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# Molecular mechanisms highlighting the potential role of COVID-19 in the development of neurodegenerative diseases

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition to the pulmonary manifestations, COVID-19 patients may present a wide range of neurological disorders as extrapulmonary presentations. In this view, several studies have recently documented the worsening of neurological symptoms within COVID-19 morbidity in patients previously diagnosed with neurodegenerative diseases (NDs). Moreover, several cases have also been reported in which the patients presented parkinsonian features after initial COVID-19 symptoms. These data raise a major concern about the possibility of communication between SARS-CoV-2 infection and the initiation and/or worsening of NDs. In this review, we have collected compelling evidence suggesting SARS-CoV-2, as an environmental factor, may be capable of developing NDs. In this respect, the possible links between SARS-CoV-2 infection and molecular pathways related to most NDs and the pathophysiological mechanisms of the NDs such as Alzheimer's disease, vascular dementia, frontotemporal dementia, Parkinson's disease, and amyotrophic lateral sclerosis will be explained.

## KEYWORDS

COVID-19, neurodegenerative diseases, molecular mechanisms, SARS-CoV-2, neurodegeneration

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## INTRODUCTION

Pandemic COVID-19 is caused by SARS-CoV-2, structurally a large enveloped non-segmented positive-sense RNA virus [1]. This virus, along with its spike protein (S), makes contact with cells and binds to several host proteins (known as virus receptors) that assist in its entry into cells [1]. After entry into the host cell, viral pneumonia (fever, cough, dyspnea, hypoxemia) [2–5], acute tubular necrosis (loss of brush border, vacuolar degeneration, luminal dilatation) [6], and gastrointestinal manifestations (diarrhea, diminished appetite, nausea, vomiting, abdominal pain) [4, 7] are commonly seen in humans. The expression of specific receptors is necessary for SARS-CoV-2 binding and entering the target cells. In this regard, CD147, a member of the immunoglobulin superfamily was a suggested receptor that plays a role in virus binding [8]; however, newer studies have ruled out the role of this transmembrane glycoprotein [9]. Following SARS-CoV-2 binding, an androgen-responsive serine protease, namely transmembrane protease serine 2 facilitates virus entry and activation by cleavage of the virus S protein. This protease is highly expressed in epithelial cells of the respiratory, gastrointestinal, urogenital tract, and brain cell lines [10]. In addition, it has been shown that angiotensin-converting enzyme 2 (ACE2) is the main protein responsible for the cellular accumulation of SARS-CoV-2 [11–13]; this is an enzyme that converts angiotensin II to angiotensin and is distributed throughout the body and the brain. In the brain, ACE2 is expressed both on neurons and glial cells and on endothelial and arterial smooth muscle cells. ACE2 is also expressed in different central nervous system (CNS) compartments such as the temporal lobe and hippocampus [14]. Its expression can be enhanced by cytokines, such as interferon [15] or other inflammatory responses [16], and maybe regulated by excitotoxicity [17]. Also, it has been reported that heparan sulfate proteoglycans (HSPGs) can facilitate virus binding to the receptor ACE2 [18].

Altogether, the data mentioned illustrate that SARS-CoV-2, capable of infecting the brain and the nervous system, can present nervous system symptoms in COVID-19 patients. SARS-CoV-2, due to its spread to the brain through the olfactory route [19], the hematogenous route [20] and the enteric-vagal routes [21] is associated with a variety of other symptoms and clinical manifestations [2], such as dysfunction of the central (fatigue, headache, confusion, stroke [22], dizziness, syncope [23], seizure, anorexia, and insomnia [24–27]), peripheral (anosmia, ageusia, myoclonus [28], neuropathic pain, and myalgias) [5, 24, 29]) combined central-peripheral (Guillain Barre syndrome [30]) and enteric nervous systems (diarrhea [31]). It has been documented that SARS-CoV-2 enters CNS via ACE2 receptors present on brain endothelial cells, which constitute the blood-brain barrier (BBB). Subsequently, reduction in tight junction protein gene expression levels in endothelial cells would be induced, which leads to alteration in BBB integrity and permeability, resulting in neuro-invasion of SARS-CoV-2 and neuro-inflammatory responses [32–34].

A broad spectrum of neurological diseases has been categorized as neurodegenerative diseases (NDs). The activation of glial cells and the following related happenings, as inflammatory responses, are categorized as a set of the underlying mechanisms of this kind of disease [35]. Likewise, an increase in proinflammatory cytokines and consequent neuroinflammation can also be associated with SARS-CoV-2 infection. Also, several studies have recently documented the worsening of neurological symptoms within COVID-19 morbidity in patients previously diagnosed with NDs. These mentioned documentations under the shadow of the history of

controversial relation between the post-infectious detected encephalitis lethargica and NDs raise a major concern about the possible role of SARS-CoV-2 infection in triggering and/or exacerbating the well-known NDs such as Alzheimer's disease (AD) and Parkinson's disease (PD). Accordingly, this paper tries to explain this possible role based on the ability of SARS-CoV-2 infection in inducing neuropathogenic alterations similar to those explicitly observed in different human NDs. Section "Coronavirus-mediated neuropathogenesis" details the possible pathways that may lead to nerve degeneration due to COVID-19, and the pathways documented in this section can be common to all neurodegenerative diseases. However, afterward, in Section "The possible interactions…", the pathways that may be specifically associated with developing the well-known neurodegenerative disease mentioned in each subsection are stated.

## HISTORY OF THE LINK BETWEEN VIRUSES AND NEURODEGENERATIVE DISEASES

The destructive effect on the nervous system is not limited to SARS-CoV-2 infection. Previous studies have shown that some viruses associated with different types of NDs can injure neurons by gaining access to neurons through the BBB system, causing cell lysis and neuronal death. In this regard, it has been reported that there is a link between human immunodeficiency viruses and dementia [36], in which the death of neurons is caused by inflammation and apoptosis [37]. On this line, based on the pertinent studies, the influenza virus can produce neurodegenerative diseases such as PD, one of the progressive neurological disorders [38]. The Austrian physician von Economo described a peculiar condition, postencephalitic parkinsonism, which was controversially ascribed to the influenza pandemic between 1916 and 1929. This condition is associated with movement, psychiatric and sleep disorders, and results from a post-infectious and/or autoimmune process [39]. Several research studies have also proposed neurological complications, such as PD to be a sequela of influenza infection [40, 41]. In addition, it has been shown that the Epstein–Barr virus has a major role in inflammation and neurodegeneration, which can cause multiple sclerosis and encephalitis [42, 43]. The documentations mentioned above accentuate the link between viruses and CNS damage, which can result in neurodegeneration. Thus, it is essential to deepen our knowledge about the influence of viruses on the progression of NDs, which represent a significant burden to human health worldwide. In the following sections, the possible effects of the virus SARS-CoV-2 on the progression of NDs will be discussed.

## CORONAVIRUS-MEDIATED NEUROPATHOGENESIS

Regardless of the disease type, this section points out the possible pathways that may lead to nerve degeneration due to COVID-19, and the pathways demonstrated in this section can be common to all neurodegenerative conditions.

Based on the pertinent studies, SARS-CoV-2 can bring about a hyper-inflammatory condition through its interaction with macrophages, microglia, and astrocytes in the CNS and the subsequent release of cytokines [44]. Such status can give rise to increased BBB permeability, cerebrovascular endothelial dysfunction, and BBB destruction, which eventuates to the entrance

of more inflammatory factors into the CNS, leading to neurological disorders and neurodegenerative diseases [32, 33, 45–60].

In addition, SARS-CoV-2 can induce or inhibit various mitochondrial processes [61], leading to exacerbated and uncontrolled oxidative stress, which hampers the optimal functioning of cells such as neurons [62–65], resulting in NDs [66–68]. Also, in SARS-CoV-2 infected patients, misfolded protein aggregation and endoplasmic reticulum (ER) stress have occurred, which have major roles in ND progression. Protein folding is a process in which a proper 3D structure is formed in the ER, which can be disrupted, resulting in misfolded protein aggregation and ER stress by several external factors such as toxic substances, ischemia, and oxidative stress and several internal factors such as the production of truncated proteins caused by genetic abnormalities. ER stress and the subsequent adaptive cellular responses are known as the unfolded protein response (UPR). The chaperone BiP engages misfolded proteins and their segregation from IRE1, PERK, and ATF6 complex ER, which gives rise to the activation of these proteins [69, 70]. Each of the mentioned proteins is capable of mediating UPR through the parallel signaling pathways, which can eventually promote the production of cytoprotective molecules such as molecular chaperones in ER, as well as reduce the burden of newly synthesized unfolded proteins on ER by the suppression of the protein translation, and potentiating the degradation rate of misfolded proteins [69]. Although the UPR has protective results for cells, in response to an excessive load of misfolded proteins such as that associated with higher viral load, prolonged UPR may have uncompensated outcomes. In this view, high/chronic ER stress may also promote cell death by degradation of the antiapoptotic proteins' mRNAs mediated by IRE1 [71, 72]. The activation of IRE$\alpha$ can cause the decay of select microRNAs, which normally have a role in repressing the translation of caspase-2 mRNA. Therefore, IRE1 activity can reraise the protein levels of Casp-2, which initiates the mitochondrial apoptotic pathway [73–75]. Under persistent ER stress, the influx of Ca2+ into mitochondria may happen following the outflow of Ca2+ from ER. This can also lead to apoptotic cell death by activating caspase-9 and -3 [76, 77]. Furthermore, PERK activation results in expressing ATF4 and producing the transcription factor C/EBP homologous protein (CHOP), which can induce the downregulation of Bcl-2 and lead to apoptosis [78]. In addition, it has been demonstrated that IRE1 and ATF6 also mediate the proapoptotic activity of CHOP in the CNS in ER stress [79, 80]. On the other hand, the catabolic process, autophagy, has been shown to have a prominent role in cell survival. However, its excessive activation is thought to lead to cell death [81, 82]. In this way, the interplay between ER stress signaling and autophagy has been suggested in NDs. Accordingly, different ER stress-related signaling branches such as IRE1-sXBP1 and PERK-elf2$\alpha$ arms probably play a role in developing NDs through the interaction with several autophagy-related proteins [83, 84]. Furthermore, the IFN-$\gamma$–stimulated ATF6–C/EBP-$\beta$–signaling pathway also induces autophagy [85]. In addition, it has been suggested that ER stress signaling also has a potential role in CNS-associated neuroinflammation and the development of NDs [86]. In NDs such as AD and amyotrophic lateral sclerosis (ALS), the destructive role of a subset of molecularly characterized microglia, namely disease-associated microglia, has been recognized [86, 87]. Interestingly, it has been shown that in microglia, ATF6$\alpha$ has a regulatory effect on the NF-$\kappa$B-mediated inflammatory response, which in turn postulates the role of ER stress signaling in the regulation of inflammatory response in the CNS [88]. Several lines of studies have demonstrated that coronaviruses actuate ER stress. The overexpression of SARS-CoV-2 S protein can induce all three branches of UPR resulting from the activation of IRE1, PERK, and ATF6. In parallel, ORF8, a

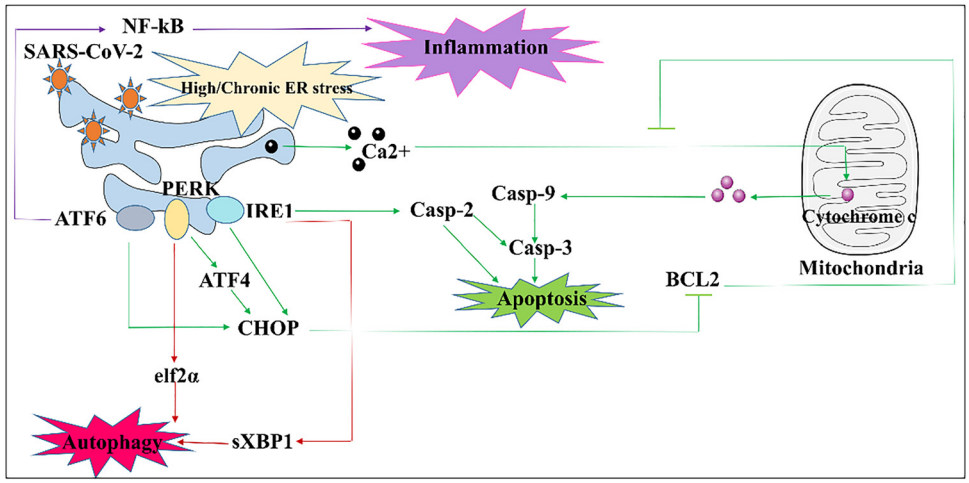


*Fig. 1.* Schematic figure showing the calcium outflow, PERK, IRE1, ATF6 associated signaling pathways within a neuron which possibly lead to the development of neurodegeneration under the effect of SARS-CoV-2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 [69, 89–91, 95]

rapidly evolving accessory protein of SARS-CoV-2, can activate both the IRE1$\alpha$ and ATF6 UPR branches [89]. Moreover, through the common nsp2 interactors, this virus can be involved in ER calcium signaling [90]. Accordingly, SARS-CoV-2 is considered a factor capable of inducing neurodegeneration and neuronal cell death by induction of UPR and ER stress [69, 91] (shown in Fig. 1). Regarding pathophysiological mechanisms of NDs such as PD, the interactions between environmental and genetic factors activate molecular events resulting in the progression of such diseases [92]. Therefore, the accumulation of misfolded proteins and ER stress are noticeable events in NDs progression (Aoe T. 2020).

Considering the ER stress-inducing effect of SARS-CoV-2 and the role of ER stress in the progression of NDs [93] through the promotion of neurotoxicity by activating inflammation and apoptosis [94] and autophagy [95] (shown in Fig. 1), it is suggested that this virus, as an environmental factor, may be capable of triggering and/or exacerbating the NDs in individuals associated with predisposing factors such as genetic makeup. This is a possibility that may result in neurodegeneration in an overall view.I In the following sections, we will discuss specific NDs in which the SARS-CoV-2 infection may relate to their underlying pathophysiological mechanisms.

## THE POSSIBLE INTERACTIONS OF CORONAVIRUS WITH NEURODEGENERATIVE DISEASES

The previous section, section “Coronavirus-mediated neuropathogenesis”, indicated the possible pathways that may lead to nerve degeneration due to COVID-19, which can be common to all neurodegenerative conditions. Nonetheless, in this section, the pathways that may be significantly associated with developing the well-known neurodegenerative diseases are detailed.

## Alzheimer's disease (AD)

AD is the most common form of dementia which gradually progresses caused by the degeneration of the cells in the brain, leading to the progressive alteration of several functions, such as difficulty in remembering recent events [96]. As the disease advances, patients can have problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, self-neglect, and behavioral issues [97]. Following that, slowly, functions of the body are lost, leading to death at last. It has been shown that AD's pathology is associated with amyloid-beta (A$\beta$) plaques [98–100], tau proteins [101], neurofibrillary tangles (NFT) [102], reduced levels of dopamine (DA) and its receptors [103–105], glial hypertrophy, myelin disruption [106], the loss of neuronal connections [107], neuronal death, and oligodendroglial degeneration in the brain.

***The possible link between SARS-CoV-2 infection and the development of AD.*** The connection between COVID-19 and AD is unclear, but literature reports of cognitive and memory impairment after COVID-19 have been documented. In this view, 30–40% of patients reported problems with memory four months after COVID-19 hospitalization [108]. Likewise, younger individuals are at risk for COVID-19-related cognitive symptoms, even without the severe disease. Also, it has been shown that SARS-CoV-2 may actually induce memory loss eight months after having a mild case of the condition [109]. Moreover, several evidence shows that SARS-CoV-2 infection has a possible impact on developing AD. In this respect, ACE2, the main protein responsible for the cellular accumulation of SARS-CoV-2 may be expressed in the temporal lobe and hippocampus, representing cerebral regions involved in the pathogenesis of AD [14]. Furthermore, it has been shown that SARS-CoV-2 has a possible role in AD underlying pathophysiology such as A$\beta$ plaques and tau proteins. In this view, the significant increasing effect of this virus on phosphorylation of the tau protein has been detected in infected brain organoids [110]. The tau protein is a phosphoprotein expressed in the axon of neurons, which promotes microtubule assembly and plays a role in maintaining neuronal integrity and axonal transport [111, 112]. Tau pathology and its intracellular aggregation, which results from tau detachment from the microtubules can be developed by hyperphosphorylation induced by the activation of several kinases such as glycogen-synthetase kinase 3 b, cyclin-dependent kinase 5 and cdc2 protein kinase, mitogen-activated kinase including extracellular signal-regulated kinase, c-Jun N-terminal kinase and p38 MAP kinase [113]. This, in turn, induces filamentous lesions in neurons and sometimes in glia which are sufficient to cause tauopathies (a heterogeneous group of NDs) such as AD [114]. Also, this virus plays a role in the accumulation of A$\beta$. A$\beta$ is the main component of amyloid plaques which are the extracellular deposits found in the brains of people with AD, produced by activating secretase family enzymes. It has been reported that the inhibition of secretases and kinases is caused by ACE2-related pathways, and the process of inhibiting these signaling pathways can be caused by the COVID-19 virus resulting in long-term neurological sequels following the activation of AD triggering signaling pathways [115] (shown in Fig. 2). Moreover, oxidative stress induced by SARS-CoV-2 can lead to A$\beta$ accumulation. In this regard, glutamine synthetase (GS) is an enzyme that interacts with A$\beta$ and prevents A$\beta$ fibrillogenesis, the process by which a peptide forms insoluble aggregates of amyloid. However, following oxidative stress, GS activity is inhibited, leading to structural alteration of the enzyme. This alteration can prevent the GS-induced modification effect on the fibrillogenic and toxicologic properties of A$\beta$, playing a pivotal role in neurotoxicity in the AD

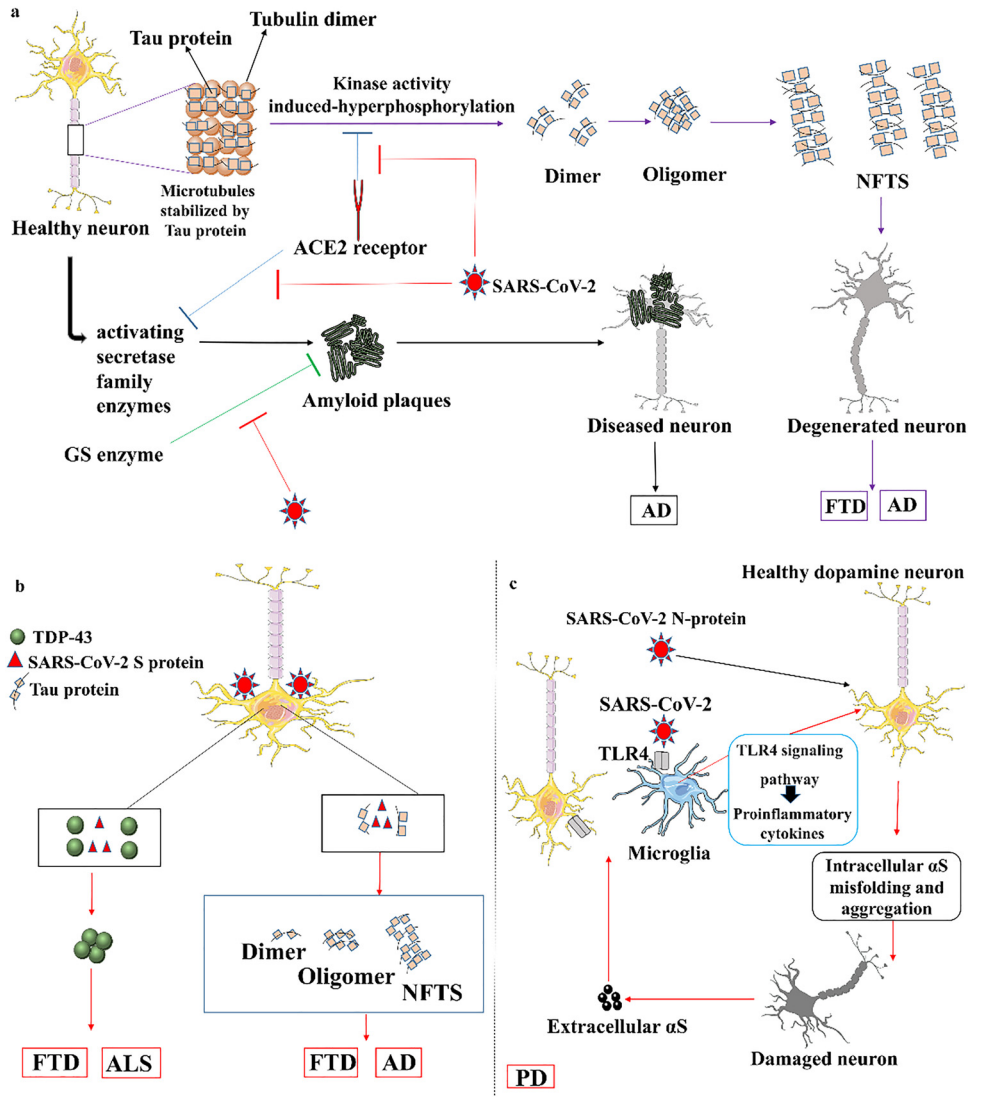


*Fig. 2.* Schematic figure explaining pathways that result in neurodegenerative diseases via SARS-CoV-2: (a) The interaction of SARS-CoV-2, ACE2 receptor, and GS enzyme leading to the development of AD and FTD. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GS, glutamine synthetase; AD, Alzheimer's disease; FTD, Frontotemporal disorder [110, 115]; (b) S protein of SARS-CoV-2 can interact with the heparin-binding proteins tau and TDP-43, which may give rise to the aggregation of tau and TDP-43 and, subsequently, the development of FTD, ALS, and AD. TDP-43, TAR DNA-binding protein 43; ALS, Amyotrophic lateral sclerosis [110, 170]; (c) The vicious cycle which induces PD. TLR4 signaling pathway initiating innate immune response can be elevated by SARS-CoV-2, which is a potential factor capable of inducing αS misfolding and aggregation resulting in dopaminergic neuronal damage. Afterward, αS can be released extracellularly and potentiates immune responses in a TLR4-dependent manner. Also, αS aggregation can be accelerated via direct interaction with SARS-CoV-2 N-protein; PD, Parkinson's disease; TLR4, Toll-like receptor; αS, alpha-synuclein [192, 194, 196, 199]

brain [116–118] (shown in Fig. 2). Based on SARS-CoV-2-induced uncontrolled oxidative stress, it can be considered that SARS-CoV-2 infection may have a role in aggregating A$\beta$ in this way. Overall, since tau protein and A$\beta$ aggregation are the pathophysiological mechanisms in AD and regarding the effect of SARS-CoV-2 infection on increased phosphorylation of tau [110] and A$\beta$, it can be suggested that SARS-CoV-2 infection may have a role in inducing and intensifying AD. This possible effect will be elucidated in the clinic in the coming times.

## Vascular dementia

Vascular cognitive impairment (VCI) is a heterogeneous group of disorders due to vascular etiology, with varying severity of cognitive deficits. In this regard, vascular dementia (VaD), which is considered as a major VCI, is the most severe form of VCI [119]. VaD is the second most common subtype of dementia after AD, estimated to represent 20% of dementia cases in North America and Europe (112–114). According to VCCCS (Vascular Impairment of Cognition Classification Consensus Study) conceptualization, VaD is made up of different main subtypes comprising post-stroke dementia, subcortical ischemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias (combination between vascular and neurodegenerative diseases) [120], which result from small-, large-, and mixed- small/large vessel diseases [121].

Small vessel disease (SVD) consists of different pathological findings such as small infarcts, microscopic infarcts, microbleeds, arteriolosclerosis, intracranial atherosclerosis, and cerebral amyloid angiopathy [119]. According to various studies, SVD is the most common cerebrovascular pathology found in examined samples of VaD patients [122–124]. In this respect, it is noticeable that SVD is associated with factors such as age, diabetes mellitus, hypertension and stroke, [125]and the key pathophysiological mechanisms underlying SVD are linked to ischemia, inflammation, and oxidative stress [124, 126]. It has been demonstrated that following ischemia and inflammation, endothelial activation takes place. Endothelial activation, which is deemed as the overexpression of adhesion molecules such as VCAM-1, ICAM-I, P-selectin and E-selectin, is linked to endothelial dysfunction [126, 127]. The effect of vascular inflammation and endothelial dysfunction on the structural and functional cerebrovascular alterations in SVD is documented [128, 129]. On this line, renin-angiotensin–aldosterone system (RAAS) activation is shown to have a role in provoking oxidative stress, small cerebral-vessel inflammation, endothelial dysfunction, and subsequent increased BBB permeability via the influence of angiotensin II (Ang II) [126, 130, 131]. In this respect, the effect of aldosterone on promoting cerebrovascular inflammation and endothelial dysfunction is also demonstrated [132].

In another respect, it is noteworthy to mention that one of the other subtypes of VaD, namely Post-stroke Dementia results from stroke. In this way, dementia can develop in 10% of patients after the first stroke and in a third of patients following recurrent stroke [124]. Stroke is the second leading cause of death; it is a medical condition in which significant complications such as cell death are caused by poor blood flow to the brain. There are two main types of stroke: ischemic, due to interruption of blood flow, and hemorrhagic, which is caused by bleeding [133]. In this view, it has been shown that dementia may develop following each of them [124]. The key events contributing to stroke pathology are inflammation, rapid reduction of ATP, loss of homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, impairment of the BBB, activation of glial cells, and infiltration of leukocytes [134–141].

***The possible link between SARS-CoV-2 infection and the development of VaD.*** According to several lines of studies, it is suggested that COVID-19 infection may drive the onset of hypertension through increasing the signaling of Ang II, which is one of the key effectors in RAAS [142, 143]. SARS-CoV-2 causes the downregulation of ACE2 [144]; subsequently, it would lead to the accumulation of Ang II [145]. Ang II, in turn, through its effect on the angiotensin 1 receptor, enhances aldosterone production. Ang II in concert with aldosterone can also exert pro-inflammatory effects by the mediation of angiotensin 1 receptor and mineralocorticoid receptor, respectively, which can result in cerebrovascular inflammation and endothelial dysfunction [132]. Accordingly, recent compelling evidence suggests that the pro-inflammatory action of Ang II and aldosterone can flare up under the influence of SARS-CoV-2 [146]. As mentioned above, several studies have shown that SVD is the most common cerebrovascular pathology found in VaD [124]. In addition, the role of vascular inflammation and endothelial dysfunction in SVD is documented [128, 129]. In this relevance, several studies have demonstrated the association of Ang II and aldosterone with cerebral SVD [147, 148]. This association is reasonable considering the pro-inflammatory action of Ang II and aldosterone, which can result in cerebrovascular inflammation and endothelial dysfunction. Taking into account the enhancing effect of SARS-CoV-2 on the pro-inflammatory action of Ang II and aldosterone [146], and the positive association of Ang IIa and aldosterone with SVD [147, 148], it is proposed that SARS-CoV-2 may have a role in the development of SVD and VaD. On the other hand, it has been stated above that hypertension is one of the risk factors for SVD and VaD [124, 125]. In this respect, if the control of high blood pressure becomes poor, the alterations related to hypertension, such as small vascular lesions and inflammatory reactions, will take place gradually in small cerebral vessels [149]. Considering the above-mentioned fact that SARS-CoV-2 may cause hypertension and according to the presumed effect of hypertension on SVD progression, the possible role of SARS-CoV-2 infection in the development of hypertension and subsequent SVD and VaD would be highlighted.

In another respect, it has been reported that the risk of ischemic stroke during COVID-19 is roughly 5%, but COVID-19-related hemorrhagic strokes are far less common than ischemic strokes [150]. In this view, it has been shown that SARS-CoV-2 infection affects the initiation of stroke and the intensification of stroke as a preexisting neurological disorder [151, 152]. This is a noticeable subject that is caused by cytokine storm, hypoxia-induced ischemia secondary to severe pulmonary disease, thrombotic microangiopathy, endotheliopathy, and coagulation [153]. Thus, SARS-CoV-2 infection has a role in progressing stroke; clinically, this has also been reported in several cases of COVID-19 presenting stroke symptoms [34, 154–160].

As mentioned earlier, studies have documented that stroke can be a significant factor for biochemical dysfunction in the brain, ultimately leading to VaD [124]. By considering the role of SARS-CoV-2 infection in the progression of stroke, as well as the association of stroke with VaD, this virus may also have a role in developing post-stroke dementia. These matters need to be evaluated clinically in the future.

## Frontotemporal disorder

Frontotemporal disorder (FTD), and its pathological presentation, namely Frontotemporal Lobar Degeneration, encompasses several types of dementia involving the frontal and temporal lobes [161, 162]. FTD was first described by Pick in 1892 (Neary et al., 2005). FTD is presented

as behavioral or language disorders, including significant social and personal behavior changes, apathy, blunting of emotions, deficits in both expressive and receptive language, and frontal and temporal lobe atrophy [163–165]. It has been shown that FTD's pathology is associated with three main proteins, namely the fused in sarcoma protein (FUS) in FTLD-FUS, the microtubule-associated protein Tau in FTLD-Tau [114], and TAR DNA-binding protein 43 (TDP- 43) in FTLD-TDP, which are sufficient to cause these types of NDs [166, 167]. In this regard, these proteins in CNS can induce widespread neurotoxicity and cell death due to the accumulation of misfolded tau, FUS, and TDP-43 intracellular inclusions [162, 168, 169].

***The possible link between SARS-CoV-2 infection and the development of FTD.*** It has been reported that SARS-CoV-2 exposure is associated with altered distribution of tau protein from axons to soma and aberrant tau phosphorylation (hyperphosphorylation), which lead to neurodegeneration and apparent neuronal death [110]. In this view, to have more explanation, tau phosphorylation is induced by the activation of several kinases, whose activation is inhibited by ACE2-related pathways. However, the process of inhibiting these signaling pathways can be caused by the COVID-19 virus resulting in tau phosphorylation [113, 115] (shown in Fig. 2). Also, the SARS-CoV-2 S protein can interact with the heparin-binding site. In this site, there are several heparin-binding proteins such as tau and TDP-43, which are aggregation-prone. Viruses enter the cell via HSPG-mediated endocytosis and use the endosomal pathway to travel through the cytoplasm and reach the nucleus to initiate their replication and infection. On this line, there is a possibility that due to the interaction between SARS-CoV-2 S protein and the proteins tau and TDP-43, the aggregation of the proteins mentioned will be increased; this eventually can lead to the development of NDs such as FTD. Thus, this binding can induce aggregation of these proteins, which leads to NDs such as FTD [170, 171] (shown in Fig. 2). Since aggregation of tau and TDP-43 are considered pathophysiological mechanisms underlying FTD, it can be suggested that SARS-CoV-2 infection may have a role in developing FTD. This possible effect of SARS-CoV-2 remains to be evaluated in the future.

## Parkinson's disease (PD)

PD is a long-term degenerative disease of the central nervous system that mainly involves the motor system, increasing with age, such as those above 60 years [172, 173]. The prodromal features usually emerge slowly, and as the disease worsens, the non-motor symptoms become more common. In this regard, hyposmia is one of the most common non-motor symptoms in PD [174]. The core symptoms of PD are tremor, rigidity, slowness of movement, and difficulty with walking [175]; these motor presentations mainly result from the death of cells in the substantia nigra (SN), leading to midbrain dopaminergic neuron deficit [176]. Also, cognitive and behavioral problems occur with depression, anxiety, and apathy detected in people with PD [177]. The neuropathological hallmarks of PD include progressive dopaminergic neuronal cell loss in the SN and other brain regions such as the locus ceruleus, as well as abnormal accumulation of the protein alpha-synuclein ($\alpha$S) in the form of Lewy bodies and Lewy neurites which is induced by misfolding of $\alpha$S [178].

***The possible link between SARS-CoV-2 infection and the development of PD.*** The initiation of PD symptoms that were previously reported in 8 cases of COVID-19 [179–185] supports the possible influence of SARS-CoV-2 infection on the development of PD. Also, there is some

evidence that SARS-CoV-2 infection has a possible role in inducing and progressing PD, summarized in this section. The ability of coronaviruses to enter the CNS through the nasal cavity with subsequent neuronal death has been shown in animal studies [186, 187]. As reported, hyposmia has been induced in COVID-19 patients without nasal obstruction and rhinorrhea, which is a common prodromal feature of PD [188–191]. Moreover, as mentioned earlier, SARS-CoV-2 can induce inflammation, which may damage dopaminergic neurons through αS modification [192]. In this regard, Toll-like receptors (TLRs) such as TLR4 (a signaling receptor in innate immunity that is a specific immunologic response to infection), which possesses a strong binding affinity to SARS-CoV-2 S protein [193], can be elevated by the SARS-CoV-2-induced inflammatory process, induce proinflammatory cytokines through the TLR4 signaling pathway in microglia [194]. The resulting inflammation is a potential factor capable of inducing αS misfolding, and aggregation in neurons can give rise to neuronal damage [195]. As a vicious cycle, different forms of αS can be released extracellularly from the damaged neurons activating TLR4 and leading to further inflammatory signals in the neural network [194] (shown in Fig. 2). This process spreads from cell to cell and hampers the brain, since αS toxicity has a role in cellular dysfunction such as mitochondrial abnormalities, axonal transport deficits, and synaptic transmission alterations [62, 194, 196–200]. Also, recently, direct interaction between the nucleocapsid protein (N-protein) of SARS-CoV-2 and αS has been documented in a way that SARS-CoV-2 N-protein speeds up the αS aggregation process [199] (shown in Fig. 2). In addition, it has been shown that lesions on basal ganglia may occur through thromboembolic encephalopathy and cytokines induced by SARS-CoV-2 infection [201–204]. By taking into consideration the SN, which is a midbrain dopaminergic nucleus, and its critical role in modulating motor movement as a part of the basal ganglia circuitry, and the lesion-inducing effect of SARS-CoV-2 on basal ganglia, it can be assumed that dopaminergic neurons may be damaged via this virus leading to motor disturbances.

Further, there is a possible influence of SARS-CoV-2 infection on the development of PD via accumulation of angiotensin II. In this view, in a study on the regulatory role of angiotensin II in the synthesis of the enzymes involved in catecholamine biosynthesis such as DA has been documented [205]. In another study, the ACE2 receptor has been detected in the mitochondria isolated from cell cultures derived from dopaminergic neurons [206]. Also, it is assumed that SARS-CoV-2 can cause downregulation of ACE2 [144], which can lead to the accumulation of angiotensin II [145], resulting in DA metabolic dysfunction [207]. Thus, the mentioned data illustrate that SARS-CoV-2 through ACE2 located on dopaminergic neurons and accumulation of angiotensin II may promote the development of PD in COVID-19 patients.

According to significant observational literature discussed above, since protein misfolding and aggregation along with DA deficit are a set of pathophysiological mechanisms in PD, and considering the inducing effect of SARS-CoV-2 infection on protein misfolding and aggregation and oxidative stress in dopaminergic neurons [192], it can be suggested that SARS-CoV-2 infection may also have a role in triggering PD. On this line, as mentioned above, the initiation of PD manifestations in 8 cases of COVID-19 [179–185] upholds the feasible influence of SARS-CoV-2 infection on the development of PD; however, the long-term observation of persons with a past medical history of COVID-19 along with conducting research experiments will assess the validity of this assumption in the future (Table 1). In another aspect, a cohort study has demonstrated a significant worsening of motor and nonmotor symptoms in PD patients during

*Table 1.* COVID-19 related cases of parkinsonism

| | Case I | Case II | Case III | Case IV |
|---|---|---|---|---|
| Age & Gender | 35-year-old female | 45-year-old male | 58-year-old Male | 64-year-old Female |
| Clinical presentations of COVID-19 | Fever, cough, sneezing, rhinorrhea, diarrhea, myalgia, anosmia, hypogeusia | Fatigue, shortness of breath, chest pain without fever, and loss of smell | Dry cough, fever, nausea, and shortness of breath | Fever, fatigue, and loss of smell |
| COVID-19 severity | Mild | Moderate requiring hospitalization | Severe with desaturation requiring ICU admission | Mild |
| COVID-19 to PD features interval | 10 days | 2–3 weeks | 32 days | 5 days |
| Core features of PD | Right side rigidity, bradykinesia | Tremor, bradykinesia, rigidity in right side more than left side | Right side–dominant hypokinetic-rigid syndrome with rest and postural tremor | Left side bradykinesia rigidity and rest tremor |
| Nonmotor symptoms of PD | Hypophonia, hypomimia, gait impairment, and slow saccades | None | None | Hypomimia |
| Prodromal PD symptoms | None | None | None | Constipation |
| Underlying medical conditions | None | Hypertension | Hypertension and dyslipidemia | ND |
| Family history of PD | None | ND | None | None |
| Brain imaging | Reduced The function of the nigrostriatal dopamine system, akin to PD | Reduced function of the nigrostriatal dopamine system, akin to PD | Reduced function of the nigrostriatal dopamine system, akin to PD | Reduced right putamen uptake |
| Genetic testing for familial PD | ND | Negative | ND | ND |
| Drug treatment | Levodopa/benserazide | Pramipexole | Spontaneously | ND |
| Reference | (Faber et al., 2020) [180] | (Cohen et al., 2020) [181] | (Méndez-Guerrero et al., 2020) [182] | (Makhoul and Jankovic, 2021) [183] |
| | Case V | Case VI | Case VII | Case VIII |
| Age & Gender | 35-year-old female | 72-year-old male | 66 -year-old male | 74 -year-old male |
| Clinical presentations of COVID-19 | Fever, Hyposmia, encephalitis | Fever, chills, cough, and breathlessness | Cough, hoarseness of voice, and one episode of a generalized tonic-clonic seizure | ND |
| COVID-19 severity | ND | ND | ND | ND |

*(continued)*

**Table 1.** Continued

| | Case V | Case VI | Case VII | Case VIII |
|---|---|---|---|---|
| COVID-19 to PD features interval | ND | 5 days | One week | 8 weeks |
| Core features of PD | Tremor, cogwheel rigidity, bradykinesia, & postural instability | Cogwheel rigidity, postural instability, and bradykinesia | Rigidity in his right upper and lower limbs with severe bradykinesia | rigidity, postural instability, and motor slowing |
| Nonmotor symptoms of PD | Hypomimia | Loss of smell, | None | ND |
| Prodromal PD symptoms | None | ND | ND | ND |
| Underlying medical conditions | ND | Orthostatic hypotension | ND | ND |
| Family history of PD | ND | ND | ND | ND |
| Brain imaging | Bi pallidal lesion | ND | Gliosis in bilateral temporal lobes, periventricular punctate white matter ischemic changes in bilateral frontal and parietal lobes and age- related cerebral and cerebellar atrophy. | Ischemic changes in periventricular white matter |
| Genetic testing for familial PD | ND | ND | ND | ND |
| Drug treatment | Levodopa/carbidopa | ND | Levodopa-carbidopa | Levodopa- carbidopa |
| Reference | (Ayele et al., 2021) [185] | (Rao et al., 2022) [184] | (Rao et al., 2022) [184] | (Rao et al., 2022) [184] |

ND: not determined.

the COVID-19 illness [208]. This, in turn, postulates the possible role of SARS-CoV-2 infection in the exacerbation of neurological symptoms in PD patients.

### Amyotrophic lateral sclerosis (ALS)

ALS is an inevitably fatal neurological disorder that affects the upper and lower motor neurons in the motor cortex, the brain stem nuclei, and the anterior horn of the spinal cord leading to progressive muscle weakness and wasting, which affect chewing, swallowing, speaking, breathing, and cause tongue atrophy and fasciculations, which compromise the autonomy of the subject in daily life [209–212]. It has been documented that genetic causes involved in ALS are hexanucleotide expansions in chromosome 9 open reading frame 72 and mutations in superoxide dismutase 1 (SOD1), TDP-43, FUS, and TANK-binding kinase 1. Also, in both sporadic and familial ALS patients, there are cytoplasmic aggregations of TDP-43 and SOD1, which show a significant extent of neuronal damage resulting from aggregates of these proteins in various tissues that share a distinctive b-sheet-rich fibrillar ultrastructure leading to cell death [213–218].

***The possible link between SARS-CoV-2 infection and the development of ALS.*** There is several evidence available that shows SARS-CoV-2 infection has a possible role in developing ALS. In this respect, it has been reported that the health status of ALS patients during the COVID-19 illness worsened, showing the impact of SARS-CoV-2 infection on these patients [219]. Also, ACE2 may be expressed in the motor cortex, in the cytoplasm of neurons, which represent cerebral regions involved in the pathogenesis of ALS [220]. Further, it can be proposed that SARS-CoV-2 has a possible role in ALS underlying pathophysiology such as TDP-43 aggregations [170]. In this view, based on the effect of SARS-CoV-2 on protein misfolding resulting from SARS-CoV-2-induced oxidative stress, this virus may aggregate TDP-43 in the brain, which can be considered the crucial reason behind ALS [170] (shown in Fig. 2). Also, as mentioned earlier, binding of the SARS-CoV-2 S protein to heparin-binding proteins can induce aggregation of TDP-43, leading to neuron damage. There have not yet been any reports of cases of ALS in patients following COVID-19. However, based on the effect of SARS-CoV-2 on the aggregation of TDP-43, which is considered part of the pathophysiological mechanism underlying ALS, it can be suggested that SARS-CoV-2 infection may have a role in developing ALS.

## CONCLUSION

As mentioned above, COVID-19 is a contagious disease caused by SARS-CoV-2. SARS-CoV-2 gets into contact with cells and binds to its receptors that assist in its entry into cells, including brain cells. This virus can infect the brain and the nervous system, presenting nervous system symptoms in COVID-19 patients. The COVID-19 patients may present various neurological disorders such as dementia, one of the most devastating diseases [221].

Interestingly, several cases presenting parkinsonian features, five days to 8 weeks after initial COVID-19 symptoms, have been recently reported [183], which raises the possibility of NDs development following COVID-19 infection. In this review, we culled the documentation in which the inducing effect of SARS-CoV-2 on ER stress and prolonged UPR may have a role in the progression of NDs due to activation of the pathways of apoptosis, autophagia and inflammation. In continuation, the inducing effect of SARS-CoV-2 on the progression of

pathophysiological mechanisms that are exclusive for the well-known NDs such as VaD, AD, PD, FTD, and ALS was explained.

The molecular pathways stated here are not the only mechanisms that can flare up the clinical presentations of the NDs under the effect of SARS-CoV-2. In another aspect of view, it has to be mentioned that during the COVID-19 pandemic, noticeable psychological disturbances such as anxiety have been detected in patients with NDs. Pertinently, the reason is more ascribed to the factors such as changes in daily life, the imposition of quarantine measures, the fear of becoming infected with the virus SARS-CoV-2, and worrying about drug availability [222, 223]. Several analytical studies have displayed the association of anxiety with a rise in the risk of all-cause dementia [224]. This critical topic highlights that the exacerbation of the NDs can also be affected by the COVID-19 pandemic-related psychological status.

According to the possible mechanisms that highlight the impact of SARS-CoV-2 infection on the initiation of NDs, nowadays, there is an underdebated line of thought maintaining that the COVID-19 pandemic might be associated with the boost in the epidemic of NDs [225]. In this regard, viral infection has been identified only as one of the potential risk factors for NDs and other risk factors such as genetic. Therefore, it is not clear whether or not we will face a coming epidemic of NDs, and this is a topic that needs to be elucidated in the future. In other views, based on the before-mentioned molecular pathways showing a possible role for SARS-CoV-2 infection in developing the NDs, SARS-CoV-2 infection is not only capable of intensifying the clinical presentations of patients with NDs but may also shift the time of disease onset to an earlier age. This is another subject that remains to be clarified clinically in the future.

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## REFERENCES

1. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndr 2020; 14(4): 407–12. https://doi.org/10.1016/j.dsx.2020.04.020.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.
3. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease. N Engl J Med 2020; 382(18): 1708–20. https://doi.org/10.1056/NEJMoa2002032.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061–9. https://doi.org/10.1001/jama.2020.1585.
6. Benedetti C, Waldman M, Zaza G, Riella LV, Cravedi P. COVID-19 and the kidneys: an update. Front Med (Lausanne) 2020; 7: 423. https://doi.org/10.3389/fmed.2020.00423.
7. Wang D, Ju X, Xie F, Lu Y, Li F, Huang H, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Zhonghua Er Ke Za Zhi 2020; 58(4): 269–74. https://doi.org/10.3760/cma.j.cn112140-20200225-00138.
8. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep 2020; 16(3): 434–40. https://doi.org/10.1007/s12015-020-09976-7.
9. Shilts J, Crozier TW, Greenwood EJ, Lehner PJ, Wright GJ. No evidence for basigin/CD147 as a direct SARS-CoV-2 spike binding receptor. Sci Rep 2021; 11(1): 413. https://doi.org/10.1038/s41598-020-80464-1.
10. Qiao J, Li W, Bao J, Peng Q, Wen D, Wang J, et al. The expression of SARS-CoV-2 receptor ACE2 and CD147, and protease TMPRSS2 in human and mouse brain cells and mouse brain tissues. Biochem Biophys Res Commun 2020; 533(4): 867–71. https://doi.org/10.1016/j.bbrc.2020.09.042.
11. Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Sarnelli G. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? Brain Behav Immun 2020; 87: 93–4. https://doi.org/10.1016/j.bbi.2020.04.060.
12. Perrotta F, Matera MG, Cazzola M, Bianco A. Severe respiratory SARS-CoV2 infection: does ACE2 receptor matter? Respir Med 2020; 168: 105996. https://doi.org/10.1016/j.rmed.2020.105996.
13. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 2020; 181(4): 894–904. e9. https://doi.org/10.1016/j.cell.2020.03.045.
14. Dong M, Zhang J, Ma X, Tan J, Chen L, Liu S, et al. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. Biomed Pharmacother 2020; 131: 110678. https://doi.org/10.1016/j.biopha.2020.110678.
15. Ziegler CG, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 2020; 181(5): 1016–35. e19. https://doi.org/10.1016/j.cell.2020.04.035.
16. Li M-Y, Li L, Zhang Y, Wang X-S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020; 9(1): 45. https://doi.org/10.1186/s40249-020-00662-x.
17. Xu J, Sriramula S, Lazartigues E. Excessive glutamate stimulation impairs ACE2 activity through ADAM17-mediated shedding in cultured cortical neurons. Cell Mol Neurobiol 2018; 38(6): 1235–43. https://doi.org/10.1007/s10571-018-0591-8.
18. Hao W, Ma B, Li Z, Wang X, Gao X, Li Y, et al. Binding of the SARS-CoV-2 spike protein to glycans. Sci Bull (Beijing) 2021; 66(12): 1205–14. https://doi.org/10.1016/j.scib.2021.01.010.
19. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021; 24(2): 168–75. https://doi.org/10.1038/s41593-020-00758-5.
20. Patrì A, Vargas M, Buonanno P, Annunziata MC, Russo D, Staibano S, et al. From SARS-CoV-2 hematogenous spreading to endothelial dysfunction: clinical-histopathological study of cutaneous signs of COVID-19. Diagn Pathol 2021; 16(1): 16. https://doi.org/10.1186/s13000-021-01075-6.
21. Deffner F, Scharr M, Klingenstein S, Klingenstein M, Milazzo A, Scherer S, et al. Histological evidence for the enteric nervous system and the choroid plexus as alternative routes of neuroinvasion by SARS-CoV2. Front Neuroanat 2020; 14: 596439. https://doi.org/10.3389/fnana.2020.596439.

22. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020; 91(8): 889–91. https://doi.org/10.1136/jnnp-2020-323586.
23. Ebrille E, Lucciola MT, Amellone C, Ballocca F, Orlando F, Giammaria M. Syncope as the presenting symptom of COVID-19 infection. HeartRhythm Case Rep 2020; 6(7): 363–6. https://doi.org/10.1016/j.hrcr.2020.04.015.
24. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020; 288(3): 335–44. https://doi.org/10.1111/joim.13089.
25. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care 2020; 24(1): 176. https://doi.org/10.1186/s13054-020-02882-x.
26. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir (Wien) 2020; 162(7): 1491–4. https://doi.org/10.1007/s00701-020-04374-x.
27. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7(7): 611–27. https://doi.org/10.1016/S2215-0366(20)30203-0.
28. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, Parra-Serrano J, Toledo-Alfocea D, Sánchez-Tejerina D, et al. Generalized myoclonus in COVID-19. Neurology 2020; 95(6): e767–72. https://doi.org/10.1212/WNL.0000000000009829.
29. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6): 683–90. https://doi.org/10.1001/jamaneurol.2020.1127.
30. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020; 382(26): 2574–6. https://doi.org/10.1056/NEJMc2009191.
31. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology 2020; 158(6): 1518–9. https://doi.org/10.1053/j.gastro.2020.02.054.
32. Reynolds J, Mahajan SD. SARS-COV2 alters blood brain barrier integrity contributing to neuro-inflammation. J Neuroimmune Pharmacol 2021; 16(1): 4–6. https://doi.org/10.1007/s11481-020-09975-y.
33. Sashindranath M, Nandurkar HH. Endothelial dysfunction in the brain: setting the stage for stroke and other cerebrovascular complications of COVID-19. Stroke 2021; 52(5): 1895–904. https://doi.org/10.1161/STROKEAHA.120.032711.
34. Chong Z-Z, Souayah N. SARS-CoV-2 induced neurological manifestations entangles cytokine storm that implicates for therapeutic strategies. Curr Med Chem 2022; 29(12): 2051–74. https://doi.org/10.2174/0929867328666210506161543.
35. Kwon HS, Koh S-H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 2020; 9(1): 42. https://doi.org/10.1186/s40035-020-00221-2.
36. Brew BJ, González-Scarano F. HIV-associated dementia: an inconvenient truth. Neurology 2007; 68(5): 324–5. https://doi.org/10.1212/01.wnl.0000252803.24176.76.
37. Mattson M, Haughey N, Nath A. Cell death in HIV dementia. Cell Death Differ 2005; 12(1): 893–904. https://doi.org/10.1038/sj.cdd.4401577.
38. Jang H, Boltz DA, Webster RG, Smeyne RJ. Viral parkinsonism. Biochim Biophys Acta Mol Basis Dis 2009; 1792(7): 714–21. https://doi.org/10.1016/j.bbadis.2008.08.001.

39. Bigman DY, Bobrin BD. Von Economo's disease and postencephalitic parkinsonism responsive to carbidopa and levodopa. Neuropsychiatr Dis Treat 2018; 14: 927–31. https://doi.org/10.2147/NDT.S153313.
40. Sadasivan S, Sharp B, Schultz-Cherry S, Smeyne RJ. Synergistic effects of influenza and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) can be eliminated by the use of influenza therapeutics: experimental evidence for the multi-hit hypothesis. NPJ Parkinsons Dis 2017; 3: 18. https://doi.org/10.1038/s41531-017-0019-z.
41. Henry J, Smeyne RJ, Jang H, Miller B, Okun MS. Parkinsonism and neurological manifestations of influenza throughout the 20th and 21st centuries. Parkinsonism Relat Disord 2010; 16(9): 566–71. https://doi.org/10.1016/j.parkreldis.2010.06.012.
42. Fernández-Menéndez S, Fernández-Morán M, Fernández-Vega I, Pérez-Álvarez A, Villafani-Echazú J. Epstein–Barr virus and multiple sclerosis. From evidence to therapeutic strategies. J Neurol Sci 2016; 361: 213–9. https://doi.org/10.1016/j.jns.2016.01.013.
43. Hashemian S, Ashrafzadeh F, Akhondian J, Beiraghi Toosi M. Epstein-Barr virus encephalitis: a case report. Iran J Child Neurol 2015; 9(1): 107–10.
44. Chowdhury B, Sharma A, Satarker S, Mudgal J, Nampoothiri M. Dialogue between neuroinflammation and neurodegenerative diseases in COVID-19. J Environ Pathol Toxicol Oncol 2021; 40(3): 37–49. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2021038365.
45. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395(10229): 1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.
46. Arcuri C, Mecca C, Bianchi R, Giambanco I, Donato R. The pathophysiological role of microglia in dynamic surveillance, phagocytosis and structural remodeling of the developing CNS. Front Mol Neurosci 2017; 10: 191. https://doi.org/10.3389/fnmol.2017.00191.
47. Yin J, Valin KL, Dixon ML, Leavenworth JW. The role of microglia and macrophages in CNS homeostasis, autoimmunity, and cancer. J Immunol Res 2017; 2017: 5150678. https://doi.org/10.1155/2017/5150678.
48. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 2005; 57(1): 67–81. https://doi.org/10.1002/ana.20315.
49. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci 2009; 32(9): 506–16. https://doi.org/10.1016/j.tins.2009.05.009.
50. Wang W-Y, Tan M-S, Yu J-T, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 2015; 3(10): 136. https://doi.org/10.3978/j.issn.2305-5839.2015.03.49.
51. Smith JA, Das A, Ray SK, Banik NL. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. Brain Res Bull 2012; 87(1): 10–20. https://doi.org/10.1016/j.brainresbull.2011.10.004.
52. Li Y, Fu L, Gonzales DM, Lavi E. Coronavirus neurovirulence correlates with the ability of the virus to induce proinflammatory cytokine signals from astrocytes and microglia. J Virol 2004; 78(7): 3398–406. https://doi.org/10.1128/jvi.78.7.3398-3406.2004.
53. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv [Preprint]. 2020:2020.02.10.20021832. https://doi.org/10.1101/2020.02.10.20021832.
54. Onyango IG, Khan SM, Bennett, Jr JP. Mitochondria in the pathophysiology of Alzheimer's and Parkinson's diseases. Front Biosci (Landmark Ed) 2017; 22(5): 854–72. https://doi.org/10.2741/4521.
55. Banks WA, Kastin AJ. Blood to brain transport of interleukin links the immune and central nervous systems. Life Sci 1991; 48(25): PL117–21. https://doi.org/10.1016/0024-3205(91)90385-o.

56. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol 2015; 14(4): 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5.
57. Hirsch EC, Vyas S, Hunot S. Neuroinflammation in Parkinson's disease. Parkinsonism Relat Disord 2012; 18 Suppl 1:S210–2. https://doi.org/10.1016/S1353-8020(11)70065-7.
58. Muhammad S, Haasbach E, Kotchourko M, Strigli A, Krenz A, Ridder DA, et al. Influenza virus infection aggravates stroke outcome. Stroke 2011; 42(3): 783–91. https://doi.org/10.1161/STROKEAHA.110.596783.
59. Chen C, Zhang X, Ju Z, He W. Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019. Zhonghua Shao Shang Za Zhi 2020; 36(6): 471–5. https://doi.org/10.3760/cma.j.cn501120-20200224-00088.
60. Xia X, Wang Y, Zheng J. COVID-19 and Alzheimer's disease: how one crisis worsens the other. Transl Neurodegener 2021; 10(1): 15. https://doi.org/10.1186/s40035-021-00237-2.
61. Ajaz S, McPhail MJ, Singh KK, Mujib S, Trovato FM, Napoli S, et al. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. Am J Physiol Cell Physiol 2021; 320(1): C57–65. https://doi.org/10.1152/ajpcell.00426.2020.
62. Guo JD, Zhao X, Li Y, Li GR, Liu XL. Damage to dopaminergic neurons by oxidative stress in Parkinson's disease. Int J Mol Med 2018; 41(4): 1817–25. https://doi.org/10.3892/ijmm.2018.3406.
63. Roy J, Galano JM, Durand T, Le Guennec JY, Chung-Yung Lee J. Physiological role of reactive oxygen species as promoters of natural defenses. FASEB J 2017; 31(9): 3729–45. https://doi.org/10.1096/fj.201700170R.
64. Dandekar A, Mendez R, Zhang K. Cross talk between ER stress, oxidative stress, and inflammation in health and disease. Methods Mol Biol 2015; 1292: 205–14. https://doi.org/10.1007/978-1-4939-2522-3_15.
65. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev 2017; 2017: 8416763. https://doi.org/10.1155/2017/8416763.
66. Nikam S, Nikam P, Ahaley S, Sontakke AV. Oxidative stress in Parkinson's disease. Indian J Clin Biochem 2009; 24(1): 98–101. https://doi.org/10.1007/s12291-009-0017-y.
67. Zhou C, Huang Y, Przedborski S. Oxidative stress in Parkinson's disease: a mechanism of pathogenic and therapeutic significance. Ann N Y Acad Sci 2008; 1147: 93–104. https://doi.org/10.1196/annals.1427.023.
68. Lovell MA, Markesbery WR. Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. Nucleic Acids Res 2007; 35(22): 7497–504. https://doi.org/10.1093/nar/gkm821.
69. Aoe T. Pathological aspects of COVID-19 as a conformational disease and the use of pharmacological chaperones as a potential therapeutic strategy. Front Pharmacol 2020; 11: 1095. https://doi.org/10.3389/fphar.2020.01095.
70. Hetz C, Papa FR. The unfolded protein response and cell fate control. Mol Cell 2018; 69(2): 169–81. https://doi.org/10.1016/j.molcel.2017.06.017.
71. Iurlaro R, Muñoz-Pinedo C. Cell death induced by endoplasmic reticulum stress. FEBS J 2016; 283(14): 2640–52. https://doi.org/10.1111/febs.13598.
72. Logue SE, Cleary P, Saveljeva S, Samali A. New directions in ER stress-induced cell death. Apoptosis 2013; 18(5): 537–46. https://doi.org/10.1007/s10495-013-0818-6.
73. Upton J-P, Wang L, Han D, Wang ES, Huskey NE, Lim L, et al. IRE1$\alpha$ cleaves select microRNAs during ER stress to derepress translation of proapoptotic Caspase-2. Science 2012; 338(6108): 818–22. https://doi.org/10.1126/science.1226191.
74. Reyes NA, Fisher JK, Austgen K, VandenBerg S, Huang EJ, Oakes SA. Blocking the mitochondrial apoptotic pathway preserves motor neuron viability and function in a mouse model of amyotrophic lateral sclerosis. J Clin Invest 2010; 120(10): 3673–9. https://doi.org/10.1172/JCI42986.

75. Puccini J, Dorstyn L, Kumar S. Caspase-2 as a tumour suppressor. Cell Death Differ 2013; 20(9): 1133–9. https://doi.org/10.1038/cdd.2013.87.
76. Bahar E, Kim H, Yoon H. ER stress-mediated signaling: action potential and Ca2+ as key players. Int J Mol Sci 2016; 17(9): 1558. https://doi.org/10.3390/ijms17091558.
77. Ye Z, Wong CK, Li P, Xie Y. A SARS-CoV protein, ORF-6, induces caspase-3 mediated, ER stress and JNK-dependent apoptosis. Biochim Biophys Acta Gen Subj 2008; 1780(12): 1383–7. https://doi.org/10.1016/j.bbagen.2008.07.009.
78. Rozpedek W, Pytel D, Mucha B, Leszczynska H, Diehl JA, Majsterek I. The role of the PERK/eIF2$\alpha$/ATF4/CHOP signaling pathway in tumor progression during endoplasmic reticulum stress. Curr Mol Med 2016; 16(6): 533–44. https://doi.org/10.2174/1566524016666160523143937.
79. Xu W, Lu X, Zheng J, Li T, Gao L, Lenahan C, et al. Melatonin protects against neuronal apoptosis via suppression of the ATF6/CHOP pathway in a rat model of intracerebral hemorrhage. Front Neurosci 2018; 12: 638. https://doi.org/10.3389/fnins.2018.00638.
80. Hu H, Tian M, Ding C, Yu S. The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum stress-induced apoptosis and microbial infection. Front Immunol 2019; 9: 3083. https://doi.org/10.3389/fimmu.2018.03083.
81. Yan C, Liu J, Gao J, Sun Y, Zhang L, Song H, et al. IRE1 promotes neurodegeneration through autophagy-dependent neuron death in the Drosophila model of Parkinson's disease. Cell Death Dis 2019; 10(11): 800. https://doi.org/10.1038/s41419-019-2039-6.
82. Banerjee R, Beal MF, Thomas B. Autophagy in neurodegenerative disorders: pathogenic roles and therapeutic implications. Trends Neurosci 2010; 33(12): 541–9. https://doi.org/10.1016/j.tins.2010.09.001.
83. Hosoi T, Nomura J, Tanaka K, Ozawa K, Nishi A, Nomura Y. Link between endoplasmic reticulum stress and autophagy in neurodegenerative diseases. Endoplasmic Reticulum Stress Dis 2017; 4(1): 37–45. https://doi.org/10.1515/ersc-2017-0004.
84. Kouroku Y, Fujita E, Tanida I, Ueno T, Isoai A, Kumagai H, et al. ER stress (PERK/eIF2 $\alpha$ phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. Cell Death Differ 2007; 14(2): 230–9. https://doi.org/10.1038/sj.cdd.4401984.
85. Gade P, Ramachandran G, Maachani UB, Rizzo MA, Okada T, Prywes R, et al. An IFN-$\gamma$–stimulated ATF6–C/EBP-$\beta$–signaling pathway critical for the expression of Death Associated Protein Kinase 1 and induction of autophagy. Proc Natl Acad Sci U S A 2012; 109(26): 10316–21. https://doi.org/10.1073/pnas.1119273109.
86. García-González P, Cabral-Miranda F, Hetz C, Osorio F. Interplay between the unfolded protein response and immune function in the development of neurodegenerative diseases. Front Immunol 2018; 9: 2541. https://doi.org/10.3389/fimmu.2018.02541.
87. Deczkowska A, Keren-Shaul H, Weiner A, Colonna M, Schwartz M, Amit I. Disease-associated microglia: a universal immune sensor of neurodegeneration. Cell 2018; 173(5): 1073–81. https://doi.org/10.1016/j.cell.2018.05.003.
88. Ta HM, Le TM, Ishii H, Takarada-Iemata M, Hattori T, Hashida K, et al. Atf6$\alpha$ deficiency suppresses microglial activation and ameliorates pathology of experimental autoimmune encephalomyelitis. J Neurochem 2016; 139(6): 1124–37. https://doi.org/10.1111/jnc.13714.
89. Echavarría-Consuegra L, Cook GM, Busnadiego I, Lefèvre C, Keep S, Brown K, et al. Manipulation of the unfolded protein response: a pharmacological strategy against coronavirus infection. Plos Pathog 2021; 17(6): e1009644. https://doi.org/10.1371/journal.ppat.1009644.

90. Davies JP, Almasy KM, McDonald EF, Plate L. Comparative multiplexed interactomics of SARS-CoV-2 and homologous coronavirus nonstructural proteins identifies unique and shared host-cell dependencies. ACS Infect Dis 2020; 6(12): 3174–89. https://doi.org/10.1021/acsinfecdis.0c00500.
91. Septyaningtrias DE, Susilowati R. Neurological involvement of COVID-19: from neuroinvasion and neuroimmune crosstalk to long-term consequences. Rev Neurosci 2021; 32(4): 427–42. https://doi.org/10.1515/revneuro-2020-0092.
92. Golpich M, Rahmani B, Ibrahim NM, Dargahi L, Mohamed Z, Raymond AA, et al. Preconditioning as a potential strategy for the prevention of Parkinson's disease. Mol Neurobiol 2015; 51(1): 313–30. https://doi.org/10.1007/s12035-014-8689-6.
93. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. Nat Rev Neurol 2017; 13(8): 477–91. https://doi.org/10.1038/nrneurol.2017.99.
94. Sprenkle NT, Sims SG, Sánchez CL, Meares GP. Endoplasmic reticulum stress and inflammation in the central nervous system. Mol Neurodegener 2017; 12(1): 42. https://doi.org/10.1186/s13024-017-0183-y.
95. Balakrishnan B, Lai K. Modulation of SARS-CoV-2 Spike-induced Unfolded Protein Response (UPR) in HEK293T cells by selected small chemical molecules. bioRxiv [Preprint]. 2021:2021.02.04.429769. https://doi.org/10.1101/2021.02.04.429769.
96. Leyhe T, Müller S, Milian M, Eschweiler GW, Saur R. Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. Neuropsychologia 2009; 47(12): 2464–9. https://doi.org/10.1016/j.neuropsychologia.2009.04.018.
97. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996; 46(1): 130–5. https://doi.org/10.1212/wnl.46.1.130.
98. Behrendt G, Baer K, Buffo A, Curtis MA, Faull RL, Rees MI, et al. Dynamic changes in myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. Glia 2013; 61(2): 273–86. https://doi.org/10.1002/glia.22432.
99. Dean DC, Hurley SA, Kecskemeti SR, O'Grady JP, Canda C, Davenport-Sis NJ, et al. Association of amyloid pathology with myelin alteration in preclinical Alzheimer disease. JAMA Neurol 2017; 74(1): 41–9. https://doi.org/10.1001/jamaneurol.2016.3232.
100. Zhan X, Jickling GC, Ander BP, Stamova B, Liu D, Kao PF, et al. Myelin basic protein associates with A$\beta$PP, A$\beta_{1\text{-}42}$, and amyloid plaques in cortex of Alzheimer's disease brain. J Alzheimers Dis 2015; 44(4): 1213–29. https://doi.org/10.3233/JAD-142013.
101. Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci 1993; 16(11): 460–5. https://doi.org/10.1016/0166-2236(93)90078-z.
102. Brion J-P. Neurofibrillary tangles and Alzheimer's disease. Eur Neurol 1998; 40(3): 130–40. https://doi.org/10.1159/000007969.
103. Burns J, Galvin J, Roe C, Morris J, McKeel D. The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. Neurology 2005; 64(8): 1397–403. https://doi.org/10.1212/01.WNL.0000158423.05224.7F.
104. Gibb W, Mountjoy C, Mann D, Lees A. The substantia nigra and ventral tegmental area in Alzheimer's disease and Down's syndrome. J Neurol Neurosurg Psychiatry 1989; 52(2): 193–200. https://doi.org/10.1136/jnnp.52.2.193.
105. Storga D, Vrecko K, Birkmayer J, Reibnegger G. Monoaminergic neurotransmitters, their precursors and metabolites in brains of Alzheimer patients. Neurosci Lett 1996; 203(1): 29–32. https://doi.org/10.1016/0304-3940(95)12256-7.

106. Benitez A, Fieremans E, Jensen JH, Falangola MF, Tabesh A, Ferris SH, et al. White matter tract integrity metrics reflect the vulnerability of late-myelinating tracts in Alzheimer's disease. Neuroimage Clin 2014; 4: 64–71. https://doi.org/10.1016/j.nicl.2013.11.001.
107. Tsai J, Grutzendler J, Duff K, Gan W-B. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat Neurosci 2004; 7(11): 1181–3. https://doi.org/10.1038/nn1335.
108. Gordon MN, Heneka MT, Le Page LM, Limberger C, Morgan D, Tenner AJ, et al. Impact of COVID-19 on the onset and progression of Alzheimer's disease and related dementias: a roadmap for future research. Alzheimers Dement 2022; 18(5): 1038–46. https://doi.org/10.1002/alz.12488.
109. Søraas A, Bø R, Kalleberg KT, Støer NC, Ellingjord-Dale M, Landrø NI. Self-reported memory problems 8 months after COVID-19 infection. JAMA Netw Open 2021; 4(7): e2118717. https://doi.org/10.1001/jamanetworkopen.2021.18717.
110. Ramani A, Müller L, Ostermann PN, Gabriel E, Abida-Islam P, Müller-Schiffmann A, et al. SARS-CoV-2 targets neurons of 3D human brain organoids. EMBO J 2020; 39(20): e106230. https://doi.org/10.15252/embj.2020106230.
111. Ebneth A, Godemann R, Stamer K, Illenberger S, Trinczek B, Mandelkow E-M, et al. Overexpression of tau protein inhibits kinesin-dependent trafficking of vesicles, mitochondria, and endoplasmic reticulum: implications for Alzheimer's disease. J Cell Biol 1998; 143(3): 777–94. https://doi.org/10.1083/jcb.143.3.777.
112. Hirokawa N. Microtubule organization and dynamics dependent on microtubule-associated proteins. Curr Opin Cell Biol 1994; 6(1): 74–81. https://doi.org/10.1016/0955-0674(94)90119-8.
113. Buée L, Bussière T, Buée-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Rev 2000; 33(1): 95–130. https://doi.org/10.1016/s0165-0173(00)00019-9.
114. Petrucelli L, Dickson D, Kehoe K, Taylor J, Snyder H, Grover A, et al. CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. Hum Mol Genet 2004; 13(7): 703–14. https://doi.org/10.1093/hmg/ddh083.
115. Kermanshahi S, Gholami M, Motaghinejad M. Can infection of COVID-19 virus exacerbate Alzheimer's symptoms? Hypothetic possible role of angiotensin-converting enzyme-2/Mas/brain-derived neurotrophic factor axis and Tau hyper-phosphorylation. Adv Biomed Res 2020; 9: 36. https://doi.org/10.4103/abr.abr_72_20.
116. Butterfield DA, Hensley K, Cole P, Subramaniam R, Aksenov M, Aksenova M, et al. Oxidatively induced structural alteration of glutamine synthetase assessed by analysis of spin label incorporation kinetics: relevance to Alzheimer's disease. J Neurochem 1997; 68(6): 2451–7. https://doi.org/10.1046/j.1471-4159.1997.68062451.x.
117. Moreira PI, Honda K, Liu Q, Aliev G, Oliveira CR, Santos MS, et al. Alzheimer's disease and oxidative stress: the old problem remains unsolved. Curr Med Chem Cent Nerv Syst Agents 2005; 5(1): 51–62. https://doi.org/10.2174/1568015053202714.
118. Aksenov MY, Aksenova M, Butterfield D, Hensley K, Vigo-Pelfrey C, Carney J. Glutamine synthetase-induced enhancement of $\beta$-amyloid peptide A$\beta$ (1–40) neurotoxicity accompanied by abrogation of fibril formation and A$\beta$ fragmentation. J Neurochem 1996; 66(5): 2050–6. https://doi.org/10.1046/j.1471-4159.1996.66052050.x.
119. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, et al. Vascular cognitive impairment and dementia: JACC scientific expert panel. J Am Coll Cardiol 2019; 73(25): 3326–44. https://doi.org/10.1016/j.jacc.2019.04.034.
120. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, et al. Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study. Alzheimers Dement 2018; 14(3): 280–92. https://doi.org/10.1016/j.jalz.2017.09.007.

121. Ying H, Jianping C, Jianqing Y, Shanquan Z. Cognitive variations among vascular dementia subtypes caused by small-, large-, or mixed-vessel disease. Arch Med Sci 2016; 12(4): 747–53. https://doi.org/10.5114/aoms.2016.60962.
122. Skrobot OA, Attems J, Esiri M, Hortobágyi T, Ironside JW, Kalaria RN, et al. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. Brain 2016; 139(11): 2957–69. https://doi.org/10.1093/brain/aww214.
123. Strozyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, et al. Contribution of vascular pathology to the clinical expression of dementia. Neurobiol Aging 2010; 31(10): 1710–20. https://doi.org/10.1016/j.neurobiolaging.2008.09.011.
124. Parsi MM, Duval C, Ariëns RA. Vascular dementia and crosstalk between the complement and coagulation systems. Front Cardiovasc Med 2021; 8: 803169. https://doi.org/10.3389/fcvm.2021.803169.
125. Khan U, Porteous L, Hassan A, Markus HS. Risk factor profile of cerebral small vessel disease and its subtypes. J Neurol Neurosurg Psychiatry 2007; 78(7): 702–6. https://doi.org/10.1136/jnnp.2006.103549.
126. Parfenov VA, Ostroumova OD, Ostroumova TM, Kochetkov AI, Fateeva VV, Khacheva KK, et al. Vascular cognitive impairment: pathophysiological mechanisms, insights into structural basis, and perspectives in specific treatments. Neuropsychiatr Dis Treat 2019; 15: 1381–402. https://doi.org/10.2147/Ndt.S197032.
127. Quick S, Moss J, Rajani RM, Williams A. A vessel for change: endothelial dysfunction in cerebral small vessel disease. Trends Neurosci 2021; 44(4): 289–305. https://doi.org/10.1016/j.tins.2020.11.003.
128. Low A, Mak E, Rowe JB, Markus HS, O'Brien JT. Inflammation and cerebral small vessel disease: a systematic review. Ageing Res Rev 2019; 53: 100916. https://doi.org/10.1016/j.arr.2019.100916.
129. Poggesi A, Pasi M, Pescini F, Pantoni L, Inzitari D. Circulating biologic markers of endothelial dysfunction in cerebral small vessel disease: a review. J Cereb Blood Flow Metab 2016; 36(1): 72–94. https://doi.org/10.1038/jcbfm.2015.116.
130. Zhang M, Mao Y, Ramirez S, Tuma R, Chabrashvili T. Angiotensin II induced cerebral microvascular inflammation and increased blood–brain barrier permeability via oxidative stress. Neuroscience 2010; 171(3): 852–8. https://doi.org/10.1016/j.neuroscience.2010.09.029.
131. Gomolak JR, Didion SP. Angiotensin II-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation. Front Physiol 2014; 5: 396. https://doi.org/10.3389/fphys.2014.00396.
132. Dinh QN, Young MJ, Evans MA, Drummond GR, Sobey CG, Chrissobolis S. Aldosterone-induced oxidative stress and inflammation in the brain are mediated by the endothelial cell mineralocorticoid receptor. Brain Res 2016; 1637: 146–53. https://doi.org/10.1016/j.brainres.2016.02.034.
133. Greenlund KJ, Neff LJ, Zheng Z-J, Keenan NL, Giles WH, Ayala CA, et al. Low public recognition of major stroke symptoms. Am J Prev Med 2003; 25(4): 315–9. https://doi.org/10.1016/s0749-3797(03)00206-x.
134. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010; 87(5): 779–89. https://doi.org/10.1189/jlb.1109766.
135. Grønberg NV, Johansen FF, Kristiansen U, Hasseldam H. Leukocyte infiltration in experimental stroke. J Neuroinflammation 2013; 10(1): 115. https://doi.org/10.1186/1742-2094-10-115.
136. Goodfellow JA, Dani K, Stewart W, Santosh C, McLean J, Mulhern S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: an important cause of stroke in young people. Postgrad Med J 2012; 88(1040): 326–34. https://doi.org/10.1136/postgradmedj-2011-130326.
137. Allen CL, Bayraktutan U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. Int J Stroke 2009; 4(6): 461–70. https://doi.org/10.1111/j.1747-4949.2009.00387.x.
138. Kim JY, Park J, Chang JY, Kim S-H, Lee JE. Inflammation after ischemic stroke: the role of leukocytes and glial cells. Exp Neurobiol 2016; 25(5): 241–51. https://doi.org/10.5607/en.2016.25.5.241.

139. Moro MA, Almeida A, Bolaños JP, Lizasoain I. Mitochondrial respiratory chain and free radical generation in stroke. Free Radic Biol Med 2005; 39(10): 1291–304. https://doi.org/10.1016/j.freeradbiomed.2005.07.010.
140. Ormstad H, Aass HCD, Amthor K-F, Lund-Sørensen N, Sandvik L. Serum cytokine and glucose levels as predictors of poststroke fatigue in acute ischemic stroke patients. J Neurol 2011; 258(4): 670–6. https://doi.org/10.1007/s00415-011-5962-8.
141. Khatri R, McKinney AM, Swenson B, Janardhan V. Blood–brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. Neurology 2012; 79(13 Suppl 1): S52–7. https://doi.org/10.1212/WNL.0b013e3182697e70.
142. Chen G, Li X, Gong Z, Xia H, Wang Y, Wang X, et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. PLoS One 2021; 16(4): e0250815. https://doi.org/10.1371/journal.pone.0250815.
143. Akpek M. Does COVID-19 cause hypertension? Angiology 2021: 00033197211053903. https://doi.org/10.1177/00033197211053903.
144. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020; 76: 14–20. https://doi.org/10.1016/j.ejim.2020.04.037.
145. Santamarina MG, Boisier D, Contreras R, Baque M, Volpacchio M, Beddings I. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit Care 2020; 24(1): 395. https://doi.org/10.1186/s13054-020-03125-9.
146. Lumbers ER, Head R, Smith GR, Delforce SJ, Jarrott B, H Martin J, et al. The interacting physiology of COVID-19 and the renin-angiotensin-aldosterone system: key agents for treatment. Pharmacol Res Perspect 2022; 10(1): e00917. https://doi.org/10.1002/prp2.917.
147. Yuan Y, Li N, Liu Y, Zhu Q, Heizhati M, Zhang W, et al. Positive association between plasma aldosterone concentration and white matter lesions in patients with hypertension. Front Endocrinol (Lausanne) 2021; 12: 753074. https://doi.org/10.3389/fendo.2021.753074.
148. Li CC, Chen WX, Wang J, Xia M, Jia ZC, Guo C, et al. Nicotinamide riboside rescues angiotensin II–induced cerebral small vessel disease in mice. CNS Neurosci Ther 2020; 26(4): 438–47. https://doi.org/10.1111/cns.13276.
149. Liu Y, Dong Y-H, Lyu P-Y, Chen W-H, Li R. Hypertension-induced cerebral small vessel disease leading to cognitive impairment. Chin Med J 2018; 131(05): 615–9. https://doi.org/10.4103/0366-6999.226069.
150. Spence JD, De Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, et al. Mechanisms of stroke in COVID-19. Cerebrovasc Dis 2020; 49(4): 451–8. https://doi.org/10.1159/000509581.
151. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. Stroke 2020; 51(9): e254–8. https://doi.org/10.1161/STROKEAHA.120.031208.
152. Qin C, Zhou L, Hu Z, Yang S, Zhang S, Chen M, et al. Clinical characteristics and outcomes of COVID-19 patients with a history of stroke in Wuhan, China. Stroke 2020; 51(7): 2219–23. https://doi.org/10.1161/STROKEAHA.120.030365.
153. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointerv Surg 2021; 13(3): 202–6. https://doi.org/10.1136/neurintsurg-2020-016794.
154. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain 2020; 143(10): 3089–103. https://doi.org/10.1093/brain/awaa239.
155. Tan Y-K, Goh C, Leow AS, Tambyah PA, Ang A, Yap E-S, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis 2020; 50(3): 587–95. https://doi.org/10.1007/s11239-020-02228-y.

156. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020; 143(10): 3104–20. https://doi.org/10.1093/brain/awaa240.
157. Zhang L, Sun W, Wang Y, Wang X, Liu Y, Zhao S, et al. Clinical course and mortality of stroke patients with coronavirus disease 2019 in Wuhan, China. Stroke 2020; 51(9): 2674–82. https://doi.org/10.1161/STROKEAHA.120.030642.
158. Fan S, Xiao M, Han F, Xia P, Bai X, Chen H, et al. Neurological manifestations in critically ill patients with COVID-19: a retrospective study. Front Neurol 2020; 11: 806. https://doi.org/10.3389/fneur.2020.00806.
159. Keller E, Brandi G, Winklhofer S, Imbach LL, Kirschenbaum D, Frontzek K, et al. Large and small cerebral vessel involvement in severe COVID-19: detailed clinical workup of a case series. Stroke 2020; 51(12): 3719–22. https://doi.org/10.1161/STROKEAHA.120.031224.
160. Yuen KC, Sharf V, Smith E, Kim M, Yuen AS, MacDonald PR. Sodium and water perturbations in patients who had an acute stroke: clinical relevance and management strategies for the neurologist. Stroke Vasc Neurol 2021:svn-2021-001230. https://doi.org/10.1136/svn-2021-001230.
161. Neary D, Snowden J, Mann D. Frontotemporal dementia. Lancet Neurol 2005; 4(11): 771–80. https://doi.org/10.1016/S1474-4422(05)70223-4.
162. Nolan M, Talbot K, Ansorge O. Pathogenesis of FUS-associated ALS and FTD: insights from rodent models. Acta Neuropathol Commun 2016; 4(1): 99. https://doi.org/10.1186/s40478-016-0358-8.
163. Dickson DW. Neuropathology of Pick's disease. Neurology 2001; 56(11 Suppl 4): S16–20. https://doi.org/10.1212/wnl.56.suppl_4.s16.
164. Hodges JR, Miller B. The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: Part I. Neurocase 2001; 7(1): 31–5. https://doi.org/10.1093/neucas/7.1.31.
165. Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004; 56(3): 399–406. https://doi.org/10.1002/ana.20203.
166. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 2006; 351(3): 602–11. https://doi.org/10.1016/j.bbrc.2006.10.093.
167. Snowden JS, Hu Q, Rollinson S, Halliwell N, Robinson A, Davidson YS, et al. The most common type of FTLD-FUS (aFTLD-U) is associated with a distinct clinical form of frontotemporal dementia but is not related to mutations in the FUS gene. Acta Neuropathol 2011; 122(1): 99–110. https://doi.org/10.1007/s00401-011-0816-0.
168. Olney NT, Spina S, Miller BL. Frontotemporal dementia. Neurol Clin 2017; 35(2): 339–74. https://doi.org/10.1016/j.ncl.2017.01.008.
169. Rademakers R, Cruts M, Van Broeckhoven C. The role of tau (MAPT) in frontotemporal dementia and related tauopathies. Hum Mutat 2004; 24(4): 277–95. https://doi.org/10.1002/humu.20086.
170. Idrees D, Kumar V. SARS-CoV-2 spike protein interactions with amyloidogenic proteins: potential clues to neurodegeneration. Biochem Biophys Res Commun 2021; 554: 94–8. https://doi.org/10.1016/j.bbrc.2021.03.100.
171. Tavassoly O, Safavi F, Tavassoly I. Heparin-binding peptides as novel therapies to stop SARS-CoV-2 cellular entry and infection. Mol Pharmacol 2020; 98(5): 612–9. https://doi.org/10.1124/molpharm.120.000098.
172. De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006; 5(6): 525–35. https://doi.org/10.1016/S1474-4422(06)70471-9.
173. Han S, Kim S, Kim H, Shin H-W, Na K-S, Suh HS. Prevalence and incidence of Parkinson's disease and drug-induced parkinsonism in Korea. BMC Public Health 2019; 19(1): 1328. https://doi.org/10.1186/s12889-019-7664-6.

174. Roos DS, Twisk JW, Raijmakers PG, Doty RL, Berendse HW. Hyposmia as a marker of (non-) motor disease severity in Parkinson's disease. J Neural Transm 2019; 126(11): 1471–8. https://doi.org/10.1007/s00702-019-02074-0.
175. Armstrong RA. Visual signs and symptoms of Parkinson's disease. Clin Exp Optom 2008; 91(2): 129–38. https://doi.org/10.1111/j.1444-0938.2007.00211.x.
176. Triarhou LC. Dopamine and Parkinson's disease 2013. In: Madame curie bioscience database [Internet]. Austin, TX: Landes Bioscience. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6271/.
177. Kirsch-Darrow L, Marsiske M, Okun MS, Bauer R, Bowers D. Apathy and depression: separate factors in Parkinson's disease. J Int Neuropsychol Soc 2011; 17(6): 1058–66. https://doi.org/10.1017/S1355617711001068.
178. Recasens A, Dehay B. Alpha-synuclein spreading in Parkinson's disease. Front Neuroanat 2014; 8: 159. https://doi.org/10.3389/fnana.2014.00159.
179. Brundin P, Nath A, Beckham JD. Is COVID-19 a perfect storm for Parkinson's disease? Trends Neurosci 2020; 43(12): 931–3. https://doi.org/10.1016/j.tins.2020.10.009.
180. Faber I, Brandao PR, Menegatti F, de Carvalho Bispo DD, Maluf FB, Cardoso F. Coronavirus disease 2019 and parkinsonism: a non-post-encephalitic case. Mov Disord 2020; 35(10): 1721–2. https://doi.org/10.1002/mds.28277.
181. Cohen ME, Eichel R, Steiner-Birmanns B, Janah A, Ioshpa M, Bar-Shalom R, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. Lancet Neurol 2020; 19(10): 804–5. https://doi.org/10.1016/S1474-4422(20)30305-7.
182. Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, Ruiz-Ortiz M, Blanco-Palmero VA, Azcarate-Diaz FJ, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. Neurology 2020; 95(15): e2109–18. https://doi.org/10.1212/WNL.0000000000010282.
183. Makhoul K, Jankovic J. Parkinson's disease after COVID-19. J Neurol Sci 2021; 422: 117331. https://doi.org/10.1016/j.jns.2021.117331.
184. Rao AR, Hidayathullah SM, Hegde K, Adhikari P. Parkinsonism: an emerging post COVID sequelae. IDCases 2022:e01388. https://doi.org/10.1016/j.idcr.2022.e01388.
185. Ayele BA, Demissie H, Awraris M, Amogne W, Shalash A, Ali K, et al. SARS-COV-2 induced Parkinsonism: the first case from the sub-Saharan Africa. Clin Park Relat Disord 2021; 5: 100116. https://doi.org/10.1016/j.prdoa.2021.100116.
186. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008; 82(15): 7264–75. https://doi.org/10.1128/JVI.00737-08.
187. Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, Reznikov LR, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J Infect Dis 2016; 213(5): 712–22. https://doi.org/10.1093/infdis/jiv499.
188. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277(8): 2251–61. https://doi.org/10.1007/s00405-020-05965-1.
189. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis 2020; 71(15): 889–90. https://doi.org/10.1093/cid/ciaa330.
190. Lovato A, De Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. Ear Nose Throat J 2020; 99(9): 569–76. https://doi.org/10.1177/0145561320920762.

191. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004; 56(2): 173–81. https://doi.org/10.1002/ana.20160.
192. Mahalaxmi I, Kaavya J, Mohana Devi S, Balachandar V. COVID-19 and olfactory dysfunction: a possible associative approach towards neurodegenerative diseases. J Cell Physiol 2021; 236(2): 763–70. https://doi.org/10.1002/jcp.29937.
193. Quitadamo PA, Comegna L, Cristalli P. Anti-infective, anti-inflammatory, and immunomodulatory properties of breast milk factors for the protection of infants in the pandemic from COVID-19. Front Public Health 2021; 8: 589736. https://doi.org/10.3389/fpubh.2020.589736.
194. Conte C. Possible link between SARS-CoV-2 infection and Parkinson's disease: the role of toll-like receptor 4. Int J Mol Sci 2021; 22(13): 7135. https://doi.org/10.3390/ijms22137135.
195. Tomé CML, Tyson T, Rey NL, Grathwohl S, Britschgi M, Brundin P. Inflammation and $\alpha$-synuclein's prion-like behavior in Parkinson's disease—is there a link? Mol Neurobiol 2013; 47(2): 561–74. https://doi.org/10.1007/s12035-012-8267-8.
196. Pasqualetti G, Brooks DJ, Edison P. The role of neuroinflammation in dementias. Curr Neurol Neurosci Rep 2015; 15(4): 17. https://doi.org/10.1007/s11910-015-0531-7.
197. Bright F, Werry EL, Dobson-Stone C, Piguet O, Ittner LM, Halliday GM, et al. Neuroinflammation in frontotemporal dementia. Nat Rev Neurol 2019; 15(9): 540–55. https://doi.org/10.1038/s41582-019-0231-z.
198. Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J Immunol 2004; 173(6): 3916–24. https://doi.org/10.4049/jimmunol.173.6.3916.
199. Semerdzhiev SA, Fakhree MAA, Segers-Nolten I, Blum C, Claessens MMAE. Interactions between SARS-CoV-2 N-protein and $\alpha$-synuclein accelerate amyloid formation. ACS Chem Neurosci 2022; 13(1): 143–50. https://doi.org/10.1021/acschemneuro.1c00666.
200. Bendor JT, Logan TP, Edwards RH. The function of $\alpha$-synuclein. Neuron 2013; 79(6): 1044–66. https://doi.org/10.1016/j.neuron.2013.09.004.
201. Garretti F, Agalliu D, Lindestam Arlehamn CS, Sette A, Sulzer D. Autoimmunity in Parkinson's Disease: the role of $\alpha$-synuclein-specific T cells. Front Immunol 2019; 10: 303. https://doi.org/10.3389/fimmu.2019.00303.
202. Arlehamn CSL, Garretti F, Sulzer D, Sette A. Roles for the adaptive immune system in Parkinson's and Alzheimer's diseases. Curr Opin Immunol 2019; 59: 115–20. https://doi.org/10.1016/j.coi.2019.07.004.
203. Block ML, Zecca L, Hong J-S. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 2007; 8(1): 57–69. https://doi.org/10.1038/nrn2038.
204. Haddadi K, Ghasemian R, Shafizad M. Basal ganglia involvement and altered mental status: a unique neurological manifestation of coronavirus disease 2019. Cureus 2020; 12(4): e7869. https://doi.org/10.7759/cureus.7869.
205. Aschrafi A, Berndt A, Kowalak JA, Gale JR, Gioio AE, Kaplan BB. Angiotensin II mediates the axonal trafficking of tyrosine hydroxylase and dopamine $\beta$-hydroxylase mRNAs and enhances norepinephrine synthesis in primary sympathetic neurons. J Neurochem 2019; 150(6): 666–77. https://doi.org/10.1111/jnc.14821.
206. Costa-Besada MA, Valenzuela R, Garrido-Gil P, Villar-Cheda B, Parga JA, Lanciego JL, et al. Paracrine and intracrine angiotensin 1-7/Mas receptor axis in the substantia nigra of rodents, monkeys, and humans. Mol Neurobiol 2018; 55(7): 5847–67. https://doi.org/10.1007/s12035-017-0805-y.
207. Hernández VS, Zetter MA, Guerra EC, Hernández-Araiza I, Karuzin N, Hernández-Pérez OR, et al. ACE2 expression in rat brain: implications for COVID-19 associated neurological manifestations. Exp Neurol 2021; 345: 113837. https://doi.org/10.1016/j.expneurol.2021.113837.
208. Cilia R, Bonvegna S, Straccia G, Andreasi NG, Elia AE, Romito LM, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. Mov Disord 2020; 35(8): 1287–92. https://doi.org/10.1002/mds.28170.

209. Galvin M, Gaffney R, Corr B, Mays I, Hardiman O. From first symptoms to diagnosis of amyotrophic lateral sclerosis: perspectives of an Irish informal caregiver cohort—a thematic analysis. BMJ Open 2017; 7(3): e014985. https://doi.org/10.1136/bmjopen-2016-014985.
210. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol 2020; 27(10): 1918–29. https://doi.org/10.1111/ene.14393.
211. Min YG, Choi S-J, Hong Y-H, Kim S-M, Shin J-Y, Sung J-J. Dissociated leg muscle atrophy in amyotrophic lateral sclerosis/motor neuron disease: the 'split-leg'sign. Sci Rep 2020; 10(1): 15661. https://doi.org/10.1038/s41598-020-72887-7.
212. Watts CR, Vanryckeghem M. Laryngeal dysfunction in amyotrophic lateral sclerosis: a review and case report. BMC Ear Nose Throat Disord 2001; 1(1): 1. https://doi.org/10.1186/1472-6815-1-1.
213. Benkler C, O'Neil AL, Slepian S, Qian F, Weinreb PH, Rubin LL. Aggregated SOD1 causes selective death of cultured human motor neurons. Sci Rep 2018; 8(1): 16393. https://doi.org/10.1038/s41598-018-34759-z.
214. Mackenzie IR, Rademakers R, Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. Lancet Neurol 2010; 9(10): 995–1007. https://doi.org/10.1016/S1474-4422(10)70195-2.
215. Ling JP, Pletnikova O, Troncoso JC, Wong PC. TDP-43 repression of nonconserved cryptic exons is compromised in ALS-FTD. Science 2015; 349(6248): 650–5. https://doi.org/10.1126/science.aab0983.
216. Liu C, Zhang Y. Nucleic acid-mediated protein aggregation and assembly. Adv Protein Chem Struct Biol 2011; 84: 1–40. https://doi.org/10.1016/B978-0-12-386483-3.00005-7.
217. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med 2017; 377(2): 162–72. https://doi.org/10.1056/NEJMra1603471.
218. van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. Lancet 2017; 390(10107): 2084–98. https://doi.org/10.1016/s0140-6736(17)31287-4.
219. Cabona C, Ferraro PM, Meo G, Roccatagliata L, Schenone A, Inglese M, et al. Predictors of self-perceived health worsening over COVID-19 emergency in ALS. Neurol Sci 2021; 42(4): 1231–6. https://doi.org/10.1007/s10072-020-04997-z.
220. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem 2008; 107(6): 1482–94. https://doi.org/10.1111/j.1471-4159.2008.05723.x.
221. Srivastava G, Tripathi RK, Tiwari SC, Singh B, Tripathi SM. Caregiver burden and quality of life of key caregivers of patients with dementia. Indian J Psychol Med 2016; 38(2): 133–6. https://doi.org/10.4103/0253-7176.178779.
222. Salari M, Zali A, Ashrafi F, Etemadifar M, Sharma S, Hajizadeh N, et al. Incidence of anxiety in Parkinson's disease during the coronavirus disease (COVID-19) pandemic. Mov Disord 2020; 35(7): 1095–6. https://doi.org/10.1002/mds.28116.
223. El Haj M, Altintas E, Chapelet G, Kapogiannis D, Gallouj K. High depression and anxiety in people with Alzheimer's disease living in retirement homes during the covid-19 crisis. Psychiatry Res 2020; 291: 113294. https://doi.org/10.1016/j.psychres.2020.113294.
224. Santabárbara J, Lipnicki DM, Olaya B, Villagrasa B, Bueno-Notivol J, Nuez L, et al. Does anxiety increase the risk of all-cause dementia? An updated meta-analysis of prospective cohort studies. J Clin Med 2020; 9(6): 1791. https://doi.org/10.3390/jcm9061791.
225. Verkhratsky A, Li Q, Melino S, Melino G, Shi Y. Can COVID-19 pandemic boost the epidemic of neurodegenerative diseases? Biol Direct 2020; 15(1): 28. https://doi.org/10.1186/s13062-020-00282-3.