Nervous System Involvement in COVID-19: a Review of the Current Knowledge

Mahnaz Norouzi[1] · Paniz Miar[2] · Shaghayegh Norouzi[3] · Parvaneh Nikpour[2,4]

Abstract

The current pandemic of the new human coronavirus (CoV), i.e., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created an urgent global condition. The disease, termed coronavirus disease 2019 (COVID-19), is primarily known as a respiratory tract infection. Although SARS-CoV-2 directly invades the lungs, COVID-19 is a complex multi-system disease with varying degrees of severity and affects several human systems including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems. From the existing data, most COVID-19 cases develop a mild disease typically presented with fever and respiratory illness. However, in some patients, clinical evidence suggests that COVID-19 might progress to acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and septic shock resulting in a critical condition. Likewise, specific organ dysfunction seems to be related to the disease complication, worsens the condition, and increases the lethality of COVID-19. The neurological manifestations in association with disease severity and mortality have been reported in COVID-19 patients. Despite the continuously increasing reports of the neurological symptoms of SARS-CoV-2, our knowledge about the possible routes of nervous system involvement associated with COVID-19 is limited. Herein, we will primarily describe the critical aspects and clinical features of SARS-CoV-2 related to nervous system impairment and then discuss possible routes of SARS-CoV-2 nervous system involvement based on the current evidence.

Keywords COVID-19 · Neurological manifestations · Nervous system · Immune system · Cytokine storm

Introduction

Coronavirus disease 2019 (COVID-19), a consequence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, emerged in Wuhan, China, in December 2019 and spread globally with a massive impact on the health system, community relations, and economics [1]. According to the World Health Organization (WHO), there are 25,327,098 confirmed cases of COVID-19 and 848,255

✉ Parvaneh Nikpour
  pnikpour@med.mui.ac.ir

1 Department of Genetics, Faculty of Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran

2 Department of Genetics and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

3 School of Health and Biomedical Sciences, RMIT University, Melbourne, VIC 3083, Australia

4 Pediatric Inherited Diseases Research Center, Research Institute for Primordial Prevention of Noncommunicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

confirmed deaths in 216 countries, areas, and territories until September 1, 2020. The SARS-CoV-2 is most closely related to the beta-coronaviruses (beta-CoVs) genus, which mainly infects the human respiratory system. Human beta-CoVs include the Middle East respiratory syndrome (MERS-CoV), severe acute respiratory syndrome (SARS-CoV), and SARS-CoV-2. They contain a single-stranded (positive-sense) RNA genome surrounded by a membrane envelope and use their spike (S) proteins to infect the host cells [2, 3]. The S protein in SARS-CoV-2 predominantly exploits human protein receptors, named angiotensin-converting enzyme 2 (ACE2), in the cell surface to invade the human cells. Considering the genomic analysis, SARS-CoV-2 has high homological sequence similarity with SARS-CoV; however, the tendency of SARS-CoV-2 to ACE2 is 10- to 20-fold higher compared to SARS-CoV [4, 5]. SARS-CoV-2 primarily invades the lungs and creates COVID-19, which is a complex multi-system disease that affects several human organs, including the respiratory, cardiovascular, gastrointestinal, and hematopoietic, as well as immune and nervous systems [6–10]. In a considerable portion of infected patients, COVID-19 presents a moderate illness. On the other hand, respiratory failure and pneumonia, as

well as multi-organ dysfunction and septic shocks, characterize patients with severe disease [10–13]. According to clinical observation, in addition to common respiratory symptoms, neurological manifestations have been reported particularly among COVID-19-hospitalized patients with severe or critical illnesses [14–17]. Concordant with other CoVs, neurological complications associated with SARS-CoV-2 have been reported. These complications generally are related to both central and peripheral nervous systems (CNS and PNS, respectively) with no distinguished underlying mechanism [16, 17]. Indeed, due to the specific immunity, including a multilayer blood-brain barrier (BBB), and effective immune responses, the nervous system is highly protected from the invasion of pathogenic agents [18, 19]. While the nervous system invasion is not a selective advantage for viruses, it has been demonstrated that some zoonotic RNA viruses, including CoVs, introduce adverse effects on the nervous system [18, 20, 21]. Neurological complications of COVID-19 may include either a rare direct infection of nerve ends or through the secondary or systemic effects of immune system malfunction and vascular system dysregulation [17, 18]. Several studies have described COVs, particularly SARS-CoV-2, as neurotropic viruses with neuroinvasive capabilities that directly invade the CNS through neuronal retrograde routes and result in neurological pathologies such as encephalomyelitis [14, 22–26]. Detection of SARS-CoV-2 and other CoVs, particularly SARS-CoV in the cerebrospinal fluid (CSF) of infected patients, provides additional support to the potential neuroinvasive contribution of SARS-CoV-2 [25–31].

One of the most widely accepted neurological complications of SARS-CoV-2 is related to immune system malfunction. Dysregulation of adaptive and innate immune system responses has been extensively reported in CoV-related infections including SARS-CoV, MERS-CoV, and severe cases of SARS-CoV-2 [11, 13, 21, 32, 33]. Accumulating evidence indicates that overreacting of the innate immune system results in the uncontrolled release of cytokines and chemokines in patients with severe COVID-19. As a result, it leads to vascular system dysfunction and consequent BBB disruption, which may provide a path for inflammatory mediators, immune cells, and virus particles to access the CNS [34–40]. Moreover, it is proposed that the overproduction of inflammatory cytokines in SARS-CoV-2 infection may lead to inflammatory damage in the brain tissue. So, it may present nonspecific complications, including headache, dizziness, taste, and smell dysfunctions, or impaired consciousness [21, 37, 41]. This aberrant immune response may lead to complicated chronic CNS features including long- and short-term effects, depending on different factors related to disease severity [42]. Furthermore, acute cerebrovascular disease (CVD) is commonly reported in middle-aged and elderly patients with severe or critical COVID-19 disease. Consequently, it can increase the risk of other neurological complications, including

coagulation and ischemic strokes, among COVID-19 patients, which may be associated with the inflammatory response and disease severity [1, 15, 16, 41–48].

Neurological manifestations, in line with evidence about SARS-CoV and MERS-CoV cerebral involvement, support the association of COVID-19 with the nervous system manifestations during the pandemic [21]. The presence of neurological complications in COVID-19 cases may increase the likelihood of misdiagnosis among patients with neurological symptoms [15, 32]. Moreover, it is proposed that the recurrence possibility of SARS-CoV-2 may be related to virus latency in the CNS [49]. These reported neurological complications highlight the importance of understanding the correlation of the SARS-CoV-2 infection with neurological damages and its association with disease severity and mortality. This review study is aimed to describe the clinical neurological complications following SARS-CoV-2 infection and the possible routes of nervous system involvement associated with COVID-19.

SARS-CoV-2 Structure and ACE2 Tissue Distribution

Coronaviruses genetically are classified into four genera, including alpha, beta, gamma, and delta. They have a diverse genome size of 26 to 32 kb and contain a changeable number of open reading frames (ORFs). The SARS-CoV-2 genome (29,903 bp) encodes 27 proteins through 14 ORFs. ORFa/b and ORF1a are located at the 5′-terminal of the genome to generate 15 nonstructural proteins (nsps). Structural and accessory proteins are furthermore encoded by remaining ORFs. The structural proteins include the membrane (M), the envelope (E), nucleocapsid (N), and S surface glycoprotein. The accessory genes distributed within the structural genes encode 8 proteins namely, 3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14 [50, 51].

CoV protein, which belongs to the typical class I viral fusion proteins, requires protease cleavage for activation. It contains two subunits S1 and S2 that contribute to attachment and membrane fusion, respectively [52]. Like SARS-CoV, SARS-CoV-2 exploits the receptor-binding domain (RBD), the most variable part of the CoVs genomes [53] in the S protein, to attach to the ACE2 receptor on the host cells. Nevertheless, the affinity rate of SARS-CoV-2 to ACE2 is higher than that of SARS-CoV [2, 5]. It has been proposed that two consecutive steps, including cleavage at "S1 and S2 junction" and "S2 cleavage site," promote activation of S protein in SARS-CoV and MERS-CoV [54, 55]. Similar to SARS-CoV, SARS-CoV-2 S protein undergoes cleavage processing on S1-S2 junction via transmembrane serine protease 2 (TMPRSS2) and cathepsin L host proteases [56]. A functional polybasic (furin) cleavage site is located at the S1-S2 boundary of the SARS-CoV-2 S protein. Although the

functional consequence of this cleavage is unknown, it may increase the infectivity of SARS-CoV-2 [57].

ACE2 is a single-peptide component of the renin-angiotensin system (RAS) and plays a pivotal role in vascular, renal, and myocardial physiology [58]. Information from databases including Protein Atlas (https://www.proteinatlas.org) and UniProt (https://www.uniprot.org), as well as published studies, has indicated that ACE2 receptor is abundantly expressed in the epithelia of the lung and small intestine [59, 60]. ACE2 receptor is also expressed in vascular endothelium and arterial smooth muscle cells of different human organs like the stomach, colon, skin, liver, kidney, and brain [59]. Furthermore, the expression of ACE2 has been detected in CNS areas including the striatum, cortex, medulla, hypothalamus, and brainstem [21, 31, 49]. Interestingly, it has been reported that both neurons and glial cells express the ACE2 receptor in the brain [29, 61].

Clinical Manifestations

COVID-19 primarily targets the human respiratory tract and thus results in a critical clinical care condition in some patients [8, 9]. The incubation period of COVID-19 varies between 3 and 14 days, leading to various ranges of clinical symptoms. However, the clinical manifestations have been remained to be elucidated completely [6, 15]. The median day at which symptoms trigger is 14, which is reduced in patients who are 70 years of age or older. The median age of death is 75, with a higher rate of infection in men [62, 63]. The spectrum of clinical presentations is complicated among COVID-19 patients and contains asymptomatic and mild cases; however, for a few, the illness can progress to severe respiratory failure, multi-organ dysfunction, and death [6, 7, 11]. In clinical evaluation, fever, cough, dyspnea, myalgia, and fatigue are the most common symptoms following the SARS-CoV-2 infection. Further uncommon symptoms, including headache, sputum production, hemoptysis, and diarrhea, have been reported as well [8, 10, 11].

To better clarify the severity of the disease, COVID-19 patients are classified into mild, severe, and critical cases [9, 10, 12]. Following fever and pneumonia, acute respiratory distress syndrome (ARDS) manifests in up to 20% of COVID-19 patients, which are considered severe cases. Progressive respiratory failure and multiple organ dysfunction besides septic shock are considerable conditions in critical cases [11, 64, 65]. Regarding laboratory findings, leucopenia and lymphopenia are the fundamental characteristics of COVID-19 infections. Most patients show elevated levels of lactate dehydrogenase (LDH), creatinine kinase (CK), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) [8, 11].

The new coronavirus is highly contagious, and older people with underlying diseases are at higher risk of severe manifestation and mortality. The most prevalent underlying comorbidities are diabetes, hypertension, cardiovascular, and CVD [10, 63, 66, 67]. In some patients, the disease progresses to pneumonia, ARDS, and death due to extreme elevation in inflammatory cytokines, including interleukin-2 (IL2), IL7, IL10, granulocyte colony-stimulating factor (GCSF), interferon-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 A (MIP1A), and tumor necrosis factor-alpha (TNFα), especially in critical cases [11, 35].

Chest computed tomography (CT) findings showed bilateral ground-glass opacity manifestation in the middle and outer zone of the lung in severe patients [9, 68, 69]. Other CT features have reported symptoms related to lung injury such as crazy paving pattern, airway changes, and reversed halo sign [70]. Furthermore, septic shock, alongside multi-organ failure, occurs in a considerable number of patients with critical condition and high fatality risk [9, 69, 70]. Indeed, systemic inflammatory response syndrome (SIRS) may result in multiple organ dysfunction syndrome (MODS), which is observed in patients with severe infection [71]. Accordingly, cardiovascular complications have been reported in a significant proportion of patients with COVID-19 [67]. Moreover, serious liver damage related to the increased level of LDH, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) has been observed. Elsewhere, increased blood urea nitrogen and creatinine levels indicated acute kidney injury presented in a significant proportion of patients with COVID-19 [15, 71].

Neurological manifestations have been reported from COVID-19 patients as a critical aspect of the disease [14, 16, 72–77]. These manifestations include specific neurological symptoms due to the direct effects of the virus on the nervous system and non-specific neurological complications that are just systemic features of the SARS-CoV-2 infection [24, 41, 73, 78, 79]. Skeletal muscle damage in association with increased CK levels and neurological manifestations are common among patients with severe infection. Neurological symptoms indicating CNS, PNS, and skeletal muscle involvements have been reported in a considerable portion of severe cases [15, 16]. Acute CVD, including ischemic stroke, intracerebral hemorrhage, and deep cerebral venous thrombosis, was reported in 0.5–5.9% of COVID-19 patients [80, 81]. Moreover, ischemic stroke is the most prevalent acute CVD and its risk of development is higher among severe or critical COVID-19 patients ranging from 0.8 to 9.8% [16, 80, 81]. There are multiple reports of Guillain-Barre syndrome (GBS), an acute disease of the peripheral nerves induced by inappropriate immune system response in patients with confirmed COVID-19 disease [82–88]. However, the aberrant function of peripheral nerve ends is evident because of the observed taste, smell, vision impairment, and nerve pain.

Likewise, other neurological symptoms, including dizziness, headache, impaired consciousness, acute CVD, ataxia, and seizure, indicate the central nervous system involvement in the severe COVID-19 [16, 45, 84]. Although the reports of the nervous system manifestations are increasing, our knowledge about this aspect of COVID-19 disease is still limited. Therefore, it is crucial to perform an extensive autopsy and biopsy investigations to accurately explain COVID-19 accurate clinical symptoms.

Nervous System Involvement in CoVs Infection

As observed in numerous other zoonotic viruses [18], and regarding the neurological manifestations of COVID-19 [12–16, 73–78, 89, 90], nervous system is likely involved in SARS-CoV-2 infection (Fig. 1). These neurological manifestations have been demonstrated in other CoV infections such as SARS-CoV and MERS-CoV, which have provided strong evidence for CoV neuroinvasive capacity [21, 91]. SARS-CoV respiratory infection was determined to represent many neurological abnormalities, including encephalitis, aortic ischemic stroke, and polyneuropathy [91]. Interestingly, several reports have documented CSF samples that were positive for

SARS-CoV RNA. Also, they have evidenced monocyte and lymphocyte infiltrations in the brain, ischemic changes of neurons, and demyelinating abnormalities [92]. Autopsy studies have reliably detected SARS-CoV in brain tissue specimens of patients manifesting with neuronal edema and meningeal vasodilation [22, 30, 93, 94]. The cerebrovascular complication and neuropathological manifestations, including ischemic stroke and GBS, respectively, have been reported in patients affected with SARS-CoV, as well [91, 95].

Several clinical studies have confirmed the presence of neurological complications in humans upon MERS-CoV infection along with other respiratory symptoms [96]. MERS-CoV is a potentially neuroinvasive virus according to clinical reports of neurological symptoms, including loss of consciousness, ischemic strokes, seizure attacks, paralysis, and other neuropathological manifestations [97–100]. MERS-CoV infection is accompanied by severe neurological diseases like encephalitis and neuromuscular disease such as GBS. Nevertheless, there is no report on MERS-CoV detection in the CNS of humans [96–98]. Likewise, the symptoms of CoVs infection in kids with encephalitis, the presence of CoVs nucleic acid in the human brain, and the ability of CoVs to infect CNS cell cultures have demonstrated the
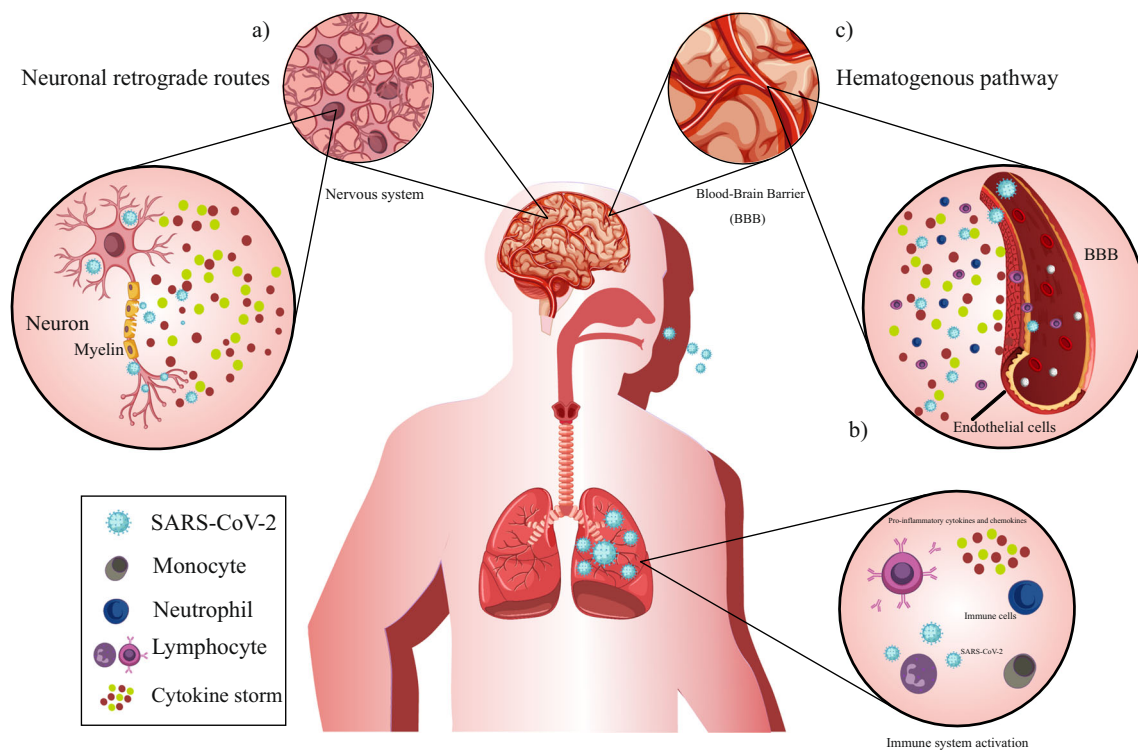
Fig. 1 Nervous system involvements in COVID-19 disease. CoVs can attack the nervous system through neuronal retrograde routes. PNS may provide an accessible route for SARS-CoV-2 to gain access to the nervous system and neurological symptoms may manifest due to a direct SARS-CoV-2 attack on the myelin or axon of PNS neuron (**a**). The activation of the immune system following the SARS-CoV-2 infection can be detrimental to the nervous system. The overexpression of pro-inflammatory cytokines and chemokines called cytokine storm may have negative effects on peripheral nerve roots and the BBB integrity (**b**). Hematogenous pathways may provide another route for SARS-CoV-2 toward CNS. Impaired BBB provides a path for inflammatory cytokines and immune cells to access the CNS. In the hematogenous pathways, the endothelial cells of BBB act as a bed for SARS-CoV-2 accession to CNS (**c**)

neurotropic properties of CoVs. Furthermore, the induced encephalitis in newborn mice has illustrated the neuroinvasive potential of CoVs [101].

The newly emerged CoV (i.e., SARS-CoV-2) involves neurological manifestations, especially in severely affected individuals [16, 17, 102, 103]. SARS-CoV-2 neurological manifestations are reported to include symptoms related to the CNS (e.g., impaired consciousness, acute CVD, corticospinal tract signs, ataxia, and seizure), PNS (e.g., taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscle damages [104–106]. Headache, myalgia, fatigue, confusion, anorexia, dizziness, malaise, and dyspnea are the most frequently reported neurological symptoms, which approximately affects one-third of patients with COVID-19 [72, 78]. Skeletal muscle damage in association with increased CK levels and neurological manifestations are common among patients with severe COVID-19 infection [15, 16]. Another most common reported neurological complication is smell and taste impairments. This problem shows the varying geographical frequency with high incidence in the studies from Europe and a lower frequency in the studies from Asian countries [16, 107]. It has been demonstrated that neurological complications commonly affect patients with severe COVID-19 infection, suggesting that neurological manifestations may be related to disease severity [73].

Neurological symptoms, including CNS, PNS, and skeletal muscle involvements, have been reported in a considerable portion of COVID-19 severe cases [15, 16]. Meningoencephalitis and encephalopathy are reported in multiple studies as other neurological presentations of COVID-19. Besides, CFS analyses have demonstrated elevated levels of inflammatory cytokines related to acute encephalopathy [25, 36, 77, 108, 109]. While the incidence of encephalitis has been reported to be lower than 1% in two retrospective studies of COVID-19 [110, 111], the CSF RT-PCR test has shown the presence of SARS-CoV-2 RNA in the CSF of four COVID-19 patients [78]. The typical neurological manifestations associated with encephalitis include irritability, confusion, and reduced consciousness, and may represent seizures, headache, and neck stiffness [46, 112, 113]. Few retrospective studies have demonstrated that seizures are common in SARS-CoV-2 infection with a frequency ranging from 0.5 to 1.4% [16, 111, 114–116]. All types of seizures, including febrile, focal, and generalized tonic-clonic seizures [114, 117–120], as well as status epilepticus myoclonic, status epilepticus, and non-convulsive status epilepticus [121–123] have been reported among the symptoms of COVID-19.

Acute CVD, including ischemic stroke, intracerebral hemorrhage, and thrombotic vascular events, has been reported in middle-aged and elderly cases of COVID-19 [1, 16, 43, 44, 110]. Cerebrovascular events related to COVID-19 are likely to share similar risk factors for stroke, e.g., older age,

hypertension, hyperlipidemia, diabetes mellitus, smoking, and prior strokes [80, 124–126]. However, accumulating reports have been reported about the large vessel strokes among COVID-19 patients without significant vascular risk factors, suggesting additional etiologies specific to SARS-CoV-2 [14, 72, 127–130]. Acute CVD involves the brain parenchyma or subarachnoid space in COVID-19 patients. Furthermore, hypercoagulable states (increased prothrombin time and elevated levels of a fibrin degradation product called D-dimer) have been reported in some COVID-19-related strokes [14, 124].

Another neurological disease reported in COVID-19 is GBS and its variants. GBS is an acute disease that affects peripheral nerves. This health problem is characterized by rapidly progressive symmetrical limb weakness and sensory symptoms in SARS-CoV-2 infection. GBS is associated with inappropriate immune system response and all the variants of GBS like acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and *acute motor and sensory axonal neuropathy* (AMSAN) have been reported in COVID-19 patients [82–84, 131–135]. Other variants like Miller Fisher syndrome and facial diplegic variants have been also described [113, 136, 137]. Furthermore, GBS with no respiratory symptoms of COVID-19 has been reported in some individuals affected with SARS-CoV-2 [41, 78, 138]. Demyelinating disorders, including acute disseminated encephalomyelitis (ADEM), exacerbation of multiple sclerosis (MS) plaque, and the clinically isolated syndrome, have been reported in COVID-19 patients, as well [78, 139]. ADEM (a multifocal demyelination syndrome) and myelitis (defined as inflammation of the spinal cord) have been considered post-infectious diseases reported in COVID-19 patients [120, 140, 141].

Although the neurological symptoms have been reported in a considerable number of COVID-19 patients, the underlying molecular mechanisms of the nervous system involvement has not been well understood yet [15, 21]. In this regard, understanding the SARS-CoV-2 correlation with the reported neurological complication in COVID-19 patients is critical from this diagnostic and therapeutic outlook. The following section will dedicate the possible routes of nervous system involvement.

Direct Infection of the Nervous System (the Neuronal Retrograde Routes)

The inherent and specific characteristic of the nervous system immunity preserves the CNS from the invasion of pathogenic agents [19]. Due to the devastating and lethal nature of CNS infection, the capacity to invade the nervous system is a rather poor evolutionary feature [20]. However, some zoonotic RNA viruses like West Nile virus (WNV) and Nipah virus (NiV) have the potential to infect fully differentiated neurons [18]. In

the case of the COVID-19 pandemic with the increasing trends in reporting of neurological manifestations, it is plausible that SARS-CoV-2 has the potential to infect the nervous system [15, 16, 21, 49]. The evidence of cerebral involvement in other CoVs (SARS-CoV and MERS-CoV) and the presence of SARS-CoV-2 genomic RNA in the CSF of COVID-19 patients [25, 27, 30, 78] have reinforced the assumption of CNS infection with the SARS-CoV-2 [31, 142]. Moreover, it has been suggested that the abnormal function of the cardio-respiratory center in the brain stem due to the neuroinvasive potential of SARS-CoV-2 might be the cause of respiratory failure in COVID-19 patients [4]. However, a recent report claims that respiratory failure in patients with COVID-19 is different from that caused by brain dysfunction [101]. This suggests that SARS-CoV-2 introduction to the brain is possible; nevertheless, it is a rare phenomenon due to non-specific symptoms observed in COVID-19 patients [101]. Overall, like other CoVs, there is no adequate evidence to prove CNS access by SARS-CoV-2, although it is proposed that described routes for other pathogens may provide a path to the brain for SARS-CoV-2 [4, 21, 31, 101].

Neuronal retrograde routes are one of the essential pathways for the respiratory neurotropic virus entry to the CNS (Fig. 1a) [42]. Indeed, the PNS provides accessible routes for this virus to gain access to the nervous system [18, 21]. Regarding this point, the transition of SARS-CoV-2 to the brain through the olfactory nerve is plausible. The evidence of alteration in the sense of smell (anosmia) supports this theory [4, 15, 21, 31]. However, bioinformatics analysis on bulk and single-cell RNA-Seq datasets for SARS-CoV2 receptor expression at the olfactory system showed that two critical genes for SARS-CoV-2 invasion (i.e., *ACE2* and *TMPRSS2*) did not express at olfactory neurons. This study also showed that SARS-CoV-2-related proteins are expressed at non-neuronal olfactory system cells, probably leading to anosmia following COVID-19 contamination [143]. Nevertheless, other PNS components such as neuromuscular junctions might participate in the neurological complication of COVID-19. Increased levels of CK and myalgia or fatigue, which is observed among a significant portion of hospitalized COVID-19 patients, support the assumption that SARS-CoV-2 may aggress the myelin or axon of muscular neurons (Fig. 1a) [143, 144]. Another scenario in the nerve ends involvement is proposed since GBS has been reported in several cases associated with COVID-19 [82, 87, 132, 134, 144–146]. Although respiratory tract or gastrointestinal infection has been reported in two-thirds of GBS patients before the neuropathy manifestation, a pattern of the parainfectious profile was reported in GBS associated with COVID-19. GBS mechanism, which mimics autoimmune diseases, is commonly related to campylobacteriosis and viral infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and Zika virus [82, 84, 133].

While the underlying mechanism of the GBS manifestation in COVID-19 patients has not been elucidated, the immune system attack through inflammatory cytokine or antibodies against specific gangliosides is proposed in this regard [84]. Further investigation of the association of GBS with the COVID-19 infection can reveal neurological complications of the disease [38, 147]

Immune Response Dysfunction

Immune responses caused by a viral infection can damage the nervous system. Therefore, comprehensive knowledge about the brain reaction against viral infections is critical to combat neurological viral conditions. The activation of the immune system following the SARS-CoV2 infection (Fig. 1b) can be detrimental to the nervous system [19, 21]. It has been suggested that both viral and host factors participate in CoV pathogenicity. However, it is the uncontrolled immune response that leads to immune pathogenesis of the CoVs, including pulmonary tissue damage and reduced lung capacity. Therefore, the innate immune response can play a protective or destructive role in CoVs infection [148]. Elevated levels of neutrophils, monocytes, and macrophages have been observed in severe SARS-CoV and MERS-CoV infections [147].

As expected, such an increase in the number of leukocytes and neutrophils has been observed in patients with severe COVID-19. Moreover, lymphopenia and pneumonia, the most prevalent characteristics observed in patients with severe COVID-19 infection, are related to innate immune system dysfunction [138, 147]. Therefore, the aberrant immune system function, which is observed among severe cases of COVID-19, might be caused by a decline in the number of T lymphocytes, especially CD4$^+$ T-cells. Furthermore, the elevated levels of neutrophil-to-lymphocyte ratio (NLR), which is a reliable marker of systemic inflammation and infection, indicated the serious immunologic condition in patients with severe COVID-19. Moreover, consistent with SARS-CoV and MERS-CoV infections, the overactive inflammatory response in patients with severe COVID-19 is plausible, regarding the elevated serum levels of the pro-inflammatory cytokine and chemokines (TNF-α, IL-1, IL-6, IL-7, IL-8, IL-9, IP10, GCSF, MCP1, and MIP1A) at their blood samples. Since the immune system dysregulation causes aberrant inflammation in COVID-19 patients, the correlation of these conditions with neurological manifestation is plausible [62, 138].

Inflammation, the immune system reaction to tissue damage, may have negative effects on the recovery process from an injury. So, many protective efforts have been triggered to overcome this detrimental condition [149]. All types of CNS cells, including neurons, macroglia, and microglia, participate in neuroinflammation responses [150]. Because of the paradoxical effects of cytokines in cells, cytokine functions are

critical to determining the protective or destructive function of the immune system in the case of any pathogen exposure. Indeed, it is the ultimate turnover of cytokines that determines the invasion of leukocytes towered the brain parenchyma [151]. However, infection-related biomarkers such as procalcitonin, ESR, serum ferritin, CRP, and inflammatory cytokines (i.e., TNF-α, IL-2R, IL-6, IL-8, and IL10) are increased in blood samples of individuals with severe COVID-19 compared to the patients in the mild group [13, 138]. These findings suggest that lymphopenia and cytokine may play a key role in the neurological pathogenesis of novel SARS-CoV-2.

Infiltration of infected leukocytes through the "Trojan horse" mechanism is an efficient approach for some viruses to access the nervous system [18, 32]. The so-called Trojan horse mechanism, which refers to the crossing of infected leukocytes from the blood-brain barrier (BBB), is the main mechanism used by some lentiviruses like simian immunodeficiency virus (SIV) and HIV to transfer across CNS vascular barriers [152]. Previous studies have shown the ability of beta-CoVs to infect monocytes, macrophages, and dendritic cells. The SARS-CoVs can infect primary human monocytes [153], whereas MERS-CoV infects both monocytes and T cells [154]. Thus, dendritic cells could be infected by SARS-CoV-2 [64]. However, the low amounts of ACE2 receptors expressing on the cell surface of monocytes and macrophages suggest that other mechanisms might involve in communications between SARS-CoV-2 and the host innate immune response [147].

Accumulating evidence has indicated that overreacting of the innate immune system and inflammatory responses in patients with severe COVID-19 correlate with respiratory failure, ARDS, and adverse clinical outcomes [34]. This condition, which has been considered a cytokine storm syndrome, contributes to vascular permeability, leakage, and consequently devastating effects on pathological symptoms [32, 34, 64]. Cytokine storms cause BBB disruption, which protects the CNS by controlling the spread of circulating molecules, immune cells, or virus particles into the CNS. Indeed, impaired BBB provides a path for inflammatory mediators and immune cells to access the brain parenchyma (Fig. 1c). This offensive entry may occur following the CoV infection, and thereby, the brain inflammation is likely to exacerbate COVID-19-related neurological manifestations [18, 21, 32].

Hematogenous Pathways

It seems that the impairment of general hemostasis due to the pulmonary damage and MODS leads to the critical condition in COVID-19 patients [21, 155, 156]. Previous studies demonstrate that human CoVs have the potential to disseminate other regions of the human body [45]. The existence of SARS-CoV and MERS-CoV particles in the circulating blood cells, lymphoid tissue, and epithelial cells of different human tissues suggest the broad range of tissue tropism for CoVs [157]. SARS-CoV-2 has shown a multi-organ impact with significant effects on the vascular system and homeostasis maintenance [155, 158–160]. Although the hematogenous pathway is proposed as a possible route for neurotropic viruses toward the CNS, the vascular system derangements in COVID-19 patients are complicated and still unknown [90, 160, 161]. Intriguingly, human CoVs can pass through the epithelium cells and spread throughout the blood circulation pathways, thereby reaching the other regions, including CNS [42]. In the hematogenous pathways, the endothelial cells of BBB or blood-cerebrospinal fluid barrier provide a route for the accession of viruses to the CNS (Fig. 1c) [90]. The evidence of direct infection of endothelial cells by SARS-CoV-2 [161] and the presence of viral-like particles in brain capillary endothelium of COVID-19 patients [90] support the concept that the vascular system acts as a bed for SARS-CoV-2 to accesses the nervous system. Furthermore, an in vitro study has shown that SARS-CoV-2 can directly invade the engineered human blood vessel organoids; however, the evidence to support the CNS infection by CoVs particularly SARS-CoV-2 via hematogenous pathways is rare [21, 162].

Boosting inflammatory responses and the development of cytokine storm, observed in severe COVID-19 patients, contributes to vascular permeability and promotes the dysfunction of the endothelial cells [7, 155]. Accordingly, the immune system malfunction, aberrant inflammatory responses, and endothelial dysfunction participate in the induction of a prothrombotic state [156, 157]. Thrombosis, a physiological response termed immunothrombosis that involves blood coagulation and platelet aggregation, is a key effector of the innate immune response that delimitates pathogen spreading through the vascular system [163]. While the immunothrombosis state is inherently beneficial via the local control of the infection, endothelial dysfunction accompanied by the hyper-inflammation response due to SARS-CoV-2 infection might lead to a state of COVID-induced coagulopathy [155, 156, 161]. Disseminated intravascular coagulation and its related parameters like thrombocytopenia and D-dimer have been frequently reported in COVID-19 patients [155, 159, 164]. A study on 183 confirmed COVID-19 patients revealed that the levels of D-dimer are significantly higher in deceased COVID-19 patients (71.4%) compared to survivors (0.6%) [165]. Previously, in the case of SARS-CoV infection, the artery cerebral thrombosis was reported in critically ill patients with underlying conditions [166]. Likewise, the incidence of large vessel stroke has been reported among COVID-19 patients in association with the elevation of inflammatory markers and D-dimer levels [16, 18, 80, 166]. While acute ischemic stroke commonly occurs in older people [45], there are rare reports of intracerebral hemorrhage among COVID-19 patients [16, 45–48].

Despite the observed high levels of D-dimer markers and coagulation system dysfunction in COVID-19 patients, it seems likely to be associated with nervous system impairment [5]. It has not been understood that hemorrhagic events occur due to the SARS-CoV-2 infection or whether it is a coincidental situation [48]. However, the ACE2 receptor occupation on vascular endothelial cells with SARS-CoV-2 may cause aberrantly increased blood pressure and elevate the risk of intracranial hemorrhage [15, 20, 21]. Besides, it is of note that severe hypoxia development due to lung injury and respiratory failure might cause CVD-like ischemic stroke [21, 164]. Indeed, the progress of ARDS in severe COVID-19 patients leads to profound systemic hypoxemia, which may correlate with observed congestion and edema in the brain tissue [16, 89]. Furthermore, the induction of hypoxemia by lung injury and ARDS may facilitate SARS-CoV-2 access to the brain. Nevertheless, there are no adequate data to indicate that SARS-CoV-2 directly invades the CNS. So, research on the neuroinvasive potential of SARS-CoV-2 requires further consideration [89].

COVID-19 and Possible Long-Term Neurological Consequences

The accumulating information about nervous system involvement and evidence of cognitive impairment among COVID-19 patients provide an alarming document about the possible further delayed-onset neurological complications. This condition may include unpredictable outcomes, either via aggravating a pre-existing neurological disorder or causing a neurodegenerative disease in COVID-19 survivors [11, 167–169]. Although it is too early to conclude about the possible risk of developing long-term neurological consequences of COVID-19 infection, it is plausible that chronic neuroinflammation associated with SARS-CoV-2 may cause neurodegenerative diseases in the future. Moreover, the SARS-CoV-2 neuroinvasive nature may result in subsequent neurodegenerative disorders like multiple sclerosis (MS), Huntington, Parkinson's (PD), and Alzheimer's diseases (AD) [41, 79]. The significant risk of developing subsequent neurological complications in COVID-19 survivors is consistent with previous evidence that indicated other human CoVs latency in the nervous system and induced oxidative tissue injury and CNS chronic complications [42, 169, 170]. In other words, the potential neuroinvasive feature of SARS-CoV-2, as well as chronic neuroinflammation and cytokine storm associated with COVID-19 severity, spotlight the possible increased risk of neurodegeneration characteristic of this disease [171, 172]. The reports on CoVs in the CNS of patients with PD, AD, and MS raise the question of whether and how COVID-19 infection may be related to this neurodegenerative disease [173].

COVID-19 is accompanied by the impaired immune response and sustained rise of inflammatory cytokines, which can promote cognitive decline and neurodegenerative disorders [169, 174]. Available data recommend that chronic neuroinflammation associated with high levels of cytokines may implicate pathogenesis and different clinical features of neurodegenerative disorders. For instance, the COVID-19-associated cytokine storm may synergize with amyloid-stimulated type I interferon (IFN) response and exacerbate the cognitive decline in patients with AD. It has been reported that profound systemic hypoxemia complicates the presentation of dementia in AD patients that mostly manifest COVID-19 with diarrhea or drowsiness [175, 176]. These diverse clinical profiles may correspond to distinct pathogenesis and age-related concepts that influence patients with pre-existing neurological conditions [177]. Since elderly individuals are at a higher risk for developing both neurodegenerative and COVID-19 diseases, SARS-CoV2 infection may cause de novo neurodegenerative consequences like PD by accelerating aging in the brain tissue. Also, COVID-19 may complicate the clinical course of pre-existing PD, thereby resulting in worsening of its symptoms [172, 176–179]. Although the long-term effects of SARS-CoV-2 on the brain are not well characterized, the expression of ACE2 receptor in the CNS suggests that SARS-CoV-2 may infiltrate the brain regions to develop neurodegenerative disorders in the future [31, 49, 180]. The capacity of SARS-CoV-2 to reach the brain and the immunological complexity of COVID-19 can theoretically explain the likelihood of developing long-term neurodegenerative diseases. However, it is challenging to clarify the expected neurodegeneration sequelae in COVID-19 patients relying only on the conducted investigations [96, 169, 177, 178, 181]. In line with evidence from other coronavirus families that indicate their association with MS and other neurological diseases, COVID-19 complications in patients with neurodegenerative disease indicate the urgent attention that should be taken in the context of COVID-19 neurological studies [170, 181]. Overall, studies on critical outcomes and clinical presentations of COVID-19 in patients with pre-existing neurological conditions can provide valuable data to predict risk factors developing long-term brain damage and subsequent neurodegenerative diseases.

Conclusion

COVID-19 is a complex multi-system infectious disease that involves a set of currently unknown complications. The spectrum of clinical manifestations of SARS-CoV-2 is continuously broadened. Therefore, further studies are needed to evaluate whether these multi-organ failures are reflective of direct tissue viral invasion or due to the secondary or systemic effects of the virus. Neurological symptoms and complications

observed in COVID-19 patients, especially in severe cases, suggest the impact of SARS-CoV-2 on the nervous system. Although neurological manifestations can be devastating clinical complications of COVID-19, the underlying precise molecular mechanism of neuroinvasion and interaction of SARS-CoV-2 with the nervous system is poorly defined. The neurological pathogenesis of COVID-19 seems to be a complex process. In this regard, hematogenous and neuronal retrograde routes may play an essential role in CNS involvement. While there are limited reports about the direct propagation and presence of SARS-CoV-2 in the human brain tissue, it has been proposed that immune system impairment, subsequent cytokine storm, and vascular system dysfunction might facilitate SARS-CoV-2 entry to the brain. In this respect, the potential of the SARS-CoV-2 invasion to the peripheral nerves might be correlated with the neurological complication of COVID-19. However, it is currently believed that SARS-CoV-2 in concert with host immune responses may participate in the neurological complication of COVID-19 disease. Hence, experimental studies focusing to unravel the precise molecular mechanisms by which CNS or PNS is affected by COVID19 are urgently needed. These studies with shedding light on the underlying molecular mechanisms of neurological complication of COVID-19, will potentially lead to develop more efficient preventive and treatment strategies for these neurological manifestations.

Code availability Not applicable

Data Availability Not applicable

Declarations

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication The authors agree to the publication of this article.

Conflict of interest The authors declare no conflicts of interest.

References

1. Filatov A, Sharma P, Hindi F, Espinosa PS (2020) Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus 12(3):e7352
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H et al (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395(10224):565–574
3. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML, Leist SR, Schäfer A et al (2020) An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med 12(541):eabb5883
4. Li YC, Bai WZ, Hashikawa T (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 92(6):552–555
5. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367(6483):1260–1263
6. Adhikari SP, Meng S, Wu Y-J, Mao Y-P, Ye R-X, Wang Q-Z, Sun C, Sylvia S et al (2020) Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty 9(1):1–12
7. Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, Peccatori J, D'Angelo A et al (2020) Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 22(2):95–97
8. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK et al (2020) Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 34:101623
9. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109:102433
10. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, Dai J, Sun Q et al (2020) Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect 80(4):388–393
11. He F, Deng Y, Li W (2020) Coronavirus disease 2019: what we know? J Med Virol 92(7):719–725
12. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z (2020) Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med 35(5):1545–1549
13. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M et al (2020) Melino G (2020) COVID-19 infection: the perspectives on immune responses. Cell Death Differ 27(5): 1451–1454
14. Varatharaj A, Thomas N, Ellul MA, Davies NW, Pollak TA, Tenorio EL, Sultan M, Easton A et al (2020) Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 7(10):875–882
15. Jin H, Hong C, Chen S, Zhou Y, Wang Y, Mao L, Li Y, He Q et al (2020) Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists. Stroke Vasc Neurol 5(2):svn-2020-000382
16. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D et al (2020) Hu Y (2020) Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol 77(6):683–690
17. Najjar S, Najjar A, Chong DJ, Pramanik BK, Kirsch C, Kuzniecky RI, Pacia SV, Azhar S (2020) Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. J Neuroinflammation 17(1):1–14
18. Koyuncu OO, Hogue IB, Enquist LW (2013) Virus infections in the nervous system. Cell Host Microbe 13(4):379–393
19. Manglani M, McGavern DB (2018) New advances in CNS immunity against viral infection. Curr Opin Virol 28:116–126
20. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, Martinborough E, Peach R et al (2011) Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell 146(6):980–991
21. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C (2020) Nervous system involvement after infection with

COVID-19 and other coronaviruses. Brain Behav Immun 87:18–22

22. Lau K-K, Yu W-C, Chu C-M, Lau S-T, Sheng B, Yuen K-Y (2004) Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 10(2):342–344

23. Zlateva KT, Van Ranst M (2004) Detection of subgroup B respiratory syncytial virus in the cerebrospinal fluid of a patient with respiratory syncytial virus pneumonia. Pediatr Infect Dis J 23(11):1065–1066

24. Yavarpour-Bali H, Ghasemi-Kasman M (2020) Update on neurological manifestations of COVID-19. Life Sci 257:118063

25. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H et al (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 94:55–58

26. Xiang P, Xu X, Gao L, Wang H, Xiong H, Li R (2020) First case of 2019 novel coronavirus disease with encephalitis. ChinaXiv 202003:00015

27. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H (2004) Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics 113(1):e73–e76

28. Zhou L, Zhang M, Wang J, Gao J (2020) Sars-Cov-2: underestimated damage to nervous system. Travel Med Infect Dis 36:101642

29. Steardo L, Steardo L Jr, Zorec R, Verkhratsky A (2020) Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol 229(3):e13473

30. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, Li Z, Deng P et al (2005) Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin Infect Dis 41(8):1089–1096

31. Baig AM, Khaleeq A, Ali U, Syeda H (2020) Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 11(7):995–998

32. Al-Obaidi M, Bahadoran A, Wang S, Manikam R, Raju CS, Sekaran S (2018) Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. Acta Virol 62(1):16–27

33. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 8(5)

34. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Collaboration HAS (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 395(10229):1033

35. Singhal T (2020) A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 87(10223)

36. Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, Nocivelli S, Pezzini A et al (2020) Steroid-responsive severe encephalopathy in SARS-CoV-2 infection. medRxiv 88(2):423–427

37. Ye M, Ren Y, Lv T (2020) Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun 88:945–946

38. Schett G, Sticherling M, Neurath MF (2020) COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nat Rev Immunol 20(5):271–272

39. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I (2020) COVID-19 cytokine storm: the anger of inflammation. Cytokine 133:155151

40. Cao X (2020) COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 20(5):269–270

41. Chen X, Laurent S, Onur OA, Kleineberg NN, Fink GR, Schweitzer F, Warnke C (2020) A systematic review of neurological symptoms and complications of COVID-19. J Neurol 20:1–11

42. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, Talbot PJ (2020) Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 12(1):14

43. Pleasure SJ, Green AJ, Josephson SA (2020) The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: neurologists move to the frontlines. JAMA Neurol 77(6):679–680

44. Hess D, Eldahshan W, Rutkowski E (2020) COVID-19–related stroke. Transl Stroke Res 11(3):322–325

45. Calcagno N, Colombo E, Maranzano A, Pasquini J, Keller Sarmiento IJ, Trogu F, Silani V (2020) Rising evidence for neurological involvement in COVID-19 pandemic. Neurol Sci 41:1339–1341

46. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T et al (2020) Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 382(20):e60

47. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B (2020) COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 31:201187

48. Sharifi-Razavi A, Karimi N, Rouhani N (2020) COVID-19 and intracerebral haemorrhage: causative or coincidental? New microbes and new infections 27;35:100669

49. Kabbani N, Olds JL (2020) Does COVID19 infect the brain? If so, smokers might be at a higher risk. Mol Pharmacol 97(5):351–353

50. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z et al (2020) Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 27:325–328

51. Li H, Liu S-M, Yu X-H, Tang S-L, Tang C-K (2020) Coronavirus disease 2019 (COVID-19): current status and future perspective. Int J Antimicrob Agents 55(5):105951

52. Ou X, Zheng W, Shan Y, Mu Z, Dominguez SR, Holmes KV, Qian Z (2016) Identification of the fusion peptide-containing region in betacoronavirus spike glycoproteins. J Virol 90(12):5586–5600

53. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579(7798):270–273

54. Belouzard S, Chu VC, Whittaker GR (2009) Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci 106(14):5871–5876

55. Millet JK, Whittaker GR (2014) Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. Proc Natl Acad Sci 111(42):15214–15219

56. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181(2):281–292.e6

57. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF (2020) The proximal origin of SARS-CoV-2. Nat Med 26(4):450–452

58. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B et al (2000) A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 87(5):e1–e9

59. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203(2):631–637

60. Zou X, Chen K, Zou J, Han P, Hao J, Han Z (2020) Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals

the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 14(2):185–192

61. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 82(15):7264–7275

62. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506

63. Wang W, Tang J, Wei F (2020) Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol 92(4):441–447

64. Moore JB, June CH (2020) Cytokine release syndrome in severe COVID-19. Science 368(6490):473–474

65. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P et al (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4):420–422

66. Liu K, Chen Y, Lin R, Han K (2020) Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect 80(6):e14–e18

67. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X (2020) COVID-19 and the cardiovascular system. Nat Rev Cardiol 17(5):259–260

68. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D (2020) Early clinical and CT manifestations of coronavirus disease 2019 (COVID-19) pneumonia. Am J Roentgenol 215(2):338–343

69. Murthy S, Gomersall CD, Fowler RA (2020) Care for critically ill patients with COVID-19. Jama 323(15):1499–1500

70. Ye Z, Zhang Y, Wang Y, Huang Z, Song B (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 30(8):4381–4389

71. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X (2020) Analysis of 92 deceased patients with COVID-19. J Med Virol 2020:1–5

72. Wang L, Shen Y, Li M, Chuang H, Ye Y, Zhao H, Wang H (2020) Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. J Neurol 267(10):2777–2789

73. Ellul M, Benjamin L, Singh B, Lant S, Michael B, Kneen R, Defres S, Sejvar J et al (2020) Neurological Associations of COVID-19. Lancet Neurol 19:p767–p783

74. Needham EJ, Chou SH-Y, Coles AJ, Menon DK (2020) Neurological implications of COVID-19 infections. Neurocrit Care 32(3):667–671

75. Valiuddin HM, Kalajdzic A, Rosati J, Boehm K, Hill D (2020) Update on neurological manifestations of SARS-CoV-2. West J Emerg Med 21(6):45–51

76. Rahman A, Niloofa R, De Zoysa IM, Cooray AD, Kariyawasam J, Seneviratne SL (2020) Neurological manifestations in COVID-19: a narrative review. J Clin Neurosci 77:8–12

77. Das G, Mukherjee N, Ghosh S (2020) Neurological insights of COVID-19 pandemic. ACS Chem Neurosci 11(9):1206–1209

78. Favas T, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D, Mishra VN, Kumar A et al (2020) Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurol Sci 41(12):3437–3470

79. Yachou Y, El Idrissi A, Belapasov V, Benali SA (2020) Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol Sci 41(10):2657–2669

80. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L et al (2020) Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 5(3):279–284

81. Radmanesh A, Raz E, Zan E, Derman A, Kaminetzky M (2020) Brain imaging use and findings in COVID-19: a single academic center experience in the epicenter of disease in the United States. Am J Neuroradiol 41(7):1179–1183

82. Zhao H, Shen D, Zhou H, Liu J, Chen S (2020) Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 19(5):383–384

83. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M (2020) Guillain–Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 25:1–38.

84. Sedaghat Z, Karimi N (2020) Guillain Barre syndrome associated with COVID-19 infection: a case report. J Clin Neurosci 76:233–235

85. Caress JB, Castoro RJ, Simmons Z, Scelsa SN, Lewis RA, Ahlawat A, Narayanaswami P (2020) COVID-19–associated Guillain-Barré syndrome: the early pandemic experience. Muscle Nerve 62(4):485–491

86. Abrams RM, Kim BD, Markantone DM, Reilly K, Paniz-Mondolfi AE, Gitman MR, Choo SY, Tse W et al (2020) Severe rapidly progressive Guillain-Barré syndrome in the setting of acute COVID-19 disease. J Neurovirol 26(5):797–799

87. Arias A, Torres-Tobar L, Hernández G, Paipilla D, Palacios E, Torres Y, Duran J, Ugarte S et al (2017) Guillain-Barre syndrome in patients with a recent history of Zika in Cucuta, Colombia: a descriptive case series of 19 patients from December 2015 to March 2016. J Crit Care 37:19–23

88. Whittaker A, Anson M, Harky A (2020) Neurological manifestations of COVID-19: a review. Acta Neurol Scand 142(1):14–22

89. Li Z, Liu T, Yang N, Han D, Mi X, Li Y, Liu K, Vuylsteke A et al (2020) Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. Front Med 4:1–9

90. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, Sordillo EM, Fowkes M (2020) Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 92(7):699–702

91. Tsai L, Hsieh S, Chang Y (2005) Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwanica 14(3):113–119

92. Lang ZW, Wen T, He LX, Xie L, Zhou YS (2003) Detection of SARS coronavirus RNA in lung tissues from patients with severe acute respiratory syndrome by in situ reverse transcription polymerase chain reaction. Chin J Microbiol Immunol 23:926–929

93. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, Zou W, Zhan J et al (2005) Multiple organ infection and the pathogenesis of SARS. J Exp Med 202(3):415–424

94. Zhang Q, Ding Y, Hou J, He L, Huang Z, Wang H, Cai J, Zhang J et al (2003) Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with in situ hybridization. Di 1 jun yi da xue xue bao= Acad J First Med College PLA 23(11):1125–1127

95. Tsai L-K, Hsieh S-T, Chao C-C, Chen Y-C, Lin Y-H, Chang S-C, Chang Y-C (2004) Neuromuscular disorders in severe acute respiratory syndrome. Arch Neurol 61(11):1669–1673

96. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S (2020) Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol 77(8):1018–1027

97. Kim K, Tandi T, Choi JW, Moon J, Kim M (2017) Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. J Hosp Infect 95(2):207–213

98. Kim J-E, Heo J-H, H-o K, Song S-h, Park S-S, Park T-H, Ahn J-Y, Kim M-K et al (2017) Neurological complications during treatment of middle east respiratory syndrome. J Clin Neurol 13(3):227–233

99. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M et al (2014) Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 29:301–306

100. Arabi YM, Balkhy HH, Hayden FG, Bouchama A, Luke T, Baillie JK, Al-Omari A, Hajeer AH et al (2017) Middle East respiratory syndrome. N Engl J Med 376(6):584–594

101. Turtle L (2020) Respiratory failure alone does not suggest central nervous system invasion by SARS-CoV-2. J Med Virol 28:116–126

102. Azhideh A (2020) COVID-19 neurological manifestations. Int Clin Neurosci J 7(2):54–54

103. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N et al (2020) Extrapulmonary manifestations of COVID-19. Nat Med 26(7):1017–1032

104. Klopfenstein T, Toko L, Royer P-Y, Lepiller Q, Gendrin V, Zayet S (2020) Features of anosmia in COVID-19. Med Mal Infect 50(5):436–439

105. Levinson R, Elbaz M, Ben-Ami R, Shasha D, Levinson T, Choshen G, Petrov K, Gadoth A et al (2020) Anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. medRxiv 52(8):600–602

106. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 10(7):806–813

107. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S et al (2020) 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 277(8):2251–2261

108. Farhadian S, Glick LR, Vogels CB, Thomas J, Chiarella J, Casanovas-Massana A, Zhou J, Odio C et al (2020) Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. BMC Neurol 20(1):248

109. Huang YH, Jiang D, Huang JT (2020) SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun 87:149

110. Jain R, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, Bilaloglu S, Hochman K et al (2020) COVID-19 related neuroimaging findings: a signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. J Neurol Sci 414:116923

111. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, González E, Redondo-Peñas I et al (2020) Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology 95(8):e1060–e1070

112. Li Y, Li H, Fan R, Wen B, Zhang J, Cao X, Wang C, Song Z et al (2016) Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. Intervirology 59(3):163–169

113. González-Pinto T, Luna-Rodríguez A, Moreno-Estébanez A, Agirre-Beitia G, Rodríguez-Antigüedad A, Ruiz-Lopez M (2020) Emergency room neurology in times of COVID-19: malignant ischemic stroke and SARS-COV2 infection. Eur J Neurol 27(9):e35–e36

114. Sohal S, Mossammat M (2020) COVID-19 presenting with seizures. Epilepsy Behav 112:107335

115. Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D (2020) Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Crit Care 24(1):1–4

116. Mahammedi A, Saba L, Vagal A, Leali M, Rossi A, Gaskill M, Sengupta S, Zhang B et al (2020) Imaging in neurological disease of hospitalized COVID-19 patients: an Italian Multicenter Retrospective Observational Study. Radiology 297(2):201933

117. Karimi N, Sharifi Razavi A, Rouhani N (2020) Frequent convulsive seizures in an adult patient with COVID-19: a case report. Iran Red Crescent Med J 3(22):20200301

118. Kadono Y, Nakamura Y, Ogawa Y, Yamamoto S, Kajikawa R, Nakajima Y, Matsumoto M, Kishima H (2020) A case of COVID-19 infection presenting with a seizure following severe brain edema. Seizure 80:53–55

119. Hepburn M, Mullaguri N, George P, Hantus S, Punia V, Bhimraj A, Newey CR (2020) Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? Neurocritical Care 34(1):139–143

120. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, Fontanella MM (2020) SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir:1–4

121. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, Calabresi P (2020) Focal status epilepticus as unique clinical feature of COVID-19: a case report. Seizure 78:109–112

122. Somani S, Pati S, Gaston T, Chitlangia A, Agnihotri S (2020) De novo status epilepticus in patients with COVID-19. Ann Clin Translat Neurol 7(7):1240–1244

123. Scullen T, Keen J, Mathkour M, Dumont AS, Kahn L (2020) COVID-19 associated encephalopathies and cerebrovascular disease: the New Orleans experience. World Neurosurg 141:e437–e446

124. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X et al (2020) Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 382(17):e38

125. Zhai P, Ding Y, Li Y (2020) The impact of COVID-19 on ischemic stroke: a case report. Diagn Pathol 15(1):78

126. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, Glaser A, Elsayegh D (2020) COVID-19 presenting as stroke. Brain Behav Immun 87:115–119

127. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H et al (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama 323(11):1061–1069

128. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229)

129. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, Mouchtouris N, Philipp L et al (2020) Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry 91(8):846–848

130. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt J-D et al (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 191:9–14

131. El Otmani H, El Moutawakil B, Rafai M-A, El Benna N, El Kettani C, Soussi M, El Mdaghri N, Barrou H et al (2020) Covid-19 and Guillain-Barré syndrome: more than a coincidence! Rev Neurol 176(6):518–519

132. Coen M, Jeanson G, Almeida LAC, Hübers A, Stierlin F, Najjar I, Ongaro M, Moulin K et al (2020) Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. Brain Behav Immun 87:111–112

133. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, Viganò M, Giovannelli G et al (2020) Guillain-Barré syndrome related to COVID-19 infection. Neurol-Neuroimmunol Neuroinflamm 7(4):e741

134. Padroni M, Mastrangelo V, Asioli GM, Pavolucci L, Abu-Rumeileh S, Piscaglia MG, Querzani P, Callegarini C et al

(2020) Guillain-Barré syndrome following COVID-19: new infection, old complication? J Neurol 267(7):1877–1879

135. Rana S, Lima AA, Chandra R, Valeriano J, Desai T, Freiberg W, Small G (2020) Novel coronavirus (COVID-19)-associated Guillain–Barré syndrome: case report. J Clin Neuromuscul Dis 21(4):240

136. Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, Harpe J, Greer C et al (2020) COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology 95(5):221–223

137. Benito-León J, Méndez-Guerrero A, Gutiérrez-Ortiz C (2020) Author response: Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology 95(9):409–409

138. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K et al (2020) Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 71(15):762–768

139. Domingues RB, Mendes-Correa MC, de Moura Leite FBV, Sabino EC, Salarini DZ, Claro I, Santos DW, de Jesus JG et al (2020) First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. J Neurol 267(11):3154–3156

140. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S (2020) Acute myelitis after SARS-CoV-2 infection: a case report. MedRxiv 5: 100091

141. AlKetbi R, AlNuaimi D, AlMulla M, AlTalai N, Samir M, Kumar N, AlBastaki U (2020) Acute myelitis as a neurological complication of Covid-19: a case report and MRI findings. Radiol Case Rep 15(9):1591–1595

142. Nath A (2020) Neurologic complications of coronavirus infections, Wolters Kluwer Health Inc on behalf of the American Academy of Neurology. Neurology 94(19):809–810

143. Brann D, Tsukahara T, Weinreb C, Logan DW, Datta SR (2020) Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. Sci Adv 6(31):eabc5801

144. Guidon AC, Amato AA (2020) COVID-19 and neuromuscular disorders. Neurology 94(22):959–969

145. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, de Aragón-Gómez F (2020) Benito-León J (2020) Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology 95(5):e601–e605

146. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, Franciotta D, Baldanti F et al (2020) Guillain–Barré syndrome associated with SARS-CoV-2. N Engl J Med 382:2574–2576

147. Prompetchara E, Ketloy C, Palaga T (2020) Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 38(1):1–9

148. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W et al (2020) Coronavirus infections and immune responses. J Med Virol 92(4):424–432

149. Cederberg D, Siesjö P (2010) What has inflammation to do with traumatic brain injury? Childs Nerv Syst 26(2):221

150. Carson MJ, Thrash JC, Walter B (2006) The cellular response in neuroinflammation: the role of leukocytes, microglia and astrocytes in neuronal death and survival. Clin Neurosci Res 6(5):237–245

151. Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G (2017) Neuroinflammation pathways: a general review. Int J Neurosci 127(7):624–633

152. McGavern DB, Kang SS (2011) Illuminating viral infections in the nervous system. Nat Rev Immunol 11(5):318–329

153. Law HK, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, Nicholls JM, Peiris JM et al (2005) Chemokine up-regulation in sars-coronavirus–infected, monocyte-derived human dendritic cells. Blood 106(7):2366–2374

154. Chu H, Zhou J, Wong BH-Y, Li C, Chan JF-W, Cheng Z-S, Yang D, Wang D et al (2016) Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. J Infect Dis 213(6):904–914

155. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G (2020) Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta 507:167–173

156. Wang J, Saguner AM, An J, Ning Y, Yan Y, Li G (2020) Dysfunctional coagulation in COVID-19: from cell to bedside. Adv Ther 37(7):3033–3039

157. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, Trilling M, Lu M et al (2020) Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 92(5):491–494

158. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G et al (2020) Hematological findings and complications of COVID-19. Am J Hematol 95(7):834–847

159. Thachil J, Tang N, Gando S, Falanga A, Levi M, Clark C, Iba T (2020) Laboratory haemostasis monitoring in COVID-19. J Thromb Haemost 18(8):2058–2060

160. Zaim S, Chong JH, Sankaranarayanan V, Harky A (2020) COVID-19 and multi-organ response. Curr Probl Cardiol 45(8):100618

161. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA et al (2020) Endothelial cell infection and endotheliitis in COVID-19. Lancet 395(10234):1417–1418

162. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E et al (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181(4):905–913.e7

163. Gaertner F, Massberg S Blood coagulation in immunothrombosis—at the frontline of intravascular immunity. Semin Immunol 28(6):561–569

164. Roberts CM, Levi M, McKee M, Schilling R, Lim WS, Grocott MP (2020) COVID-19: a complex multisystem disorder. Br J Anaesth 125(3):238–242

165. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18(4):844–847

166. Umapathi T, Kor AC, Venketasubramanian N, Lim CT, Pang BC, Yeo TT, Lee CC, Lim PL et al (2004) Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 251(10):1227–1231

167. Serrano-Castro P, Estivill-Torrús G, Cabezudo-García P, Reyes-Bueno J, Petersen NC, Aguilar-Castillo M, Suárez-Pérez J, Jiménez-Hernández M et al (2020) Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? Neurología 35(4):245–251

168. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C et al (2020) Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 382(23):2268–2270

169. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R (2020) Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther 12(1):69

170. Mishra R, Banerjea AC (2020) Neurological damage by coronaviruses: a catastrophe in the queue! Front Immunol 11:565521

171. Abate G, Memo M, Uberti D Impact of COVID-19 on Alzheimer's disease risk: viewpoint for research action. Healthcare 8(3):286

172. Salles-Gándara P, Rojas-Fernandez A, Salinas-Rebolledo C, Milan-Sole A (2020) The potential role of SARS-COV-2 in the pathogenesis of Parkinson's disease. Front Neurol 11:1044

173. Matías-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu J (2020) Should we expect neurological symptoms in the SARS-CoV-2 epidemic? Neurología 35(3):170–175

174. Iwashyna TJ, Ely EW, Smith DM, Langa KM (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. Jama 304(16):1787–1794

175. Covino M, De Matteis G, Santoro M, Sabia L, Simeoni B, Candelli M, Ojetti V, Franceschi F (2020) Clinical characteristics and prognostic factors in COVID-19 patients aged≥ 80 years. Geriatr Gerontol Int 20(7):704–708

176. Naughton SX, Raval U, Pasinetti GM Potential novel role of COVID-19 in Alzheimer's disease and preventative mitigation strategies. J Alzheimers Dis 76(1):21–25

177. Ferini-Strambi L, Salsone M (2020) COVID-19 and neurological disorders: are neurodegenerative or neuroimmunological diseases more vulnerable? J Neurol:1–11

178. Victorino DB, Guimaraes-Marques M, Nejm M, Scorza FA, Scorza CA (2020) COVID-19 and Parkinson's disease: are we dealing with short-term impacts or something worse? J Parkinsons Dis 10(3):899–902

179. Bauer K, Schwarzkopf L, Graessel E, Holle R (2014) A claims data-based comparison of comorbidity in individuals with and without dementia. BMC Geriatr 14:10

180. Gomez-Pinedo U, Matias-Guiu J, Sanclemente-Alaman I, Moreno-Jimenez L, Montero-Escribano P, Matias-Guiu JA (2020) Is the brain a reservoir organ for SARS2-CoV2? J Med Virol 92(11):2354–2355

181. Willis M, Robertson N (2020) Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. J Neurol 267(5):1567–1569