharmacological supplementation with Se can enhance GPX4 activity by upregulating its transcription through coactivation of the transcription factor activating protein 2 gamma and the specificity protein 1 that effectively protects neurons against GPX4-dependent ferroptosis.[79] Furthermore, activation of the nuclear factor E2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (KEAP-1)-GPX4 pathway also exhibits excellent antiferroptosis effects by inhibiting lipid peroxidation by upregulation of GPX4 and SLC7A11 transcription and increases in NADPH and GSH levels.[80]

(3) Lipid ROS regulation: Inactivation of SLC7A11 and GSH depletion leads to ROS accumulation. Hydroxyl radicals formed by the Fenton reaction can react with polyunsaturated fatty acids (PUFAs) in lipid membranes in the presence of reduced iron, leading to lipid peroxidation.[81] ROS production and detoxification imbalance leads to oxidative stress and subsequent free radical-mediated damage to DNA, proteins, and lipids.[82] In this regard, lipid antioxidants (for example, vitamin E, ferrostatin-1 (Fer-1), and liprostatin-1) can decrease intracellular lipid peroxidation and inhibit ferroptosis,[83,84] thus showing neuroprotection after acute brain injuries (for example, ICH and traumatic brain injury).[85–90]

(4) Iron regulation: Iron exists in the forms of Fe^{2+} or Fe^{3+} and maintains a dynamic balance in vivo. Iron regulating proteins (eg, ceruloplasmin, transferrin, membrane protein transferrin receptor 1, prostate 6 transmembrane epithelial antigen 3 (Steap3), divalent metal transporter 1 (DMT1) or family of zinc-iron regulatory proteins 8/14, and ferritin) participate in iron-binding, iron transport, and maintain iron homeostasis.[91–93] In a pathologic state, an increase in iron absorption and a decrease in iron storage lead to intracellular iron accumulation and ferroptosis,[68] which can reprogram iron uptake, production, utilization, and storage of intracellular iron.[93] Iron chelators (eg, deferoxamine and deferiprone) can bind to free iron to inactivate iron-containing enzymes and inhibit Fenton reactions, as well as down-regulate hepcidin expression.[94,95] A new study showed that the iron chelator PBT434 [5,7-dichloro-2-((ethylamino)methyl)-8-hydroxy-3-methylquinazolin-4(3H)-one] chelates interstitial iron to inhibit iron uptake and stimulate iron efflux in brain microvascular endothelial cells and other cells of the neurovascular unit.[96] In addition, the tetracycline class antibiotic minocycline, an iron-chelating agent, has an anti-inflammatory effect.[97] Various iron chelators exhibit cerebral protection against acute traumatic and non-traumatic brain injuries.[12,89,98] For example, the brain-permeable iron chelator VK28 (5-[4-(2-hydroxyethyl) piperazine-1-ylmethyl]-quinoline-8-ol), the lipid-permeable iron chelator 2.2'-dipyridyl, and the iron chelator deferoxamine currently in clinical use decrease iron accumulation, ROS production, microglial activation, and neuronal death. Treatment with these iron chelators can protect the brain against iron toxicity and improve neurologic recovery after ICH.[99]

(5) Regulation of PE biosynthesis: The members of the long-chain family of acyl-coenzyme A synthase 4 and the lysophosphatidylcholine acyltransferase 3 involved in PE biosynthesis are vital enzymes that can regulate lipid peroxidation and ferroptosis.[100,101] A new study showed that energy- or stress-mediated activation of AMP protein kinase inhibits ferroptosis by phosphorylation and inactivation of acetyl-CoA carboxylase and subsequently decreases PUFA biosynthesis.[102] Therefore, given that inhibition of the expression of members of the long-chain family of acyl-coenzyme A synthase 4 attenuates oxidative stress, BBB damage, brain edema, and behavioral and cognitive deficits after subarachnoid hemorrhage,[14] it is necessary to investigate whether inhibition of ferroptosis can prevent or reduce brain injury in patients with COVID-19.

The Potential Role of Ferroptosis in COVID-19-Related Brain Injury
Ferroptosis May Exist in COVID-19-Related Brain Injuries

The brains of patients with COVID-19 could be susceptible to ferroptosis. Ferroptosis involves the following three factors: iron, amino acids, and unsaturated fatty acids.[103] Iron is the most abundant trace metal in the brain and is needed for normal cell metabolism and contributes to physiologic processes such as oxygen transport, energy production, and transmission of

neurotransmitters.[104] The brain is sensitive to oxidative stress and lipid peroxidation due to its high level of PUFAs.[103] PUFA phospholipids are constituents of the cell membrane and carry out various physiologic functions (eg, neuronal synaptic connection, neuronal plasticity, and network development, as well as neurotransmitter release). They are also involved in the pathogenesis of ferroptosis.[105] The neuron cell membranes are rich in PUFAs and cholesterol that are susceptible to ROS-mediated oxidation caused by a cytokine storm in COVID-19.[103] The enzyme activity of GPX4 and superoxide dismutase is much lower in brain tissues compared to other tissues, indicating that neurons could be highly susceptible to iron overload.[90] SLC7A11 (also known as system Xc-) expressed in glial cells enhances glutamate release, thus inducing neuronal ferroptosis.[106] Astrocytes can store iron and prevent iron overload in neuronal synapses.[107] Nrf2 overexpression in astrocytes inhibits ferroptosis, probably due to the outward release of GSH from astrocytes.[108] Meanwhile, inducible loss of GPX4 expression in neurons can induce ferroptosis.[67]

Neuronal death and the resultant neurologic dysfunction occur in patients with brain injuries, and ferroptosis is one of the death mechanisms. Ferroptosis is pathogenic in aging, tissue repair, tumor development, cerebral ischemia[109] and ICH,[86,110] and is involved in the pathogenesis of spinal cord injury,[111] subarachnoid hemorrhage,[14] traumatic brain injury,[112] epilepsy,[113] Alzheimer's disease,[15] Parkinson's disease,[16] and other neurodegenerative diseases. In addition, the disruption of iron homeostasis is present in almost all neuropathological specimens of neurological disorders,[67] including COVID-19-related brain injuries.[1] Therefore, like other brain diseases, ferroptosis may also exist in COVID-19 brain injury and plays a vital role in the process of brain injuries.

The pathogenesis of various complications of COVID-19 and brain injury, in particular, may be closely related to an imbalance of intracellular iron homeostasis that leads to ferroptosis.[1] Ferritin stores large amounts of iron within a cell. The level of ferritin in the CSF may reflect the level of iron in the brain.[114] Two recent studies revealed elevated serum levels of iron and ferritin associated with cerebral ischemia or disease severity in COVID-19 patients.[115,116] A cohort study with 39 COVID-19 patients demonstrated that serum ferritin levels are correlated with the severity of COVID-19 disease[116] and are related to hyperferritinemia syndrome.[117] Since iron and ferritin levels are associated with ferroptosis,[118] we speculated that the severity of COVID-19 is also related to the occurrence of ferroptosis. Another study of 6 patients with COVID-19 complicated with ischemic stroke revealed that all 6 patients were in a high-grade prethrombotic state, with high blood levels of D-dimer and ferritin.[115] Patients with COVID-19 and stroke have higher ferritin levels than patients with stroke alone, and ICH patients have higher serum ferritin levels than patients with ischemic stroke.[119] Although, to date, no reports have directly linked ferroptosis and COVID-19-related brain injury, these biomarkers of ferroptosis are altered in COVID-19-related brain injury, suggesting that ferroptosis may exist and indeed play an underlying role in disease progression.

Three contributing factors may cause ferroptosis in COVID-19-related brain injury according to recent studies: i) hepcidin release, the principal regulator of systemic iron homeostasis; ii) excessive iron influx through the transferrin receptor during SARS-CoV-2 replication; and iii) SARS-CoV-2 attack on hemoglobin and release of free iron into the circulation.[120–124] IL-6 can initially stimulate the synthesis of ferritin and hepcidin in a COVID-19-related cytokine storm.[120,121] The amino acid sequence at the distal end of the cytoplasmic tail of the SARS-CoV-2 spike glycoprotein has highly similar to that of the hepcidin protein.[122] Hepcidin and hepcidin-like proteins bind to ferroportin, the cellular iron exporter, causing its degradation, thus preventing iron outflow and increasing intracellular ferritin.[123] In addition, iron is required for SARS-CoV-2 replication and enters cells through transferrin receptors.[124] Excess intracellular iron interacts with molecular oxygen to trigger the Fenton reaction and induce ferroptosis when GPX4 does not eliminate excess lipid ROS.

Furthermore, hemoglobin, attacked by SARS-CoV-2, dissociates porphyrin from iron and releases free iron into the circulation, resulting in iron overload.[125,126] Dysfunctional iron metabolism in COVID-19 finally leads to ferroptosis, releasing intracellular ferritin and causing ferritinemia.[118] Together, this current evidence suggests that ferroptosis may exist in COVID-19-related brain injury and that ferroptosis plays a role in brain complications in COVID-19.

The Potential Role of Ferroptosis Underlies COVID-19-Related Brain Injury

Ferroptosis can induce the release of pathogen-associated molecular patterns and damage-associated molecular patterns, together with excessive oxidative stress.[127] Ferroptosis can cause local brain damage, leading to neuronal death and neural network damage.[104] Additionally, the sensitivity of oligodendrocytes to iron can cause axonal damage through

ferroptosis.[104] Ferroptosis can also induce tau phosphorylation and form neurofibrillary tangles, leading to cognitive impairment.[76] Ferroptosis is also immunogenic and proinflammatory and creates a positive feedback loop.[127] As a result, ferroptosis may be one of the causes of COVID-19-related enhanced inflammatory reaction and multiple organ failure syndromes involving the brain with CNS symptoms[17] (Figure 2). COVID-19-related brain injury contains many kinds of brain disease, such as stroke. Our previous studies have shown that stroke can cause ferroptosis.[98,128] Iron toxicity contributes to stroke-induced early brain damage, and ferroptosis plays a significant role in the secondary brain injury from stroke.[12] Therefore, ferroptosis may be the effect of COVID-19-related stroke, but in turn, it plays a vital cause in the secondary brain injury of COVID-19-related stroke and further aggravate brain damage.

After SARS-CoV-2 infection, transferrin recognized by transferrin receptors carries excess Fe^{3+} into cells. The metal reductase Steap3 in the endoplasmic reticulum reduces Fe^{3+}, and ferric iron enters the cytoplasm to form LIP. Under conditions of intracellular iron overload, the interaction between excess intracellular iron and molecular oxygen induces a Fenton reaction, producing excessive hydroxyl radicals.[129] Phospholipid hydroperoxide is produced by lipoxygenase/arachidonic acid lipoxygenase-mediated peroxidation of PE phospholipids containing PUFA.[76] When GPX4 activity is inhibited, phospholipid hydroperoxide enhances lipid peroxidation of plasma membranes, nucleic acids, and proteins, causing oxidative damage and ferroptosis.[72] Finally, damage-associated molecular patterns and alarmins (HMGB1, IL-33, and TNF) are released, exacerbating inflammation, cell death, and neurodegeneration.[127]
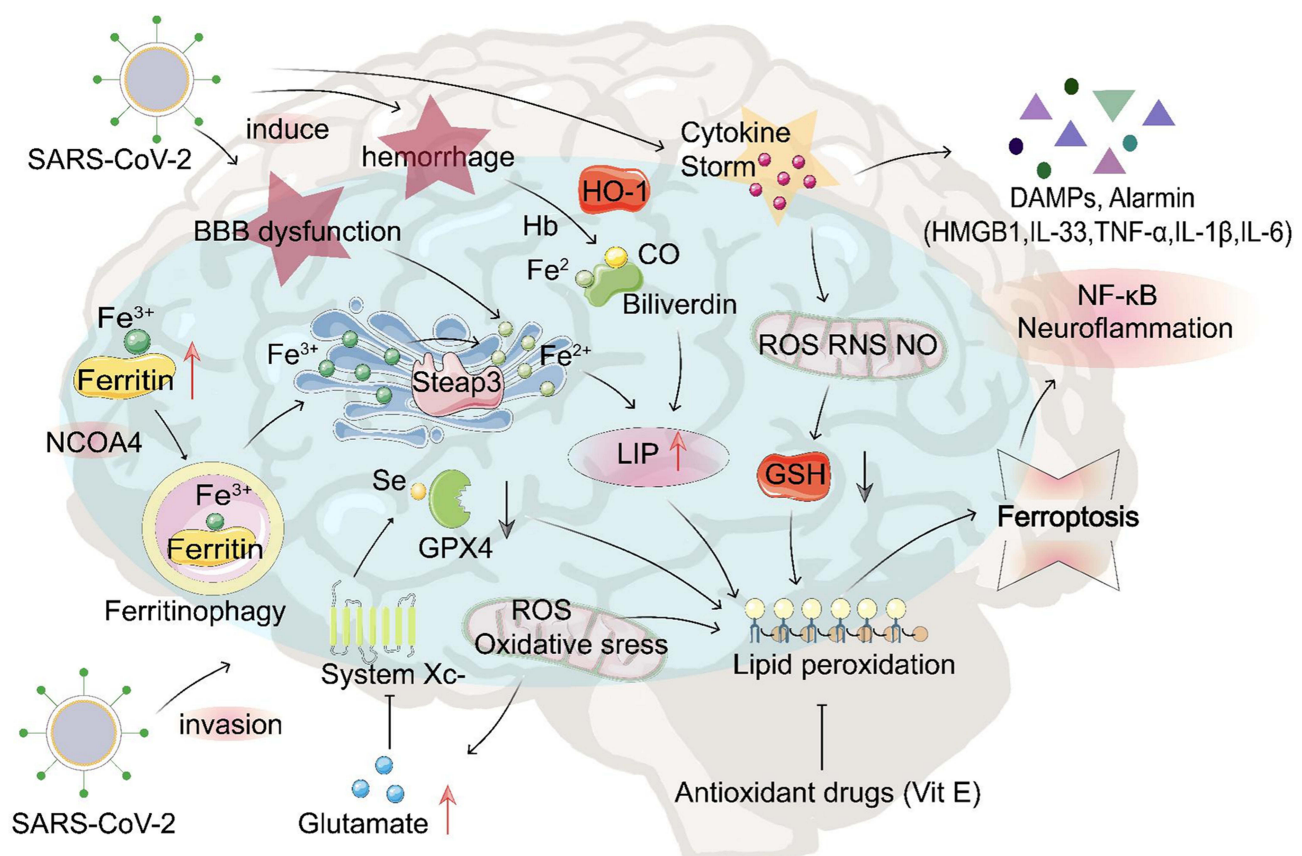

Figure 2 The potential role of ferroptosis in COVID-19-related brain injury. After SARS-CoV-2 infection, transferrin receptors recognize transferrin that carries Fe^{3+}, which enters cells through endocytosis to form endosomes. IL-6 promotes ferritin synthesis, which stores Fe^{3+} and releases Fe^{3+} through ferritinophagy; after that, the endoplasmic reticulum metal reductase Steap3 reduces Fe^{3+} into Fe^{2+} to form LIP. GPX4 protects the cell against lipid peroxidation and inhibits ferroptosis. Under iron overload conditions combined with GPX4 depletion or inhibition, mitochondria generate large amounts of ROS, leading to lipid peroxidation, cell membrane damage, and ferroptosis. Excess ROS depletes intracellular GSH, and this depletion forms a positive feedback loop and aggravates lipid peroxidation. During this peroxidation, damage-associated molecular patterns and alarmins (eg, HMGB1, IL-33, TNF-α, IL-1 β, and IL-6) are released that activate NF-kB and other proinflammatory signaling pathways, eventually leading to neuroinflammation and cell death. SARS-CoV-2 infection can damage the brain, resulting in BBB disruption and bleeding accompanied by a cytokine storm.

During the cytokine storm in COVID-19, levels of proinflammatory mediators (eg, NF-κB, TNF-α, and IL-1β) are increased in the brain, leading to increased expression of AQP4 that promotes brain edema.[130] These factors are also involved in the mechanisms of cell ferroptosis.[90] The iron accumulation in the area surrounding the edema can cause secondary brain damage.[12] The formation and enlargement of edema in the brain can cause a compressive effect and increased intracranial pressure, leading to brain herniation and death.[131] GPX4 overexpression reduces cerebral edema, while treatment with Fer-1, an inhibitor of lipid peroxidation, reduces the proinflammatory cytokine levels (eg, NF-κB, TNF-α, and IL-1β) in the brain and reduces cerebral edema.[132]

As discussed in SARS-CoV-2 Invasion with Subsequent Brain Injuries, the cytokine storm can cause BBB dysfunction,[34] which, together with inflammation in the injured brain of COVID-19 patients, allows more iron to enter the brain. Ferritin transported to the brain must pass through the BBB under the control of DMT1.[133] However, the gene that encodes DMT1 has binding sites for AP-1 and NF-κB,[133] both of which are potent inflammatory factors. Since COVID-19-induced cytokine storm produces numerous proinflammatory factors, including AP-1 and NF-κB,[134] it can lead to increased DMT1 expression, thus in turn, more iron is transported to the brain, causing iron accumulation or overload, thereby causing neuronal death and aggravated brain damage.[135] Previous studies have shown that intracellular iron influx and increased DMT1 expression are early downstream responses of NF-kB activation that accelerate neuronal damage in the brain.[133] A study involving four COVID-19 patients revealed that three patients had an elevated CSF/serum albumin index, indicating BBB dysfunction; simultaneously, the CSF level of the inflammatory cytokine IL-6 was increased in two patients, indicating a proinflammatory response in the brain.[36] The cytokine storm in COVID-19 produces substantial oxidative stress, which inactivates transferrin. Releasing a large amount of "free iron" increases serum iron levels,[68] leading to ferritinemia.[118]

Elevated iron levels in the brains of COVID-19 patients can damage brain tissue. The toxic effects of iron overload on carbohydrates, lipids, proteins, and nucleic acids in the brain have been established.[136] Iron deposition leads to lipid peroxidation,[12,103] the most effective inducer of ferroptosis.[137] During the severe cytokine storm of COVID-19, excessive increases in the circulating "free iron" will aggravate the proinflammatory response and induce morphological changes in red blood cells and fibrin. The resulting production of hydroxyl free radicals causes oxidative stress. It generates a remarkable procoagulation state that promotes the formation of dense clots in the brain and leads to ischemic stroke.[117]

A recent study documented the formation of cerebral thrombosis and the appearance of stroke in patients with COVID-19.[138] The cerebral blood vessels rupture after a hemorrhagic stroke in COVID-19 patients, allowing blood to accumulate within the brain parenchyma. Heme oxygenase degrades hemoglobin metabolites into ferrous iron, biliverdin, and carbon monoxide in the brain.[125,126] This metabolic pathway modulates secondary brain injury.[139] Iron released into the extracellular space can generate free radicals and ROS through the Fenton reaction, causing oxidative damage to molecules such as PUFAs, DNA, and proteins, thus further aggravating tissue damage.[13,140] ROS activates microglia and astrocytes to release proinflammatory cytokines and increase the release of Fe^{2+} from LIP, leading to iron-dependent oxidative damage and neuronal cell death, exacerbating secondary brain injuries.[90] Compared to controls, mice with ischemic stroke had lower GPX4 activity and GSH levels. A subsequent increase in iron deposition and lipid peroxidation eventually resulted in ferroptosis.[109] In ICH, hemoglobin breaks down and releases large amounts of ferrous iron and mitochondrial atrophy; both are features of ferroptosis.[86,87,141] Furthermore, lipid peroxidation inhibitors such as Fer-1 protect against damage caused by ischemic and hemorrhagic stroke.[142] Similar pathogenic mechanisms can lead to COVID-19-related stroke.

Potential Therapeutic Targets for COVID-19-Related Brain Injury

Investigating the potential role of ferroptosis in COVID-19-related brain injury is an emerging research direction and may yield therapeutic targets (Table 3). Regulation of iron and ROS, Nrf2/KEAP1 pathway, GPX4-GSH pathway, as primary targets, can make a difference through antimalarial drugs, antioxidants, iron chelators, (-)-epicatechin, etc. These ferroptosis inhibitors may serve as a potential intervention to protect neurons against various brain injuries and patients with COVID-19-related brain injuries.[71,110] Antimalarial drugs inhibit the expression of iron transporters and the activity of Fe^{2+}/H^+ cotransporters, thus reducing iron and iron-catalyzed free radicals in brain tissues.[135] Tocotrienol, a component of vitamin E, inhibits ferroptosis of neurons.[108] Nrf2 is also a promising target for reducing ferroptosis

Table 3 Potential Therapeutic Targets for COVID-19-Related Brain Injury

Potential Therapeutic Targets	Molecular Mechanisms	Potential Drugs	References
Iron uptake	Inhibits the expression of iron transporters and the activity of Fe^{2+}/H^+ cotransporters	Antimalarial drugs	[135]
ROS	Inhibits lipid peroxidation and decreases lipid ROS in cellular membranes	Antioxidants (eg, tocotrienol, vitamin E, Fer-1, liprostatin-1, zileuton)	[71,83,84,108,110,175]
LIP	Binds to free iron to inactivate iron-containing enzymes and decreases iron accumulation to inhibit Fenton reaction	Iron chelators (eg, deferoxamine, deferiprone, PBT434, minocycline, VK28,2,2'-dipyridyl)	[71,94–98,128]
Nrf2/KEAP1 pathway	Activates the Nrf2-dependent and Nrf2-independent pathways	(-)-Epicatechin (a brain-permeable flavanol)	[88,143,144]
GPX4-GSH pathway	Enhances GPX4 activity by upregulating its transcription	Se	[79]

Abbreviations: Fer-1, ferrostatin-1; GPX4, glutathione peroxidase 4; GSH, glutathione; KEAP1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor E2-related factor 2; LIP, liable ferrous iron pool; ROS, reactive oxygen species.

and treating brain injuries.[143] In this sense, we have shown that (-)-epicatechin, a brain-permeable flavanol, protects against ICH by activating the Nrf2-dependent and Nrf2-independent pathways and may serve as a potential intervention for patients with ICH[88,144] or patients with COVID-19-related brain injuries.

Concluding Remarks

The SARS-CoV-2 vaccines are essential to prevent further morbidity and mortality from COVID-19.[145] Although studies have found an increased risk of neurological complications in individuals who have been vaccinated against COVID-19, the risk of these complications is greater after testing positive for SARS-CoV-2.[146] Expert opinions indicate that it is advisable to correct the iron deficiency before administering the COVID-19 vaccine.[147] Iron is a nutrient required for immunity, and iron deficiency reduces the efficacy of vaccines.[147] However, no studies have investigated the role of the COVID-19 vaccine on ferroptosis. In theory, vaccination against COVID-19 would reduce the risk of COVID-19 infection, therefore reducing ferroptosis-mediated brain damage. We could only speculate that COVID-19 vaccines may reduce the occurrence of ferroptosis and may help recover from the disease on ferroptosis. This is an excellent direction for us to further research COVID-19.

Due to inflammation, iron and vitamin deficiencies, anemia is a common manifestation in COVID-19.[148] Studies have shown that serum iron levels are abnormally low in severe infections, but iron overload is high in pulmonary fibrotic tissue and the brain.[118,149] Similarly, a significant serum iron deficiency can be detected in patients with COVID-19.[122,150] Anemic patients with COVID-19 had elevated levels of inflammation markers (IL-6 levels and C-reactive protein) compared to those without anemia and survived a more severe course of COVID-19,[151,152] but did not directly influence mortality.[148] Various evidence indicates that anemia and low serum iron concentration are independent risk factors associated with severe illness and poor outcomes in hospitalized patients and death from COVID-19.[150,153,154] A case report showed an 8.2 times greater chance of developing severe pneumonia in patients with anemia.[148,151] In a cohort study, patients with anemia were more likely to have one or more comorbidities and severe COVID-19 illness compared to patients without anemia.[153]

Furthermore, previous studies showed a significant association between prior iron deficiency anemia and ischemic stroke.[155] Transfusions have remained a considerable way to manage stroke so far.[156] Since no articles report the relationship, we could only speculate that anemia may be associated with COVID-19-related brain injury. Thus, immune-mediated disruption of iron homeostasis and ferroptosis, releasing intracellular ferritin and causing ferriminemia in

patients with COVID-19, with a strong possibility of progressing to severe CNS disease.[157] The effects of anemia and iron deficiency severity on subsequent CNS manifestations will be worthwhile exploration.

The epidemiological survey showed that the median time from the onset of the first symptom to dyspnea was 5.0 days, 7.0 days to hospital admission, and 8.0 days to the intensive care unit.[20] The incubation period may be long enough for the virus to enter and destroy medulla neurons, leading to brain damage.[47] However, there have been no experiments or studies that investigate the time frame of ferroptosis in COVID-19. Changes in biomarkers of ferroptosis (eg, transferrin receptor, transferrin, and hepcidin) have not been reported in COVID-19.[158] Based on the hypothesis we put forward that ferroptosis occurs and aggravates brain injuries in COVID-19, ferroptosis can occur early or late after COVID-19 infection. Whether it is associated with neuropsychiatric disturbances in COVID-19 depends on whether it affects neuropsychiatric pathways, which needs further research. The effect of inhibiting ferroptosis by iron chelation on COVID-19-related injury may be an excellent direction worth exploring in depth.

Increasing evidence indicates that SARS-CoV-2 infection can cause various brain injuries with neuropsychiatric symptoms. Ferroptosis may be the basis for the pathogenic mechanisms of various brain injuries associated with the COVID-19 virus. BBB dysfunction and neuroinflammation in COVID-19 allow more iron to flow into brain tissues. Free iron released into the extracellular space generates free radicals, causing oxidative damage to molecules such as PUFAs, DNA, and proteins. Ferroptosis can also be induced by free iron and further aggravates brain tissue damage.[13,140] Although there is no direct evidence linking ferroptosis with brain injuries from COVID-19, the rationale exists. Now we hypothesize that ferroptosis occurs and aggravates brain injuries in COVID-19. The potential role of ferroptosis in COVID-19-related brain injuries warrants careful study to identify promising therapeutic targets to combat SARS-CoV-2-induced brain injuries with neuropsychiatric symptoms.

Abbreviations

BBB, blood-brain barrier; CNS, central nervous system; GPX4, glutathione peroxidase 4; GSH, glutathione; Hb, hemoglobin; HMGB1, high mobility group box-1; HO-1, heme oxygenase-1; IL, interleukin; LIP, labile iron pool; NCOA4, nuclear receptor coactivator 4; NF-kB, nuclear factor kappa B; RNS, reactive nitrogen species; ROS, reactive oxygen species; Se, selenocysteine; Steap3, prostate 6 transmembrane epithelial antigen 3; TNF, tumor necrosis factor; VitE, vitamin E.

Acknowledgements

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors declare no conflicts of interest in this work.

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