Pathophysiological Clues to How the Emergent SARS-CoV-2 Can Potentially Increase the Susceptibility to Neurodegeneration

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Abstract

Along with emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, a myriad of neurologic symptoms, associated with structural brain changes, were reported. In this paper, we provide evidence to critically discuss the claim that the survived patients could possibly be at increased risk for neurodegenerative diseases via various mechanisms. This virus can directly invade the brain through olfactory bulb, retrograde axonal transport from peripheral nerve endings, or via hematogenous or lymphatic routes. Infection of the neurons along with peripheral leukocytes activation results in pro-inflammatory cytokine increment, rendering the brain to neurodegenerative changes. Also, occupation of the angiotensin-converting enzyme 2 (ACE-2) with the virus may lead to a decline in ACE-2 activity, which acts as a neuroprotective factor. Furthermore, acute respiratory distress syndrome (ARDS) and septicemia induce hypoxemia and hypoperfusion, which are locally exacerbated due to the hypercoagulable state and micro-thrombosis in brain vessels, leading to oxidative stress and neurodegeneration. Common risk factors for COVID-19 and neurodegenerative diseases, such as metabolic risk factors, genetic predispositions, and even gut microbiota dysbiosis, can contribute to higher occurrence of neurodegenerative diseases in COVID-19 survivors. However, it should be considered that severity of the infection, the extent of neurologic symptoms, and the persistence of viral infection consequences are major determinants of this association. Importantly, whether this pandemic will increase the overall incidence of neurodegeneration is not clear, as a high percentage of patients with severe form of COVID-19 might probably not survive enough to develop neurodegenerative diseases.

Keywords COVID-19 · Neurodegeneration · Alzheimer disease · Parkinson disease · ACE-2

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Introduction

In December 2019, a novel coronavirus causing severe acute respiratory syndrome (SARS), shortly named SARS coronavirus 2 (SARS-CoV-2), emerged in China. Until now, this outbreak has been accompanied by a high burden on physical health as well as causing a lot of social, economic and political distress, all over the world [1]. The long-term consequences of the virus, including its effects on physical health, however, might be a way more serious threat to the world. Importantly, this viral infection can cause or even present with neurologic symptoms such as cerebrovascular accident, impaired consciousness, confusion, agitation, seizure, ataxia, headache, anosmia, ageusia, neuropathies, and encephalitis or encephalopathy [2–5]. In addition, brain structural changes associated with COVID-19 have been confirmed by imaging techniques, both in both surviving patients and non-survivors [6, 7]. Furthermore, based on the evidence for invasion of the virus to the CNS, it has been speculated that different levels of respiratory distress observed in SARS-CoV-2 infection, could be attributed to the effects of the

virus on the nervous system [8–10]. There is some evidence that human corona viruses can remain latent in the neuronal cell lines [11] and it has been demonstrated that COVID-19 is associated with widespread gene expression changes in the brain, highlighting its long-standing and extensive effects on neurologic function [12]. Thus, apart from the neurologic symptoms in acute phase of infection with the virus, the long-term neurologic sequelae of SARS-CoV-2, for instance neurodegenerative diseases, are of great importance [5].

Neurodegenerative diseases, a group of neurologic diseases characterized by demise of neurons mostly occurring in old age, cause a major burden due to high rates of disability and mortality [13, 14]. A myriad of factors from genetic predispositions to metabolic and environmental risk factors, via various mechanisms including misfolded protein accumulation, impairments in autophagy, mitochondrial dysfunction, neuronal apoptosis, and synaptic impairment, as well as oxidative stress and neuroinflammation contribute to demise of specific neurons in CNS, constituting the pathophysiology of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [15, 16].

Coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV [17] as well as coronavirus disease 2019 (COVID-19) [10] have been shown to cause neurologic disorders after resolution of infection. For instance, it has been determined that viral infections can be associated with some chronic neurological sequelae known as postencephalitic parkinsonism following encephalitis lethargica, which is marked by a set of extrapyramidal symptoms and pathological alterations in substantia nigra and other subcortical nuclei. This entity was first described following influenza pandemics in 1918, but there is no report of such sequelae for human corona virus outbreaks, although there is some indirect evidence for involvement of Corona virus infections in neurodegenerative diseases [18, 19]. Furthermore, human corona virus (HCoV) infection along with other respiratory virus infections such as influenza virus is shown to spread throughout CNS especially temporal region and hippocampus associated with learning/cognitive changes [20]. Whether this hippocampal damage might perpetuate neurodegenerative changes is not clear but AD-specific tau pathology following viral infection-related inflammation associated with cognitive impairments has been confirmed in animal studies [21].

Even ignoring the potential consequences of invasion of the virus to the CNS, COVID-19 is associated with a noticeable increment in inflammatory cytokines which are suggested to lead to a cascade of deleterious mechanisms contributing to neurodegeneration [22]. In addition to direct invasion of the virus to the nervous system and the inflammatory reactions resulting from viral infection, various other mechanisms such as the neuroendocrine axis, cytokine storm, metabolic changes, gut microbiome changes, and hypoperfusion as well as the common underlying risk factors in patients afflicted with

SARS-CoV-2 may contribute to the acceleration of neurodegenerative processes. In this article, we aim to revisit the possible pathomechanisms that may contribute to susceptibility to neurodegeneration, especially Alzheimer's disease and Parkinson's disease, in patients afflicted with this virus (summarized in Table 1). This might pave the way for designing therapeutic interventions in the future to prevent neurodegeneration in these patients.

Direct or Indirect Penetration to CNS: Neuroinvasive Potential

It has been revealed that SARS-CoV-2 can invade human cells through interaction between the virus S1 spike protein and angiotensin-converting enzyme-2 (ACE-2), which is abundantly expressed in multiple brain tissues [73]. Previously, it was shown that SARS-CoV mRNA, which similarly binds to ACE-2, could be found in brain tissue of the patients infected with this virus [74]. On the whole, the differential levels of respiratory distress, the observed neurologic symptoms in some patients, and structural brain changes in patients have been suggested as clues to the neuroinvasive potential of virus [3, 6–10, 75], although some studies based on CSF analysis, and neuroimaging evidence suggest that neuroinvasion is less likely to be responsible for encephalopathy [37].

Multiple routes have been suggested for SARS-CoV-2 entry into CNS [2, 76]:

1) Interaction of the SARS-CoV-2 with ACE-2 receptor in the capillary endothelium could result in endotheliitis [77] and thereby invasion of the virus into CNS through the destroyed Blood-brain barrier (BBB) could be facilitated. Consistent with this hypothesis, virus RNA and markers of intrathecal inflammation in cerebrospinal fluid (CSF) of patients with COVID-19 infection have been detected [78, 79].

2) Another route proposed for virus entry is hematogenous spread of the virus or its dissemination through lymphatics [80]. Until recently, the commonly held opinion was that brain does not possess characteristic lymphatic drainage, but Loveau et al. (2015) have shown that there exist some lymphatic vessels in the brain which could constitute a proper route for SARS-CoV-2 entry into the brain [23]. In fact, post-mortem studies have revealed that endothelial cells of various tissues could be infected with the virus and the resultant endotheliitis could facilitate virus dissemination through lymphatics and blood vessels resulting in meningitis/encephalitis [77].

3) According to the high rates of anosmia and ageusia observed in patients afflicted with SARS-CoV-2, and its persistence even after recovery from infection in a portion of patients, it has been suggested that SARS-CoV-2 can penetrate nervous system via olfactory bulb, be further

Table 1 Summary of the mechanisms and risk factors linking COVID-19 infection and neurodegenerative diseases

Mechanism/risk factors involved in PD/AD/both pathophysiology	Evidence for mechanism/risk factor in COVID-19	Evidence for mechanism/risk factor in PD/AD/both
Olfactory bulb involvement	- Smell impairment in COVID-19 [2, 23] even after recovery from infection [24]. - Olfactory bulb asymmetry detected on post-mortem MRIs [6]. - Invasion of the virus into brain through of ACE-2 and TMPRSS receptors in glia in brain cortex and olfactory bulb [25–28].	- Anosmia and olfactory bulb involvement revealed by imaging in both AD and PD [29–31] - Expression of ACE-2 and TMPRSS receptors in glia in olfactory bulb, substantia nigra, and cerebral cortex, the areas involved in PD and AD [25–28].
Cytokine production	- Increased IL-6, IL-8, IL-10, and TNF-α was detected in COVID-19 patients with meningoencephalitis [32].	-Increased IL-1β in AD patients compared to controls, and higher IL-6 in PD patients compared to controls, as well as increased TNF-α has been detected [33, 34].
Microglial activation	- SARS-CoV-2 open reading frame 3a (ORF-3a) protein stimulates NLRP3 inflammasomes, thereby accelerates the microglial activation [35, 36]. - Due the BBB breakdown in viral infections, monocytes can penetrate BBB [37]. - Severe microglial activation in post-mortem COVID-19 infection [38, 39].	-Microglial activation aggravates neurodegeneration in AD and PD [40, 41]. - NLRP3 inflammasomes play a role in microglia- mediated IL-1β release in AD [42] and chronic inflammation in PD can induce mitochondrial dysfunction through NLRP3 inflammosome [43].
T cell infiltration	- Mild perivascular infiltration of T cells was noted in post-mortem CNS analysis of patients who died of COVID-19 infection [38, 39].	- CNS-infiltrating CD4+ and CD8+ cells in close contact to blood vessels or in the vicinity of melanized DA neurons in the SN in PD were detected [44]. - T cells were found in the hippocampus of AD patients with an increased number of CD8+ cells compared to CD4+ cells [45].
Oxidative stress	- SARS-CoV-2 can cause ARDS and the resultant hypoxia due to ARDS as well as hypercoagulation and thrombosis can cause oxidative stress which is associated with RONS production and the consequent organ injury [5].	- Evidence of greater α-synuclein aggregation in PD [46], and higher beta-amyloid peptide accumulation in AD [47] in response to oxidative stress, through neuroinflammation and other mechanisms.
ACE axis imbalance	- ACE-2 acts as a receptor for SARS-CoV-2 spike protein, allowing its entry to cells [48]. Binding of SARS-CoV-2 to ACE-2 can result in ACE-2 depletion, which can aggravate multiple organ injury, through downregulating ACE-2/Angiotensin (1-7)/Mas axis [49].	- ACE-2 activity is reduced in AD and is an important regulator of the central classical ACE-1/Ang II/AT1R axis of RAS [50]. - ACE-2/Ang 1-7/Mas axis can protect neurons against neurodegenerative mechanisms [51].
Gut microbiota	- Alteration of gut microbiota composition, known as gut microbiome dysbiosis has been detected in Covid-19 patients [52, 53].	- The increased permeability of intestine and BBB induced by gut microbiota dysbiosis disturbance is involved in development of neurodegenerative disorders [54].
Amyloid-beta/tau/alpha-synuclein accumulation	- SARS-CoV spike protein can hijack protein machinery in endoplasmic reticulum and promote unfolded protein response and accumulation of misfolded proteins [55]. - Impaired proteostasis in SARS-CoV infection due to interactions of ORF-9b [56].	- Accumulation of misfolded proteins, such as Amyloid-beta and tau accumulation in AD and alpha-synuclein accumulation in PD, due to impaired proteostasis is the mainstay of neurodegenerative diseases [57].
Synaptic dysfunction	- In SARS-CoV infection IFN-α and IFN-β have been shown to be effective in limiting virus reproduction [58].	- IFN activates microglia and stimulates a pro-inflammatory response and promotes synapse elimination [59].
Mitochondrial dysfunction	- SARS-CoV ORF-9b of SARS-CoV induces autophagy of the host cell, as well as inducing ubiquitination, and impairing proteostasis in mitochondria [56].	- Mitochondrial dysfunction, impaired proteostasis, autophagy and lysosomal dysfunction are involved in pathophysiology of neurodegenerative diseases [60].
ApoE e4 allele	- Serum cholesterols bind to ApoE receptors and induce ACE-2 receptor transport to the cell surface [61]. - ApoE e4e4 genotype acts as a risk factor for severe SARS-CoV-2 infection [62, 63].	- ApoE e4 increases the risk for AD nearly 14-fold by increasing formation and deposition of beta-amyloid, and tau aggregates and disrupting dendritic spine formation and synaptic plasticity [64].
Metabolic syndrome/ factors	- Obesity and metabolic syndrome increase the susceptibility for affliction with this infection [65]. - Metabolic consequences following SARS-CoV has been reported [66].	- Obesity, metabolic syndrome, lipid metabolism alterations and diabetes mellitus increase the risk for developing neurodegenerative disorders through multiple mechanisms [67].

Table 1 (continued)

Mechanism/risk factors involved in PD/AD/both pathophysiology	Evidence for mechanism/risk factor in COVID-19	Evidence for mechanism/risk factor in PD/AD/both
HPA axis abnormalities	- Cytokine production in acute phase of SARS-CoV-2 can potentially stimulate HPA axis [68, 69].	- Higher cortisol levels can enhance tau hyperphosphorylation, apoptosis, synaptic loss and mitochondrial dysfunction [70].
Delayed autoimmune response	- SARS-CoV-2 may remain latent in neurons [11] and autoimmune responses against SARS-CoV-2 can cause autoimmune neurologic entities [10] [71].	-Autoimmune mechanisms can promote neuroinflammation and anti-CoV antibodies have been identified in CSF of individuals with Parkinson's disease [72].

Abbreviations: *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *SARS-CoV*, severe acute respiratory syndrome coronavirus; *RONS*, reactive oxygen and nitrogen species; *HPA*, hypothalamic-pituitary-adrenal; *BBB*, blood-brain barrier; *CNS*, central nervous system; *ACE-2*, angiotensin-converting enzyme 2; *ACE-1*, angiotensin-converting enzyme 1; *Ang II*, angiotensin 2; *Ang 1-7*, angiotensin 1-7; *ORF-9b*, open reading frame 9b; *ORF-3a*, open reading frame 3a; *IFN*, interferon; *TNF-α*, tumor necrosis factor alpha; *IL-6*, interleukin-6; *IL-8*, interleukin 8; *IL-10*, interleukin 10; *IL-1β*, interleukin 1 beta; *NLRP3*, NOD-like receptor protein 3

disseminated throughout the brain via axonal transport [2, 81]. Additionally, evidence of olfactory bulb asymmetry in a post-mortem brain MRI study on COVID-19 patients was observed [6], although a recent study has suggested that anosmia in COVID-19 patient results from transient edema of olfactory cleft [82]. As ACE-2 and transmembrane serine protease 2 (TRPMSS2), the putative receptors for the virus, are widely expressed on olfactory epithelium a recent study on human olfactory neurons has suggested that virus entry to olfactory neurons occurs via TRPMSS2 receptor, as its expression has been upregulated in olfactory neurons infected with the virus [29]. On the other hand, olfaction dysfunction and structural changes in olfaction-associated areas is an early observation in neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) [24, 30, 31]. Importantly, persistent hyposmia after recovery from COVID-19 is prevalent among patients with this infection especially in older patients [25]. Accordingly, although the mechanism for post-viral hyposmia is poorly understood [25], but due to expression of both ACE2 and TMPRSS2 in the oligodendrocyte precursor cells and the astrocytes in the substantia nigra, ventricles, and cortex as well as in olfactory bulb pericytes [26–28, 83], it has been suggested to be potentially an early sign of Parkinson's or Alzheimer's disease [2]. Clinically, this fact might necessitate caution regarding differential diagnosis of anosmia in otherwise asymptomatic patients diagnosed with COVID-19. Mechanistically, the potential of olfactory bulb as a route of virus entry, the probable pathophysiologic changes associated with neurodegenerative diseases, like neuroinflammatory processes or changes in neuronal protein machinery, and the relationship between these conditions should be addressed by further research.

4) Sensory neurons and dorsal root ganglion (DRG) neurons can express ACE-2, as well as other virus receptors such as TMPRSS2 and FURIN [84]. As well, SARS-CoV-2 may find way to the brain through free nerve terminals at the external layers of skin or epithelium of luminal organs [85]. Enteric nervous system and vagus nerve is also considered a potential route of virus entry, compatible with gastrointestinal symptoms observed in patients [86]. Similarly, Parkinson's disease α-synuclein pathology has been suggested to follow the same pattern of progression, starting from enteric nervous system [87].

Once the virus enters the nervous system, it can bind to the widely expressed ACE-2 in brain tissue and disseminate throughout the brain. As an example, post-mortem electron microscopy performed by Paniz-Monodolfi et al. (2020) on patients with COVID-19 has revealed presence of the virus in the frontal lobe [88]. Importantly, SARS-CoV has been shown to lead to death of neurons in infected mice without causing encephalitis [89]. As well, recently, widespread brain transcriptional changes associated with COVID-19 have been detected [12]. As stated earlier, HCoV infection as well as other respiratory infections, can get disseminated across brain especially temporal and hippocampal regions and there is evidence of AD-specific pathology in hippocampal regions in animal models with viral infections although it is not clear whether it is the result of inflammation or direct viral infiltration [20, 21]. Furthermore, according to Braak hypothesis and staging system in PD, disease-specific pathologic changes in brain regions of patients with PD occur in a characteristic order, starting from enteric nervous system and/or olfactory bulb and then extended through limbic system and cerebral cortices, although this pattern is not universal and there are some controversies over it [87], which is almost consistent with the proposed mechanisms for invasion of the virus.

Cytokine Storm: Neuroimmune Mechanisms

Although there has been a report on SARS-CoV-2 detection in CSF [78], in two reported cases of severe SARS-CoV-2

meningoencephalitis, viral RNA was not detectable, which may be suggestive of transient or undetectable amounts of viral RNA in CNS [90, 91]. On the other hand, cytokine storm, the noticeable increment in circulating levels of cytokines, has been considered one of the main mechanisms responsible for SARS-CoV-2-induced damage to the lungs and death, similar to other members of HCoV family. Upregulation in levels of pro-inflammatory cytokines including interleukin-6 (IL-6) has been detected in patients with COVID-19, especially those with more severe disease [32, 92]. This observation might raise the question that whether it is the peripheral inflammation, rather than direct viral infiltration, that leads to severe meningoencephalitis or other neurologic symptoms. Consistently, high levels of cytokines such as Intelukin-6 (IL-6), IL-8, IL-10, and Tumor Necrosis Factor alpha (TNF-α) as well as positive anti-S1 IgM have been detected in three cases of COVID-19 meningoencephalitis [93]. Indeed, high levels of peripheral cytokines can pass BBB directly and initiate neuroinflammatory reactions or compromise BBB integrity allowing permeation of virus-infected peripheral white blood cells and especially monocytes leading to uncontrolled production of cytokines, microglial activation and neuroinflammation [33, 94]. Immune response dysregulation, on the other hand, is recognized as a main mechanism involved in pathophysiology of neurodegenerative diseases and increment in levels of pro-inflammatory cytokines such as IL-1β and IL-6 is observable in these patients [34, 95]. Although it is not clear whether neuroinflammation can be a trigger for neurodegenerative processes but it has been shown that it can at least accelerate these mechanisms and lead to promotion of neurodegeneration in patients at preclinical stages [95]. Furthermore, it has been revealed that systemic inflammation marked by high cytokine levels can contribute to subsequent hippocampal atrophy, as observed in severe sepsis [96, 97]. Indeed, increased levels of pro-inflammatory cytokines, increase BBB permeability to both cytokines and peripheral leukocytes infected/activated by the virus, which activate resident brain microglia and promote their maturation into the M1 neurotoxic phenotype [40]. This persistent microglial activation can further activate other microglia, promote oxidative stress, propagate tau hyperphosphorylation and protein aggregation, and lead to mitochondrial dysfunction and apoptosis, as well as impairing synaptic plasticity and neurotransmission [41, 98]. Additionally, cytokines resulting from infection, by reaching the brain, can alter synthesis of dopamine, and potentially increase the susceptibility to PD [58]. In cases of SARS-CoV-2, an increased number of CD8 T cells producing interferons including IFN-γ were reported [93], and in SARS-CoV infection, IFN-α and IFN-β have been shown to be effective in limiting virus reproduction [59]. Interferons, like other cytokines, can enhance synaptic loss by activating microglia [99] and in the presence of β-amyloids, these peptides act as part of host immune system and can entrap viral particles, promoting

the post-viral inflammatory response induced by interferons [35].

The upregulation in cytokine levels can be, at least partly, attributed to Corona virus open reading frame 3a (ORF3a) protein and aggravated by the associated Acute Lung Injury (ALI), which are recognized to induce NOD-like receptor protein 3 (NLRP3) inflammasome activity and promote cytokine production, namely IL-1β [36, 100]. On the other hand, systemic inflammation, through activation of NLRP3 inflammasome, impairs immune homeostasis in the brain, promotes production of pro-inflammatory cytokines particularly IL-1β and propagates aggregation of peptides in form of pathogenic fibrils, as well as causing mitochondrial dysfunction and apoptosis thereby contributing to neurodegeneration, as in AD and PD [42, 43, 71]. All such evidence highlights the fact that NLRP3 inflammasome might act as the cross-road in potential neurodegenerative consequences of SARS-CoV-2 infection.

An important question that will be raised is whether SARS-CoV-2 infection has long-standing effects and whether the resultant cytokine storm will persist and can potentially lead to neuropathologic changes associated with neurodegenerative diseases. Actually, answer to this question might depend on multiple factors such as the extent to which there is an underlying ground for inflammation, the extent of potential neuroinvasion or migration of peripheral leukocytes to the brain, or the presence of autoimmune reactions due to mechanisms such as molecular mimicry following the viral infection. In this regard, COVID-19 has been known to cause autoimmune reactions by molecular mimicry mechanisms causing cranial neuropathies [85], multiple sclerosis [101], Guillain–Barré syndrome [10], or encephalomyeloradiculitis [72]. In keeping with this, higher levels of anti-corona virus antibodies have been detected in CSF sample of PD patients [102] and it has been determined that specific variants of the virus such as mutations in glycoprotein (S) by inducing immune reactions can precipitate glutamate excitotoxicity and thereby contribute to neurodegeneration [103]. Furthermore, it has been determined that under inflammatory conditions especially in old ages, BBB integrity is compromised and myeloid cells infected with the virus can migrate to CNS and perpetuate neuroinflammation by cytokine production and prompting microglial activation [104, 105]. Over time, these leukocytes may remain infected with the HCoV and act as a persistent source of inflammation in the brain, contributing to the neurodegenerative milieu [106].

Adoptive and Cellular Immune System: Immune Cells in Brain

The role of cellular immune system in COVID-19 infection has been highlighted in some recent studies. Actually, it has

been revealed that SARS corona virus structural and non-structural antigens activate CD4 and CD8 T cell response, occurring proportionate to the severity of infection [107, 108]. In mild cases, the CD8 T cell response against virus is dominant, but in severe cases, the humoral immune response and CD4 T cells take over the antiviral immune response more prominently, which might itself even contribute to immuno-pathology [108]. Furthermore, the systemic inflammatory response induced by viral infection could alter the anti-inflammatory conditions in favor of inflammatory conditions [108]. Whether or not the cellular and adoptive immune system activation in periphery influence central nervous system is not clear, but it has been revealed that in viral infections, due the BBB breakdown, white blood cells could further penetrate BBB and perpetuate infection in brain and culminate in neuroinflammatory processes [76]. In COVID-19 infection, elevations in cellular markers of inflammation, such as increased white blood cells, were not observed in CSF samples in a study with a small sample size [79], although in some cases, pleocytosis in CSF samples has been reported [37, 38]. In post-mortem histopathological analysis of patients who died of COVID-19 infection, severe microglial activation and mild perivascular infiltration of T cells was noted in CNS [39, 45]. This might suggest that although prominent immune cell activation is not common in mild and moderate infections, in severe forms of the disease, cellular components of immune system infiltrate in CNS. As mentioned earlier, infiltration of microglia in CNS is associated with dysregulated production of cytokines, disruption of neurotransmission, and even hippocampal atrophy [97] as well as propagation of neurodegenerative mechanisms and apoptosis [41, 98]. Furthermore, evidence T cell infiltration in the CNS has been detected in both AD [44] and PD [109]. This inflammatory, cytotoxic polarization of immune cells would more possibly occur in the old patients with COVID-19 infection [110] and further propagate the neurodegenerative mechanisms, which may have already been triggered by misfolded protein accumulations due to aging [57]. On the whole, due to the variable cellular immune response in different phases of infection, and in mild or severe forms of infection [108], the effects of such changes on neurodegenerative processes, especially in the long run, cannot be clearly predicted.

Interactions of Viral Proteins: Protein Aggregation and Mitochondrial Dysfunction

Infection of dopaminergic neurons expressing α-synuclein with respiratory viruses such as H1N1 has culminated in α-synuclein aggregate formation and suppression of autophagy, the main mechanisms involved in priming neurodegeneration in PD [111]. On the other hand, SARS-CoV-2 proteins can interact with human proteins, including proteins associated

with aging such as those related to ubiquitination, mitochondrial activity, RNA processing, or vesicle trafficking [55]. It was determined that SARS-CoV infection can hijack endoplasmic reticulum (ER) machinery for synthesis of viral proteins, and its spike protein by interacting with ER chaperons activates PERK pathway which in turn stimulates glucose-regulated protein 78 (GRP78), and GRP94, inducing the unfolded protein response (UPR), thereby enhancing protein misfolding [56]. On the other hand, Open Reading Frame 9b (ORF-9b) of SARS-CoV can induce autophagy of the host cell, as well as inducing ubiquitination, and impairing proteostasis in mitochondria [112]. Furthermore, SARS-CoV proteins, ORF-3a, ORF-3b, ORF-6, ORF-7a, can induce apoptosis of host cells, which is mediated by caspase-3 and ER stress and Janus Kinase (JNK) pathways [113]. Although such evidence is not available for SARS-CoV-2 yet, but the structural and mechanistic behavior similarity of these viruses makes these assumptions so likely that targeting ER stress has been suggested as a treatment for SARS-CoV-2 [114, 115]. Thus, it is possible that COVID-19 infection, enters the neurons, by hijacking protein machinery disrupts ER and mitochondrial function and upregulates accumulation of misfolded proteins, thereby triggers mitochondrial oxidative stress and contributes to apoptosis and degeneration of neurons [55, 60, 116].

Gut Microbiome: Shared Mechanisms of Immune System and Gastrointestinal Tract

According to a recent systematic review and meta-analysis study, around 7.8% and 5.5% of patients with COVID-19 infection experience gastrointestinal symptoms such as diarrhea and nausea/vomiting, respectively, as well as other symptoms like abdominal pain and GI bleeding. This indicates virus infiltration in the GI epithelium, possibly through ACE receptors, although the mechanism is not well determined [52, 117]. Importantly, shedding of the virus in feces of afflicted patients has been observed in five weeks or more after infection [53]. Furthermore, various genetic and environmental factors including infections are key to the composition of gut microbiota and such alterations have been detected in COVID-19 patients [54, 118]. On the other hand, as mentioned earlier, it is mechanistically possible that pathogens find their way into CNS via peripheral nerve endings and contribute to neurodegeneration and gut microbiota dysbiosis can potentially play a prominent role in dissemination of the virus and its invasion into CNS. Furthermore, based on the findings in animal models and humans, it has been speculated that some alterations in GI tract, e.g. GI lesions and increased permeability of intestinal epithelium, occurs decades before development of neurodegenerative disease-specific

pathologies and might contribute to development of neurodegenerative diseases [119].

Besides the possible contribution of gut microbiota dysbiosis to direct invasion of the virus into CNS, by mechanisms like increasing GI permeability, molecular mimicry, and oxidative stress upregulates immune system activation, which along with altering neurotransmission balance it can contribute to neurodegenerative processes [119]. Having such facts in mind, it might be possible that SARS-CoV-2 infection, by modifying gut microbiota renders the patients to developing neurodegenerative diseases [119]. However, it is not clear whether any potential alterations in composition of gut microbiome would be permanent and whether it depends on the severity of infection and the presence of gastrointestinal symptoms. In this regard, the recent systematic review on GI manifestations of COVID-19 has shown that there is no significant difference in prevalence of GI symptoms in severe and non-severe forms of the disease [52].

Furthermore, gut microbiota composition plays an important role in maintaining the immunological equilibrium and is suggested as a determinant for rates of affliction with infectious and inflammatory diseases including COVID-19 [48, 120]. For instance, old age, as a common risk factor for severe form of COVID-19 infection and neurodegenerative diseases is associated with less variety in gut microbiota [120]. This fact might indicate that since the diversity of gut microbiota acts as a common risk factor for COVID-19 infection and development of neurodegeneration, the odds for developing neurodegenerative diseases would be higher in patients surviving COVID-19.

Considering all of mentioned links between gut microbiome, COVID-19 infection and neurodegeneration, will illuminate that personalized nutritional modifications and maybe fecal transplantation methods might have a preventive role for COVID-19 infection and even be beneficial in diminishing the risk of neurodegeneration in patients with history of COVID-19 infection [120].

Angiotensin-Converting Enzymes: Neuroprotective and Neurotoxic Features

Angiotensin-converting enzymes (ACE), consisting of ACE-1 and ACE-2, are key components of renin-angiotensin system (RAS). ACE-2 is a membrane-bound enzyme expressed on many cell types, which is responsible for cleavage of angiotensin II into smaller proteins such as angiotensin (1-7) which bind to Mas receptor, forming ACE-2/angiotensin (1-7)/Mas axis [49]. As mentioned earlier, ACE-2 acts as a receptor which binds to SARS-CoV-2 spike protein, thereby allowing its entry to cells [51]. Binding of SARS-CoV-2 to ACE-2 can potentially lead to ACE-2 depletion, which can further perpetuate multiple organ injury, as ACE-2/

angiotensin (1-7)/Mas axis is known to have protective effects [50]. On the other hand, similar protective role of ACE-2/angiotensin (1-7)/Mas axis in neurodegeneration has been addressed, contrary to ACE-1 and angiotensin II which are shown to be involved in augmentation of oxidative stress, neuroinflammation, and apoptosis, thereby contributing to neurodegeneration [121]. Lower levels of ACE-2 and angiotensin (1-7) activity, and higher levels of ACE-1 activity and angiotensin II, in association with higher levels of Aβ and phosphorylated tau, in AD patients compared to controls [68], as well as similar evidence in animal AD models [69] has also been detected.

Apart from the role of ACE-2 and its downstream axis in demise of neurons, gene expression studies have revealed that ACE-2 gene shows the most significant co-expression with dopamine decarboxylase, which is responsible for conversion of L-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine. This indicates that ACE-2 downregulation, induced by SARS-CoV-2 infection, might be associated with concomitant alterations in dopamine synthetic pathway, which is implicated in pathophysiology of PD [122]. Furthermore, ACE-2 gene polymorphisms have been shown to influence susceptibility to infection with COVID-19 and its complications such as multi-organ failure, although the exact association has not been determined [123, 124], while specific ACE-2 polymorphisms can potentially increase the risk for PD [125] and AD [70].

Accordingly, ACE inhibitors by reducing angiotensin II levels have shown promise in preventing progression of neurodegenerative diseases [121, 126]. Then again the question that will be raised is whether such alterations in ACE-2 levels will persist or not. Moreover, whether or not ACE inhibitor administration would halt perpetuation of organ injury and the potential for progression to neurodegeneration in patients with severe COVID-19 infection remains a question.

Hypothalamic-Pituitary Axis: Neuroendocrine Mechanisms

The over-activation of immune system and cytokine production in acute phase of viral infections is speculated to stimulate hypothalamic-pituitary-adrenocortical (HPA) axis [68, 69]. This phenomenon will lead to secretion of higher amounts of glucocorticoids, which downregulate activation of inflammatory cells and production of excessive amounts of cytokines, in order to prevent the deleterious effects of cytokine storm [122]. In addition to the increased production of glucocorticoids as a physiologic response to the viral infection, administration of exogenous glucocorticoids in the critically ill patients with COVID-19 might further add to the increased levels of glucocorticoids in these patients. Importantly, prolonged amounts of glucocorticoids are known to accelerate

neurodegenerative processes through a myriad of mechanisms. Disturbances in glucocorticoids can lead to mitochondrial dysfunction and enhance apoptosis, activate hyperphosphorylation of tau, the key cytoskeleton protein, and thereby contribute to synaptic loss and impaired neurotransmission [127]. Consistent with this, in patients with de novo PD, HPA axis abnormality is observed as a common finding [128].

On the other hand, SARS-CoV can express certain sequences of amino acid which are structurally similar to adrenocorticotropic hormone (ACTH), and the host immune response by forming antibodies, can destroy the endogenous ACTH [129]. Moreover, it is suggested that SARS-CoV infection, reduces ACE-2 expression in various tissues such as lung and heart [130, 131]. On the other hand, ACE-2 overexpression in corticotropin-releasing hormone (CRH) producing cells in hypothalamus is associated with a decrement in HPA axis activation [132]. It is not clear whether SARS-CoV-2 infection reduces ACE-2 expression in these hypothalamic neurons [133], but if so, this mechanism will further lead to HPA axis activation [132]. Despite the changes in HPA axis described in acute phase of viral infections, 3 months after recovery from SARS-CoV a subset of patients showed HPA axis hypo-activity without any abnormalities in HPA axis prior to or during viral infection [134]. This phenomenon can be attributed to some cytokines such as transforming growth factor-beta (TGF-β) and TNF-α, which are suggested to downregulate activation of HPA axis under certain circumstances and are shown to be involved in severe SARS-CoV-2 infection [135, 136]. However, additional data is required to determine whether the effects of COVID-19 infection on HPA axis function is similar to SARS-CoV, whether TGF-β mediates such effects and what would be the long-term consequences of this infection on HPA axis, if any.

Hypoxia and Thrombosis: Systemic or Local Insults to the Brain

Acute respiratory distress syndrome (ARDS), considered the most serious clinical presentation of COVID-19 [137], especially when requiring long-term mechanical ventilation, is accompanied by higher rates of subsequent cognitive impairment and executive dysfunction in survivors, even years after hospital discharge [138]. The risk for developing dementia and/or progressive neurodegeneration in patients with ARDS depends on multiple factors like pre-existing neurologic injury, dementia, amyloid-beta pathology or delirium, and presence of concomitant hypoperfusion or hypoxemia, cytokine levels, and incompetent BBB integrity [138]. Actually, ARDS-related hypoxemia and systemic inflammation/sepsis as well as increased BBB permeability are the main mechanisms known to contribute to brain damage. Consistent with

this, a recent post-mortem study on COVID-19 patients has shown neuropathological changes consistent with hypoxic injury in majority of patients, despite minimal SARS-CoV-2 infection in brain tissue [5]. Also recently, it has been revealed that in patients even with moderate SARS-CoV-2 infection, the levels of glial fibrillary acidic protein (GFAP) and neurofilament light chain protein (NFL) are elevated, which are indicators of astrocytic reaction and axonal injury, respectively [139]. Nevertheless, it has been determined that hippocampal damage, specifically in CA1 and CA2, is attributable more to high levels of cytokines rather than hypoxemia [140]. Indeed, upregulation in levels of peripheral cytokines and sepsis is associated with alterations in function of epithelial cells in BBB and subsequent tendency towards amyloid-beta peptide build-up and AD pathology [141]. As stated earlier, sepsis can also trigger neuroinflammatory processes in the brain, alter glucose metabolism and neurotransmission, and increase brain tissue vulnerability to systemic insults such as oxidative stress [142]. As well, septic shock, especially when associated with hypercapnia, can impair auto-regulatory mechanisms for cerebral blood circulation [143], further contributing to hypoxemia. Apart from ARDS and the subsequent blood circulation alterations, local vascular obstruction in CNS may be precipitated by sepsis-induced coagulopathy, which is the tendency towards formation of micro-thrombosis in end-organs induced by systemic inflammation and is prominent in critically ill COVID-19 patients, causing defects in brain circulation and render patients to hypoxic-ischemic changes [144, 145]. Furthermore, SARS-CoV-2 by binding to ACE-2 can potentially cause ACE-2 depletion and by shifting the equilibrium towards ACE1/angiotensin II, the subsequent vasoconstriction can further contribute to hypoperfusion [144]. As mentioned in the previous section, ACE-2 cleaves angiotensin II to angiotensin (1-7), which as well as inducing vasodilation, by binding to Mas receptor exerts anti-inflammatory effects and is recognized as a neuroprotective factor [146]. Importantly, it has become evident that Alzheimer-type dementia and other neurodegenerative diseases may be precipitated by chronic cerebral hypoperfusion and vascular event [46]. Moreover, thrombosis and endothelial dysfunction are associated with impaired anti-oxidant activity, which along with hypoxia results in oxidative stress and production of inflammatory cytokines, the main contributors to neurodegeneration [47]. Oxidative stress can enhance α-synuclein aggregation in PD [147], beta-amyloid peptide accumulation in AD [62] through neuroinflammation and other mechanisms.

APOE and Lipid Metabolism: Shared Genetic and Metabolic Risk Factors

Delirium and impaired consciousness is a common clinical finding, especially in severe cases of COVID-19 [75] and

pre-existing dementia has been recognized to increase the risk for severity of COVID-19 infection about three-fold as well as increasing mortality [63]. Moreover, it has been determined that a large proportion of COVID-19 reported symptoms are inheritable, especially delirium was reported to have 50% heritability, according to the study in homozygotic twins [61]. Interestingly, ApoE e4-e4 genotype is associated with a significantly increased risk for dementia and delirium [64] and it has been shown that ApoE e4 homozygotes, independent from pre-existing dementia or other comorbidities, were more probably tested positive for COVID-19 and would probably experience more severe forms of the disease [66, 148]. This same genetic predisposition increasing the risk for AD and COVID-19, might constitute a confounding factor which at least partly explains the possibly higher risks of developing AD-type dementia in patients surviving COVID-19.

Mechanistically, it has been shown that high levels of blood cholesterol by binding to ApoE receptor, improve SARS-CoV-2 entry to cells via ACE-2 receptors [149]. ApoE e4 genotype, on the other hand, favors pro-inflammatory conditions in macrophages, and has lower efficiency in delivering essential fatty acids for maintenance of neuronal membrane and myelin sheath, as well as promoting

misfolded protein accumulations, disrupting dendritic spine formation and synaptic plasticity [150].

In one study from China on patients surviving SARS-CoV, it was shown that 12 years following recovery from infection, patients developed metabolic changes especially lipid metabolism disruptions such as increase in levels of phosphatidylinositol and lysophosphatidylinositol and hyperlipidemia, associated with hyperinsulinemia, impaired glucose metabolism or cardiovascular abnormalities [151]. Such metabolic changes were suggested to be associated with high-dose pulses of methylprednisolone, as well as the severity of initial damage to the lungs [151]. Also, binding of the virus to cells led to acute T2DM during SARS-CoV infection in 50% of patients without history of Type 2 diabetes mellitus (T2DM), although only 5% of them remained diabetic after resolution of infection, with no significant difference in blood glucose levels compared to their siblings [67]. These permanent metabolic changes such as DM were especially observed in critically ill patients with complications after discharge from hospital, which might occur due to pancreatic damage or consequences of septicemia and the associated metabolic changes [65]. Additionally, type 1 diabetes mellitus (T1DM) due to autoimmune mechanisms or damage to pancreatic islet cells
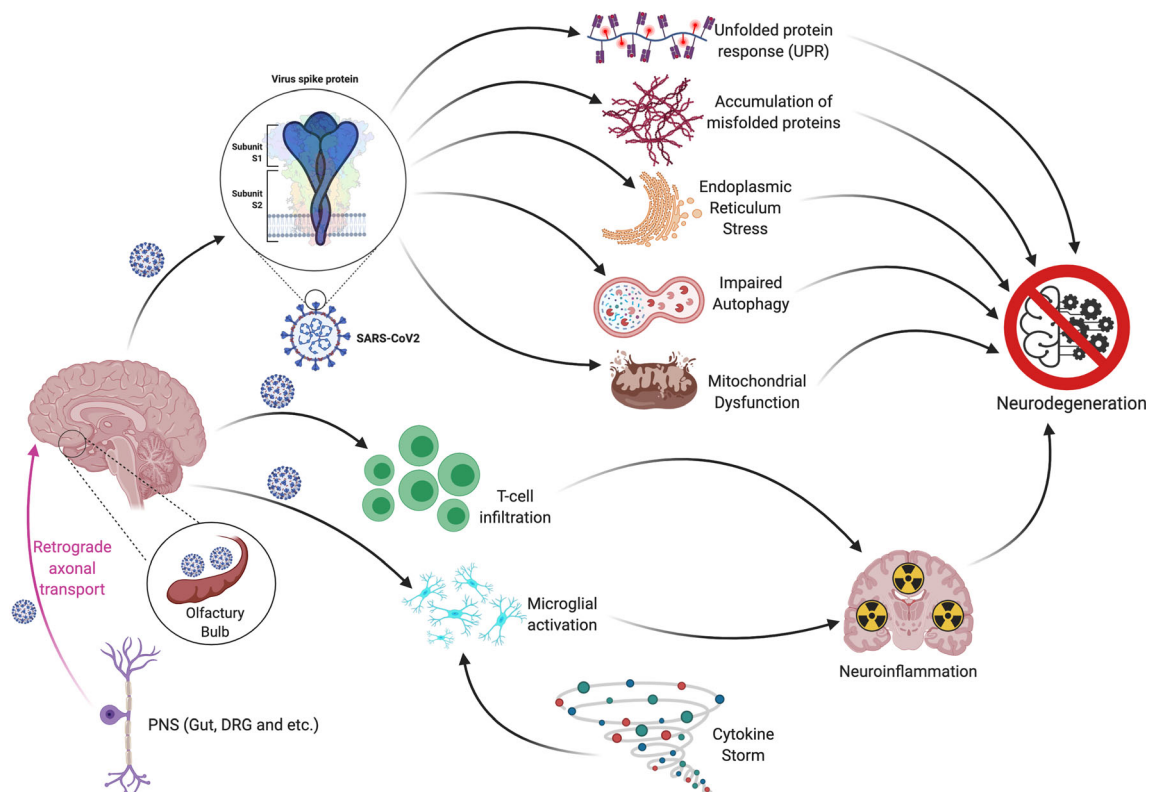

Fig. 1 Contribution of SARS-CoV-2 to neurodegeneration via invasion into CNS. SARS-CoV-2 can directly invade olfactory bulb, penetrate brain via retrograde axonal transport from peripheral nerve endings, or reach brain via hematogenous pathway. Virus invasion along with excessive peripheral cytokine production, due to the septicemia, upregulate central cytokine production and will enhance the microglial activation, which along with T cell infiltration lead to neuroinflammation and contribute to neurodegeneration. Furthermore, it has been shown that SARS-CoV spike protein can promote Endoplasmic reticulum (ER) unfolded protein response, impair autophagy and proteostasis in mitochondria and culminate in misfolded protein accumulation and apoptosis

following viral infection is a phenomenon that might occur in these patients [67]. Even more, long-term cognitive dysfunction [138], as well as depression and post-traumatic stress disorder (PTSD) [152] following ARDS and hypoxia might be associated with poor episodic and working memory and uncontrolled eating behaviors, culminating in weight gain [153]. Although occurrence of such metabolic changes, following SARS-CoV-2 infection is not established yet, but should be anticipated. Importantly, obesity, metabolic syndrome, lipid metabolism alterations and diabetes mellitus are known to increase the odds for affliction with neurodegenerative disorders [154].

Also, increment in blood glucose levels in T2DM patients may aggravate fibril formation and AD

pathology, through upregulation of interferon regulatory factor 5 (IRF5) activity [35]. Increased IRF-5 in response to high blood glucose levels, on the other hand, promotes susceptibility for COVID-19 infection [35]. Moreover, it has been recently shown that obesity and metabolic syndrome increase the susceptibility for affliction with this infection [155]. Thus, even if we assume that rate of metabolic changes following COVID-19 infection will not increase significantly, we can consider the fact that patients with pre-existing metabolic abnormalities are recognized to be at higher risk of COVID-19 and more severe form of the disease [156], and the same population, if surviving COVID-19, are at greater risk for developing neurodegenerative disorders [154].
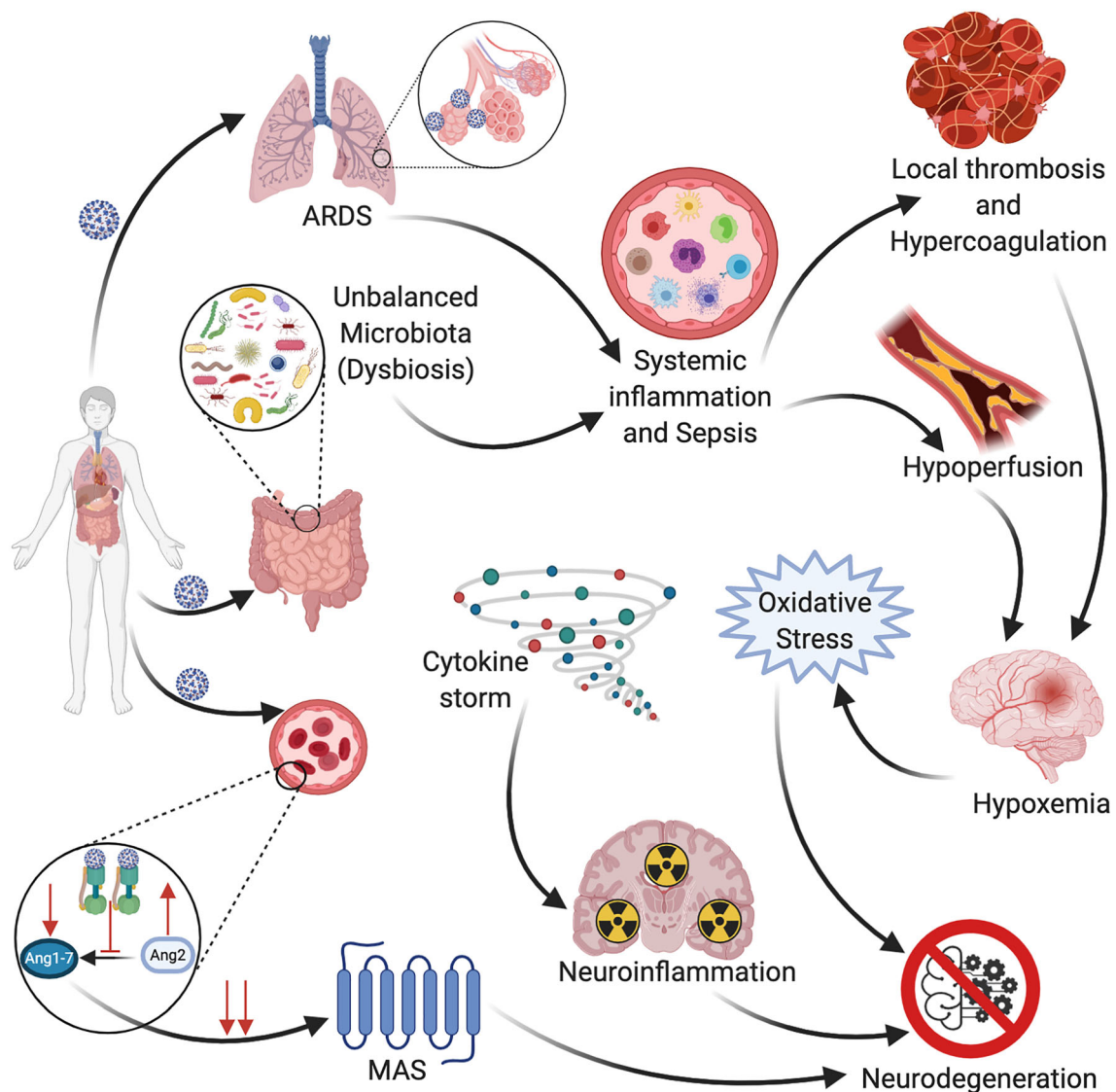

Fig 2. Contribution of SARS-CoV-2 to neurodegeneration via its systemic effects. Occupation of the angiotensin-converting enzyme-2 (ACE-2) by the virus will reduce ACE-2/Angiotensin (1-7)/Mas axis activity, which acts as a neuroprotective mechanism. Acute respiratory distress syndrome (ARDS)-induced hypoxemia along with the sepsis-induced hyper-coagulation and the resultant tendency towards formation of local thrombosis in brain vessels will cause hypoperfusion exacerbate oxidative stress and promote neurodegeneration

Conclusion

As discussed throughout this article and summarized in Table 1, Fig. 1, and Fig. 2, direct or indirect invasion of the SARS-CoV-2 into CNS and migration and infiltration of peripheral leukocytes to the brain induces production of cytokines, activates microglia, induces their polarization into M1 phenotype, and thereby contributes to the propagation of neurodegenerative processes. Viral replication can also hijack protein synthesis machinery in neurons, promote unfolded protein response, and by impairing proteostasis trigger misfolded protein accumulation. On the other hand, sepsis and elevated cytokine production will upregulate HPA axis and cortisol secretion, which can further enhance tau hyperphosphorylation. ACE-2 depletion due to its excessive occupation of with SARS-CoV-2, and the subsequent decline in ACE-2/angiotensin (1-7)/Mas axis activity will attenuate neuroprotective mechanisms and promote neurodegeneration. Additionally, ARDS as well as sepsis-induced hypercoagulation render brain to hypoxic damage, which is known to cause oxidative stress and enhance neurodegenerative processes. The shared risk factors for developing neurodegenerative diseases and infection with COVID-19 including genetic variances such as APOE e4-e4 genotype, and metabolic risk factors such as Diabetes Mellitus or hyperlipidemia, could also underlie the higher risk for developing neurodegenerative diseases in recovered patients, if any.

Whether or not such mechanisms will persist and the extent to which they can accelerate the process of neurodegeneration in patients with variable disease severity is not clear. Additionally, due to the high rates of death, especially in severe forms of the disease and in patients with comorbidities which increase the risk for neurodegeneration, as well as premature death in these patients due to other comorbidities, it is possible that the overall prevalence/incidence of neurodegenerative diseases will not increase in the upcoming years. On the whole, in this time the research on the association between these entities is based on hypothesis and for providing evidence in this regard, prospective cohort studies should be designed. Furthermore, it is noteworthy that the increased risk for development of neurodegenerative diseases in this population is not inevitable; for instance, modifying neurodegenerative mechanisms by Vitamin D supplementation has been suggested [157]. Similarly, targeting ACE and RAS system by administering ACE inhibitors may be a promising method to halt neurodegeneration.

Compliance with ethical standards

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