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REVIEW

Neurological complications associated with Covid-19; molecular mechanisms and therapeutic approaches

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Abstract

With the progression of investigations on the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), neurological complications have emerged as a critical aspect of the ongoing coronavirus disease 2019 (Covid-19) pandemic. Besides the well-known respiratory symptoms, many neurological manifestations such as anosmia/ageusia, headaches, dizziness, seizures, and strokes have been documented in hospitalised patients. The neurotropism background of coronaviruses has led to speculation that the neurological complications are caused by the direct invasion of SARS-CoV-2 into the nervous system. This invasion is proposed to occur through the infection of peripheral nerves or via systemic blood circulation, termed neuronal and haematogenous routes of invasion, respectively. On the other hand, aberrant immune responses and respiratory insufficiency associated with Covid-19 are suggested to affect the nervous system indirectly. Deleterious roles of cytokine storm and hypoxic conditions in blood-brain barrier disruption, coagulation abnormalities, and autoimmune neuropathies are well investigated in coronavirus infections, as well as Covid-19. Here, we review the latest discoveries focussing on possible molecular mechanisms of direct and indirect impacts of SARS-CoV-2 on the nervous system and try to elucidate the link between some potential therapeutic strategies and the molecular pathways.

KEYWORDS
central nervous system, Covid-19, post-COVID-19 syndrome, SARS-CoV-2

Abbreviations: ADAM17, a disintegrin and metalloproteinase domain 17; ALT, alanine aminotransferase; Ang II, Angiotensin II; APC, antigen presenting cell; ARDS, acute respiratory distress syndrome; BBB, blood-brain barrier; BLAST, basic local alignment search tool; BSG, basigin; CD147, cluster of differentiation 147; CLR, c-type lectin receptor; CNS, central nervous system; Covid-19, coronavirus disease of 2019; COX, cyclooxygenase; CSF, cerebrospinal fluid; CVD, cardiovascular disease; CXCL, (C-X-C motif) ligand; DAMPs, damage-associated molecular patterns; DIC, disseminated intravascular coagulation; DMF, dimethyl fumarate; DMTs, disease modifying therapies; EC, endothelial cell; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ENS, enteric nervous system; FAT, fast axonal transport; GBS, Guillain-Barre syndrome; G-CSF, granulocyte colony-stimulating factor; GRP78, Glucose-Regulated Protein 78; hACE2, human angiotensin converting enzyme 2; HBC, horizontal basal cell; hCoVs, human coronaviruses; HIF-1α, hypoxia inducible factor-1α; HIV, human immunodeficiency virus; HPA axis, hypothalamic-pituitary-adrenal axis; hsCRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IP-10, interferon-gamma-induced protein-10; IVIg, intravenous immunoglobulin; JAK-STAT, Janus kinase-signal transducer and activator of transcription; LDH, lactate dehydrogenase; LTs, leukotrienes; MCP-1, monocyte chemoattractant protein-1; MERS-CoV, middle east respiratory syndrome; MMP, matrix metalloproteinases; MRI, magnetic resonance imaging; MS, multiple sclerosis; NETs, neutrophil extracellular traps; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, nod-like receptor; NLRP3, NLR family pyrin domain containing 3; NRP1, neuropilin 1; NVU, neurovascular unit; OB, olfactory bulb; OE, olfactory epithelium; OSN, olfactory sensory neuron; PAMPs, pathogen-associated molecular patterns; PCF, pro-protein convertase furin; PGE, prostaglandin E; PGs, prostaglandins; PNS, peripheral nervous system; PRR, pattern recognition receptor; PT, prothrombin time; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SARS-CoV-1, severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; spO2, oxygen saturation; T2D, type 2 diabetes; TAG-1, transient axonal glycoprotein-1; TFPI, tissue factor pathway inhibitor; Th2, T helper 2; THBD, thrombomodulin; TJ, tight junction; TLR, toll-like receptor; TMPRSS2, Transmembrane Serine Protease 2; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; WHO, World Health Organization; WNV, west Nile virus; ZO-1, zonula occludens-1.

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1 | INTRODUCTION

The most recent life-threatening outbreak is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a high transmission rate, which has turned into a worldwide challenge with the first breakout reported in the Hubei province Wuhan, December 2019.[1-4] This ongoing outbreak was first known as an epidemic by the World Health Organization (WHO). Then, considering the rapid spread worldwide, the WHO declared the current outbreak a pandemic on 11 March 2020.[5] Other epidemics were also caused in the past two decades by other coronaviruses (CoVs) such as SARS-CoV and MERS-CoV in 2003 and 2012,[5,6] respectively, both inducing severe viral pneumonia with respiratory failure[1] and neurological manifestations.[2,7,8] Common respiratory viruses, including CoVs, influenza, and respiratory syncytial virus (RSV), can be associated with various neurological impairments.[5,9-12] CoVs are responsible for various respiratory, gastrointestinal, hepatic, and neurological diseases with different severity levels.[2,3] The presence of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) of some coronavirus disease 2019 (Covid-19) patients and abnormal brain magnetic resonance imaging (MRI) findings might be convincing evidence supporting Covid-19 neuroinvasion and neurovirulence.[13-16] Considering central nervous system (CNS) and peripheral nervous system (PNS) susceptibility to the SARS-CoV-2 infection, chronic or permanent changes to several parts of the nervous system could lead to multiple neurological manifestations, including encephalopathy,[17] encephalitis,[18] seizures,[19] headache,[5,7] anosmia and ageusia,[20] demyelination[21,22] and neuropsychiatric disorders,[23] which needs to be precisely investigated and treated.[24]

2 | MECHANISM OF CELLULAR VIRAL INFECTION

Coronaviruses mainly use their Spike (S) protein to enter the host cell. SARS-CoV and SARS-CoV-2 share approximately 70% of their sequence identity in the Spike protein, and both utilise the human angiotensin converting enzyme 2 (hACE2) receptor of the host cell for cell entry.[25-27] Noteworthy, the binding affinity of SARS-CoV-2 S protein to ACE2 receptor is 10–20 times higher than that of SARS-CoV due to some structural differences in the receptor binding domain of S protein.[28,29] In addition, the production of angiotensin II (Ang II) is counterbalanced by ACE2. The primary function of ACE2 is the degradation of Ang II and formation of Ang 1-7 to neutralise the vasoconstrictor effect of Ang II and maintain blood pressure.[26,27,29-31] ACE2 is highly expressed in the small intestine, kidney, heart, adipose tissue, thyroid, testis, and pancreas, whereas the muscles, brain, spleen, and blood vessels have the lowest ACE2 expression.[32,33] Besides, lungs, liver, bladder, and colon have shown a medium ACE2 expression.[33-35] Moreover, ACE2 receptor is expressed in higher levels in the lungs of smokers and type 2 diabetes (T2D) patients and in the heart of patients with cardiovascular disease (CVD), which makes them more susceptible to be infected by SARS-CoV-2.[33] In addition, an increase in mRNA levels of ACE2 in Covid-19 patients has been reported.[33] Low expression of ACE2 in respiratory tissues and high rates of infection in these tissues, lead to the speculation of plausible alternative receptors. Several experiments support the role of co-receptors and attachment factors such as transmembrane serine protease 2 (TMPRSS2), basigin (BSG) (also known as CD147), GRP78, some toll-like receptors (TLRs) and c-type lectin receptors (CLRs), heparan sulfate, and sialic acids, which facilitate and enhance the entry of the virus in the presence of ACE2.[26,33,36] Nevertheless, these co-receptors may not be sufficient for virus entry into some specific cells not expressing ACE2 although deletion of co-receptors may reduce infection.[26,33,37-39] Furthermore, Neuropilin 1 (NRP1) mainly facilitates the regulation of angiogenesis, gangliogenesis, and vascular permeability, and similarly, enhances viral infectivity and acts as a co-receptor for cell entry.[26,40] Noteworthy, NRP1 and BSG are found more than ACE2 and TMPRSS2 in the brain, including the olfactory bulb (OB).[39]

The pathogenesis of SARS-CoV-2 is mediated via the interaction between receptors and the spike protein of the virus for viral attachment, then utilising diverse endocytic pathways for entry.[41,42] To elaborate, after binding the receptor binding domain of S protein to the peptidase domain of ACE2, the SARS-CoV-2/ACE2 complex is formed. Subsequently, TMPRSS2, which activates and cleaves S protein,[25,28,29] is activated for S priming, and then the SARS-CoV-2/ACE2 complex undergoes endocytosis and forms an endosome. After acidification of the endosome and fusion of viral and lysosomal membranes,[41] encapsidated viral RNA is released to the cytoplasm for replication and transcription.[26,42,43] Complementary to this, SARS-CoV-2 may utilise CD147-mediated endocytosis for cell entry,[44] and pro-protein convertase furin (PCF) might also play a role in endocytic pathways.PCF is essential for the propagation of numerous viruses by cleavage of viral envelope glycoproteins, which may also involve the endocytosis of SARS-CoV-2.[45] Due to the expression of ACE2 and CD147 and other plausible receptors in the circumventricular organs of CNS, glial cells, and neurons,[30,31,46,47] SARS-CoV-2 can potentially invade the nervous system, which leads to neurological manifestations. Neurological impairments are not limited to direct infection by the virus. Other indirect effects of infection, including the immune response and cytokine storm, can also damage the nervous system, as explained in subsequent sections of this review.[48] Considering the high pathophysiological pathway similarity between SARS-CoV and SARS-CoV-2, they might share putative routes for CNS invasion, which are elaborated below.

3 | POTENTIOAL ROUTES OF DIRECT CNS INVASIONS

3.1 | The neuronal route of invasion

The main transmission factor of SARS-CoV-2 is the droplets of Covid-19 patients who cough and sneeze and release the droplets into the air.[49] Thus, clarifying the potential intranasal and oral routes of SARS-CoV-2 CNS invasion is required to understand the

development of anosmia, ageusia, and other nervous system dysfunctions. After entering via droplets containing SARS-CoV-2 in the nasal cavity, viruses can either reach the lung through the airway or land on the nasal mucosa and infect susceptible cells.[50] The olfactory epithelium (OE) of the nasal cavity contains olfactory sensory neurons (OSNs), basal cells, epithelial cilia, and Bowman's gland for mucus secretion and homoeostatic electrolyte balance[51] (Figure 1a). Horizontal basal cells (HBCs) of the OE are directly attached to the basal lamina and are progenitors of OSNs. It is believed that OSNs do not express ACE2; it is expressed in HBCs, which then mature into OSNs. Infected HBCs mature into bipolar unmyelinated OSNs and then penetrate the cribriform plate and access the OB by a synaptic path[39,52-54] (Figure 1b). Subsequently, the virus could infect mitral cells of the OB, which are connected to several parts of the brain, and facilitate infection of other susceptible regions of the nervous system, including the cortex, the mesolimbic cortex, hippocampus, amygdala, and eventually brainstem and spinal cord via a transsynaptic pathway, using endocytosis and exocytosis[39,48] (Figure 1d). Similar animal experiments using MERS-CoV, SARS-CoV, and SARS-CoV-2 support HBC and OSN infection as a precurser to reaching the CNS via olfactory nerves.[55-57] The majority of Covid-19 patients experience smell or taste disorders[58-61]; this neurotoxic effect of SARS-CoV-2 might be due to changes in phosphorylation pattern of proteins associated with axons and synapses in olfactory/gustatory neurons or injuries to any of VII, IX, X cranial nerves and the nucleus of solitary tract.[50,62] Moreover, the molecular mechanism of virus transportation inside PNS and brain parenchyma neurons is almost identified in the neuronal route. Due to the high length of peripheral nerve axons, the migration of the virus via diffusion could not be possible.[62] Thus, experimental results suggest another propagation mechanism named fast axonal transport (FAT), which is mainly used by hCoVs to spread along neuronal cells.[63] After the endocytosis of the virus to peripheral neurons and formation of the endosomes, the endosome lysis occurs, and the virus undergoes retrograde trafficking to the cell body and nucleus via axonal microtubules, utilising the microtubule-dependent motor proteins kinesin for anterograde and dynein for retrograde axonal transport.[48,62,64,65] Therefore, the envelope of SARS-CoV-2 should be stable during neuronal transport[66] (Figure 1c).

In addition to the olfactory nerve, the virus could utilise other peripheral nerves to reach the CNS and brainstem, including the pulmonary network and enteric nervous system (ENS) via the vagus nerve.[50,53,66,67] NRP1 and ACE2 are highly expressed in the gastrointestinal tract; meanwhile, intestinal neurons and glia highly express ACE2 and TMPRSS2 and are susceptible to being infected by SARS-CoV-2.[39,49,64] In addition, viral nucleic acid has been detected in the stool of Covid-19 patients,[68-71] which may be due to the infection of intestinal cells or self-ingestion of mucus from the airways.[72] The enteric neuronal network is directly connected to the CNS through the parasympathetic vagus nerve arising from the hindbrain, and the sympathetic nerve fibres arising from the spine.[66] Hence, transferring the infection from the intestine to the CNS is possible in animal models. At the same time, there is not sufficient evidence in humans and requires attaining more data of vagal complex ACE2 expression and the ability of trans-neuronal spread of SARS-CoV-2 in the gut-brain axis.[39] In brief, considering the anatomically close distance of the olfactory nerves to the CNS, it can be suggested as the main pathway of neuronal dissemination of SARS-CoV-2 to reach the CNS in the early stages of the infection rather than the gut-brain axis or other plausible neuronal routes.

3.2 | The haematogenous route of invasion

As the second possible infectivity route, haematogenous dissemination of viral particles could provide entry into the CNS for SARS-CoV-2 via overcoming the barriers of CNS or through circumventricular organs.[73-75] Despite the wide range of frequency in results of different studies, dissemination of SARS-CoV-2 into the blood has been reported in up to 40% of patients with Covid-19.[76] Circulating viral particles could cross the blood-brain barrier (BBB) and invade the brain parenchyma, facilitating ACE2 receptors that are expressed by brain endothelial cells (ECs) and pericytes[74,77,78] (Figure 2a). In vitro, human vessel organoids are susceptible to SARS-CoV-2 infection in an ACE2-dependent manner.[79] In line with this, clinical studies have observed the presence of viral elements in ECs of multiple organs in Covid-19 patients; more specifically, an autopsy study in which electron micrographs indicated the presence of SARS-CoV-2 viral-like proteins inside ECs of frontal lobe tissue of the brain.[80,81] Of note, there is evidence of cerebral vasculature wide expression of some SARS-CoV-2 alternative receptors such as NRP1 and BSG, which could be considered a synergistic factor for this entry route.[39,76,82] Moreover, increased secretion of pro-inflammatory cytokines and chemokines and pneumonia-induced hypoxia associated with Covid-19 compromise the BBB integrity, expedite virus entry and contribute to CNS invasion by SARS-CoV-2.[74,83,84]

The choroid plexus and circumventricular organs are other regions that could possibly act as entry gates to the brain for circulating SARS-CoV-2 particles. Termed as the blood-CSF barrier, the choroid plexus is the selectively permeable structure that restricts the free diffusion of molecules at the blood-CSF interface and contributes to CSF production.[64,78] ACE2 and TMPRSS2 are expressed by human choroid plexus cells,[85] and in vitro experiments that modelled the human choroid plexus by organoids demonstrated a high susceptibility of this tissue to SARS-CoV-2 infection.[64,86] Thus, the presence of SARS-CoV-2 in CSF, which has been reported by few case reports,[14,87,88] is likely to occur through the infection of choroid plexus; however, the indirect effects of SARS-CoV-2 on the CNS by disruption of the blood-CSF barrier due to infection of choroid plexus may play a more critical role in the exhibition of neurological manifestation in Covid-19.[86] On the other hand, circumventricular organs are highly vascularised structures adjacent to the third and fourth ventricles, characterised by their continuous fenestrated and extensively permeable vessels.[74,89] Preliminary data on the median eminence of the hypothalamus, one of the circumventricular organs, suggest the

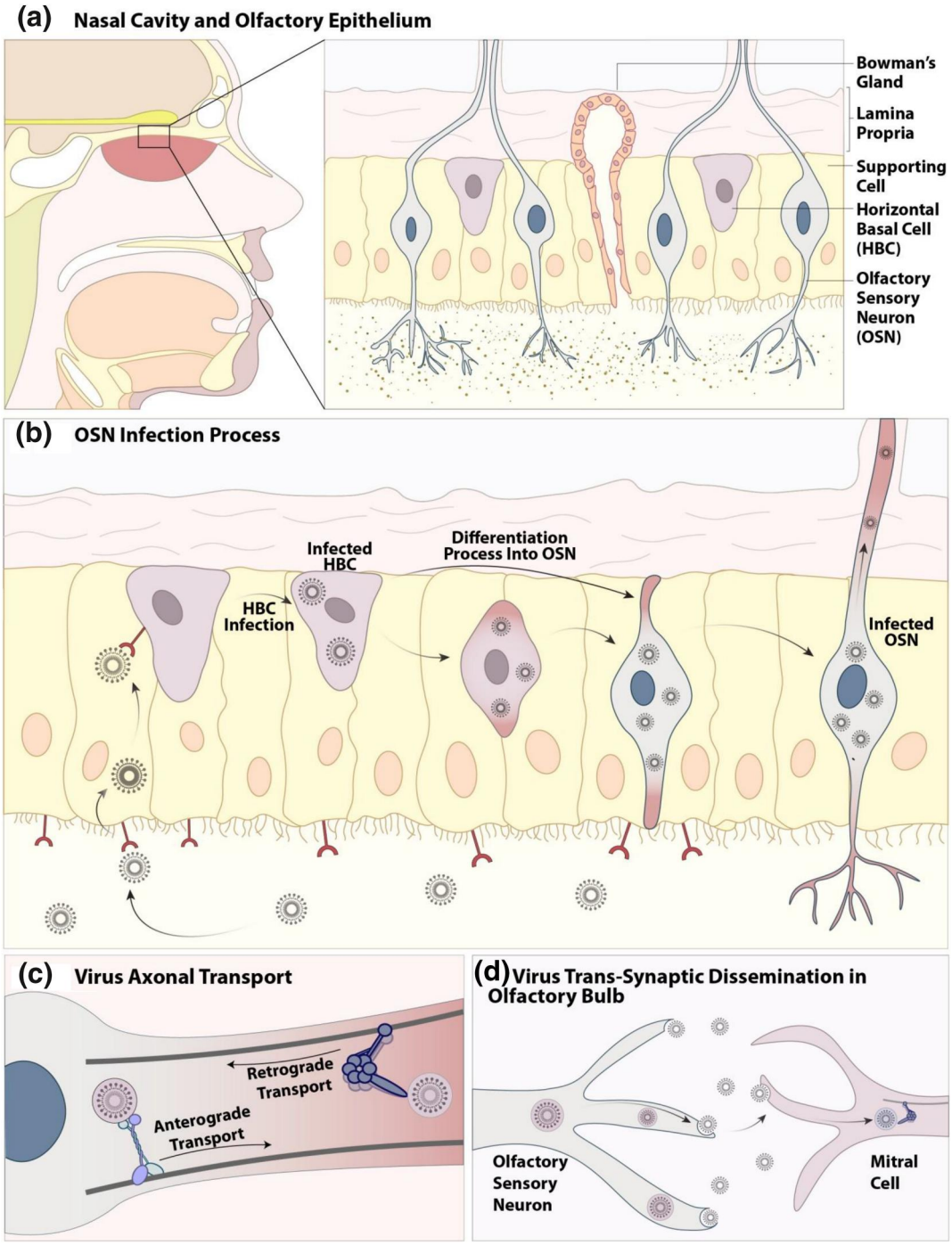

FIGURE 1 Potential route of central nervous system invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via nasal cavity and axonal transport propagation. (a) Olfactory epithelium is located in the roof of the nasal cavity and its distinct cell types; (b) Proposed mechanism of olfactory sensory neuron (OSN) infection process by infection and differentiation of horizontal basal cells (HBCs) to OSNs and propagation of viruses to the olfactory bulb (OB) through the cribriform plate; (c) Axonal transport of viruses via retrograde and anterograde dissemination utilising Dynein for retrograde and Kinesin for anterograde transport to facilitate the infection of neuronal cells; (d) Trans-synaptic pathway of virus propagation in the OB to infiltrate in the brain and infect more cells by exocytosis and endocytosis

expression of ACE2 and TMPRSS2 in this tissue.[90] This could facilitate SARS-CoV-2 entry to the hypothalamus tissue and further spread of the virus to the entire brain, owing to the widespread connection of the hypothalamus to other centres of the brain[76] (Figure 2b,c).

Dissemination of virus-infected leucocytes into the' blood circulation and subsequent extravasation of the immune cells into the brain parenchyma could serve as another gateway for the virus to the CNS. The so-called 'Trojan horse' mechanism has been well investigated previously in some of the neurotropic viruses such as

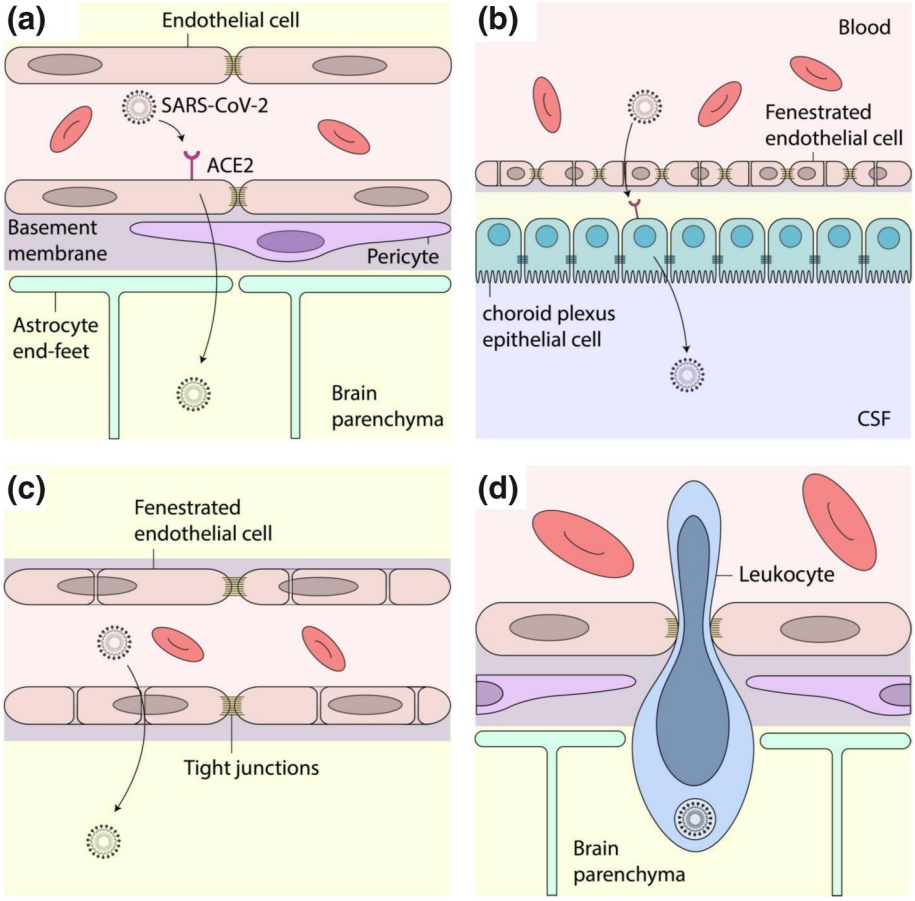

FIGURE 2 Possible mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) haematogenous route of neuroinvasion. (a) Blood-brain barrier (BBB). Brain endothelial cells (ECs) and pericytes are observed to express angiotensin converting enzyme 2 (ACE2) and other SARS-CoV-2 alternative receptors. This could facilitate the SARS-CoV-2 invasion to the brain tissue through the paracellular passage of the viral particles across the BBB; (b) choroid plexus. The barrier at the interface between the blood and the cerebrospinal fluid (CSF) consists of a more permeable endothelium due to the fenestrated structure of the ECs. Moreover, the choroid plexus epithelium cells at the apical side of the blood-CSF barrier express ACE2. With these properties, the blood-CSF barrier could serve as a SARS-CoV-2 entry gate to the CSF and then brain parenchyma; (c) circumventricular organs. Capillaries of the median eminence and other circumventricular organs lack the tightly coordinated BBB structure and consist of a continuous, fenestrated endothelium permeable to polypeptides and hormone molecules. Due to this extensive permeability, circumventricular organs could act as possible gateways to the brain tissue for SARS-CoV-2; (d) Trojan horse mechanism. SARS-CoV-2 could infect the leucocytes. Dissemination of infected leucocytes into the cerebral blood circulation and later extravasation of infected cells could facilitate SARS-CoV-2 entry to the brain parenchyma by the so-called Trojan horse mechanism

HIV and West Nile Virus (WNV).[91,92] Infected leucocytes could infiltrate into the brain through the vasculature, the meninges, and the choroid plexus. These sites have been observed as entry points for monocytes, neutrophils, and T cells.[77] There are indications that SARS-CoV could infect lymphocytes, granulocytes, monocytes, and monocyte derivatives[93]; thus, it is likely that SARS-CoV-2 also utilises this mechanism in order to invade the CNS by infecting ACE2-expressing leucocytes.[45,94] SARS-CoV-2 is shown to abortively infect dendritic cells and macrophages.[95] This evidence, in conjunction with systemic inflammation and hypoxic condition that increase the infiltration of leucocytes through the BBB during the infection,[45,96] strengthens the feasibility of SARS-CoV-2 neuroinvasion by this route (Figure 2d).

4 | COVID-19 ASSOCIATED CYTOKINE STORM

Considering various clinical observations, Covid-19 infection can promote immune dysregulation, characterised by high levels of pro- and anti-inflammatory cytokines and chemokines.[97,98] Dysregulated immune response may exhibit as severe lymphopenia[99] with hyper-activated pro-inflammatory T-cells and decreased regulatory T-cells, mostly in critically ill patients.[100] In contrast, no decrease of B-cells has been seen in Covid-19 patients.[99] Cytokines, the main indication of hyper-inflammation in Covid-19 patients, are a group of immunoregulatory cell-cell communication molecules, including chemokines, interleukins, lymphokines, monokines, and interferons.[101] Chemokines such as CXCL8 and CXCL10 act as chemotaxis cytokines

and bring leucocytes to the site of concern.[102,103] Additionally, the production of type I interferons is the fastest and first response of infected cells to slow down or stop viral replication and alert the presence of the pathogen to immune cells.[74,102] Although cytokines are essential for combating viral infections, overexpression and elevated levels of inflammatory cytokines, known as cytokine storm, could lead to immune cell infiltration to different organs, which subsequently causes multiple organ damage such as acute respiratory distress syndrome (ARDS) and CNS dysfunction or even death.[100,101,104-107] According to obtained data, the majority of severe Covid-19 patients have exhibited a significant increase in pro- and anti-inflammatory cytokines, including IL-2, IL-6, IL-7, IL-1β, tumour necrosis factor-α (TNF-α), IFN-γ, interferon-gamma-induced protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF),[108-112] and other molecules and inflammatory markers including paracalcitonin, alanine aminotransferase (ALT), lactate dehydrogenase (LDH), D-dimer, high-sensitivity C-reactive protein (hsCRP), and ferritin[98,108] which are associated with Covid-19 severity.[98,100,112,113] Interestingly, Th2 cell-secreted cytokines such as IL-4 and IL-10 have also been elevated in Covid-19 patients, which take part in inhibiting the inflammatory response.[112] Complement activation also plays a critical role in the disease severity of SARS-CoV-2 by promoting immune cell activation and pro-inflammatory states. In the same way, Increased plasma complement levels were noted in moderate and severe Covid-19 patients, making them susceptible to complement-mediated injuries.[114,115]

The generation of IFNs and other cytokines is mediated through several pattern-recognition receptors (PRRs), including TLRs and NOD-like receptors (NLRs), which are expressed in monocytes, neutrophils, macrophages, and dendritic cells.[116] PRRs detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including viral components such as RNA and molecular complexes from damaged cells.[76] As an example, TLR3 expressed on ECs recognises viral RNA and consequently increases the release of IFNs.[74] Besides, by activating the PRRs, formation of inflammasomes is promoted, and procaspase-1 converts to caspase-1, leading to converting pro-IL-1β to the active IL-1β.[106] The triggered signalling process leads to the expression or activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) as well as activation of interferon regulatory factors that mediate the type I interferon-dependent anti-viral response, which involves in the activation of innate immunity.[106,113,117] SARS-CoV-2 infection may also induce a massive release of ATP in the alveolar microenvironment that ATPs can act as DAMP and can activate P2X7R and NLRP3, which eventually results in the progression of inflammatory response and IL-1β and IL-18 release.[97,118] P2X7 receptors are widely expressed in immune, lung, and CNS cells, mainly in microglia and oligodendrocytes, and play a key role in inflammation.[119] NLRP3 inflammasome is an essential cause of activation of the innate immune response,[113] and unlike other PRRs, NLRP3 can react to other signals such as K+ efflux, production of reactive oxygen species (ROS), and Ca2+ mobilisation.[120] For instance, P2X7R activation triggers K+ efflux, which then stimulates the NLRP3 inflammasome and cytokine release.[120] Hence, upregulation of transcription of NLRP3 genes may help the recognition of PAMPs and DAMPs that may be induced by activation of purine sensing receptors such as P2X7R and results in cytokine release.[113,119]

Another involved pathway in the activation of cytokines such as type I IFNs after viral infection is the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling pathway.[121] This pathway mediates biologic activity for a large number of inflammatory cytokines, which demonstrates JAK-STAT activation contribution to critical events such as inflammation and the development of the immune system, which may lead to facilitating the invasion of SARS-CoV-2 into the CNS.[104,122] Since multiple pathways control cytokine activation,[101] the inhibition of involved pathways looks to be a promising strategy to balance the immune response.[123] However, prolonged inhibition of plausible pathways associated with cytokine release or activation may lead to a compromised anti-viral immune response, which could subsequently promote the proliferation of the SARS-CoV-2.[104,106] Therefore, clinical trials are in progress focussing on inhibiting associated inflammatory molecules or receptors and pathways to overcome the hyper-inflammation and prevent harmful effects arising from the hyper-inflammatory response of SARS-CoV-2 infection (Table 1).

5 | THE INDIRECT EFFECTS ON THE NERVOUS SYSTEM

5.1 | Blood-brain barrier disruption

Segregating the CNS from peripheral blood circulation, the BBB is a highly selective barrier formed by unique ECs and supporting cellular and non-cellular elements, including astrocytes, pericytes, and extracellular matrix (ECM). As a part of the 'neurovascular unit' (NVU), the highly coordinated activity of BBB components results in tight control of molecules and ions passage, precise delivery of oxygen and nutrients according to tissue needs, and protection of the CNS from toxins and pathogens.[124,125] The balanced permeability of BBB is crucial for the maintenance of an environment that neurons could properly function in[126]; however, emerging evidence suggests that SARS-CoV-2 infection has the potency to disturb the integrity of BBB and induce hyperpermeability in the barrier. A recent study in a BBB-on-a-chip in vitro system demonstrated that the SARS-CoV-2 spike protein could cause dysfunction and loss of integrity of the BBB.[127] In line with this, a case study of 31 Covid-19 patients with neurological manifestations reported that 58% of patients exhibited signs of BBB disruption and leakage.[128] Considering the neurotropism characteristic of previous CoVs[73,129,130] and emerging reports of neurological manifestations such as encephalopathy/encephalitis, acute disseminated encephalomyelitis, seizures, impaired consciousness, and delirium in Covid-19 patients,[6,17-19,131,132] it is feasible to attribute these neurological complications, at least partly, to BBB

TABLE 1 Clinical trials associated with Covid-19 sequels and further neurological complications

	Trial identification	Drug used	Delivery route	Drug description	Phase	Status
Inflammatory- and Autoinflammatory-related trials	NCT04334044	Ruxolitinib	Orally	Inhibits JAK1/2 and decreases IL-6 production by macrophages	1 and 2	Completed
	NCT04362137	Ruxolitinib	Orally		3	Completed
	NCT04348071	Ruxolitinib	Orally		2 and 3	Withdrawn
	NCT04354714	Ruxolitinib	Orally		2	Withdrawn
	NCT04377620	Ruxolitinib	Orally		3	Terminated
	NCT04338958	Ruxolitinib	Orally		2	Completed
	NCT04891133	Baricitinib	Orally	Inhibits JAK1 and JAK2 which leads to dampen inflammatory immune responses	2 and 3	Recruiting
	NCT04320277	Baricitinib	Orally		2 and 3	Not yet recruiting
	NCT04321993	Baricitinib	Orally		2	Recruiting
	NCT04393051	Baricitinib	Orally		2	Not yet recruiting
	NCT04421027	Baricitinib	Orally		3	Completed
	NCT04358614	Baricitinib	Orally		2 and 3	Completed
	NCT04340232	Baricitinib	Orally		2 and 3	Withdrawn
	NCT04373044	Baricitinib + Hydroxychloroquine	Orally	Hydroxychloroquine: reducing activated T cells and the production of cytokines by lymphocytes	2	Terminated
	NCT04412772	Tocilizumab	Intravenously	Blocks the IL-6 signalling pathways	3	Recruiting
	NCT04730323	Tocilizumab	Intravenously		4	Completed
	NCT04445272	Tocilizumab	Intravenously		2	Completed
	NCT04377750	Tocilizumab	Intravenously		4	Recruiting
	NCT04643678	Anakinra	Subcutanous injection	A recombinant IL-1 receptor antagonist	2 and 3	Recruiting
	NCT04603742	Anakinra	Intravenously		2	Not yet recruiting
	NCT04510493	Canakinumab	Intravenously	Anti-IL-1β monoclonal antibody which leads to neutralisation of IL-1β signalling	3	Completed
	NCT04362813	Canakinumab	Intravenously		3	Completed
	NCT04393311	Ulinastatin	Intravenously	A serine protease inhibitor	1 and 2	Not yet recruiting
	NCT04795583	Prednisone	Orally	An immunomodulatory drug	3	Not yet recruiting
	NCT04355247	MethylPREDNISolone	Intravenously	A potent anti-inflammatory drug	2	Recruiting
	NCT04329650	Siltuximab and Methylprednisolone	Intravenously	Siltuximab: IL-6 inhibitor	2	Recruiting

(Continues)

TABLE 1 (Continued)

	Trial identification	Drug used	Delivery route	Drug description	Phase	Status
	NCT04355637	Budesonide	Inhalation	Anti-inflammatory effects in the lungs, reducing expression of ACE-2 and TMPRSS2	4	Recruiting
	NCT04381364	Ciclesonide	Inhalation	Inhibits the replication of SARS-CoV-2 genomic RNA by targeting the viral endonuclease NSP15	2	Recruiting
	NCT04412252	Tofacitinib	Orally	Inhibits JAK1 and JAK3	2	Withdrawn
	NCT04415151	Tofacitinib	Orally		2	Recruiting
	NCT04280588	Fingolimod	Orally	Used for immune therapy in patients with multiple sclerosis	2	Withdrawn
	NCT04532372	Leflunomide	Orally	An immunosuppressive drug used for rheumatoid arthritis(RA)	1 and 2	Recruiting
	NCT04869358	Ofatumumab	Subcutaneously	A recombinant human monoclonal antibody to CD20 of B lymphocytes	4	Recruiting
	NCT04878211	Ofatumumab	Subcutaneously		4	Recruiting
	NCT04346797	Eculizumab	Intravenously	A monoclonal antibody against C5 which blocks the generation of pro-inflammatory molecules	2	Recruiting
	NCT04802083	Eculizumab	Intravenously		Unknown	Available
	NCT04891172	Intravenous immunoglobulin	Intravenously	Pooled polyclonal serum IgG from healthy donors	2 and 3	Recruiting
	NCT04548557	Intravenous immunoglobulin	Intravenously		3	Not yet recruiting
Hypoxia-related trials	NCT04359862	Propofol and Sevoflurane	Sevoflurane: Inhalation Propofol: Intravenously	Anaesthetics with probable neuroprotective effects	4	Terminated
	NCT04771000	Ambrisentan	Orally	A selective endothelin type A receptor antagonist	2	Recruiting
	NCT04356937	Tocilizumab	Intravenously	Blocks the IL-6 signalling pathways	3	Completed
Coagulation-related trials	NCT04743011	Heparin sodium	Inhalation	Anticoagulant	1 and 2	Not yet recruiting
	NCT04723563	Heparin	Inhalation		4	Completed
	NCT04427098	Enoxaparin	Subcutaneously injection		2	Recruiting

TABLE 1 (Continued)

Trial identification	Drug used	Delivery route	Drug description	Phase	Status
NCT04492254	Enoxaparin	Subcutaneously injection		3	Recruiting
NCT04646655	Enoxaparin	Subcutaneously injection		3	Recruiting
NCT04354155	Enoxaparin	Subcutaneously injection		2	Completed
NCT04408235	Enoxaparin	Subcutaneously injection		3	Not yet recruiting
NCT04360824	Enoxaparin	Subcutaneously injection		4	Recruiting
NCT04530578	Nebulized Heparin + Enoxaparin	Nebulized Heparin: inhalation, Enoxaparin: Subcutaneously		4	Recruiting
NCT04355026	Hydroxychloroquine + Bromhexine	Orally	Hydroxychloroquine: reducing activated T cells and the production of cytokines by lymphocytes, Bromhexine: TMPRSS2 inhibitor	4	Recruiting
NCT04332666	Angiotensin 1–7	Intravenously	Vasodilation effect and increases endothelial function and inhibits Angiotensin II-induced signalling	2 and 3	Not yet recruiting
NCT04328012	Losartan	Orally	Blocks the AT1 receptor and may be protective in stroke	2 and 3	Recruiting
NCT04312009	Losartan	Orally		2	Completed
NCT04340557	Losartan	Orally		4	Completed
NCT04643691	Losartan and Spironolactone	Orally	Losartan: blocks the AT1 receptor and may be protective in stroke, Spironolactone: a competitive aldosterone antagonist that may provide protection from SARS-CoV-2	2	Recruiting
NCT04899232	Antithrombin III	Intravenously	An anticoagulant with anti-inflammatory properties	2	Recruiting
NCT04466670	Acetylsalicylic acid (aspirin)	Orally	Inhibits platelet aggregation triggered by the release of arachidonic acid (AA) from platelet cells	2	Recruiting
NCT04363840	Acetylsalicylic acid (aspirin)	Orally		2	Not yet recruiting

(Continues)

TABLE 1 (Continued)

Trial identification	Drug used	Delivery route	Drug description	Phase	Status
NCT04424901	Dipyridamole	Orally	Antiplatelet drug	2	Recruiting
NCT04391179	Dipyridamole	Orally		2	Completed
NCT04410328	Dipyridamole and Aspirin	Orally	Dipyridamole: antiplatelet drug, Aspirin: inhibits platelet aggregation triggered by the release of arachidonic acid (AA) from platelet cells	3	Recruiting
NCT04570397	Ravulizumab	Intravenously	Inhibits C5 complement	3	Recruiting
NCT04369469	Ravulizumab	Intravenously		3	Active, not recruiting
NCT04390464	Ravulizumab and Baricitinib	Ravulizumab: Intravenously, Bariticinib: Orally	Ravulizumab: a complement C5 inhibitor, Baricitinib: Inhibitor of the Janus kinases JAK1 and JAK2 which leads to dampen inflammatory immune responses	4	Recruiting
NCT04333420	IFX-1	Unknown	A monoclonal antibody that blocks the effect of C5a	2 and 3	Recruiting
NCT04371367	Avdoralimab	Intravenously	An IgG1-κ anti-C5aR1 blocking antibody	2	Completed
NCT05010876	C1 inhibitor	Slow infusion	Inhibits lectin pathway of complement	2	Completed

Abbreviations: ACE-2, angiotensin converting enzyme 2; Covid-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, Transmembrane Serine Protease 2.

impairment followed by the infection; however, it is not precisely clear whether the initial damage to the barrier is due to the direct invasion of SARS-CoV-2 to cellular structures of the BBB, or a response of barrier components to exacerbated inflammatory state associated with Covid-19.[45,39]

As the core anatomical elements of the BBB, ECs in the brain are uniquely specialised in structure and function. Continuous intercellular tight junctions (TJs), lack of common fenestrations, and suppressed transcytosis are distinguishing characteristics of these cells, compared to ECs in other tissues, making them capable of limiting both the paracellular and transcellular passage of molecules through the neurovascular endothelium.[89,124] However, barrier properties of brain ECs could be altered directly or/and indirectly by the virus infection. Because of the fact that expression of ACE2 receptor and NRP1 has been observed in human brain microvascular ECs,[77,133] and the presence of SARS-CoV-2 particles in capillary ECs of the brain is reported in an autopsy study,[80] the direct effect of SARS-CoV-2 on ECs could be proposed as a possible route of damage to the BBB (Figure 3a); however, the indirect effect of the hyperinflammatory state is the most likely culprit of disruption of the BBB associated with Covid-19.[45] Elevation in levels of pro-inflammatory factors is strongly related to alteration in TJ function and BBB disruption. For instance,

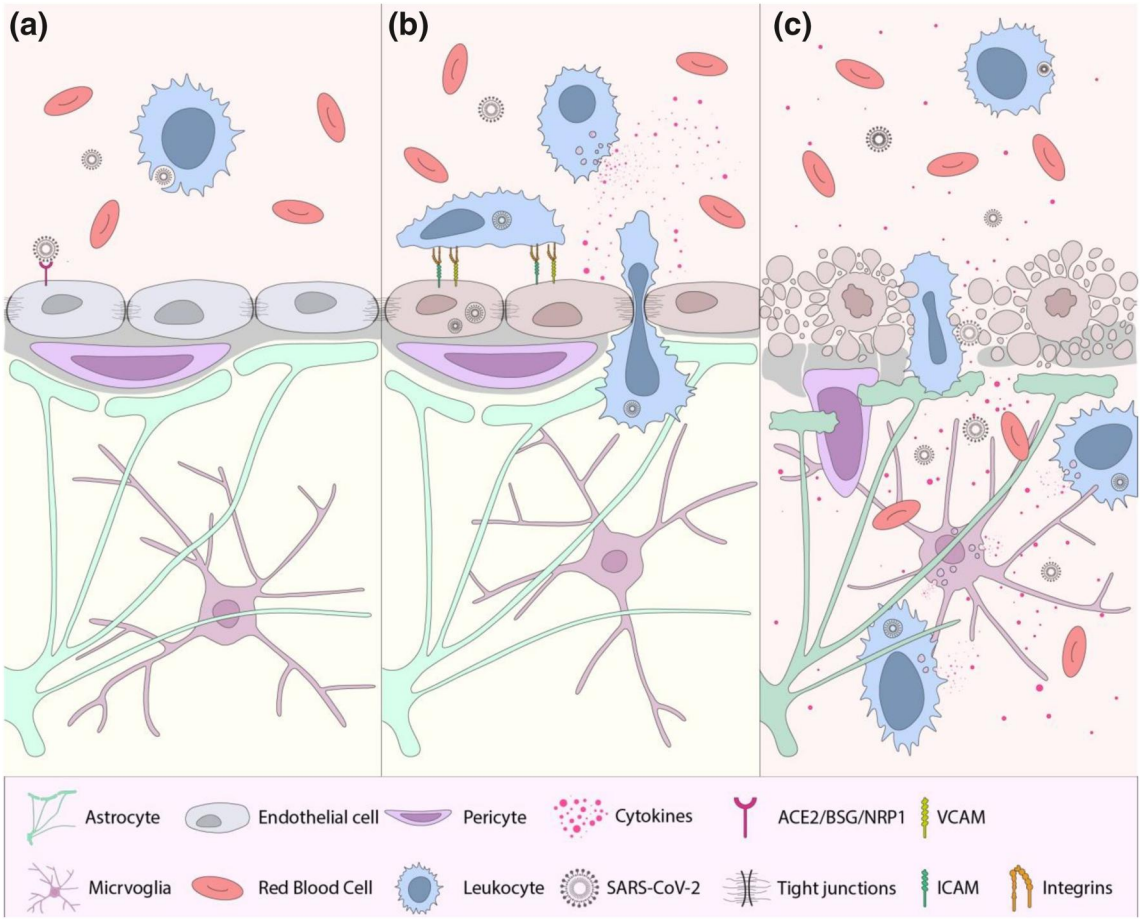

FIGURE 3 Potential mechanisms of blood-brain barrier (BBB) disruption by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. (a) Dissemination of SARS-CoV-2 into the blood circulation leads to the interaction of viral particles with ACE2, basigin, or Neuropilin 1 receptors expressed by brain endothelial cells (ECs). SARS-CoV-2 could also infect leucocytes; (b) by facilitating entry receptors, SARS-CoV-2 infects the brain ECs and promotes activation of these cells. Moreover, due to systemic inflammation associated with the infection, ECs exposure to circulating cytokines also activates these cells. ECs activation induces upregulated expression of vascular and intercellular adhesion molecules (VCAM and ICAM) and matrix metalloproteinases (MMPs). Interaction of leucocyte surface β1 and β2 integrins with adhesion molecules results in the binding of circulating leucocytes to the ECs and facilitates extravasation of leucocytes through the tight junctions and basement membrane that are already degraded by the action of MMPs. In this manner, infiltration of infected leucocytes by the 'Trojan horse' mechanism facilitates viral entry to the brain parenchyma; (c) infection of the brain ECs and hyperinflammatory state associated with Covid-19 induce apoptosis of ECs, leading to the disruption of the BBB. The compromised barrier allows extravasation of erythrocytes and leucocytes, leakage of plasma pro-inflammatory agents such as cytokines, and free passage of circulating SARS-CoV-2 particles to the brain parenchyma. The presence of viral particles and pro-inflammatory factors, as well as infiltrated leucocytes in cerebral tissue, triggers activation of astrocytes and microglia, which in turn causes further release of cytokines in the brain parenchyma, phagocytic hyperactivity of microglia, and disruption of astrocytes end feet, all results in more damage to the BBB and nervous tissue

in a rat study, an increased level of IL-1 has been indicated as a causative factor for meningitis and compromised BBB integrity.[134] Another study suggested that IL-1β induces discontinuous distribution of claudin-5, one of the TJ proteins, along the plasma membrane of brain ECs.[135] Moreover, cytokines and chemokines such as TNF-α, IL-6, IL-12, CCL2, and cxcl10 are demonstrated to cause distribution of TJ proteins (occludin, claudin-5, ZO-1, and ZO-2), modulation in the function of BBB transporters like P-glycoprotein, and alteration of adsorptive transcytosis properties, all resulting in compromised BBB permeability.[84,136]

Under the influence of systemic inflammation, activation of ECs by cytokines such as IL-6, IFN-γ, and TNF-α triggers the overexpression of different proteases, including matrix metalloproteinases (MMPs).[136,45] MMPs are critical contributors to BBB disruption by digesting TJs and basement membrane proteins associated with ECs.[137] Numerous studies have investigated the deleterious effects of dysregulated MMPs, indicating their pivotal role in CNS pathologies, such as cerebral oedema, leucocyte infiltration, haemorrhage, and exacerbated inflammatory reactions.[134] On another note, pro-inflammatory cytokines such as TNF-α and IL-1β have been shown to induce cyclooxygenase (COX) activity in several cell types, including brain ECs.[84,134,138] COX activation triggers the production of eicosanoids, including prostaglandins (PGs) and leukotrienes (LTs), which in turn affect various pathways and tissues. Studies have indicated that COX2-mediated PGs induce the expression of MMP1, leading to further alteration of TJs and damage to BBB.[139] Furthermore, prostaglandin E (PGE) production in brain ECs by COX1 or COX2 plays a vital role in exhibiting symptoms such as fever and malaise/discomfort through the hypothalamic-pituitary-adrenal (HPA) axis activation.[140] Thus, it is tempting to speculate that PG release in response to systemic inflammation is an overlooked inducer of sickness behaviour related to Covid-19 disease.

Promoted by systemic inflammation, activation of brain ECs triggers upregulated expression of the vascular and the intercellular adhesion molecules (VCAM and ICAM), which mediate immune cell infiltration into the brain parenchyma via interaction with β1 and β2 integrins expressed on the surface of leucocytes[45,134] (Figure 3b). In parallel with inflammatory mediated damage to BBB, increased extravasation of immune cells across the BBB leads to a higher presence of viral particles (by the 'Trojan horse' mechanism) and pro-inflammatory cytokines and chemokines in the brain parenchyma, where they encounter the CNS defence system represented by astrocytes and microglia. Astrocytes exposure to viral particles and pro-inflammatory mediators triggers activation and subsequent upregulated production of pro-inflammatory factors by these cells, as well as vascular endothelial growth factor (VEGF).[140,141] This ultimately results in astroglial death and disruption of astrocytic end-feet, the structural components of the BBB that form the outer layer of the mature capillaries[125,141] (Figure 3c). Moreover, secretion of VEGF-A by activated astrocytes stimulates the endothelial nitric oxide synthase (eNOS) signalling in ECs and downregulates the expression of TJ proteins such as occludin and claudin-5.[136] In parallel with this, sonic hedgehog production of astrocytes is shown to be suppressed by IL-1β. This also results in further disruption of BBB integrity; as the sonic hedgehog signalling pathway plays a key role in upregulated expression of TJ proteins in brain ECs.[142] Similar to astrocytes, activation of microglia in an infectious/inflammatory condition is followed by an exacerbating response of overproduction of pro-inflammatory mediators such as cytokines, chemokines, matrix proteases, PGs, nitric oxide, and ROS[143] (Figure 3c). Besides the impairment of the BBB permeability in a vicious circle led by pro-inflammatory factors, exaggerated response of microglia is associated with a phagocytic hyperactivity characteristic, inducing neurodegeneration, synaptic loss, and demyelination in the CNS tissue.[141] These findings are in line with the evidence derived from post-mortem case series, such as a study of 43 Covid-19 patients, in which substantial astrogliosis, microglial activation, and cytotoxic T lymphocytes infiltration were prevalent in the brain specimens; and increased phagocytic activity of microglia was indicated by detection of overexpressed lysosomal marker CD68.[144] Additionally, another study of highly multiplexed spatial analysis of CNS tissue has also identified profound immune activation in Covid-19 brains, accompanied by significant microglial alterations, parenchymal CD8 infiltration, and formation of microglial nodules, hotspots of microglia-T-cell interactions. Prominent perivascular leakage and considerable axonal damage were observed in this study to be tied with the broad neuroinflammation, indicating the association of immune activation with BBB disruption and neurodegeneration in the exhibition of neurological manifestations of Covid-19.[145]

5.2 | Hypoxic associated CNS dysfunction

Hypoxia is a major stress factor that induces BBB disruption, leading to infiltration of peripheral immune cells and leakage of blood proteins, including cytokines, to the brain.[96] Due to the infection of SARS-CoV-2 in different organs, respiratory and circulatory failure can cause moderate to severe levels of hypoxia. Hypoxaemia (low level of oxygen with no sensation of dyspnoea) caused by alveolar damage and inflammatory exudate can lead to intrapulmonary shunting, loss of lung perfusion regulation, intravascular microthrombi, and impaired diffusion capacity.[146,147] Affected cells/tissues must respond to the hypoxic condition to sustain their function and prevent cell death. Hypoxia-inducible factors (HIFs) are the most critical responses among different pathways and reactions of affected cells/tissues.[148] HIFs are heterodimeric transcription factors that possess two subunits: an oxygen-regulated alpha subunit and an oxygen-independent beta subunit,[149] and act as central regulators of tissue O_2 metabolism and are known as master regulators of oxygen homoeostasis.[150,151] SARS-CoV-2 infection induces upregulated expression of HIF-1α in immune cells, which results in further release of cytokines and causes ARDS. Pro-inflammatory cytokines such as IL-6 and TNF-α can reduce Zonula occludens-1 (ZO-1) mRNA levels and increase the phosphorylation of ZO-1 protein, which results in impairing BBB integrity. On the other hand, HIF-1α stabilisation in

microvascular ECs increases the transcription of VEGF and integrins, resulting in increased vascular permeability.[152,153]

Based on the results of a study, VEGF enhances gap formation between ECs and induces fenestration in unfenestrated human and porcine endothelial monolayers in vitro.[154] Interestingly, a later study indicated that hypoxia can downregulate the expression of ZO-1, increase the expression of HIF-1α and VEGF and upregulate the phosphorylation of ZO-1, which all together can disrupt the BBB integrity and facilitate the invasion of SARS-CoV-2 into the CNS tissue. Since HIF-1α stabilisation is directly linked to barrier disruption, It is claimed that inhibition of HIF-1α improves barrier stability and decreases BBB damages, and prevents or reduces further CNS dysfunctions caused by SARS-CoV-2.[148] Nevertheless, the function of the HIF-1α inhibitor and VEGF antibody has been investigated, and according to evidence and documents, the expression of ZO-1 has been increased by inhibiting HIF-1α and VEGF.[96] It is noteworthy that HIF-1α also activates miR-let-7b, which inhibits protein expression of ACE2 and subsequently by stimulation of ADAM17 and inhibition of TMPRSS2 takes part in decreasing SARS-CoV-2 entry to the cells.[152] Remarkably, in different intensities of Covid-19 patients, there is a high probability of survival in patients with spO2 values greater than 90% with oxygen supplementation.[155] Given that hypoxaemia/hypoxia is the marker of severity,[156] and patients may be at high mortality risk, it has been speculated that in patients with spO2 values less than 90%, despite oxygen supplementation, maximum supportive care with more drug and other therapies is needed.[155] Hence, seldom drug investigations associated with hypoxic conditions are being trialed to improve the status of Covid-19 patients with hypoxia (Table 1).

5.3 | Hypercoagulable state

Several studies have reported coagulation abnormalities and thrombotic complications as common manifestations in patients with Covid-19.[157-159] Presented with elevated prothrombin time (PT) and D-dimer (coagulation function–related indicators),[160,161] the hypercoagulable state of Covid-19 predisposes patients to thrombotic vascular events, including disseminated pulmonary microthrombi, venous thromboembolism, and brain strokes.[34,162] In a case series of Covid-19 patients in China, elevated D-dimer levels have been observed in 46.4% of 560 patients, while levels were even higher in severe cases of the disease (59.6%).[163] In another study of 288 patients, thromboembolic events and acute ischaemic strokes have been reported in 7.7% and 2.5% of patients, respectively.[164] Other case series have reported the rate of stroke incidence ranging from 1% to 3% in admitted patients and up to 6% in critically ill patients.[76] Moreover, a twofold higher risk of cryptogenic stroke has been reported in Covid-19 patients, as the incidence observed in more than 65.6% of 3556 hospitalised cases, compared to 30.4% in contemporary controls.[165] According to these clinical reports and data from previous coronavirus outbreaks,[30] hypercoagulopathy is considered a life-threatening aspect of Covid-19 pathogenesis, especially among patients with hypertension, diabetes, and other cardiovascular comorbidities.[166]

Given the complexity and multifactor dependence of the mechanism, the aetiology of hypercoagulopathy in Covid-19 is not precisely explained. Downregulation of ACE2 by SARS-CoV-2 and subsequent Ang II accumulation,[167] pneumonia-induced hypoxia,[168] and release of neutrophil extracellular traps (NETs)[169] are among proposed mechanisms for the condition. However, endotheliopathy and massive inflammatory response have been indicated as two main features of prothrombotic presentations associated with Covid-19. Resting endothelium maintains vascular homoeostasis and prevents thrombosis through the production of several anti-inflammatory and antithrombotic factors. Hence, the probable direct viral infection of ECs by SARS-CoV2 and the independent response of ECs to the systemic inflammation phase of the disease are the major contributors to the endothelial dysfunction and subsequent coagulopathy associated with Covid-19.[166] Due to the susceptibility of lung and brain ECs to SARS-CoV-2 infection,[77,80] it is plausible to suggest that the Covid-19-associated thrombosis is likely to be started in respiratory vascular tissue and then spreads into other organs, including the nervous system, through the circulation of viral particles and inflammatory agents.[170]

Anticoagulant and anti-inflammatory properties of intact vascular endothelium are massively inhibited by a viral infection and following vigorous inflammatory response. Studies have reported a down-regulated expression of 'tissue factor pathway inhibitor' (tissue factor pathway inhibitor (TFPI)) and 'thrombomodulin' (THBD), two anticoagulatory factors, in virus-infected ECs.[171,172] Other studies have suggested the impairment of thrombin generation control mechanisms such as antithrombin III, TFPI, and protein C system during inflammation by pro-inflammatory cytokines.[173] On the other hand, overproduction of cytokines and chemokines such as IL-6, IL-1β and, TNF, in synergy with a direct viral infection, induces activation of ECs and promotes further secretion of pro-inflammatory cytokines and pro-thrombotic factors, amplifying the vicious cycle of endothelial damage and vessel thrombosis.[174]

Complement activation is another aspect of the Covid-19-associated hypercoagulable inflammatory state. Studies have reported evident signs of complement hyperactivity in infected patients, indicated by the evaluation of soluble markers and histopathological observations.[114] It is plausible that SARS-CoV-2 infection induces three different pathways of complement activation, all converging in a common cascade and leading to the production of various molecules such as anaphylatoxins. These complement components are potent activators of inflammation and coagulation mechanisms, playing an essential role in the innate immune response against viral infections. However, dysregulated function of the complement system could end in thrombotic complications. For instance, anaphylatoxin 'C5a' promotes the release of 'tissue factor' from multiple sources, including ECs and neutrophils, which in turn activates another molecular cascade ending in thrombin production and clot formation. Furthermore, C5a impairs fibrinolysis by inhibiting the plasminogen/plasmin system and

stimulates neutrophils to release excessive NETs, all resulting in a higher coagulable condition.[175] Taken together, infection-triggered complement hyperactivation induces a maladaptive inflammatory and coagulatory response, which in turn, feeds back and amplifies complement activation and clot formation.[176]

Considering all the above, patients with Covid-19 are more likely to exhibit thrombotic events in multiple organs, including brain and cerebral circulation.[177,178] The covid-19 infection has been described as a risk factor for stroke.[179] Therefore, besides ongoing anticoagulant and antiplatelet trials, administration of other possible therapeutic agents such as complement inhibitors and anti-inflammatory agents are under investigation, as they could be beneficial in targeting multiple steps of coagulation-related pathways and developing a combination therapy strategy with much more efficiency[166] (Table 1).

5.4 | Autoimmune neuropathies

Based on various case reports of various autoimmune neuropathies associated with Covid-19, it is considered that SARS-CoV-2 can also possess auto-immunogenic effects mainly via molecular mimicry or other mechanisms.[180-183] Losing Immunologic tolerance to key antigenic sites on the different parts of neurons can lead to autoimmune peripheral neuropathies.[184] In other words, a potential trigger of multi-organ autoimmunity in Covid-19 could be the molecular mimicry between SARS-CoV-2 proteins and various human cell/tissue autoantigens, including the nervous system, which is involved in inflammatory polyneuropathies by analysing the peptide sharing between the virus and such protein antigens with BLAST (basic local alignment search tool).[185,186] Different parts of PNS, including the dorsal motor nucleus, nucleus ambiguous, nodose ganglion, and jugular ganglion, are potentially able to generate an autoimmune response due to having neurons presenting proteins with similar epitopes with SARS-CoV-2 proteins.[187] Moreover, the occurrence of autoimmunity caused by SARS-CoV-2 has been demonstrated in CNS. Multiple pathways of Covid-19 initiated autoimmune cascade are shown in Figure 4.[188]

Several case studies have reported Guillain-Barre syndrome (GBS) and its variants[189] in Covid-19 patients.[183,190-193] GBS is not usually known as a form of Covid-19 presentation, but as stated by a study by fragile, et al., the frequency of GBS is higher among patients with Covid-19.[194] In addition, an increased incidence of GBS has been seen during the pandemic. Given that the majority of GBS patients are Covid-19-positive, there could be a pathogenic link between Covid-19 and GBS.[195] GBS is an immune-mediated disorder in which gangliosides, molecular markers expressed on peripheral nerves,[196] are attacked by the immune response generated by SARS-CoV-2, due to molecular mimicry.[197] Various gangliosides such as GD1a, GD1b, GQ1b, GT1b, GM1, and GM2 participate in patients with GBS neuropathies and play a key role in the pathophysiology of GBS.[196] In Covid-19-positive GBS patients, expression of antibodies against these gangliosides has been reported.[198] IgG, IgM, and membranolytic attack complex could imply complement-fixing antibodies against myelinated fibres. Likewise, complement-fixing IgM antibodies against a peripheral nerve glycolipid that contains carbohydrate epitopes and various sulfated or acidic glycosphingolipids have been detected in the serum of GBS patients.[184] Additionally, animal studies demonstrate that some anti-ganglioside antibodies can cause blockade of nerve transmission and destruction of nerve terminal or may affect different membrane channels of neurons due to complement activation and formation of the membrane attack complex.[199]

Different trials concerning inhibiting the neurotoxic effects of antibodies have indicated that there is effective immunotherapy with Intravenous immunoglobulin (IVIg) in Covid-19 patients for treating autoimmune and inflammatory diseases as well as GBS[198-201] (Table 1). IVIg consists of accumulated human IgG purified from healthy donors and could improve GBS patients' status by complement scavenging, neutralisation, or enhancement of degradation of auto-antibodies, inhibition of activation of various innate immune cells, increasing the number of plasmablasts, and other plausible mechanisms.[200,202,203] Moreover, transient axonal glycoprotein-1 (TAG-1) and the expression of inhibitory $Fc_{\gamma}RIIB$ receptors on immune B cells, participate in responsiveness to IVIg treatment. Since TAG-1 polymorphism is associated with IVIg responsiveness, response to IVIg can be genetically determined.[184] Besides the above, other GBS treatments are needed to be trialed and approved to improve Covid-19 patients suffering GBS, by inhibiting the autoantibodies caused by viral infection.

Covid-19 infection in Patients with pre-existing impaired regulation of immune responses such as Multiple Sclerosis (MS) may potentially trigger a further amplification of immune responses.[204] Thus, MS patients may exhibit more acute neurologic symptoms during Covid-19 infection.[205] The relationship between Covid-19 and MS is complicated, and there is not enough immunological and physiological evidence regarding Covid-19 implications in MS-related neurodegeneration.[204] Nevertheless, it is frequently claimed that immunocompromised patients or patients receiving immunosuppressive treatments may be at increased risk of SARS-CoV-2 infection due to the impairment in the immune system caused by high-efficacy disease-modifying therapies (DMTs)[204,206-209]; or may experience a more severe course of Covid-19 compared with general population due to the limited immune response and subsequently allowing more significant viral replication.[204,210] So, it is suggested that cell-depleting DMTs would be associated with higher Covid-19 risk.[211] Other factors of MS patients such as age, sex, worse physical disability, and comorbidities can also increase the risk of infection and hospitalisation in MS patients with Covid-19.[204,207]

Ocrelizumab is one of most widely used therapeutics for MS patients,[212] to treat relapsing and primary progressive phase of the disease.[213] In patients treated by Ocrelizumab, severe infections was found to be very low compared to patients who formerly used rituximab, which is commonly used in the population of MS patients and this group of patients is at the risk of higher rates of infections.[214] As claimed by a study on a case report, rituximab enhances the rate of

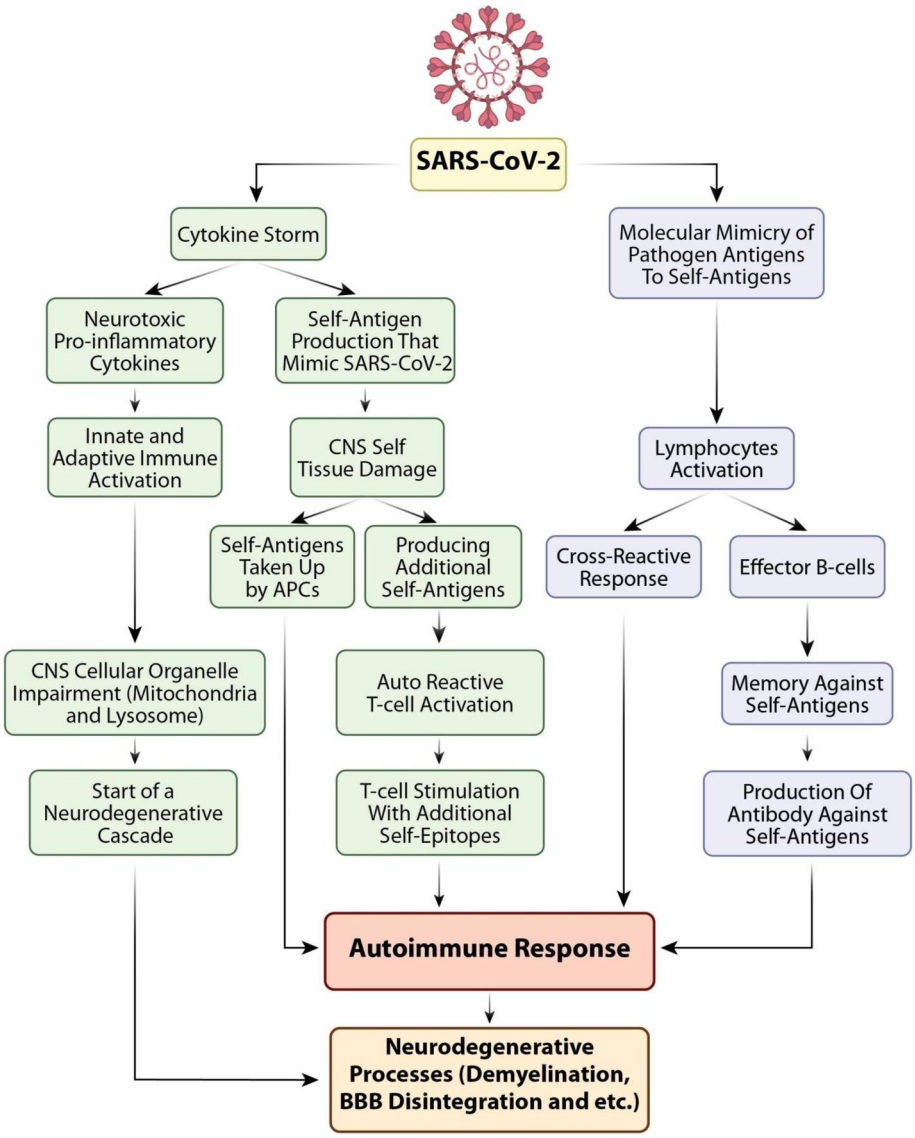

FIGURE 4 Multiple pathways of Covid-19 initiated autoimmune cascade, which may result in neurodegenerative disease severity in post-Covid-19 patients in coming decades. The cross-reactive response caused by the molecular mimicry of pathogen antigens to self-antigens, activated lymphocytes, and memory of B lymphocytes against self-antigens may lead to autoimmune response due to the interaction of antibodies with self-epitopes. Besides, initiation of central nervous system (CNS) self-tissue damage by the production of self-antigens similar to viral antigens in the structure and function of antigen presenting cells (APCs) and stimulation of T-cells by additional self-epitopes may be due to the cytokine storm and leads to an autoimmune response and further neurodegenerative complications. On the other hand, neurotoxic pro-inflammatory cytokines may have harmful effects on CNS cellular organelles such as mitochondria and lysosomes, which could be an initial point of demyelination, blood-brain barrier disintegration, and other neurodegenerative processes. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Covid-19 infection in MS patients[207] and decreases immunoglobulins, especially IgM.[214] While in other studies, it has been observed that there is no interdependence between specific DMTs and higher risk of Covid-19 in MS patients, which needs more supporting investigations. Moreover, IFN-β and glatiramer acetate are probably not related to severe infection in MS patients due to not exhibiting immunosuppressive effects.[207] It is also speculated that dimethyl fumarate (DMF) may increase the risk of Covid-19 by reducing the lymphocyte count in patients.[215] In brief, clinical trials are essential for attaining more data regarding the protective or harmful effects of immunosuppressive agents, risk factors associated with severe Covid-19, and antibody formation in MS or other autoimmune patients infected by SARS-CoV-2[216] to prevent disease activation or progression and limit the need for hospitalisation in the patients suffering autoimmune diseases[213] (Table 1).

6 | CONCLLUSION

SARS-CoV-2 could affect the nervous system in various ways. The direct invasion of the CNS by the virus could possibly occur through the infection of peripheral nerves such as OSNs,

pulmonary network, or ENS. Additionally, dissemination of viral particles and infected leucocytes from heavily involved pulmonary tissue into the systemic circulation could serve as another gateway for SARS-CoV-2 to invade the CNS. However, few studies have reported the presence of SARS-CoV-2 in CSF and brain parenchyma, which could not be indicated as consistent evidence for the direct invasion of the virus to the CNS. On the contrary, mounting evidence implicates the indirect effects of SARS-CoV-2 on the nervous system via exacerbating inflammation and pneumonia-induced hypoxia as key drivers of neurological manifestations in Covid-19. Destructive effects of infection-associated cytokine storm and hypoxia on the BBB have been well investigated, and mechanisms by which infection could cause coagulation abnormalities and autoimmune neuropathies are partly elucidated by previous studies on other types of infection. These findings are also applicable for Covid-19 infection as so many neurological symptoms in critically ill patients are linked to BBB disruption, thrombovascular events, and molecular mimicry-related neuropathies.

Here we reviewed some of the molecular mechanisms by which SARS-CoV-2 could directly or indirectly alter the structural and functional properties of the nervous system. Currently, there is no particular treatment for neurological complications associated with Covid-19, and most of the therapeutic efforts so far have gone into the development of effective vaccines. Despite the significant achievement, none of the developed vaccines are 100% protective against the infection. The pandemic is still a major public health issue, even in countries with a high vaccinated proportion of the population. Moreover, therapeutic approaches dependent on anti-viral agents have not been as effective as expected in the case of Covid-19. In this regard, further investigations are still needed to elucidate the molecular basis of the infection, which is an essential aspect of developing more effective therapeutic strategies. Several clinical trials are currently underway to evaluate the effects of anti-inflammatory agents, anticoagulants, and immunomodulatory therapies. The results of these trials could assist in the development of a combination therapy strategy that targets multiple aspects of SARS-CoV-2 pathogenesis, such as respiratory insufficiency, immune dysregulation, hypercoagulopathy, and multiple organ failure. In parallel with anti-viral therapies, targeting the deleterious side issues of Covid-19 by this strategy could aid not only in ameliorating neurological complications but also in improving disease severity and achieving a more favourable outcome.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Mohammad Mahboubi Mehrabani and **Mohammad Sobhan Karvandi:** Writing – original draft, Reviewing and Editing. **Pedram Maafi:** Reviewing, and Editing the Final manuscript. **Mohammad Doroudian:** Conceptualization; Preparation; Writing, Reviewing, and Editing the Final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as there is no new data were analysed in this study.

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