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REVIEW

Neuropathies and neurological dysfunction induced by coronaviruses

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Abstract
During the recent years, viral epidemic due to coronaviruses, such as SARS (Severe Acute Respiratory Syndrome), Middle East Respiratory Coronavirus Syndrome (MERS), and COVID-19 (coronavirus disese-19), has become a global problem. In addition to causing cardiovascular and respiratory lethal dysfunction, these viruses can cause neurodegeneration leading to neurological disorders. Review of the current scientific literature reveals the multiple neuropathies and neuronal dysfunction associated with these viruses. Here, we review the major findings of these studies and discuss the main neurological sequels and outcomes of coronavirus infections with SARS, MERS, and COVID-19. This article analyzes and discusses the main mechanisms of coronavirus-induced neurodegeneration according to the current experimental and clinical studies. Coronaviruses can damage the nerves directly through endovascular dysfunctions thereby affecting nerve structures and synaptic connections. Coronaviruses can also induce neural cell degeneration indirectly via mitochondrial dysfunction inducing oxidative stress, inflammation, and apoptosis. Thus, coronaviruses can cause neurological disorders by inducing neurovascular dysfunction affecting nerve structures and synaptic connections, and by inducing inflammation, oxidative stress, and apoptosis. While some of these mechanisms are similar to other RNA viruses, the neurotoxic mechanisms of COVID-19, MERS, and SARS-CoV viruses are unknown and need detailed clinical and experimental studies.

Keywords Coronavirus · Neurodegeneration

Introduction

Coronavirus disease (COVID)-19 is a lethal syndrome characterized by severe acute respiratory syndrome induced by coronavirus 2 (SARS-CoV2) infections. COVID-19 has become a global pandemic that started in 2019 that became a public health emergency killing over 2 million people in the first year (Spinelli and Pellino 2020; Watkins 2020). Coronaviruses have an average diameter of 100 nm with a spherical or oval shape. The name of coronavirus refers to the large spikes of glycoproteins in the membrane on this virus causing a typical crown-like shape under electron microscopy (Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007). These coronaviruses are single-stranded RNA viruses with a genome length of approximately 26–32 kb representing the largest genome of currently known RNA viruses (Satija and Lal 2007; Anand et al. 2002). These coronaviruses enter the host cell via ACE2 receptors, and its mechanism of replication is represented in Fig. 1. Coronaviruses induce multiple disorders including respiratory, cardiovascular, hepatocellular, and renal dysfunction (Wu et al. 2020; Xu et al. 2020; Madjid et al. 2020; Eckerle et al. 2013) (Fig. 2). However, some viruses such as SARS (severe acute respiratory syndrome), Middle East respiratory coronavirus syndrome (MERS), and coronavirus disese-19 (COVID-19) can become lethal with severe long-term respiratory and cardiovascular dysfunctions (Madjid et al. 2020; Xiong et al. 2020; Guo et al. 2019). One of the fatal consequences of coronavirus infection is a lasting neurodegeneration and neuropathy even in those patients surviving the infection (Nagashima et al. 1979; Bergmann et al. 2006; Yeh et al. 2004). Multiple studies show that coronaviruses are neurotropic as they can

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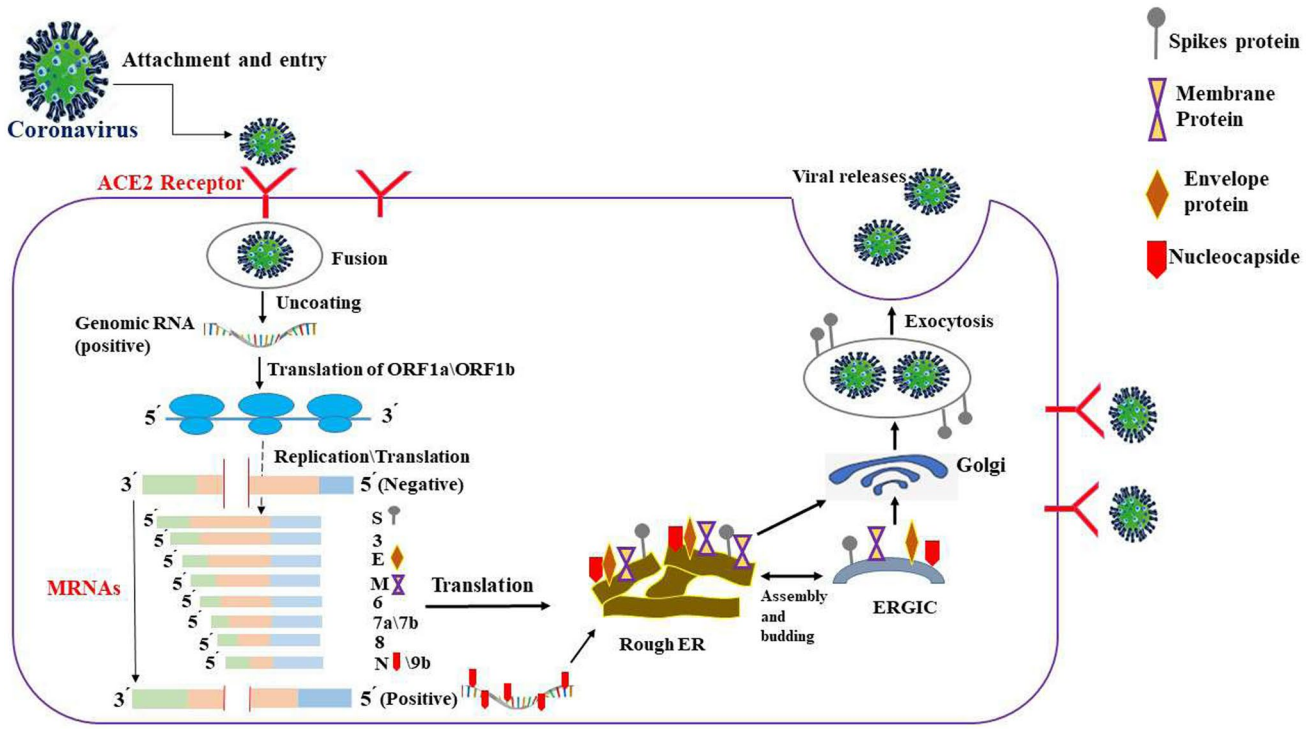

Fig. 1 The life cycle of coronavirus: At the beginning, S protein binds to the ACE2 receptor in host cells. Then, the conformation of S protein is changed and causes the virus envelope to merge with the cell membrane via the endosomal pathway. Next coronavirus releases its RNA into the host cell. Genome RNA is translated to viral replicas polyproteins pp1a and 1ab. That polyproteins disparted to small proteins by proteinases. Polymerase makes some of subgenomic mRNAs by discontinuous transcription and finally translated to viral proteins. Viral proteins and genome RNA are assembled to the ER and Golgi. After that, it transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment

invade nervous tissues and infect the microglia or astrocytes in the CNS (Desforges et al. 2014a; Li et al. 2020a). Clinical studies show that COVID-19 patients can have seizures and loss of consciousness that can become fatal. Latest studies report that approximately 36% of COVID-19 patients exhibit neurological symptoms such as stroke, headache, impaired consciousness, and paresthesia (Wu et al. 2020; Bagheri et al. 2020). COVID-19 patients can also exhibit neurobehavioral symptoms such as anxiety and depression, as well as cognitive dysfunction especially in elderly patients, which are the most susceptible to the infection (Khan et al. 2020; Watanabe et al. 1983). Autopsies of COVID-19 patients show edema, neuronal degeneration, and viral encephalitis as common neurological consequences of the infection (Barton et al. 2020; Jacomy and Talbot 2003; Jacomy et al. 2006). This critical impact of COVID-19 on the nervous system and its social and clinical implications has fostered many investigators to analyze the molecular mechanisms mediating this neurotoxicity (Jacomy et al. 2006; Tsukamoto et al. 1990). The neurotropic potential of these viruses was first suggested by their concentrations in the cerebrospinal fluid, but their pathological mechanisms are still moot (Hung et al. 2003; Doenges et al. 2016). Here, we review the clinical and experimental studies to discuss the key mechanisms of coronavirus-induced neuropathies. We report the major findings, clinical management strategies, and therapies related to neuropathies induced by these coronaviruses. This information provides to clinicians better neurotoxicity and neuropathies induced by the coronaviruses.

Effects of multiple main types of coronaviruses on nervous system

SARS-CoV neurological sequels

In 2002–2003, there was a global epidemic of severe acute respiratory syndrome (SARS), a zoonotic respiratory disease that started in Asia and spread worldwide (Ong et al. 2020). SARS patients typically have respiratory-related symptoms associated with fever, chills, dry cough, and difficult breathing, as well as neurological manifestations that were rarely described (Paybast et al. 2020; Zegarra-Valdivia et al. 2020). Neurological signs included axonopathic polyneuropathy, myopathy, encephalitis, and ischemic aortic stroke (Zegarra-Valdivia et al.

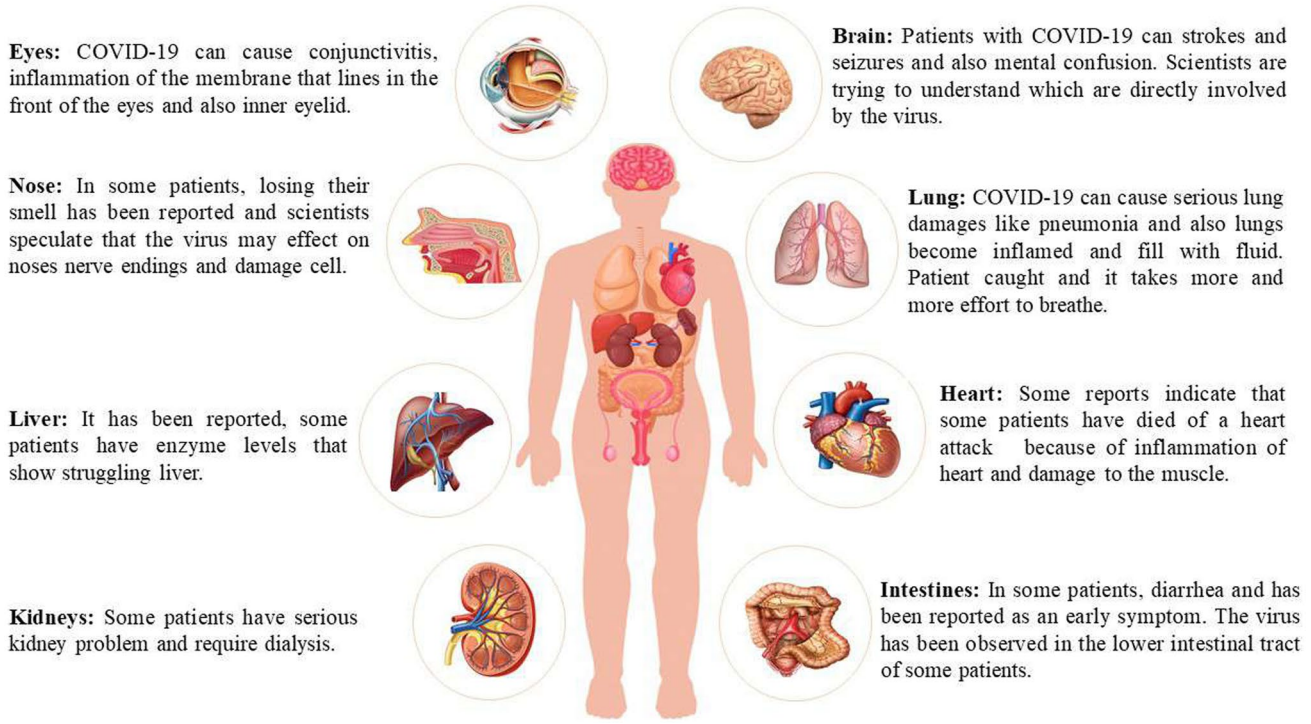

Fig. 2 Multiple effects of infection with Coronaviruses Family, such as SARS (Severe Acute Respiratory Syndrome), Middle East Respiratory Coronavirus Syndrome (MERS) and COVID-19 (coronavirus disese-19), on body organs and systems

2020; Calcagno et al. 2020). Myopathic and neuropathic complications have also been reported in SARS patients, and clinicians should be aware of the potential neuromuscular complaints (Ding et al. 2004; Lau and Chan 2005). SARS-CoV infection can cause transient ischemic attack, partial epilepsy, and mild cognitive impairments (Umapathi et al. 2004; Lin et al. 2020). Some authors suggested that neurobehavioral symptoms such as agitation and mood-related behavior can be signs of SARS-CoV infection associated with cerebral edema and meningeal vasodilation (Iroegbu et al. 2020; Chevance et al. 2020).

Leukocytes, such as monocytes and lymphocytes, were also increased in the vessel wall of the brain of SARS-CoV patients, leading to ischemic and inflammatory changes in the nerves and in extreme cases demyelination of nerve fibers (Paniz-Mondolfi et al. 2020; Conde et al. 2020). Several studies showed the presence of these viral particles and genome in the cerebrospinal fluid (CSF) to confirm the direct effects of SARS-CoV on brain tissues (Paniz-Mondolfi et al. 2020; Conde et al. 2020).

MERS-CoV neurological sequels

The Middle East respiratory syndrome (MERS), caused by MERS-CoV, was first reported in Saudi Arabia in June 2012 and also originated from bats with camels reported as intermediate host (Alfaraj et al. 2019; Banik et al. 2015). MERS-CoV causes extreme respiratory infections leading to acute respiratory distress (ARDS) syndrome, which causes pneumonia, fever, myalgia, cough, dyspnea, septic shock, multiple organ failure, and death (Zumla et al. 2015; Group WM-CR 2013). Previous reported MERS-CoV is a neuroinvasive and neurotrophic virus that can trigger neurological effects such as loss of consciousness, paralysis, ischemic stroke, Guillain–Barre syndrome, and other neuropathies (Desforges et al. 2014a; Li et al. 2020a; Yashavantha Rao and Jayabaskaran 2020). MERS-CoV induces widespread, bilateral, hyper-intensive lesions in the white matter and subcortical areas of the basal ganglia, corpus callosum, frontal, temporal, and parietal lobes (Desforges et al. 2014a; Coupanec et al. 2015). The presence of MERS-CoV in the cerebrospinal fluid (CSF) has not been confirmed, but its neurotoxicity has been well accepted (Desforges et al. 2014a; Coupanec et al. 2015).

SARS-CoV-2 (COVID-19)

The genetic similarity between SARS-CoV-2 and SARS-CoV is 79.5%. Therefore, these two viruses are expected to have similar pathological mechanisms (Lai et al. 2020; Zhang et al. 2020). SARS-CoV-2 causes multiple symptoms, such as

fever, mild pneumonia cough, and multiple organ dysfunctions with a mortality rate of 2–4% (Zheng et al. 2020; Velavan and Meyer 2020). COVID-19 induces neurological effects including headache, epilepsy, and impaired consciousness (Baig 2020; Ye et al. 2020). Anosmia and dysgeusia with sudden loss of odor or taste can occur in COVID-19 patients (Moein et al. 2020; Eliezer et al. 2020; Lechien et al. 2020). Recent genome sequencing analyses confirmed the presence of SARS-CoV-2 in cerebrospinal fluids associated with some cases of viral encephalitis caused by COVID-19. Clinical reports have shown that patients with extreme COVID-19 infection can have headaches, projectile vomiting, vision impairment, and limbs paralysis (Wu et al. 2020; Li et al. 2020b).

Mechanisms of coronavirus-induced neurological dysfunction

According to recent neurological studies, coronaviruses can induce neurotoxicity through (1) direct neuronal damage or (2) indirect mechanisms, such as pathological inflammation of the nerve, oxidative stress, and apoptosis (Fig. 3).

Direct neuronal damage is mediated through the following pathways:

1. Entering CNS through bloodstream and inducing endovascular dysfunction

a) Invasion by infected circulating leukocytes:

Coronaviruses can enter the nervous system without infecting neurons, as they can infect leukocytes, which circulate in the bloodstream and can penetrate the parenchyma of the brain (Zhong et al. 2003; Nowacki and Charley 1993). This mechanism of neuronal penetration and infection is not completely understood (Nowacki and Charley 1993; Desforges et al. 2014b), but it is described in literature as the "Trojan horse" entry, as the pathogens concealed inside the leukocytes can cross the blood-brain-barrier (Paniz-Mondolfi et al. 2020; Talbot et al. 2011). Although this mechanism has not been confirmed yet, indirect evidence showing the involvement of monocytes/macrophages in the pathogenesis strongly supports their contribution to viral penetration into the brain (Paniz-Mondolfi et al. 2020; Mesel-Lemoine et al. 2012). Coronaviruses primarily target $CD4^+$ T-lymphocytes and macrophages/microglia, which are specialized phagocytic and antigen-presenting cells in the CNS, and astrocytes expressing CD4 cell surface receptor (Pewe and Perlman 2002; Bergmann et al. 2004). The replication of coronaviruses is greatly affected by the immune responses with multiple cytokines and chemokines modulating its potential to enter the CNS (Brian and Baric 2005). Thus, CNS invasion may occur depending on the immune responses and the immunologic state (Desforges et al. 2014b, 2013). Infected monocyte/macrophage, which are involved in the coronaviruses pathogenicity, can cross the blood–brain-barrier and differentiate into perivascular microglia (Brian and Baric 2005). Replication of the virus in microglia and subsequent induction of inflammatory cytokines damages the CNS causing neurodegeneration and causing symptoms such as seizures and un-conciseness (Bergmann et al. 2006; Talbot et al. 2011; Parra et al. 1997). The role of coronavirus in peripheral nervous

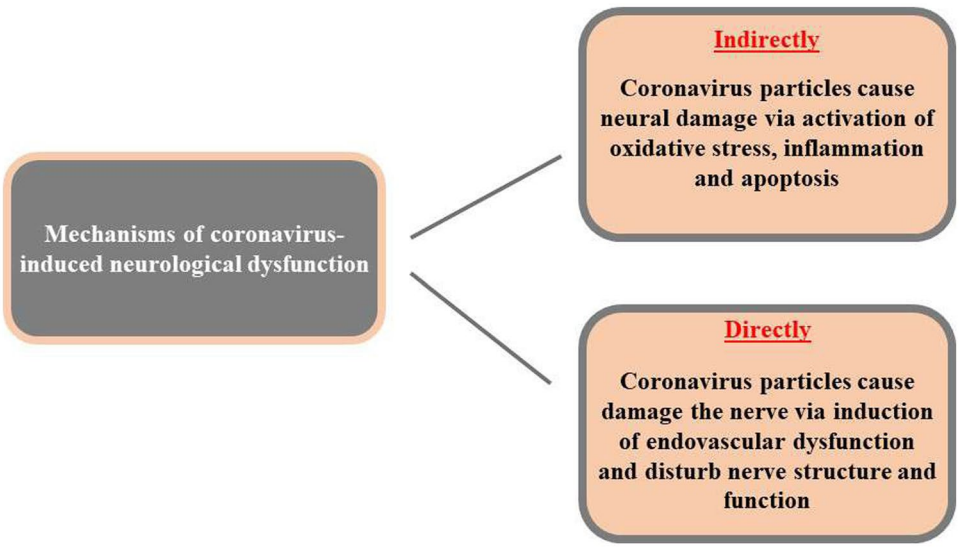

Fig. 3 Mechanisms of coronavirus-induced neurological dysfunction via directly damaging the virus particle to the nerve or microvascular system and indirectly activating of pathological mechanisms such as inflammation of the nerve, oxidative stress and apoptosis was indicated. Each of these two pathways was effect on the neural system via downstream specific mechanisms which mentioned and described in diagram

system has not been well studied, but axonopathic polyneuropathy has been reported in patients with SARS-CoV (Zegarra-Valdivia et al. 2020; Li et al. 2020c). Coronavirus can also infect oligodendrocytes (cell-producing myelin) and astrocytes, leading to fatal inflammatory disorders in the brain and degenerative symptoms such as seizures (Turner et al. 2004; Dandekar et al. 2005) (Fig. 3).

b) Infection via brain microvascular endothelium

Viral particles in the circulatory system can reach and infect brain microvascular endothelial cells (BMVECs), the major constituent of blood-brain barrier. This phenomenon occurred in RNA viruses such as coronaviruses, but the details of this mechanism are not known (Argyris et al. 2003; Liu et al. 2002). BMVEC activation can cause brain inflammation and thus neurological disorders (Wu et al. 2020; Liu et al. 2002). BMVEC activation can cause brain inflammation and thus neurological disorders (Wu et al. 2020). For example, encephalitis and meningitis may be caused by BMVEC in a percentage of infected people with coronaviruses (Wu et al. 2020). Coronavirus CNS infections are frequently associated with immune dysfunction allowing viral replication and viremia (Bergmann et al. 2006, 2004). Certain coronavirus neuropathogenesis produced by the disruption of the blood-brain barrier may allow immune cells to enter the brain and cause neurodegeneration (Wu et al. 2020; Desforges et al. 2014b; Gallagher and Buchmeier 2001). This infection not only affects the integrity of tight junction proteins, in both epithelial and endothelial cells, but also induces inflammatory factors that can degrade the basement membrane (Gallagher and Buchmeier 2001; Miner and Diamond 2016; Sun and Guan 2020). As a result, leukocytes can cross the capillaries into the surrounding tissue and produce inflammatory cytokines (Chen et al. 2001). It has been proposed that BMVECs are the only type of cells that can mediate coronavirus entry into the brain (Chen et al. 2001; Cabirac et al. 1995). Coronavirus CNS infection is also associated with increased production of pro-inflammatory cytokines (IL1, TNFα, IL12, and IL18) and creatine, with cause microglia and astrocyte activation and neurological disorders (Cabirac et al. 1995; Conti et al. 2020). A major infection can cause fatal neurodegeneration in sensory neurons and induce abnormalities such as dysosmia and dysgeusia (Keyhan et al. 2019; Lao et al. 2020). In addition to BMVECs, coronaviruses can also affect astrocytes, pericytes, neurons, microglial cells, and even neural stem cells (Chen et al. 2001; Cabirac et al. 1995). During infections, astrocytes and microglial cells can produce copious quantities of inflammatory cytokines and induce fetal neurodevelopmental disorders (Dörries 2001; Edwards et al. 2000). Virus infection of BMVECs induces the expression of inflammatory cytokines and chemokines, disrupting the blood-brain barrier and causing inflammatory neurological disorders and encephalitis (Chen et al. 2001; Desforges et al. 2007). Although the invasion of the nervous system by coronaviruses via the bloodstream is rare, there is evidence that these viruses cause vascular endothelial system disturbances that are likely to disrupt the blood-brain barrier allowing coronaviruses to enter the CNS (Wu et al. 2020; Sun and Guan 2020). Other studies have indicated that these viruses replicate in the body in mononuclear macrophages and increase cytokine production, thus raising the risk of blood-brain barrier disorders and contribute to meningitis or encephalitis (Sun and Guan 2020). After the virus reaches the nervous system, viral proteins can cause neuronal damage (Bergmann et al. 2006; Sun and Guan 2020). Some studies suggest that viruses can infect sensory or motor nerve endings, inducing retro or anterograde neuronal transport through the motor proteins such as dynein and kinesins (Bergmann et al. 2006) (Fig. 3).

2. Entering CNS through various nerve ending and disrupting nerve structures

a) Invasion of sensory nerve endings

Recent studies indicate that coronaviruses may enter the peripheral nervous system (PNS) by binding to sensory and autonomic axon-terminal receptors that convey sensory and visceral information; this phenomenon has occurred in SARS-CoV inducing axonopathic polyneuropathy (Zegarra-Valdivia et al. 2020; Li et al. 2020c). Although the mechanism and route of coronaviruses entering the PNS is unknown, it appears to be mediated by cellular adhesion molecules, especially in SARS-CoV (Heerssen et al. 2004). Coronavirus particles reach sensory nerve endings via membrane fusion and can use dynein motors for retrograde transport to the neuronal cell body (81). Virus capsids will dock at the nuclear pore, and the viral RNA is instilled into the nucleus for an acute or quiescent, latent infection (Walker and Ghildyal 2017; Prone 2007). By infecting these sensory neurons, coronaviruses can penetrate into the brain tissue through the direct connections between the peripheral and central nervous system (Wu et al. 2020) (Fig. 3).

b) Invasion of motor neurons at neuromuscular junctions (NMJs)

NMJs are specialized synapses between motor neurons and muscles to control movements and represent a gateway into the CNS for some viruses (Lai and Ip 2003; Turgay et al. 2015). Most motor neurons have their cell bodies in the spinal cord where they can connect with the brain's motor centers (Turgay et al. 2015). There are no data showing coronaviruses infecting motor neurons, but preliminary results show acute flaccid paralysis (AFP) in human coronavirus patients (Turgay et al. 2015; Guidon and Amato 2020). However, about 1% of coronavirus infections result in motor neuron infection leading to some motor dysfunction and paralysis (Guidon and Amato 2020; Cokyaman et al. 2015). Coronavirus receptors can be expressed in axonal membranes (Dubé et al. 2018). Viral particles can enter motor neuronal axons in the NMJ by binding unknown receptors or neural cell adhesion molecules (NCAMs) (Bergmann et al. 2006; Bender and Weiss 2010). Trans-neuronal spread occurs exclusively between synoptically bound neurons and the muscle with the virus moving directly into the muscles and upstream neurons, which can lead to paralysis or neurodegeneration (Hirano et al. 2004; Cowley and Weiss 2010). The analyses of motor neurons at neuromuscular junctions may define their effects on the musculoskeletal system, which is likely to depend on the genetic status of the patient (91) (Cowley and Weiss 2010) (Fig. 3).

c) Invasion via the olfactory epithelium and olfactory neurons

The olfactory system provides a special and direct gateway for coronaviruses to enter the CNS (Mori et al. 2005). The neurons that act as bipolar olfactory receptor have many branches of dendrites in the olfactory epithelium at the roof of the nasal-pharyngeal cavity where odors are detected (Mori et al. 2005; Riel et al. 2015). Dysosmia and dysgeusia are typical signs of viral infection strongly suggesting their causative effects in olfactory receptors (Keyhan et al. 2019; Lao et al. 2020). The olfactory nerve, which is part of the PNS, originates from the olfactory epithelium to the olfactory bulb in the CNS proper (Keyhan et al. 2019; Lao et al. 2020). The olfactory epithelium is well protected from most common infections by mucus and several pathogen recognition receptors (Koyuncu et al. 2013). Multiple studies suggested that coronaviruses may cause olfactory dysfunction through multiple mechanisms (Keyhan et al. 2019; Lao et al. 2020). Coronaviruses can enter the CNS through a trans-neuronal route and spread through neuroanatomic pathways to multiples brain regions (Desforges et al. 2014b). Coronaviruses tend to infect the CNS through the olfactory system after intranasal infection (Desforges et al. 2014b; Sun and Perlman 1995). For instance, human coronavirus (HCoV) can enter the CNS through the olfactory bulb, causing inflammation and demyelination (Desforges et al. 2014a; St-Jean et al. 2004). Then, the virus can infect the entire brain and CSF in less than 7 days and can cause demyelination as reported in several studies (Yeh et al. 2004; Murray et al. 1992). Neurons are highly polarized, with distinct dendrite and axonal processes (Murray et al. 1992). The maintenance and communication of distal axons with their cell bodies requires highly specialized signal transduction, intracellular sorting, trafficking, and membrane systems; coronaviruses as neurotrophic viruses are dependent on these cellular processes for migration into brain tissue (Dubé et al. 2018) (Fig. 3).

Indirect brain damage is mediated by the following molecular and cellular pathological pathways:

1) Nerve inflammation

Neurotropic RNA viruses like coronaviruses are increasingly associated with central neurological disorders (Rejdak and Grieb 2020) and can cause immune-mediated CNS pathogenesis (Hosking and Lane 2010). This immune-mediated process has been well documented with coronaviruses (Bender and Weiss 2010). Mechanisms such as the "cytokine storm" caused by an over production of inflammatory factors after the viral infection can disrupt the blood-brain barrier (Bergmann et al. 2006; Dandekar and Perlman 2005). Local production of cytokines and chemokines in the CNS can also disrupt the blood-brain barrier and reduce tight junction's stability (Weiss and Navas-Martin 2005; Weiss and Leibowitz 2011; Dörries et al. 1986). For instance, the expression of chemokine monocyte chemoattractant protein-1 (MCP-1, CCL2) is increased during coronavirus and other viral infections (Jiang et al. 2005; Law et al. 2005), and these proteins disrupt tight junction (Cheung et al. 2005). The effects of coronavirus infection on neuroinflammation depend on the host's immune response; RNA replication interferes with multiple signaling pathways, disrupting the expression of cytokines, chemokines, prostaglandins, leukotrienes, and neurotrophins that regulate neuronal survival and function and apoptosis-related genes contributing to neurodegeneration (Cheung et al. 2005; Tirotta et al. 2013). One of the main processes is the so called cytokine storm, and it is

reported as the leading critical cause of death in COVID-19 patients (Channappanavar et al. 2017). The "cytokine storm" is one of the key factors inducing neurodegeneration and neuronal dysfunction, due to the over production of inflammatory cytokines (IFNα, IL1β, IL6, IL12, IL18, IL33, TNFα, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) to SARS-CoV and other coronavirus infections (Channappanavar et al. 2017; Tisoncik et al. 2012). Likewise, severe MERS-CoV infection also increased serum levels of IL6, IFNα, CCL5, CXCL8, and CXCL10 (Cheung et al. 2005; Thiel and Weber 2008). The cytokine storm triggers became more dangerous than the original infection and causes multiple organ failure and neurodegeneration contributing to neurological disorder (Thiel and Weber 2008). This process is also observed in experimental animal models, and coronaviruses infect both neuronal and non-neuronal cells (i.e. glial cells), inducing inflammatory responses leading to degenerative processes (Edwards et al. 2000; Whitman et al. 2009). A similar process has been reported with influenza infection, with inflammation leading to neurological and cognitive effects (Jang et al. 2009; Studahl 2003). Multiple studies show increased production of inflammatory cytokines and activation of microglia in coronavirus infection (Studahl 2003; Chiara et al. 2012). Elevated levels of multiple cytokines have been detected in SARS-CoV cerebrospinal fluids associated with acute encephalopathy (Wu et al. 2020; Bergmann et al. 2006). Although the molecular inflammatory mechanisms inducing neurological disorders are not known, primate and rodent models show that complex innate and adaptive immune responses are involved, including abnormal Th1/Th2 balance and defective T-cell proliferation during coronavirus infection (Zakhartchouk et al. 2005; Gupta et al. 2006). The inflammatory processes induced by coronaviruses can also affect the neuropathogenicity of other viruses and pathogens (Ng et al. 2003). These inflammatory responses have both an antiviral effect but also a detrimental effect in the nervous system (Chen et al. 2019). Thus, glia activation can induce both antiviral responses, while long-term glia activation may cause neuropathogenic processes (Chen et al. 2019). The innate immune responses induce the recruitment and activation of other peripheral immune cells via chemokines, modulating the blood-brain barrier and cell-cell interactions (Wu et al. 2020; Bergmann et al. 2006). Immune cell penetration is essential for viral infection in the CNS, but it may pro-

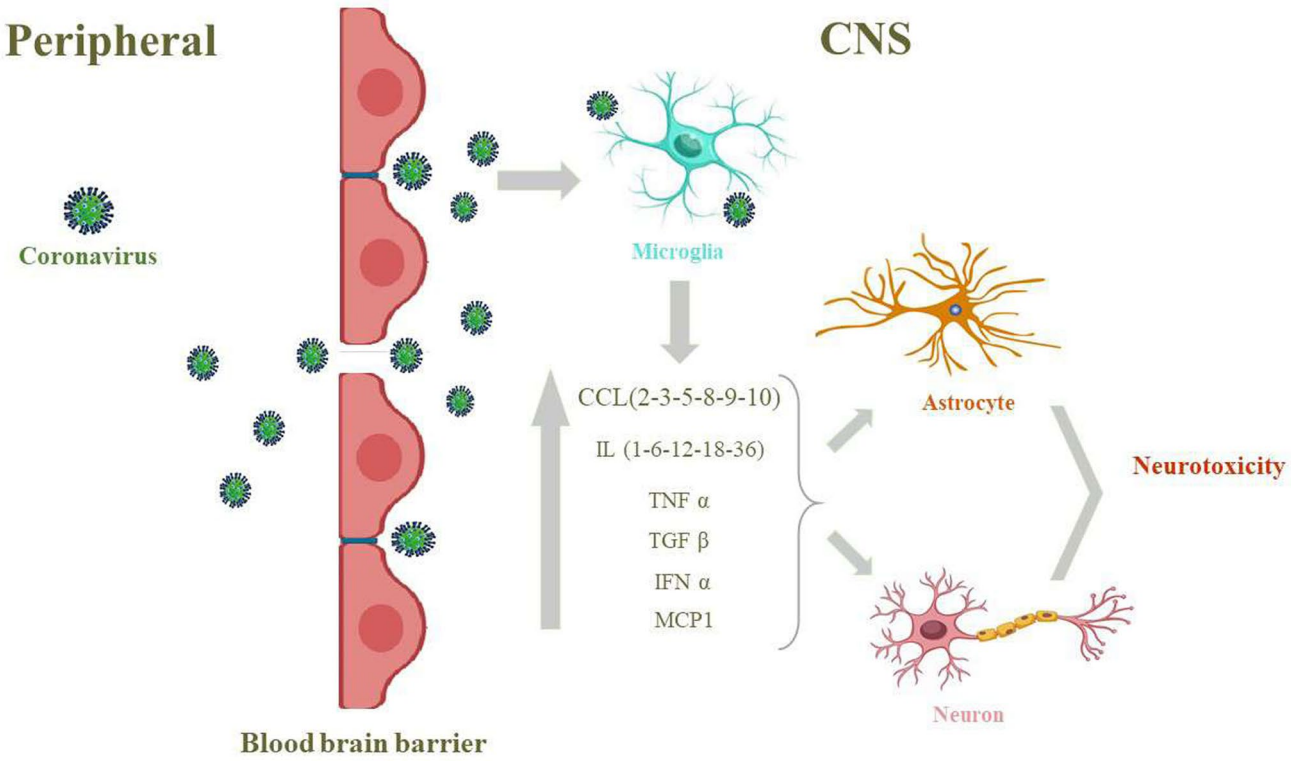

Fig. 4 Coronaviruses induced neural neuro-inflammation was mediated via production of some cytokine and chemokine such as Interleukin (IL)-1,6,12,18,36 and Tumor Necrosis Factor alpha(TNF-α) and Interferon alpha(IFN-α) and Tumor Growth Factor beta(TGF-β) and some proteins such as chemokine chemoattractant protein-1 (CCL2) such as activation**,** monocyte chemoattractant protein-1(MCP-1). All this biomarkers cause initiation of inflammatory signaling in astrocyte and neuron which led to activation of extrinsic pathway of apoptosis in neuronal cell and lead neurodegeneration

mote immune invasion resulting in neurological disorders (Bergmann et al. 2006) (Fig. 4). Taken together, these studies suggest that infection activates microglia to produce inflammatory cytokines. If unregulated, these cytokines can become detrimental and cause neurotoxicity and neurological dysfunction (Figs. 3, 4).

2) Nerve oxidative stress

Viral infections trigger neurological disorders through a variety of pathological mechanisms such as mitochondrial dysfunction and oxidative stress (Shi et al. 2014; Liu et al. 2006). Coronaviruses also target mitochondria function and cause oxidative stress damage (Liu et al. 2006). Coronaviruses target both neuronal and glial cells and affect patients of all ages (Liu et al. 2006; Padhan et al. 2008). Viruses may undergo lytic replication in the cells and spread to other cells, until viral gene expression may be limited for viral latent infection (Lavi and Weiss 1989). Viral products and host mediators can cause tissue damage and, depending on the cell type and the nervous system area, this damage can lead to meningitis, neuritis, myelitis, encephalitis, vasculitis, or demyelination (Wu et al. 2020; Padhan et al. 2008). The molecular mechanisms by which coronavirus infections cause neurological dysfunction are not known (Wu et al. 2020). Multiple studies provide critical information about the potential of coronaviruses to activate the immune system, but it is unknown how this inflammatory response can become so detrimental in some patients and disrupt neural metabolism and cause neurological dysfunction or death (Wu et al. 2020; Poyiadji et al. 2020). The production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) can become an important common pathway of tissue damage during viral infections (Ntyonga-Pono 2020; Hiffler 2020). ROS and RNS can be initiated within cells by redox reactions associated with normal physiological processes or enzymatic and non-enzymatic mechanisms associated with pathological processes induced by coronaviruses (Karadag et al. 2009). ROS and RNS are free radicals that have one or more unpaired electrons with a high ability to oxidize organelles, macromolecules, and key membrane and nucleic acid components (Karadag et al. 2009; Fransen et al. 2012). The most important examples of free radicals ROS and RNS include superoxide ($O2^{-}$), hydroxyl (OH), nitric oxide (NO), and nitric dioxide (NO2). Examples of non-radical ROS and RNS include hydrogen peroxide (H2O2) and peroxynitrite (ONOO2) (Fransen et al. 2012; Seifried et al. 2007). Viral infections increase the production of ROS and RNS which confer their effects to O2- and NO (Valko et al. 2007), this free radical is the result of inflammatory processes (Groot-Mijnes et al. 2005). O2- and other ROS are produced by infiltration of NADPH oxidase-expressing phagocytic cells in viral inflamed tissues and by humoral reactions involving xanthine oxidase (XO) (Drummond et al. 2011). NO is mainly produced by the inducible synthase of nitric oxides (iNOS), expressed in multiple cell types including phagocytic cells (Qidwai and Jamal 2010; Lirk et al. 2002). NO and ROS, especially O2-, can form reactive nitrogen oxides such as peroxynitrite, which are potent protein oxidants, nucleic acids, and membrane-unsaturated lipids (Pohanka 2013). MDA is electrophilic species that can covalently modify and damage neural macromolecules (135). Coronavirus infection increase MDA levels in the brain (Namiduru et al. 2012; Engin and Bakir 2010). Some neurological disorders induced by coronaviruses are due to MDA, ROS, and NOS production (Desforges et al. 2014a; Savarin and Bergmann 2018). On the other hand, steady-state levels of oxidative damage occurred after the balance of tissue damage caused by ROS / RNS levels and antioxidant activity rates (Poljsak et al. 2013; Costantini and Verhulst 2009). Previous studies have shown that this balance is disrupted by viral infections such as coronaviruses (Delgado-Roche and Mesta 2020). Components of the antioxidant defense system include enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT)(Delgado-Roche and Mesta 2020; Cheng 2020). Neurotrophic viral infections cause mitochondrial dysfunction in infected cells and reduce the activity of antioxidant enzymes (Shi et al. 2014; Yuan et al. 2006). Host functions and antioxidant defenses of neuronal cells are disrupted by coronaviruses and prevents normal cell and brain performance (Yuan et al. 2006). In addition, carbonylated proteins produced by coronavirus infection can cause DNA damage in brain tissues (Horner et al. 2015). In contrast, free radicals, such as ROS and NOS, damage arachidonic acid (AA) and docosahexaenoic acid (DHA) to produce inflammation affecting neuronal activity (Horner et al. 2015; Barnhart et al. 2013). This disturbance in AA affects the integrity of gray and white matter (Barnhart et al. 2013). Viral infection-induced oxidative damage is mediated by the generation of ROS and RNS, which can have a direct effect on the cells and trigger inflammation in the host (Valyi-Nagy and Dermody 2005). Other prominent molecules involved in viral oxidative stress induced is inducible iNOS, which have a prominent role in coronavirus infections and induces neurological dysfunction (Steer and Corbett 2003; Gomez et al. 2003). In most viral infections, regulated oxidative responses play beneficial roles by limiting viral replication through multiple mechanisms not well understood (Gomez et al. 2003). How-

ever, when unregulated these oxidative stress became detrimental to the host (Gomez et al. 2003; Li et al. 2009). For example, pharmacologic or genetic inhibition iNOS in mice is associated with reduced tissue damage during viral infection, so oxidative damage is also likely to contribute to coronavirus infections (Li et al. 2009). Coronavirus and other virus can induce ROS and RNS production in the CNS through an unknown mechanism (Delgado-Roche and Mesta 2020), but most likely mediated by viral components tohat can induce mitochondrial dysfunction and cytotoxic effects (Ntyonga-Pono 2020; Delgado-Roche and Mesta 2020). Glutathione is the main target of viral infections, it is an antioxidant cytosolic protein that plays a critical role in scavenging ROS and NOS (Cai et al. 2003). Glutathione (GSH) is a small thiol, the – SH group of its cysteine is extremely sensitive to oxidation, mainly by peroxide (Cai et al. 2003; Yang et al. 2017). However, when GSH is oxidized, GSH disulfide (GSSG) is formed and can be reduced by a specific enzyme, glutathione reductase (GSSG) (Yang et al. 2017). GSSG has detrimental effects and its concentration is increased during viral infections (Cai et al. 2003; Yang et al. 2017). Thus, coronavirus infections induce production of free radicals such as ROS and NOS, and reduce antioxidant capacity such as SOD, GPx, GR, and glutathione. These effects affect neural connectivity and survival leading to neuronal dysfunction and neurodegeneration. Although many of these mechanisms are not confirmed in coronavirus infections, they are expected to produce a pathophysiology similar to that reported other RNA viruses (Figs. 3, 5).

3) Nerve cell death , apoptosis, and autophagy

The term of "apoptosis" was introduced based on the Greek word meaning "falling off" or "dropping off" in analogy to leaves falling off the trees or petals from flowers (Saikumar et al. 1999). There are two apoptotic pathways named: extrinsic or intrinsic apoptosis (Lockshin and Zakeri 2004; Love 2003). In the extrinsic pathway, ligands activate receptors, such as TRAIL and FAS, and thereby pro-caspase and caspase-8 and caspase-10, which activate caspase-3 and caspase-7, to trigger apoptosis. In the intrinsic pathway, mitochondrial damage, such as DNA damage or hypoxia, causes release of cytochrome C, which led to the production of apoptosome and there-

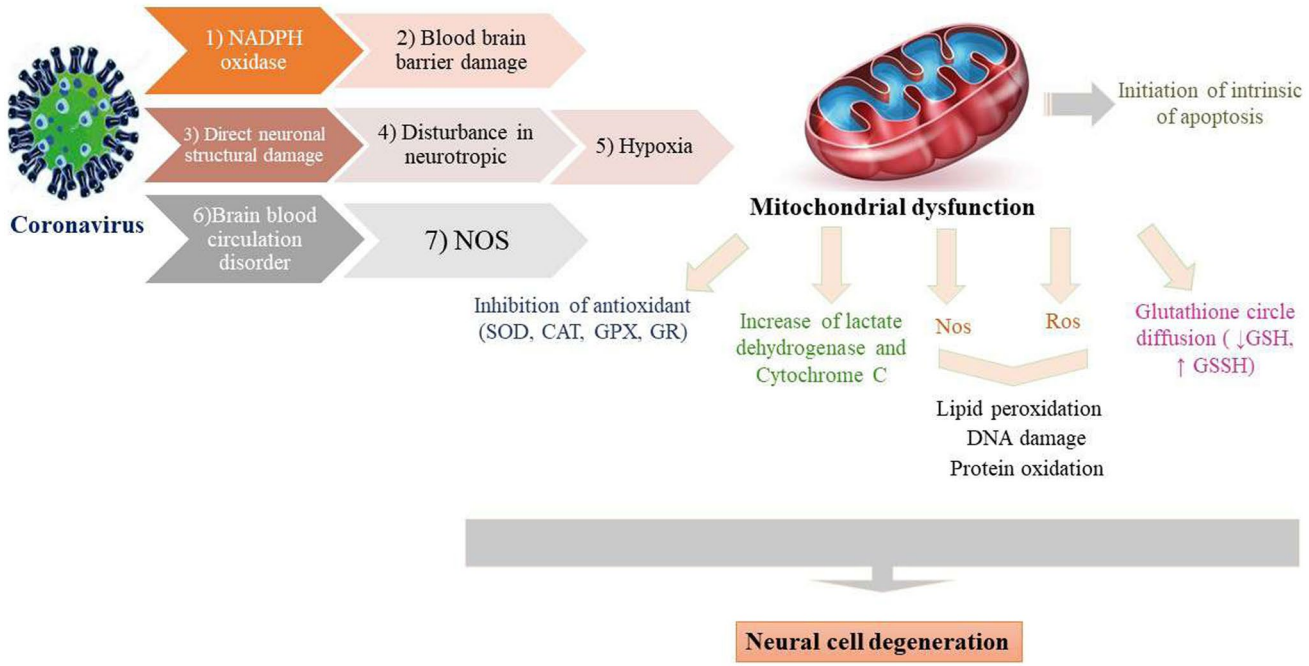

Fig. 5 Coronaviruses induced neural oxidative stress which was mediated via some parameters such as activation of NADH oxidase, induction of blood barriers barrier damage, induction of damage to neural structure, induction of hypoxia, induction of disturbances in neurotrophic factor, and activation of nitric oxide synthase enzyme (NOS).This parameters causes mitochondrial dysfunction which lead to production of Reactive oxygens specie(ROS) and Nitrogen Oxygen Species (NOS) and cause disturbances in glutathione pathway and antioxidant enzymes such as superoxide dismutase(SOD), Glutathione peroxidase(GPx) and Glutathione Reductase(GR), also causes occurrences of apoptosis and secretion of lactate dehydrogenases(LDH) and cytochrome C enzyme which all this event causes neurodegeneration

fore to the activation of caspasce-9, caspase-3, and caspase-7 and apoptosis. Some proteins such as BCL-2 and BCL-XL inhibit BAX, which stabilizes MOMP protein causing mitochondrial survival and preventing apoptosis. On the other hand, SMAC inhibits XIAP, which is a caspase-3 and caspase-7 inhibitor. Excessive apoptosis can contribute to the development or enhancement of neurodegenerative disorder (Sastre et al. 2000; Mattson 2000).

a) Coronavirus induced apoptosis

Coronavirus-induced oxidative stress and inflammation can ultimately cause apoptosis (Maadidi et al. 2014; Orzalli and Kagan 2017). Cell death following viral infection is one of the most common causes of multi-organ dysfunction and death (Fung and Liu 2014; Yan et al. 2004). Mitochondrial dysfunction and the production of reactive oxygen species play an important role in the progression from cell dysfunction to apoptosis or autophagy (Liu et al. 2006). Cell death pathogenesis in coronavirus-mediated neural dysfunction is still not fully understood (Liu et al. 2006; Padhan et al. 2008). Although, it appears that dysfunction in lipid metabolism, protein synthesis, reduction in mitochondrial ß-oxidation, and alteration of the redox state contributes to coronavirus-induced neural dysfunction and death (Shi et al. 2014; Liu et al. 2006). Indirect evidence indicate that apoptosis could be a main mechanism for cell damage caused by MERS and SARS-CoV infections, but there is inadequate knowledge of the apoptotic pathways in COVID-19 (Liu et al. 2006; Padhan et al. 2008). Previous studies have shown that apoptosis in cardiorespiratory and neuronal cells is a significant pathological characteristic of MERS and SARS-Cov infections in both experimental and human subjects (Li et al. 2020a). Early studies confirmed the activation of caspases in the cardiorespiratory and neural systems during coronavirus infection (Li et al. 2020a, 2020d). Increased Bax as an apoptotic protein and decreased Bcl2 as an anti-apoptotic protein have been shown in MERS and SARS-Cov-infected cells (Rockx et al. 2020). These results show that coronaviruses can cause apoptosis and ultimately neuronal damage and death (Yan et al. 2004; Tan et al. 2004). Viral infection can cause cell damage by activating multiple apoptotic cascades that can cause DNA damage responsible for multiple cell death (Xu et al. 2011). The extent of apoptosis appears associated with viral burden and underlying disorders in infected patients (Xu et al. 2011). Experimental studies have shown that MERS and SARS-Cov induce cell death in both in vivo and in vitro (Yang et al. 2003; Gurwitz 2020). MERS and SARS-Cov infections stimulate both the intrinsic and extrinsic apoptotic pathways (Yang et al. 2003; Gurwitz 2020). The role of this mechanism in COVID-19 is still unknown at this time. Several studies indicated that MERS and SARS-Cov-induced apoptosis in neurons is due to mitochondrial dysfunction (Gurwitz 2020; Xie and Chen 2019). As described above, viral infection initiates mitochondrial dysfunction to produce ROS and induce apoptosis (Xie and Chen 2019). On the other hand, as the virus proliferates in the lung cells, it induces alveolar and interstitial inflammatory exudation, and edema. This mechanism contributes to alveolar gas exchange disorders that cause hypoxia in the CNS, increasing anaerobic metabolism in brain cell mitochondria, and apoptosis (Wu et al. 2020; Zanin et al. 2020). Accumulation of acid may cause cerebral vasodilation, swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion (Zanin et al. 2020). If hypoxia persists, cerebral edema and circulation disorder will worsen (Felice et al. 2020). This hypoxia is the primary cause of apoptosis (Felice et al. 2020; Arabi et al. 2015). RNA mediated extrinsic apoptosis has been shown by the activation of Fas / Fas-ligand and TNF 1 / TNFα systems (Law PT-w. 2005). Given that brain cells also express Fas receptors, the death of neurons in infected patients can occur through detrimental inflammation as discussed above (Cowley and Weiss 2010; Law PT-w. 2005) (Figs. 3, 6).

The pathology of severe coronavirus infections is linked to systemic inflammation. These inflammatory reactions may be triggered by an extrinsic apoptotic pathway to cause neural death in infected patients (Dandekar and Perlman 2005; Memish et al. 2013). The persistence of coronavirus infections and its ability to infect macrophages, microglia, and astrocytes in the CNS are particularly important. These viruses can activate glial cells and induce inflammatory and apoptosis pathways. Inflammatory factors such as IL6, IL12, IL15, and TNFα are increased during coronavirus infections and all of these biomarkers can activate Fas receptor (Thiel and Weber 2008). On the other hand, clinical studies indicated that the mortality rate of COVID-19 in elderly and patients with underlying heart and respiratory conditions is significantly higher (Thiel and Weber 2008). The reduction of ACE2 expression appears to be one of the main reasons for this higher mortality rate (Burrell et al. 2012; Shenoy et al. 2010). ACE2 is a potent cardio-pulmonary protective protein that plays an important role preventing cardiovascular events and can also regulate the respiratory and nervous systems

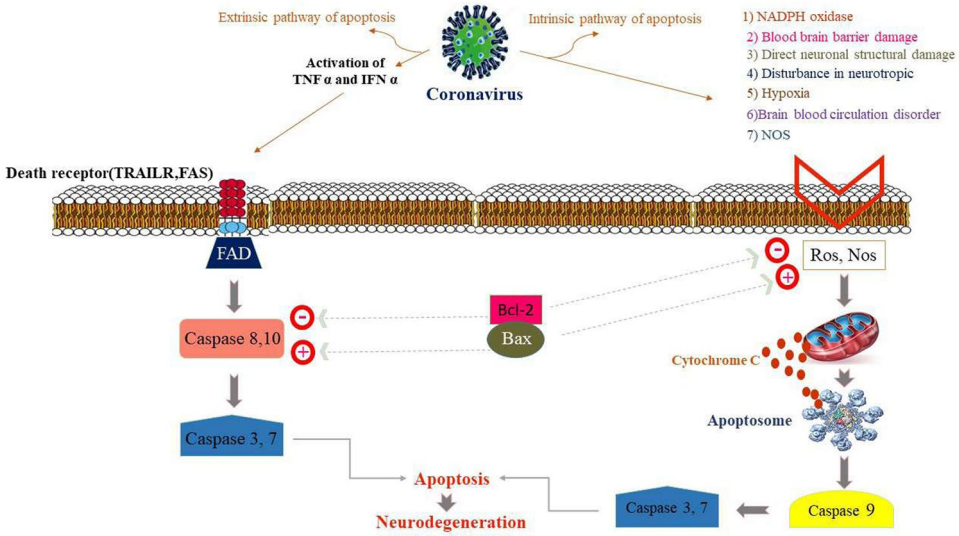

Fig. 6 Coronaviruses causes apoptosis in both intrinsic and in-extrinsic pathways. In the extrinsic pathway of apoptosis, death ligand such as TRAIL and FAS causes activation of death receptor, which lead to the activation of pro-caspase and caspase 8 and 10, which consequently activated caspase 3 and 7 and lead to apoptosis in the intrinsic pathway of apoptosis. This family viruses causes mitochondrial damage via activation of NADH oxidase, induction of blood barriers barrier damage, induction of damage to neural structure, induction of hypoxia, induction of disturbances in neurotrophic factor, and activation of nitric oxide synthase enzyme (NOS).Which lead to release of cytochrome C and production of apoptosome and therefore causes activation of caspasce-9, caspase 3 and 7 and, finally, apoptosis. Some proteins such as BCL-2 cause inhibition of Bax, which has led to the stability and mitochondrial survival and inhibited the process of apoptosis. FADD: Fas-associated protein with death domain, TRAIL: TNF-related apoptosis-inducing ligand,, Bcl-2: B-cell lymphoma 2, mitochondrial outer membrane permeabilization

(Shenoy et al. 2010; Uhal et al. 2013; Cole-Jeffrey et al. 2015). Angiotensin-converting enzyme 2 (ACE2) produces angiotensin (Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) [Ang-(Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020)] from angiotensin-2 (AngII). Previous studies have shown that the ACE2-Ang-(Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) axis plays a critical role regulating normal cardiovascular and respiratory physiology and it can be a therapeutic target in cardiopulmonary and neurological diseases (Shenoy et al. 2010; Dai et al. 2015). Some previous studies have shown that ACE2 can prevent cell death in cardiac and pulmonary systems and showed that this protein can inhibit apoptosis and autophagy-related signaling pathways and prevent cell death in various organs (Shenoy et al. 2010; Uhal et al. 2013, 2012; Cole-Jeffrey et al. 2015). Ang (Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) activates AT2R, the type-2 receptor for angiotensin. ACE-2/Ang(Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) /Mas causes Bcl-2/Beclin1 or Bcl-2/Bax complex stability and inhibits autophagy and apoptosis in the cardio-respiratory system, respectively (Dai et al. 2015; Meng et al. 2014). Ang (Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) can also inhibit phosphorylation by the c-Jun N-terminal kinas e(JNK). Apoptosis and autophagy are regulated by the complexes Bcl-2/Beclin1 and Bcl-2/Bax. Bcl-2 is an anti-apoptotic protein that interacts with Beclin1 (the key protein involved in autophagy) and Bax (the main protein involved in autophagy) when it is un-phosphorylated. Bcl-2 phosphorylation induced by autophagic or apoptotic pathways, such as the ACE-2-Mas-Ang pathway, in patients with cardio-respiratory diseases (Ferrario 2011; Uhal et al. 2011; Su et al. 2006). These pathway evokes JNK to phosphorylate and inactivate Bcl-2 by inducing its dissociation from Beclin1 or Bax, and thereby autophagia or apoptosis (Sadasivan et al. 2008; Ohishi et al. 2013). Some indirect evidence suggests that the lower expression and inactivation of ACE2-Mas-Ang (Spinelli and Pellino 2020; Watkins 2020; Ziebuhr 2004; Siddell et al. 1983; Satija and Lal 2007; Anand et al. 2002; Wu et al. 2020) in the cardiovascular system is one of the primary causes of increased mortality in high-risk patients with COVID-19. This mechanism

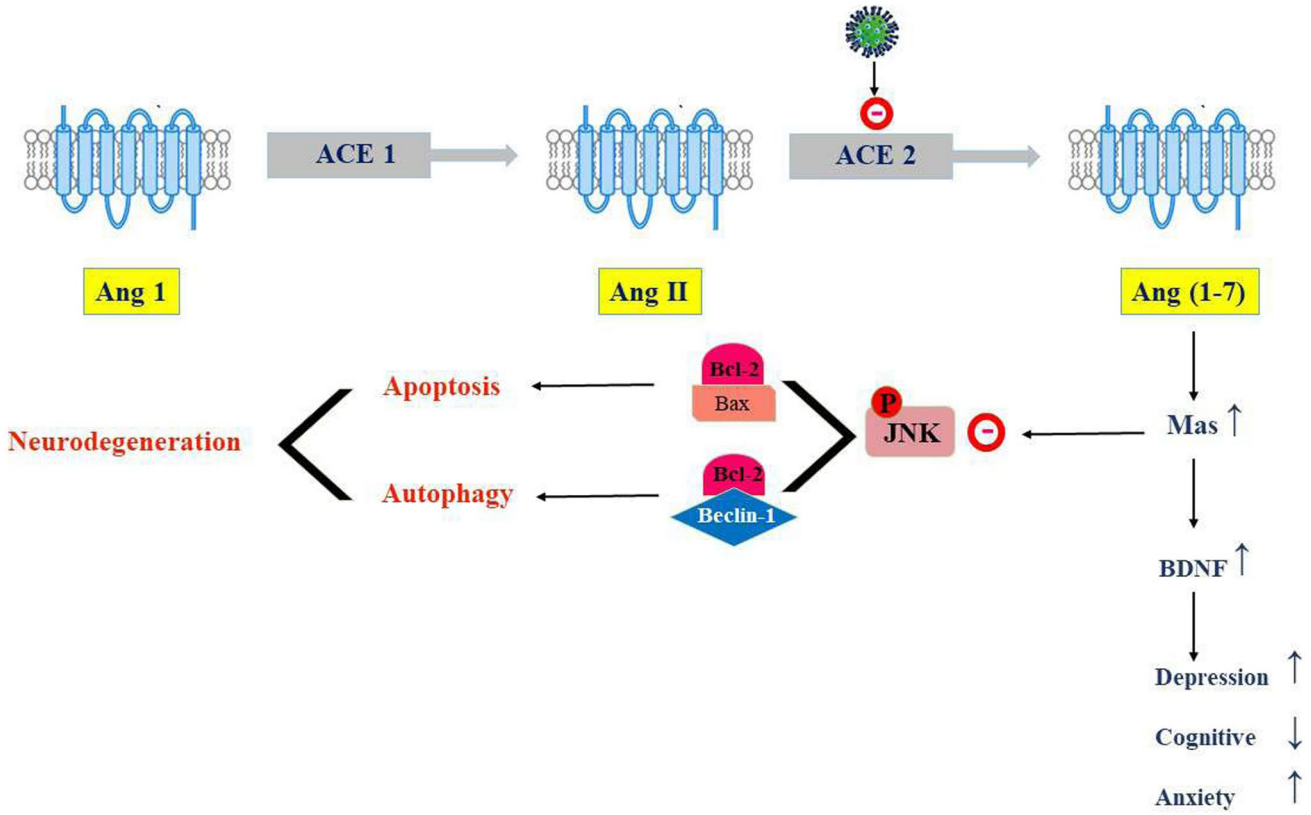

Fig. 7 The angiotensin-converting enzyme 2(ACE2) induces angiotensin (1–7) [Ang-(1–7)] development of angiotensin-2(AngII). Ang(1–7) causes AT2R, which is the angiotensin receptor type-2.On the other hand, it has been shown that ACE-2/Ang(1–7)/Mas causes Bcl-2/Beclin1 or Bcl-2/Bax complex stability and inhibits autophagy and apoptosis in the cardio-respiratory system respectively. Ang(1–7) can inhibit phosphorylation by the c-Jun N-terminal kinase(JNK). Apoptosis and autophagy are regulated by the complexes Bcl-2/Beclin1 and Bcl-2/Bax. Bcl-2 is an anti-apoptotic protein that interacts with Beclin1 (the key protein involved in autophagy) and Bax(the main protein involved in autophagy) in an unphosphorylated form. Induction of Bcl-2 phosphorylation after indications of autophagy or apoptosis such as dysfunction in the signaling pathway of ACE-2/Mas / Ang (1–7), which occurred in patient with underlying cardio-respiratory disease, activating JNK which led to phosphorylation (inactivation) of Bcl-2 and dissociation of this protein from Beclin1 or Bax and thus causes autophagy or apoptosis in respiratory and cardiac tissue of patients and increased their mortality rate. Some indirect evidence indicates that one of the key causes of increased mortality rates in high-risk patients with COVID-19 virus infection is lower expression and inactivation of ACE-2/Mas / Ang (1–7) in the cardiovascular system, resulting in activation of JNC / Bcl-2-Beclin1 or JNC / Bcl-2-bax signaling pathway and initiation of autophagy or apoptosis and thus death signal

causes the activation of JNC/Bcl2-Beclin1 or JNC/Bcl2-bax signaling pathway and induces autophagy or apoptosis (Sadasivan et al. 2008; Wang et al. 2011). These pathways affect neural connectivity and survival leading to neurodegeneration (Sadasivan et al. 2008; Wang et al. 2011). These pathways affect neural connectivity and survival leading to neurodegeneration (Sadasivan et al. 2008; Ohishi et al. 2013). Such degeneration contributes to neurological dysfunction, and although many of these mechanisms have not been well characterized in COVID-19, they are well documented in other similar RNA viruses, and predicted for coronavirus infections (Figs. 3, 7).

Conclusion

Taken together, the studies on the neurological effects of COVID-19, MERS, and SARS-CoV indicate that these lethal RNA viruses can cause direct damage to the nervous system by entering the CNS through the bloodstream and nerve endings. Viral infection directly damages the nerve structures and causes endovascular dysfunctions. Coronaviruses can also trigger detrimental inflammation, oxidative stress, and apoptosis, and all these mechanisms can induce neurotoxicity, neurodegeneration, and neurological dysfunction. While some of these mechanisms were reported in similar RNA viruses, the mechanisms inducing neurological

dysfunction in COVID-19, MERS, and SARS-CoV viruses are not well known at this time and need further evaluation both in clinical settings and experimental animal models.

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