Review article

SARS-CoV-2 mediated neurological disorders in COVID-19: Measuring the pathophysiology and immune response

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ABSTRACT

The emergence of beta-coronavirus SARS-CoV-2 gets entry into its host cells by recognizing angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRESS2) receptors, which are responsible for coronavirus diseases-2019 (COVID-19). Global communities have been affected by COVID-19, especially caused the neurological complications and other critical medical issues. COVID-19 associated complications appear in aged people with underlying neurological states, especially in Parkinson's disease (PD) and Alzheimer's disease (AD). ACE2 receptors abundantly expressed in dopamine neurons may worsen the motor symptoms in PD and upregulates in SARS-CoV-2 infected aged patients' brain with AD. Immune-mediated cytokines released in SARS-CoV-2 infection lead to an indirect immune response that damages the central nervous system. Extreme cytokines release (cytokine storm) occurs due to aberrant immune pathways, and activation in microglial propagates CNS damage in COVID-19 patients. Here, we have explored the pathophysiology, immune responses, and long-term neurological impact on PD and AD patients with COVID-19. It is also a crucial step to understanding COVID-19 pathogenesis to reduce fatal outcomes of neurodegenerative diseases.

1. Introduction

Coronavirus diseases (COVID-19) is declared as an infectious disease, the highly transmitted SARS-CoV-2 infected approximately 523 million persons and caused more than 6.27 million deaths worldwide as of 20 May 2022. In early February 2020, World Health Organization (WHO) officially issued the name COVID-19, which turned into a pandemic by SARS-CoV-2 transmission. SARS-COV-2 variants such as delta (first reported in India) and Omicron (first reported in South Africa and Botswana) are considerably more infectious and transmissible than severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV). Many countries imposed a strict policy due to the viral transmission through social contagion. However, clinical outcomes of human infection of SARS-CoV-2 remains unclear and the possibility of progressing neural disorders. The infection of SARS-CoV-2 leads to frail individuals aged people affected by pre-existing chronic pathogenesis and prone to severe COVID-19 [1]. The neurological manifestations of SARS-CoV-2 transmission and infectivity showed various neurological conditions. SARS-CoV-2 infection is associated with systemic effects [2], multi-organ damage [3], and a pro-

inflammatory state [4]. The infection pattern of SARS-CoV-2 in the human brain remains impugnable. Other β-coronaviruses like SARS-CoV and MERS-CoV indicate dynamic neuro-invasive. Clinicians have reported Meningoencephalitis in COVID-19 patients except for confirmation of the neuropathological state [5]. The molecular findings of neuropathology in COVID-19 patients' brains are emergency for a clear understanding. The neurological conditions with the underlying pathophysiological mechanism have still been explored in the context of COVID-19 [6]. Furthermore, long COVID is a burning question among those neurological disorders. Thus, this emerging clinical concept is not well understood. Few researchers found the pattern of symptoms is potentially involved in long COVID. The WHO has taken steps to gather the case information depicting a clinical image subordinated by coalescence of cognitive symptoms, especially impaired memory that requires daily functioning and lasts over three months after onset of acute COVID-19 [7].

This review depicts COVID-19 associated with neuropathological and immunological changes in Parkinson's and Alzheimer's patients' brains. We have explored PubMed, Google Scholar, Scopus, and *bioRxiv*. We delineated the COVID-19 associated neuroimmunological disorders

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through all published case reports, case series, and the cohort of studies. The latest search has done on 03 May 2022.

2. SARS-CoV-2 infection with the aged brain in Parkinson's and Alzheimer's patients

A large number of similarities have been linked between Parkinson's disease (PD) and Alzheimer's disease (AD) based on recent clinical, pathological findings and genetic data. The etiology of one disease may shed light on the other [8]. For a few decades, the infectious etiology of PD and AD has suggested the vital role of various infectious agents associated with inflammatory pathways [9]. AD is strongly associated with neurodegeneration and decreased cognition in terms of the effect of this disease [10]. Viral invasion in the cortical region of the human brain alters signals and is associated with olfaction. Current MRI findings reveal the slight olfactory bulb changes in the COVID-19 patient brain [11]. PD usually occurs when cells in the brain that produce the neurotransmitter dopamine stop working or die. Lack of dopamine leads to both motor symptoms (bradykinesia, rigidity, postural instability) and non-motor symptoms (olfactory dysfunction, cognitive impairment, dementia, and autonomic dysfunction) [12]. At present, no effective treatment owing to SARS-CoV-2 infected PD and AD patients. It represents an imminent threat to the health span of the senior population in the world.

3. Factor increase the PD and AD risk in COVID-19 patients

3.1. Alpha-synuclein and SARS-CoV-2

SARS-CoV-2 Spike protein attached to the ACE2 receptor through its receptor-binding domain (RBD) is activated proteolytically by human proteases. A hallmark progression of PD is associated with α-synuclein, which originates in both nasal and intestinal mucosa [13]. Expression of α-synuclein increased in the peripheral neurons in PD due to pathogen infection that leads to high-molecular-weight aggregates of misfolded proteins [14]. α-Synuclein is defended by the infectious agent along the vagus nerve that controls specific physiological function and the immune system or olfactory nerve that conveys the sense of smell to either the dorsal motor nucleus of the vagus nerve or the olfactory bulb. Afterward spreads the signal to neighboring neurons via the connectome of the brain. This process represents a geographical evaluation of the diseases [15]. Thus, neuroinflammation triggers central PD pathology following viral infection manifested as activation of microglial and enhanced the production of cytokine levels in Substantia nigra. Earlier evidence provides hints that West Nile and SARS-CoV are similar [16]. Consequently, neurodegeneration occurs due to the expression of analogous α-synuclein that upregulation during SARS-CoV-2 infection. H1N1 influenza infection maintains the optimal viral load by interrupting protein clearance and rendering infected host cells incapable of

counterbalancing its accumulation [17]. Furthermore, the SARS-CoV-2 infection is responsible for interfering with the clearance of α-synuclein attached to the human protein trafficking molecule involved in the function of endoplasmic regulation that leads to the uncontrollable aggregation of α-synuclein [18] (Fig. 1).

### 3.2. Beta-amyloid and tau level impact during SARS-CoV-2 infection

Aβ is a pharmacological component for plaque formation in AD patients' brains. Aβ can bind with a few viral membrane proteins. It has a high affinity to SARS-CoV-2 spike protein S1 subunit and viral ACE2. Spike protein S1 subunit RBD also attaches to heparin and accelerates Aβ and tau aggregation in the human brain as a part of an innate immune response, leading to AD [19] (Fig. 2). Several studies suggest that Aβ may relate to an increase in developing AD among COVID-19 patients [20]. $Aβ_{1-42}$ strengthened the S protein S1 subunit to the ACE2 and enhanced viral entry [21]. Furthermore, the infection model of SARS-CoV-2 pseudovirus revealed IL-6 production [22]. The expression level of ACE2 is found high in AD patients. The ACE2 is also upregulated even in mild cases. Hence, SARS-CoV-2 infection results in a higher degree of viral entry into the brain in AD patients [23]. Tau is a microtubule-related protein abundant in neurons that forms insoluble filaments and accumulates as neurofibrillary tangles in AD-related tauopathies. Tau maintains the stability of microtubules in axons under physiological conditions. Recent work demonstrated neuron infection of 3D brain organoids model with SARS-CoV-2 and exhibits the SARS-CoV-2 infection enhanced Tau protein level in the somas of neurons [24].

3.3. Apolipoprotein E (ApoE) associates with increased risk of SARS-CoV-2 infection

Apolipoprotein E (ApoE) ε4 allele confers a gain of toxic functions and a genetic risk factor for the pathogenesis of AD. ApoE has also linked to increased risk of other neurodegeneration, such as dementia with Lewy bodies and Parkinson's disease dementia [25]. ApoEε4 also implicates a vital link with AD and SARS-CoV-2 infection (Table 1). Serum cholesterols can bind with the ApoE receptor and enhance the transport of the ACE2 receptor on the cell surface. High cholesterol levels facilitating two-fold SARS-CoV-2 entry appear in super-resolution imaging [26]. Interestingly, ApoE and ACE2 are expressed abundantly in alveolar type II cells. ApoE ε4 also governs the pro/anti-inflammatory state in macrophages [27]. Contrary, ApoE acts in link to Apolipoprotein C1 and ApoJ/clusterin. Thus, maintain the dendritic recognition, synaptic turnover, and myelin and neural membranes through cholesterol transports. ApoE works like an Aβ chaperone that transports Aβ to lysosomes. ApoE ε4 allele is increased and responsible for Aβ formation and deposition. Moreover, in vivo model findings of ApoE $ε4^{(+ve)}$ mice also increased tau protein accumulation [28]. People over 60 years carrying the ApoE ε4 allele have a higher chance of developing AD than
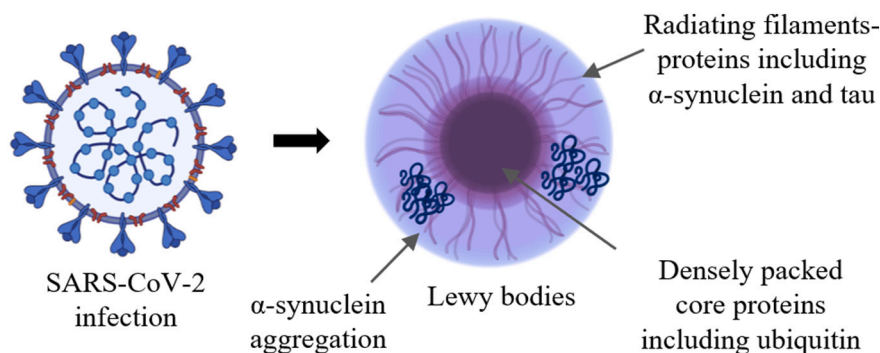
Fig. 1. Impact of SARS-CoV-2 on α-synuclein metabolism. SARS-CoV-2 infection exacerbates α-synuclein misfolding, aggregation, and interruption with α-synuclein clearance.
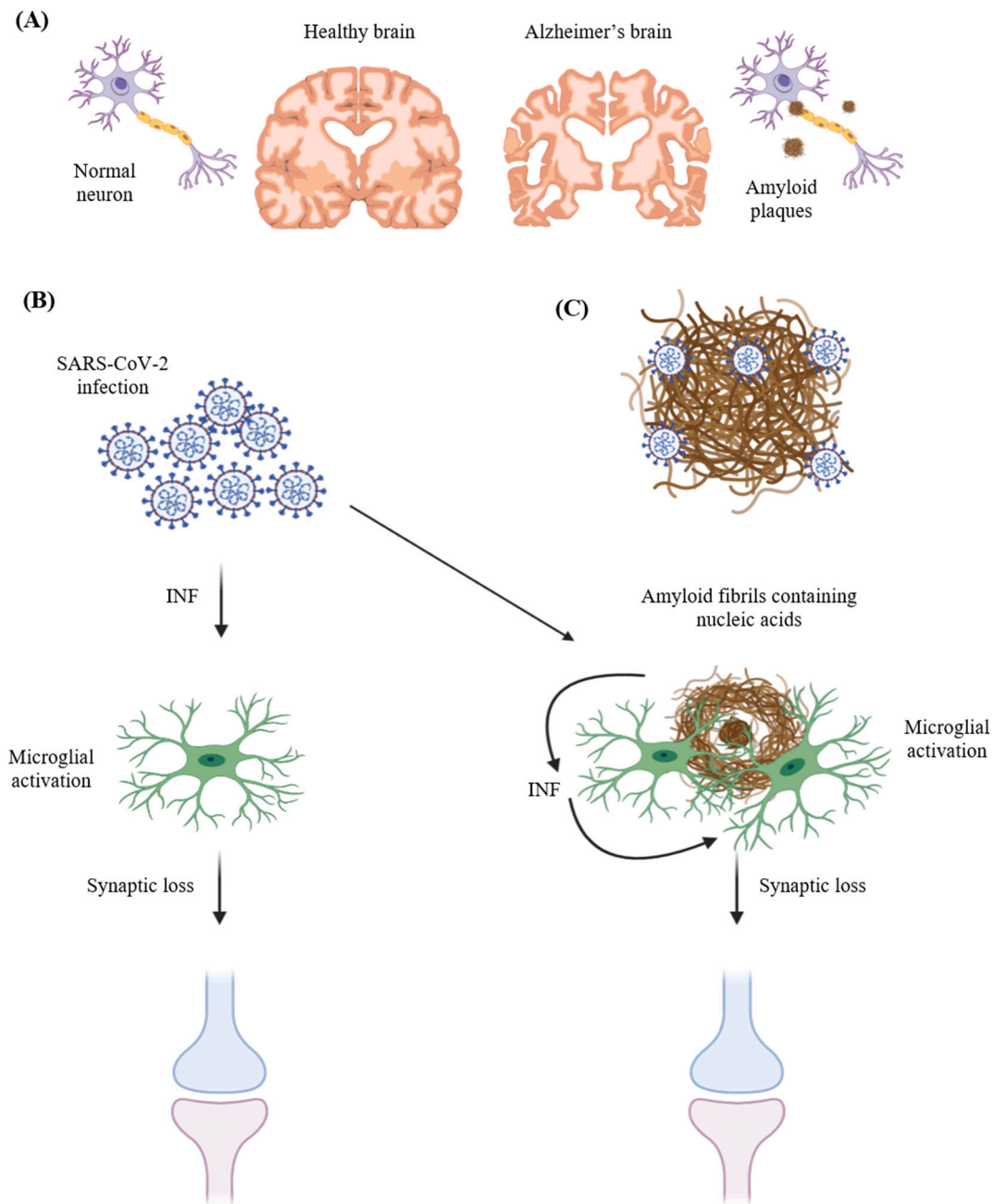
Fig. 2. Role of Amyloid-beta in Alzheimer's disease (AD) patient's infected by SARS-CoV-2. (A) Aβ is responsible for plaque formation in AD patients' neurons. (B) Potential Interactions between SARS-COV-2 infection and AD. Viral infection causes inflammation due to Type I IFN elevation. Synaptic loss occurs with nucleic acid-containing amyloid fibrils. (C) Aβ deposition further traps SARS-CoV clearance and may lead to further AD pathology.

PD, and a greater chance of SARS-CoV-2 infection leads to extensive immune cell production such as cytokine and chemokine caused inflammation. In addition, ApoE also significantly modulates the chance of developing PD. The stratified analysis revealed a positive PD progression history in the family. The ApoE has most dominated among the family members. Li et al. detected a positive and negative association between ApoE ε3 and ApoE ε4 with age at onset in PD [29].

3.4. SARS-CoV-2 infection and mitochondrial dysfunction

Mitochondria are inevitable cell organelles that play a particular role in the host's response to viral infection and immunity [30]. It also maintains normal cell function and cellular homeostasis. Cellular dysfunction and cell apoptosis or necrosis occur due to the impairment

of cell mitochondrial functions (Fig. 3). Reported evidence is in conjunction with the progression of different kinds of disease in COVID-19 patients. The hyper-inflammatory state is termed a "cytokine storm" involved in the systemic perturbations [31]. Mitochondria damage and the accumulation of mitochondrial DNA (mtDNA) induce significant changes in cellular physiology. Thus, macromolecules damage by reducing energy availability and enhancing the production of reactive oxygen species (ROS) [32]. Recent findings in human blood and tissue biopsies revealed that the heteroplasmy and mtDNA copy numbers provide the information for aging and age-related diseases based on mitochondrial functioning [33]. A direct connection has been observed between the mitochondrial dysfunction and PD, a vital component of the electron transport chain, mitochondrial complex 1, which caused energy depletion and subsequently dopaminergic cell death [34]. α-Synuclein

Table 1

The effects of cholesterol-binding protein Apolipoprotein E (ApoE ε4) in COVID-19 AD patients. SARS-CoV-2 infection increased amyloid beta deposition rather than clearance. Pro-inflammatory cytokines promote macrophages. BBB integrity and synaptic plasticity are decreasing. It also causes the misfolding of proteins accumulation.

	Increased	Decreased
Apolipoprotein E (ApoE ε4)	Amyloid beta deposition	Amyloid beta clearance Fatty acid delivery
	Promote pro-inflammatory condition in macrophages	
		Blood-brain barrier integrity
	Promoting misfolding protein accumulation	
		Synaptic plasticity
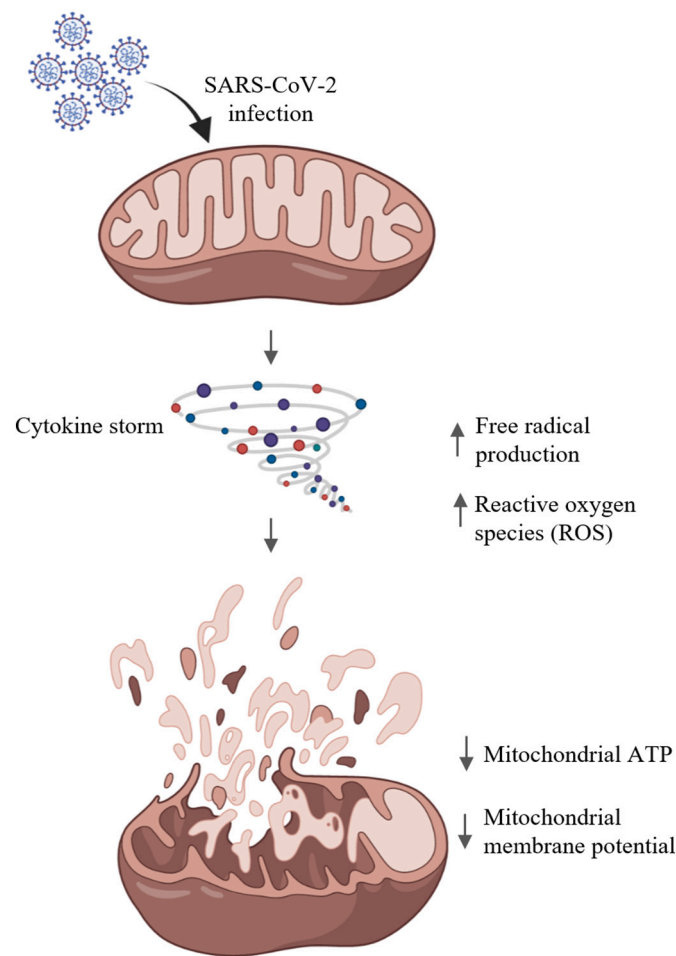
Fig. 3. Cytokine storms impact SARS-CoV-2 infection and mitochondrial function. Apoptosis initiates through viral RNA entry into the mitochondria. Cytokines production is combined with microglial activation and immune cells responsible for mitochondrial dysfunction.

accumulation in dopaminergic neurons due to their intrinsic properties selectively makes them vulnerable. Mitochondrial basal oxidative phosphorylation elevates due to high-level bioenergetic demand and proceeds to high axon terminal density. Axonal arborization and impairment of proteostasis also happen for an extensive axonal size [13]. Wu et al. findings help us understand the preferential localization of SARS-CoV-2 RNA into the mitochondria. Hence, the ROS generation increased due to the energy reduction and the functional impairment of

mitochondria. Dopaminergic neurons need a high amount of energy for cellular functioning. A spare energy reserve is inaccessible to maintain the cellular and bioenergetic stress of COVID-19 infection. Thus, the neurodegeneration threshold happens to the susceptible neurons [35]. ACE2 can cleave angiotensin 2 into angiotensin 1–7 and regulates mitochondrial functions [36]. Impairment of mitochondrial respiration was observed together with reducing ATP production in ACE2-knockout mice. ACE2 overexpression helps to recuperate the functional impairment of mitochondria. Another recent study reported insight into the pathological impact of spike protein on mitochondrial function in brain endothelial cells (ECs) [37]. The outcomes exerted the mitochondrial metabolic profile affected in brain ECs exposed to spike protein which explains the critical pathological role of spike protein in the brain ECs. It has been reported that the Open Reading Frame 9b (ORF-9b) of SARS-CoV that impairing proteostasis in mitochondria by inducing autophagy of the host cell [38]. However, such kind of evidence is still unclear for SARS-CoV-2.

4. Pathophysiology and cognitive impairment following viral infections

4.1. SARS-CoV-2 infection leads to neurological dysfunction

Few respiratory pathogens have been reported to access the nervous system, for instance, the influenza virus, the human metapneumovirus, respiratory syncytial virus, and Human coronaviruses (HCoVs) such as HCoV229E, HCoV-OC43, and SARS-CoV [39]. In the last couple of years, SARS-CoV-2 has been reported due to its potential neuroinvasion capability (Fig. 4). The cerebrovascular disorder is characterized by damage to brain tissues due to the disturbances of intracranial blood circulation [40]. Viral infections lead to vascular endothelial and system damage. Ultimately, a hyperactive inflammatory response caused hemorrhagic infarcts and ischemic. It is also responsible for vasculitis and thrombosis development [41]. It is also hard for the virus to the CNS penetration. CoVs neurotropism leads to invading the CNS [42]. Then it overreacts immune responses that induce meningitis and fatal encephalitis. Encephalitis occurs due to pathogen-induced inflammatory lesions. As known that immune cells and viruses can weaken the blood-brain barrier (BBB) and enters into brain. Nervous system infections imply the possibility of the COVID-19 patients related to neurological complications [43].

4.2. Invasive mechanisms of SARS-CoV-2 in the human nervous system

Two basic steps are responsible for SARS-CoV-2 entry into their host cell: First, the viral spike binds to the host cell membrane receptor and plasma membranes fusion. This process has been facilitated by ACE2 and TMPRSS2 receptors [44]. Second, envelope membrane fusion with the host cell endosome/lysosome. Spike protein presents on the virus surface, also known as Class I fusion protein, mediates viral attachment to the host cell membrane [45]. The spike protein can also attach to the cell membrane through Basigin [46] and Neuropilin-1 [47]. Basigin is a glycoprotein significantly found in the human brain. Contrary, Neuropilin-1 is a transmembrane receptor able to bind with furin cleaved substrate. It is also abundant in olfactory and respiratory epithelium. Neuropilin-1 co-expression in olfactory epithelium with other ACE2 and TMPRSS2 can potentiate SARS-CoV-2 entry in the brain. Cathepsin L, a lysosomal protease, may facilitate virus entry into their host cell. In vitro study suggested that Cathepsin L inhibitor can block the SARS-CoV-2 pseudovirus entry into hACE2 overexpressed HEK293 cells. Of note, cathepsin B-related inhibitor may not affect the virus entry [48]. The spike protein requires furin cleavage at the S1/S2, rendering less dependence on other host cell proteases for cell entry. Neurotropism appears in some CoVs with identical furin cleavage sites in spike protein [49]. A similar furin cleavage site is also present in SARS-CoV-2. Nerve tissues become susceptible due to the presence of
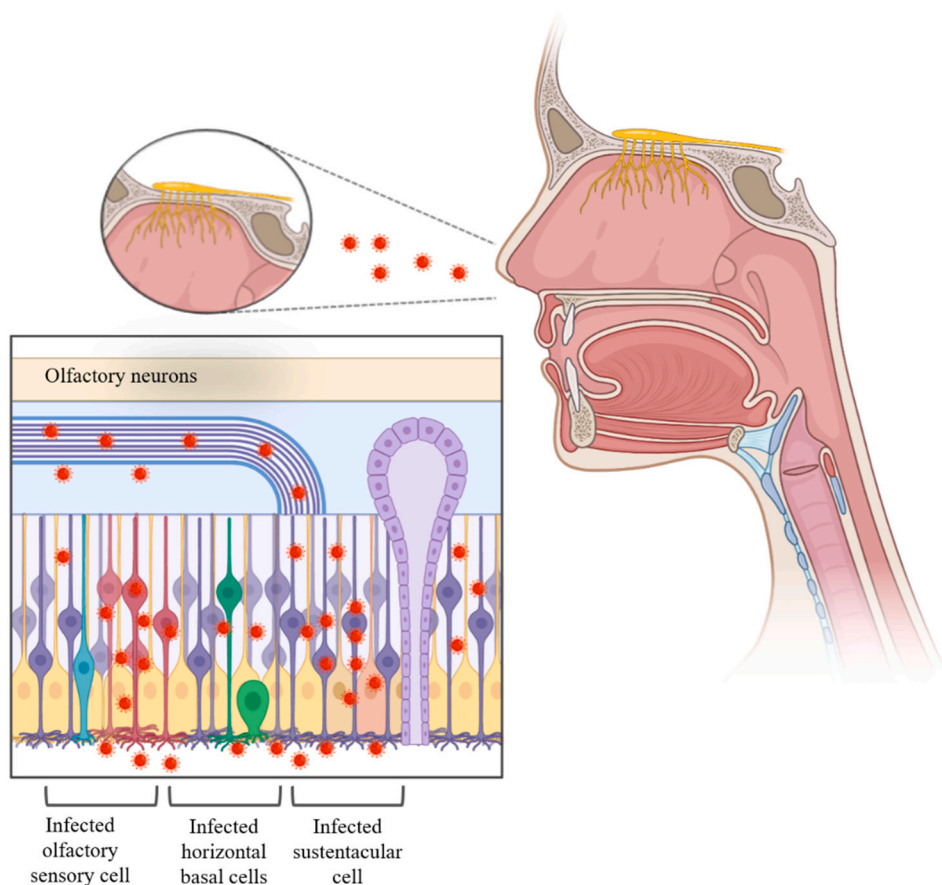
Fig. 4. SARS-CoV-2 invades the brain by targeting the olfactory nerve. SARS-CoV-2 binds to the ACE2 receptor expressed on the olfactory epithelium (OE) surface. The horizontal basal cells are connected with ACE2 receptors that are surrounded by the olfactory epithelium. The infected olfactory neurons and the olfactory bulb neurons have shared the synaptic connection. The myelin sheath of neurons may destroy by viruses and cytokine storm caused acute and chronic neuropathology.

these receptors and proteases.

4.3. Underlying molecular mechanisms of SARS-CoV-2-related neuronal injury

CNS compose of an intricate barrier system that defends the brain against the viral invasion. BBB, brain, and blood-cerebrospinal fluid barrier are included in this system. CoVs well reported that being able to reach out to the CNS caused neurovirulence [50]. The symptoms of smell loss are common in COVID-19 patients due to SARS-CoV-2 infecting the olfactory system of the brain [51]. Notwithstanding, the CoVs neuro-invading mechanism is not closely distinct. Previous findings stated that CoVs are neurovirulent, neurotropic, and neuroinvasive in animals and humans [52]. Earlier studies also reported that SARS-CoV reached out to the brain in a systemic infection model.

HCoVs can also significantly infect in vitro models of adult microglia, astrocytes, oligodendrocytes, and neural cells [53]. Neural invasion of SARS-CoV-2 particularly depends on the attachment of S protein S1 subunit to ACE2 present in neurons surface and TMPRSS2 for S protein priming [54]. According to biophysical studies, structural dissimilation in S protein RBD increased the binding affinity between SARS-CoV-2 and ACE2 receptor than other HCoVs [55]. ACE2 is also abundant in olfactory epitheliums, vascular endothelial, and tropism. For this reason, SARS-CoV-2 can infect vascular epithelial cells to cross the BBB and finally infect the CNS [56]. SARS-CoV-2 tropism was neither restricted to ACE2-expressing cells nor inclusive of some ACE2-positive cell lineages [57]. It has been observed that SARS-CoV-2 reaches the medulla oblongata and that brainstem infection may be involved in both respiratory failures in patients [58]. Ex vivo cultures also offer a unique opportunity to access the infected organ directly to observe early viral tropism [59]. MRI images showed a small ovoid lesion observed in the center of the splenium of the corpus callosum [60]. Another study reported that the ACE2 activity reduced in frontal cortex and increased parenchymal Aβ and Tau levels in hypothalamus of AD rats and in the mid-frontal cortex of AD patients [61]. SARS-CoV-2 follows a particular entry process initiated by the replication in the nerve terminal, then moves forward to the soma, thus invading the CNS. SARS-CoV-2 also can invade peripheral (trigeminal and vagus nerves) nerves. The synaptic connection via olfactory nerves may consider another mechanism by which SARS-CoV-2 directly enters the CNS [62]. Inflammation associated with SARS-CoV-2 infection can disrupt the BBB and allow the virus to enter the CNS [63].

4.4. Non-neuronal cells and their relationship with the alteration of the vascular endothelium

Earlier studies of HCoVs reported the ability of infection in neurons, non-neuronal or glial cells, astrocytes, and microglia in primary cultures. That suggests the SARS-CoV-2 may be able to use the brain as the reservoir and potentially develop neurodegenerative diseases [55]. Recent findings revealed that the expression of ACE2 in non-neuronal glial cells may become a potential target for the brain tissue during SARS-CoV-2 infection [64]. The evidence of SARS-CoV-2 RNA detection in non-neuronal cells in CNS indicates the possibility of CNS infection directly related to the vascular epithelium [65]. Glial cells of the CNS parenchyma autopsy cases reported that SARS-CoV-2 in the CNS endothelium might facilitate vascular damage and allow the virus to spread to other regions of the brain [66].

4.5. Olfactory nerve channels and trans-synaptic viral transfer

The olfactory pathway, an intranasal route is a crucial neuroinvasive point for respiratory virus entry [67]. This olfactory point seems possibly a mechanism or pathway of neuroinvasion for CoVs, including SARS-CoV-2 [68]. HCV-OC43 also follows a similar entry pattern to invade into the neuroepithelium and propagation at olfactory bulbs [69]. This research has mentioned that three days after intranasal inoculation of HCoV-OC43 was found in mice's olfactory bulb. The interface of neural mucosal is responsible for transmucosal viral entry to the nervous system. The main transport is happened by the olfactory tract of the CNS [70].

The trigeminal nerve also key transferred the process of SARS-CoV-2 to the CNS [71]. The trigeminal nerve exits in the conjunctiva through the sensory nerve ending. Zhang et al. confirmed the existence of SARS-CoV-2 RNA fragments in conjunctivitis patients [72]. Some RNA viruses can enter the CNS, for instance, the influenza virus usually uses sensory fiber of the vagus nerve [73]. Many scientific researchers have stated that SARS-CoV [74] and MERS-CoV [75] specifically infect the brain stem area. SARS-CoV-2 also follows the trans-synaptic transmission pattern to infect the brainstem from the respiratory system. Recent human brain organoids in vitro studies support the trans-synaptic transfer process where SARS-CoV-2 is found in neuronal soma and neurites [76].

4.6. Vascular endothelial cells of the blood-brain barrier (BBB) and immune cells

Several recognized neurotropic viruses caused the BBB disruption upon infection in CNS. Flaviviridae family, for instance, West Nile Virus [77] and the Zika virus [78], factors and the host cell's response may conduce BBB damage. SARS-CoV-2 could attach to the ACE2 receptors of endothelial cells when it enters the systemic circulation [79], disrupting the BBB, and causing CNS penetration with edema [67]. Earlier in vivo studies mentioned that MERS-CoV can penetrate the bloodstream and endothelial cells [80]. SARS-CoV-2 virus-like particles have been found in brain capillaries pericytes and can actively override the BBB [81]. In vitro, the blood-vessel organoids model also elicited SARS-CoV-2 invasion of brain endothelial cells and allowed for replication in the brain [82]. A review study also mentioned the COVID-19 patients' postmortem examination report where SARS-CoV-2 was found in frontal lobe tissue in brain microvascular endothelial cells [83]. Hence, multiple mechanisms affect BBB integrity during SARS-CoV-2 infection. The virus leads to a cytotoxic effect in infected cells and induces apoptosis through direct cell stress [84]. This evidence indicates that SARS-CoV-2 can cross the BBB and other HCoV.

5. Immune response for SARS-CoV-2 infection

5.1. COVID 19 and neuroimmunology disorders

Encephalitis, seizures, Guillain-Barre syndrome, and several other neurological symptoms have been characterized by COVID-19 infection [85]. High levels of systemic inflammation in the brain are a fundamental aspect of SARS-CoV-2 infection, responsible for chemokine and cytokines released with other inflammatory signals. That exacerbates neuroinflammation by significant BBB disruption [86]. This neuroinflammation has been promoted by disrupting brain hemostasis and subsequently leading to neuronal apoptosis [87]. Thus, neuroinflammation plays a critical role in functional brain damage. Clinical experience of over for behavior-associated cognitive impairments. Systemic inflammation is also responsible for abnormal neurobehavior, for example, cognitive deficits and delirium. Another side, prolonged hypoxia induces uncontrolled neuroinflammation [88].

### 5.2. The immunopathobiology of SARS-CoV-2 infection

Few viral particles are moving into systemic circulation during some viral infections. It can act through pathogen-associated molecular patterns. The infection often executes tissue damage. Indirect brain damage also occurs due to an immune reaction. In severe cases, this pattern affects the functioning. Breathing center and respiration developed due to the brainstem infection [89]. It further damages the vital part of the brain responsible for brain function, including the neocortex, hippocampus, and cerebellum [90]. Triggering the cytokine storm among COVID-19 patients is a high risk to other organs. High titers of cytokines (IL-2, IL-6, IL-8, IL-17, IL-β), TNF, granulocyte-macrophage colony-stimulating (GM-CSF) factor, interferon gamma-induced protein 10 appeared in COVID-19 patients. The IL-6 and TNF levels indicate the disease severity in COVID-19 [91]. Many secondary responses that occur after SARS-CoV-2 infection may affect neural tissue function due to the unprecedented level of the immune response. It may affect the neuron with either hemorrhagic damage or necrotizing. Such possibility included the Guillain-Barre Syndrome in patients with COVID-19 [92].

5.3. Neuroinflammation-mediated association between neuro COVID-19

Aged people increase a higher chance of SARS-CoV-2 neuro invasion by disrupting BBB. Acceleration of motor and cognitive deterioration due to the infection is considered an aggravation of neuropathological states. Usually, the general conditions, the patients with PD and AD need sufficient care and are recumbent to infections or diseases (Fig. 5). The vulnerability of patients has significantly increased in the ongoing COVID-19 pandemic. Patients are also directly dependent on this healthcare system. Host body triggered IFNs in response to viral infections. In the aspect of AD pathology, the amyloid fibrils upregulate specific gene expressions that are responsible for IFN production. IFN also causes microglia activation with amyloid plaques and stimulates a pro-inflammatory response. Furthermore, INF also activates the complement cascade that causes synapse degeneration [93]. Therefore, aged people get vulnerable to severe COVID-19 infection.

5.4. Plasma level of immune cells (cytokines and chemokines)

The "cytokine storm" is known as uncontrolled cytokines released and immune response dysregulation to a different antigen, such as infections. Usually causes dysfunction of multiple organs. The pattern of cytokine storm is slightly different in COVID-19 patients than in patients with other infections. The severe illness with a high level of proinflammatory cytokines in plasma was observed in COVID-19 patients, especially interleukin (IL) 6, compared to a moderately sick patient [94]. Several clinical studies and cases have reported that SARS-CoV-2 infection increased the cytokines in COVID-19 patients. For instance, pro-inflammatory cytokines including IL-1β, IL-6, IL-8, IL-12, IL-18, IL-33, granulocyte colony-stimulating factor (G-CSF), monocyte chemo-attractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), TNF-α, transforming growth factor (TGF)-β, IFN-α, IFN-β, IFN-γ, and anti-inflammatory cytokines IL-2, IL-4, IL-10 [95]. SARS-CoV-2 also caused the activation of immune effector cells in COVID-19 patients that release chemokines, such as C-C motif chemokine ligand (CCL)-2, CCL3, CCL5, CCL7, CCL12, C-X-C motif chemokine ligand (CXCL)-8, CXCL9, CXCL10, IFN-γ induced protein 10. Severely ill COVID-19 patients exhibit excessive levels of proinflammatory cytokines than non-severe patients [96]. The connection has been linked to the disease's severity along with the cytokine's upregulation and systemic inflammation. Generally, cytokines recruit the pro-inflammatory cells and induce the infiltration rate. As mentioned above, amyloid fibrils are responsible for interferon expression and are also involved in the innate immune response [97]. AD patients have also reported a high level of interferon-induced genes [98]. Microglia polarization is a target of multiple studies involving nerve cell preservation in diseases caused
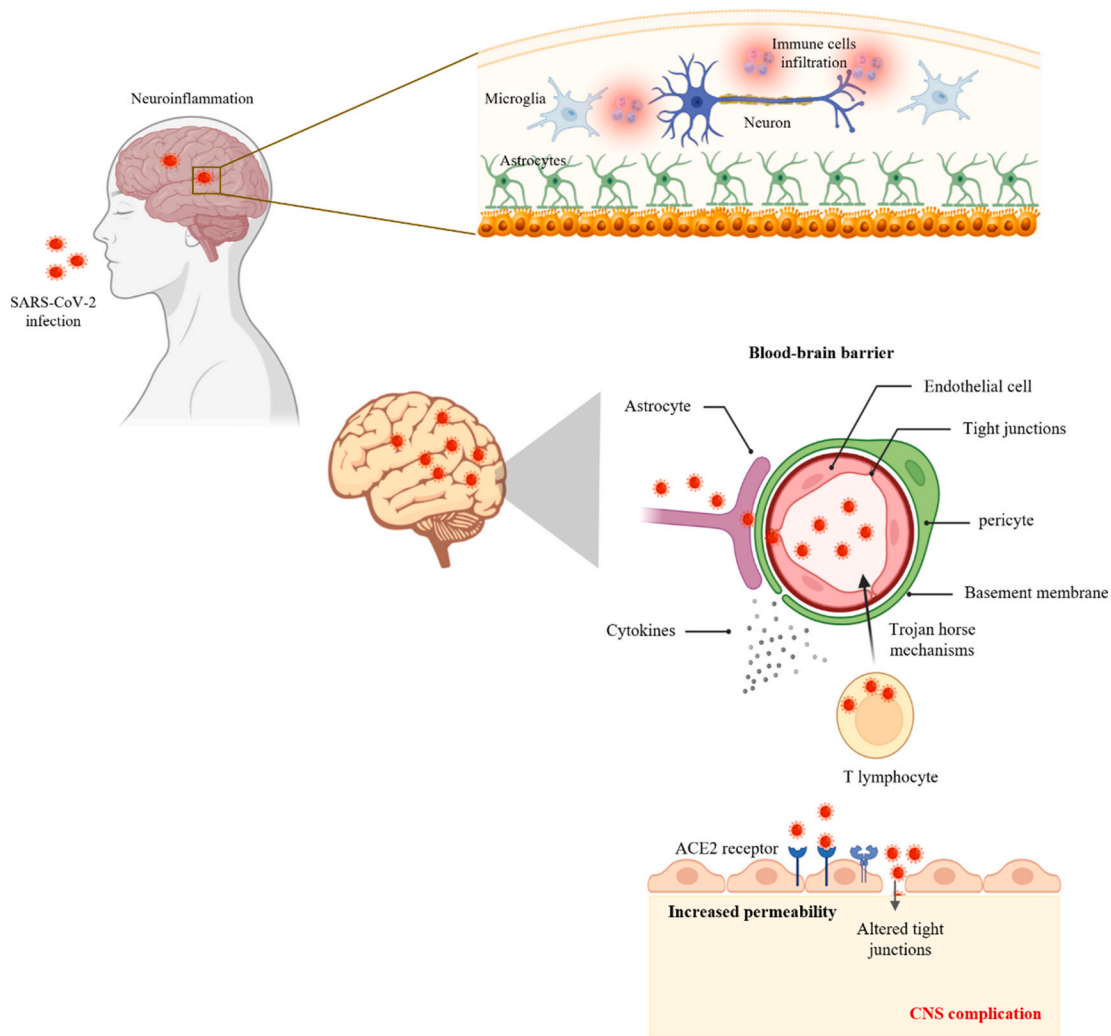
Fig. 5. SARS-CoV-2 directly enters into CNS through endocytosis and enhances the vascular permeability with the assistance of inflammatory cytokines or indirect transfer via a Trojan 'horse' mechanism. Viral particles in the bloodstream can cross the blood-brain barrier (BBB) by infecting brain microvascular endothelial cells. The infection is targeted by neurons that increase the BBB permeability which is responsible for severe neurological symptoms in COVID-19.

or aggravated by neuroinflammation. In response to viral infection, microglia are activated and polarized into the proinflammatory M1 phenotype or the anti-inflammatory M2 phenotype [99]. Earlier studies proposed that M1 and M2 microglia polarization is of key relevance for the control of viral encephalitis [100]. To assess the effects of SARS-CoV-2 infection on microglial activation and polarization in human microglial clone 3 (HMC3), we analyzed the DEGs associated with immune response and microglial polarization. SARS-CoV-2 infection, HMC3 was activated and polarized into the inflammatory M1 phenotype, producing proinflammatory cytokines [101]. Rely on the clinical evidence, pathogens like SARS-CoV-2 may be captured by amyloid fibrils and trigger a pro-inflammatory response with microglia activation (Table 2).

6. Long-term neurological impacts of COVID-19

Overwhelming COVID-19 patients are expected to recover among the most at-risk population. The neurological impacts are always negligible compared to the potential long-term lung damage. The long-term neurological events and outcomes of COVID-19 infection are still unknown [98]. Nevertheless, many reports related the symptoms remain even a month after the infection, including impaired smell and/ or taste, impaired cognition, and chronic fatigue. SARS-CoV-2 delta variant, also known as B.1.617.2 or Indian variant, quickly ramps up globally. It has been reported that severe infection ability of delta

Table 2
Cytokine storm in SARS-CoV-2 infection. SARS-CoV-2 infection increased levels of cytokines and chemokines. Moderate symptoms patients found in slightly more or remain the same levels. However, it found high level in severe COVID-19 cases.

	Cytokines	Chemokines
Pro- or anti-inflammatory factors	IL-1β	CCL 2
	IL-2R	CCL 3
	IL-6	CCL 5
	IL-8	CCL 7
	IL-10	CCL 12
	IL-12	CXCL 8
	IL-18	CXCL 9
	IL-33	CXCL 10
	TNF- α	

variant caused myalgias, loss of taste, loss of smell, fatigue, and rhinorrhea [102]. No good enough study exists to date that deciphers the pathophysiological mechanisms of COVID-19 infection [103]. The cerebellum and brainstem are two of the main areas of normal brain function that are affected during SARS-CoV-2 infections leading to activated neuroinflammatory and apoptotic cascades during acute COVID-19 infection [104]. A neuronal degeneration has been demonstrated as decreased level in glucose metabolism in long COVID patients

and may attribute to oxidative stress and mitochondrial dysfunction [105]. Direct intervention to alleviate long-term neuropsychiatric symptoms may help to understand the molecular and cellular aspects of COVID-19 brain damage [106]. Behavioral sequelae and emotional status may mitigate disease burden in long-term post-COVID-19 cognitive. Indeed, the concern about patients with lower immunity makes them more susceptible to COVID-19. If we can understand the neuropathology of COVID-19 and decipher neurodegenerative processes, that may open up new treatment strategies may develop that are related to neuroinflammation in other brain diseases. A long-term COVID-19 impact on cognition has only demonstrated the severe COVID-19 infection. A low number of T cells are debilitating in severe cases with elevated inflammatory cytokines levels. COVID-19 patients were found below the optimum levels of helper T cells and suppressor T cells. The percentage of memory helper and regulatory T cells may also decrease in severe conditions of COVID-19. A clinical study observed that among 310 patients with new neurological symptoms after COVID-19 were higher levels of neuropeptides and the C-reactive proteins in their blood, a plasma protein produced by the liver and primarily used as an indicator of inflammation. Some reasons are abaft for cognitive impairment after COVID-19 recovery [107]. Alter the bioenergetics of infected brain cells from the normal neuronal metabolism that supports the SARS-CoV-2 replication [108]. Target the mitochondria by viral infection emergence the cognitive impairment. Earlier research has elucidated that redirecting mitochondrial activity is identical during Ebola, Zika, and Influenza A virus infections [109]. Long-term cognitive outcomes will appear with the unfolding of the ongoing pandemic situation. The premature onset of dementia progresses anticipated a cognitive decline last for months among aged patients [110].

7. Conclusion

An unprecedented crisis surges among aged people in the COVID-19 pandemic. The lesson of COVID-19 we have learned in a broad spectrum of neurological disorders and immune responses has appeared to be unpredictable conditions in aged patients. Despite recent advances in understanding long-term complications after acute infectious diseases, the pathogenesis and immune response of these late effects are still unknown. In viral infections linked with neurodegenerative disorders such as PD and AD patients, causative mechanisms have never been demonstrated. The long-term neurological effects must be reconsidered on COVID-19 patients after recovering from the acute phase of the infection. The current analysis suggests us the pathophysiology and immunological response of COVID-19 will have a long-term effect on patients with neurological diseases. However, longitudinal studies would be beneficial to debunk this link.

CRediT authorship contribution statement

MSAM designed and revised the manuscript. PCH wrote and improved the English spelling. PCH and MSAM contributed to figures. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that they have no conflict of interest.

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