Overview of COVID-19 and neurological complications

Abstract: The sudden and storming onset of coronavirus 2 infection (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was associated by severe acute respiratory syndrome. Recently, corona virus disease 19 (COVID-19) has appeared as a pandemic throughout the world. The mutational nature of the virus, along with the different means of entering and spreading throughout the body has involved different organs. Thus, patients are faced with a wide range of symptoms and signs. Neurological symptoms, such as anosmia, agnosia, stroke, paralysis, cranial nerve deficits, encephalopathy, meningitis, delirium and seizures, are reported as common complications affecting the course of the disease and its treatment. In this review, special attention was paid to reports that addressed the acute or chronic neurological manifestations in COVID-19 patients who may present acute respiratory syndrome or not. Moreover, we discussed the central (CNS) and peripheral nervous system (PNS) complications in SARS-Cov2-infected patients, and also the pathophysiology of neurological abnormalities in COVID-19.

Keywords: Alzheimer’s disease; cerebrovascular disease; corona virus 2; encephalopathy; Guillain Barre syndrome; multiple sclerosis.

Introduction

In 1918, the Spanish flu, an unusually deadly influenza pandemic swept the globe, and now in the era of progress and technology, the corona virus disease 19 (COVID-19) has emerged with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (Cucinotta and Vanelli 2020). The rapid worldwide spread of this beta-coronavirus has caused serious economic, financial and social problems, and mental destruction (Ahmed et al. 2020). The ambiguous clinical presentations of the disease from respiratory (Netland et al. 2008), neurological (Montalvan et al. 2020), cardiovascular problems (Yang et al. 2020) to gastrointestinal manifestations (Pan et al. 2020) can complicate the outcome and treatment of the disease. Therefore, it is necessary to increase our knowledge about SARS-CoV-2 and its behavior in the body as much as possible in order to overcome COVID-19.

Based on genetic and antigenic criteria, corona viruses (CoVs) have been organized into three groups: α-CoVs, β-CoVs and γ-CoVs (Dhama et al. 2014; van Regenmortel et al. 2000). Currently, there are at least seven coronavirus species known to cause diseases in humans. The viruses of 229E, OC43, NL63 and HKU1 only cause common cold symptoms, which are mild. Severe illness can be caused by the remaining three viruses, namely SARS-CoVs, which resulted in the outbreak of SARS in 2002–2003 (Zhong et al. 2003). The coronaviruses, responsible for the Middle East Respiratory Syndrome (MERS-CoV), emerged in 2012 and have been circulating among camels since then (Zaki et al. 2012). SARS-CoV-2 emerged in December 2019 in Wuhan, China and measures have been taken to contain the outbreak of the disease.

So far, six families of coronaviruses have been identified, and the new SARS-CoV-2 has posed a great threat to human health. Mild seasonal respiratory illness is associated with four of these coronaviruses accounting for 15–30% of upper respiratory tract infections with a high worldwide incidence (Desforges et al. 2020). The severe acute respiratory syndrome (SARS or SARS-Cov1) and the middle east respiratory syndrome (MERS) are considered as two main coronavirus families caused by SARS-CoV and MERS CoV, which have led to serious epidemics with fatal respiratory diseases. The seventh member of the coronavirus family, named SARS-CoV-2, shares a high homology with SARS and MERS (79 and 50%, respectively) (Lu et al. 2020). Overall, coronaviruses have positive-sense single-stranded RNA genomes with glycoprotein spikes on the surface (Schoeman and Fielding 2019). Both SARS-CoV1 and SARS-CoV-2 can bind to the angiotensin-converting enzyme-2 (ACE2) (Ge...
et al. 2013), whereas MERS-CoV binds to dipeptidyl peptidase 4 (DPP4/CD26) receptors (Saad et al. 2014; Tsai et al. 2005). Therefore, it seems that SARS-CoV-1 and SARS-CoV-2 have more similar behavior patterns.

People were first infected by bats, as the primary reservoir of SARS-COV (Zheng 2020).

Basigin (BSG; CD147) (Wang et al. 2020d) and neuropilin-1 (NRP1) receptors (Cantuti-Castelvetri et al. 2020) are other targets for SARS-CoV-2, and TMPRSS11A/B, cathepsin B and L, and furin (FURIN) proteases facilitate viral entry and replication (Shang et al. 2020).

The common modes of transmission of the disease include droplets, fomites, and person-to-person contact, although transmission via stool shedding has also been reported (Chen et al. 2020b). Unfortunately, coronaviruses have zoonotic origin and are common in humans and animals, with a high rate of mutation and mortality (Zheng 2020).

The COVID-19 outbreak, caused by SARS-CoV-2, originated in December 2019 with unusual cases of pneumonia and respiratory distress with undetermined etiology (Zhu et al. 2020). On March 11, 2020, the World Health Organization (WHO) announced the COVID-19 outbreak as a pandemic associated with severe acute respiratory syndrome (Cucinotta and Vanelli 2020). This pandemic is of the most horrific kinds which, based on several evidences, targets the respiratory system; however, nervous system involvement was also reported in some experimental studies and case reports. For instance, 77 of 329 patients (39%) with severe COVID-19 diagnosis were transferred to the ICU, and 197 patients lost their lives. In eight cases (4.1% of total deaths), neurological complications were found to be the main causes of death (Romero-Sánchez et al. 2020).

There were marked variations among patients with COVID-19. For instance, age and sex (Goyal et al. 2020) can be risk factors for the prognosis of COVID-19, and patients with severe diseases were mostly male and older than those with mild diagnosis (Grasselli et al. 2020). Therefore, disease severity and mortality are higher in older individuals (Romero-Sánchez et al. 2020).

Moreover, some underlying medical conditions, such as hypertension, obesity, dyslipidemia, tobacco smoking, diabetes mellitus, and heart disease are the most common systemic comorbidities, and obesity has been reported as the only independent predictor for severe COVID-19 (Romero-Sánchez et al. 2020). The severely ill group also showed significant neurological symptoms and had less typical symptoms of coronavirus like fever and dry cough (Mao et al. 2020). SARS-CoV-2 continues to spread and there is an increased number of patients with respiratory symptoms. Furthermore, the involvement of the nervous system causes many neurological and neurocognition disturbances as the disease progresses even in the recovery period (Romero-Sánchez et al. 2020). Considering that nervous system disorders lead to cognitive problems which affect the individual and social performance of patients that have recovered from COVID-19, this review aimed to explore the impact of this disease on the nervous system.

Neurological implications

Two close relatives of SARS-CoV-2, i.e., SARS-CoV and MERS-CoV, are presented with severe respiratory complications and are associated with some neurological ailments and complications, i.e., encephalopathy, seizures, stroke, cranial nerve palsies, peripheral neuropathy and myopathy (Wu et al. 2020). The structural homology of SARS-CoV-2 with SARS-CoV and MERSCoV, its first lethal pulmonary manifestations and also the expression of SARS-CoV-2 receptor in the nervous system can be justified by the SARS-CoV-2 neurotropic actions and neurological signs (Schoeman and Fielding 2019).

Both central and peripheral neurological implications were reported in previous epidemics, i.e, SARS-CoV, MERSCoV and H1N1 influenza (Goenka et al. 2014; Kim et al. 2017). According to the classifications presented in some reports, from 4.8 million diagnosed cases of COVID-19, central nervous system (CNS) and peripheral nervous system (PNS) complications were observed in 1805–9671 and 2407–7737 patients, respectively (Ellul et al. 2020). Of course, these studies did not report any strokes associated with COVID-19. For this reason, COVID-19 patients with neurological manifestation are classified based on the CNS and PNS symptoms, and the skeletal muscle complications will be discussed later (Ahmad and Rathiore 2020). Another category is based on laboratory findings and clinical symptoms, and COVID-19 patients classified into severe, mild and moderate categorizes or NeuroCovid stage I, NeuroCovid stage II and NeuroCovid stage III (Table 1) (Fotuhi et al. 2020).

In NeuroCovid stage I, the binding of SARS-Cov2 to ACE2 receptors is related to the nasal and gustatory epithelial cells. The cytokine storm, stimulated by the virus, remains low and controlled. Patients with anosmia and ageusia are often cured without any interventions (Fotuhi et al. 2020).

NeuroCovid stage II is related to activation of a robust immune response by SARS-CoV2 with high levels of cytokines, which in turn increase the levels of ferritin, C-reactive protein and D-dimer. This hypercoagulable state triggers the formation of blood clots, arterial occlusion or venous thrombosis following strokes. The huge immune response leads to vasculitis in muscles or nerves damaging cranial
nerves, peripheral nerves and/or muscles (Fotuhi et al. 2020).

In NeuroCovid stage III, the cytokine storm damages the blood–brain barrier and leads to infiltration of inflammatory factors and other blood contents, such as the entry of viral particles into the CSF. The edema and brain injury result in delirium, encephalopathy and/or seizures. The high peripheral vascular resistance and hypertension increase the risk for intracranial hemorrhage (Fotuhi et al. 2020).

However, it seems that some brain damages, neurological symptoms in severe pneumonia, and systemic hypoxia (which indirectly cause brain damage) are related to SARS virus family—SARS-CoV-2. Inflammation and edema affect the alveolar oxygen exchange and lead to hypoxemia and subsequently brain hypoxia with vasodilation, hyperemia and brain edema (Abdennour et al. 2012; Ahmad and Rathore 2020). The peripheral vasodilatation, hypercarbia, hypoxia and anaerobic metabolism are the contributory factors which can produce neuronal swelling and brain edema and cause neurological damage (Tu et al. 2020). However, the newly published data by German researchers rejected the association of the severe hypoxia with brain damage in COVID-19. The results indicated that the causes of brain damage were probably either exaggerated immune response or viral invasion or both, especially around the brainstem (von Weyhern et al. 2020).

Headache and dizziness are featured as nonspecific neurological symptoms (Mao et al. 2020); moreover, anosmia, hypogeusia, neuralgia, vomiting, demyelination, paralysis, ataxia, cranial nerve deficits, stroke, encephalopathy, delirium, confusion, meningitis, seizures and musculoskeletal injury are other neurological complications in COVID-19 (Fotuhi et al. 2020; Helms et al. 2020; Li et al. 2020e; Mao et al. 2020; Nyati and Nyati 2013; Oxley et al. 2020; Pleasure et al. 2020; Schoeman and Fielding 2019; Wu et al. 2020). In this regard, some evidences raised awareness of cerebrovascular, dysimmune, optic neuritis, and acute inflammatory demyelinating polyradiculoneuropathy as
some neurological complications in the recovery phase of the disease (Romero-Sánchez et al. 2020).

The neurological complications that are more common in severe diseases may be related to critical illnesses. An investigation conducted by Bo Hu et al. in China demonstrated a higher incidence of neurological symptoms and signs in severe cases of COVID-19 (Mao et al. 2020). Therefore, much investigation is needed to reveal the effects of SARS-CoV-2 virus on neurological manifestations by isolating it either from CSF or dissected tissues of the brain to explore the main threatening risk factors. Overall, the neurological manifestations like encephalitis, meningitis, cerebrovascular disease and Guillain Barré Syndrome (GBS) are of great concern that will be considered in the related sections.

CNS implications

Infection with beta corona virus (HCV-OC43) induces brain inflammation, neurodegeneration and apoptosis. The acute encephalitis due to viral RNA (Jacomy et al. 2006) for several months can lead to neuronal degeneration and even death (Morfopoulou et al. 2016).

The brain is a suitable target for SARS-COV-2 which is mostly transferred through direct contact. COVID-19 mainly causes a severe and fatal respiratory syndrome with some specific neurological symptoms in the CNS, including dizziness, stiff neck, headache, acute impaired consciousness, acute cerebrovascular disease, ataxia, hyposmia, hypogeusia, neuralgias and seizure (Fotuhi et al. 2020; Li et al. 2020e; Schoeman and Fielding 2019). The onset of these symptoms may indicate that the virus can enter the brainstem through synaptic connections with lungs (Wong et al. 2020).

Although the exact relationship between the virus attack to the brainstem and respiratory insufficiency in COVID-19 patients is not clearly specified some believe that SARS-CoV-2 can enter the brain and cause respiratory failure in patients (Li et al. 2020c).

Meanwhile, there are still others who think that respiratory involvement alone does not imply central nervous system complications related to SARS-CoV-2 (Guan et al. 2020; Turtle 2020).

In some cases, SARS-CoV-2 may contribute to certain nervous system complications; however, its importance is still unclear. In an observational study on 41 patients with COVID-19, headache and myalgia and dizziness were found in 8 and 12% of the patients, in that order (Huang et al. 2020). Another study reported similar results about myalgias (17.2%), headache (14.1%) and dizziness (6.1%) (Romero-Sánchez et al. 2020). It is important to note that patients with COVID-19 with acute headache, nuchal rigidity, seizure and confusion may also experience meningitis (Moriguchi et al. 2020). Confusion is a common clinical manifestation in patients, but it is not clear if this is due to the illness and low oxygen level or brain infection (Rutkowski 2020). The meninges contain blood vessels and high levels of ACE2 (Li et al. 2020a). Damage to these blood vessels and inflammation in the brain and spinal cord meninges can lead to meningitis (Li et al. 2020a). Overall, anosmia and dysgeusia are currently the first clinical manifestations of COVID-19. They are more frequent in mild-to-moderate illness and are often improved within weeks; however, the possibility for a central etiology remains unlikely (Fotuhi et al. 2020). Loss of smell (85.6%) and taste (88.0%) have also been reported among 417 European patients with mild-to-moderate illness (Giacomelli et al. 2020). Also, 18.6% of 59 Italian patients lost their senses of smell and taste (Lovato et al. 2020). However, among 214 hospitalized patients in China (Wuhan) with severe or non-severe COVID-19 symptoms, 5.1% of the patients with mild and 5.6% of patients with severe COVID-19 experienced taste loss (Mao et al. 2020). Interestingly, in acute onset of anosmia, nasal mucosa and olfactory bulb volume were found normal in MRI reports of Iranian patients.

Hyperkinetic movement disorders are other neurological symptoms known with excessive, abnormal and involuntary movements that have been reported in COVID-19 patients. Among all 841 hospitalized patients, hyperkinetic movement were disorders diagnosed in 0.7% of COVID-19 patients (Romero-Sánchez et al. 2020).

In the presence of some neurological symptoms, laboratory tests may not show traces of virus in the brain. Duong et al. reported a case with headache, fever, disorientation, seizure and hallucination complications, despite negative head CT and CSF (Duong et al. 2020). Similarly, the head CT and CSF of a 64-year-old man with COVID-19 and acute onset of lethargy, irritability, dissociated speech and confusion were negative (Yin et al. 2020). This may suggest an indirect effect of virus or systemic inflammatory mechanisms which cause neurological complications. However, researchers could not precisely determine whether neurologic problems were due to SARS-CoV-2 infection or other factors like cross-immunity, inflammatory reaction, or if they were the side effects of treatment.

Encephalopathy

Encephalopathy is a general term that refers to a brain disease, damage, or malfunction with a very broad spectrum of symptoms like memory loss, personality changes,
dementia, seizures, coma or even death (Wendon and Lee 2008). Encephalopathy is manifested by an altered mental state, sometimes accompanied by physical manifestations such as poor coordination of limb movements. In general, encephalopathy is not just one disease, but it is an umbrella term for damage or disease with an alteration in mental status (Takei et al. 2010).

The main underlying etiology of encephalitis or acute brain inflammation includes viral infections like severe acute respiratory coronavirus (SARS-CoV), Middle East respiratory virus (MERS-CoV) infections (Glaser et al. 2006; Granerod et al. 2010) and recently SARS-CoV-2 (Algahtani et al. 2016; Duong et al. 2020; Jacomy et al. 2006). Encephalopathy can occur after extubation, possibly due to long-term effects of sedation or mechanical ventilation and often resolves in a few days. Encephalopathy can continue for several weeks or even months and can be aggravated by bacterial infection during ventilation (Waterman 2020).

A 15-year-old child with upper respiratory symptoms and subsequent HCoV-OC43 showed mild respiratory infections (Yeh et al. 2004), while some MERS-CoV infected patients demonstrated severe neurological manifestations like acute disseminated post-infectious encephalomyelitis and post-infectious brainstem encephalitis due to potential neurotropic traits (Algahtani et al. 2016).

Based on the results of some studies, coronavirus infection in mice was associated with myelin degeneration in their spinal cords in the acute phase of infection after 2–3 weeks. Acute disseminated encephalomyelitis (ADEM), demyelinating inflammation of the brain and spinal cord from acute viral infection are associated with HCoV-OC43 positive cerebrospinal fluid (CSF) and nasopharyngeal specimens (Fehr and Perlman 2015; Savarin et al. 2008; Yeh et al. 2004). A case study report in the USA showed ADEM symptoms following dysphagia and dysarthria in a woman with COVID-19 disease (Zhang et al. 2020a). Another report showed that MERS-CoV infection caused new lesions in the periventricular deep white matter, corpus callosum, bilateral pons, midbrain, left cerebellum, and upper cervical cord within 24 days (Algahtani et al. 2016). Hemorrhagic ring-enhancing lesions consistent with acute necrotizing encephalitis were seen in the bilateral thalami, medial temporal lobes and sub-insular regions on an MRI image (Poyiadji et al. 2020).

Also, encephalopathy occurred in 16 (7%) of the 214 patients with COVID-19 in China, and 40 (69%) of 58 patients in intensive care units with COVID-19 in France (Ellul et al. 2020). Moreover, a retrospective study in China showed that about 20 of 113 COVID-19 patients suffered from hypoxic encephalopathy (Chen et al. 2020a). Some patients had altered mental status with unspecified encephalopathy, whereas others had both clinical symptoms and signs of encephalopathy and evidences for CNS inflammation (Varatharaj et al. 2020).

The first confirmed case of COVID-19 associated viral encephalitis was a 24-year-old man with a stiff neck and fever followed by seizure and unconsciousness in Japan. Despite his normal brain CT, the diffusion-weighted imaging (DWI) showed an evidence of patchy pneumonia on his chest CT with hyperintensity in the right lateral ventricle. His nasopharyngeal swab and PCR assay were negative; however, his CSF sample was positive for COVID-19 (Moriguchi et al. 2020). In contrast, based on another report, a positive nasopharyngeal swab test may be accompanied by negative CSF infection analysis. The authors reported a woman with a history of fever, cough and altered mental status. She was hospitalized with COVID-19 diagnosis after the detection of SARS-Cov-2 nucleic acid in a nasopharyngeal swab although her CSF analysis was free from bacteria, HSV1 and HSV2, varicella zoster virus, and West Nile virus, and her head CT scan was normal with symmetrical bilateral medial thalamic hypoattenuation (Huang et al. 2020).

Acute necrotizing encephalopathy (ANE) is a rare complication of viral infections like influenza, but Poyiadji et al. reported a case of COVID-19 associated acute hemorrhage with ANE diagnosis. The proposed mechanism is likely linked to cytokine storm, which results in both a disruption of blood–brain barrier and damage to the brain parenchyma. Poyiadji et al. also proposed that ANE may be associated with SARS-CoV-2 and subsequent high cytokine levels because the severity of COVID-19 is associated with several interleukins (Poyiadji et al. 2020).

It is necessary to carefully consider all causes of encephalopathy, such as hypoxia, drugs, toxins and metabolic derangement in patients with altered consciousness or agitation.

Infection can influence the brain via inflammatory responses and cause encephalopathy; thus encephalitis should be taken into consideration when CSF pleocytosis, imaging changes, focal seizures, or histological changes indicate clinical evidence of brain inflammation (Ellul et al. 2020). Encephalitis may not be diagnosed even if the virus is detected in CSF unless there is an evidence of brain inflammation. The analysis of the limited literature on COVID-19 so far suggests that SARS-Cov2 triggers an immune-mediated encephalopathy more than a direct viral encephalopathy (Wu et al. 2020).

A 35-year-old Turkish female has been reported with a case of COVID-19 with encephalitis mimicking a glioma (Efe et al. 2020). She was hospitalized for refractory seizures and underwent a left anterior temporal lobectomy. She was reported as a COVID-19 patient with viral encephalitis.
diagnosis and neurological signs, i.e., cerebellar ataxia and disturbance in consciousness.

Moreover, patients with possible peripheral nerve disease must undergo CSF examination for evidences of albuminocytological dissociation (an elevated CSF protein level with a normal CSF cell count), nerve conduction studies (NCSs), and electromyography (EMG) during recovery, even if they cannot be done acutely (Ellul et al. 2020). It is difficult to explain the relationship between neuropathy, cerebrovascular disease, and ADEM in patients or the host’s response to viral infection, especially when their nasopharyngeal swab tests are negative.

Peripheral nervous system manifestations and complications

SARS-CoV-2 infection, like the other family, SARS-CoV1, can also exhibit certain PNS complications, such as injuries to muscles or severe cranial and peripheral nerves injuries. For example, weakness in both legs and inability to walk accompanied by numbness and tingling in stocking distribution related to axonal polyneuropathy were observed in a patient with severe MERS-CoV respiratory infection (Algahtani et al. 2016). There is another case report about three patients who developed motor-predominant peripheral nerve disorders, neuropathy and myopathy three weeks after the onset of the disease (Camdessanche et al. 2020). Currently, the pattern of clinical symptoms and acute response to intravenous immunoglobulin (IVIG) indicate an immune-related etiology and pathogenesis for peripheral and cranial neuropathy in COVID-19 (Fotuhil et al. 2020). Muscle injury and high levels of creatine kinase (Mao et al. 2020) in ICU patients with COVID-19 can be attributed to critical care neuropathy and myopathy.

An observational study on 214 COVID-19 patients revealed that about 8.9% of the patients presented PNS symptoms including hypoguesia, hyposmia, hypoplasia and neuralgia (Xu et al. 2020b). According to Toscano et al., COVID-19 patients can show severe facial weakness and sensory ataxia with signs of enhancement of facial nerves in brain MRI (Toscano et al. 2020). The prognosis of some patients with various degrees of cranial nerve and limb weakness were promising. However, some PNS symptoms are less intense and include neuralgia and impairments in taste, smell or vision. Unlike CNS, laboratory findings are not helpful for patients with PNS involvement. Lower lymphocyte and platelet counts in addition to higher BUN levels were demonstrated in severe diseases where CNS is involved (Guan et al. 2020).

It is important to consider some problems, such as limb weakness and sensory changes in patients because it is crucial to distinguish diseases associated with peripheral nerves involvement (e.g., GBS) compared to inflammation of the spinal cord by CSF. In this regard, CSF examination, neurophysiological examinations and spinal imaging can be helpful. Also, for the patients, under critical care, it is probably difficult to determine if neuropathy or myopathy is the nonspecific manifestation of critical illness or if they are specific to the virus itself (Guidon and Amato 2020). This problem is due to lack of reliable markers to detect the neurological disease caused by critical illnesses, although they tend to occur after several weeks. However, neuroinvasion of SARS-CoV2 to the brainstem weakens the muscles of ICU patients with ARDS; consequently, it deserves investigation (Baig et al. 2020; Hamming et al. 2004; Li et al. 2020d). Multiple reports have documented acute autoimmune polyneuropathy in patients infected with corona virus families: SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (Algahtani et al. 2016; Mao et al. 2020; Tsai et al. 2004).

Moreover, patients with a chemosensory dysfunction, i.e., anosmia or hyposmia, also experienced altered or loss of taste (Yan et al. 2020). Anosmia refers to the loss of the sense of smell and hyposmia is defined as a reduced ability to smell. In fact, anosmia/hyposmia can be the only evident symptoms in many patients. According to a case study, a patient with no symptoms of COVID-19 presented with a sudden onset of anosmia, while her test result for SARS-CoV-2 was positive (Gane et al. 2020). According to the finding, females, compared to males, are more susceptible to olfactory and gustatory dysfunctions (Lechien et al. 2020).

The close relationship between olfactory and gustatory functions may account for problems in distinguishing tastes or a complete loss of taste, while the patient may have just lost his/her sense of smell (Small and Prescott 2005). Several studies have demonstrated that taste dysfunction in COVID-19 occurs more than olfactory dysfunction, and about 10.2–22.5% of patients have impaired taste without olfactory dysfunction (Giacomelli et al. 2020; Lechien et al. 2020; Vaira et al. 2020a; Yan et al. 2020). Thus, ageusia is probably a special symptom of COVID-19 which differs from the loss of olfactory function in flu-like upper respiratory congestion or difficulties in distinguishing tastes (Vaira et al. 2020b). Generally, it seems that in ambulatory cases of COVID-19, the virus spreads via the nasal route, whereas in the seriously ill patients the virus infects the lungs (Vaira et al. 2020b).

Recently, a cohort study on 10,069 patients in Iran showed that 48.23% patients were suffering from anosmia and hyposmia and 83.38% patients had taste problems. Furthermore, about 75.5% of patients had flu or cold
symptoms before anosmia and 76.24% reported a sudden onset of anosmia. Taste dysfunction and anosmia were not reported in the French cohort study of COVID-19 patients (Bagheri et al. 2020).

The impairment of olfactory and gustatory functions in patients are likely due to the infection of the epithelial cells of nasal and oral mucosa (Fotuhi et al. 2020). As it will be mentioned in the following section, high expression of ACE2 is present in olfactory epithelial cells, nasopharynx, and oral mucosa. The virus probably binds to ACE2 receptors in nasal and oral mucosa; therefore, it can inhibit the function of sensory receptor cells mediating olfactory and gustatory receptors (Sungnak et al. 2020; Xu et al. 2020a). The effect of race on the percentage of COVID-19 patients in Asia and Europe, where the patients suffer from anosmia or ageusia, may need further investigations (Lechien et al. 2020).

A study from hospitalized patients in China (Wuhan) demonstrated that only 5% of patients suffered from smell and taste impairments (Lechien et al. 2020; Mao et al. 2020). This is in contrast with three European studies that reported olfactory and/or gustatory dysfunction in 33.9–88.0% of patients, within 21–25 days after the onset of COVID-19 (Lechien et al. 2020; Spinato et al. 2020).

NCSs documented momentary weakened compound muscle action potential (CMAP) amplitudes although there was no apparent evidence about slowing of nerve conduction velocity, lengthened distal motor latency, conduction block or temporal dispersion. Also, EMG results showed acute denervation and increased polyphagia. These patients with severe polyneuropathy, generally received intensive care for multiple organ complications and systemic inflammatory response syndrome (Tsai et al. 2005).

Peripheral autonomic nervous system disorder is another important issue that should be considered in COVID-19. Based on a number of reports, 2.5% out of 841 hospitalized COVID-19 patients had dysautonomia indicating excessive sympathetic or parasympathetic activity. Although there is a direct invasion of the peripheral nerves by the virus, the absence of any SARS-Cov2 in the CSF in some patients makes it unlikely. However, more detailed investigations are required in this area (Romero-Sánchez et al. 2020).

**Guillain Barre syndrome (GBS)**

Another PNS related disease is GBS with certain bacterial or viral etiology which usually occurs after gastrointestinal or respiratory illnesses. The most common known preceding infections related to GBS are influenza virus, Zika virus, and Campylobacter (Brasil et al. 2016; Nyati and Nyati 2013; Parra et al. 2016).

Currently, GBS is associated with ascending paralysis, sensory loss or cranial nerve injury as a result of cross-reactivity of natural immunoglobulins with bacterial or viral antigen containing specific proteins in myelin, axon, or neuro-muscular junctions (Ang et al. 2004).

Recently, neuromuscular disorder has been found along with SARS-CoV. Also, GBS has been reported in patients infected by SARS-Cov1 and in patients with beta coronavirus (HCV-OC43) which showed GBS with unilateral peripheral palsy and bulbar palsy presentations (Turgay et al. 2015). Moreover, sever MERS-CoV infection was associated with ophthalmoplegia, weakness in all four limbs and acute sensory neuropathy (Kim et al. 2017).

One in four MERS-CoV infected patients with GBS manifestations and hypersomolence was diagnosed with Bickerstaff’s brainstem encephalitis, a variant of GBS which has also been reported in patients with COVID-19 in China, Iran, Italy, and USA (Kim et al. 2017). A 61-year-old woman was hospitalized with acute leg weakness, fatigue and clinical signs of lymphocytopenia and thrombocytopenia, while GBS was confirmed on the fifth day. Fever and dry cough appeared on day 8 and her SARS-CoV-2 test was positive. It seems that lymphocytopenia and thrombocytopenia were early presentation of COVID-19 (Zhao et al. 2020). Five SARS-Cov-2 positive patients were diagnosed with GBS in Italy (Toscano et al. 2020). Limb paralysis and paresthesia were the primary symptoms in four patients, while one patient had facial diplegia and ataxia. The clinical and preclinical results were different in patients, for instance one of the five patients had a negative nasopharyngeal swab and bronchoalveolar lavage and two had normal protein levels in CSF. All five patients had white cell counts lower than five with negative SARS-CoV-2 real-time polymerase-chain-reaction; furthermore, three patients had fibrillation potentials in EMG, two patients showed caudal nerve roots enhancement, and one patient had facial nerve enhancement, while none of these cases were found in the MRI reports of the two other patients. The NCS/EMG signals included features of demyelinating polyneuropathy in two patients, while three patients had axonal polyneuropathy. One week after hospitalization, only one patient was able to walk independently and returned home (Toscano et al. 2020). Similarly, a diabetic Iranian male with cough, fever and temporary dyspnea symptoms showed ascending paralysis leading to quadriplegia and bilateral facial paralysis, two weeks after primary symptoms. NCS/EMG assessments confirmed acute motor sensorimotor neuropathy diagnosis (Sedaghat and Karimi 2020). In another study, a 54-year-old male from the USA tested positive for COVID-19 and was diagnosed with GBS and acute progressive ascending paralysis. This leads to respiratory
difficulty and diarrhea preceding the acute attack of weakness (Virani et al. 2020).

Another SARS-CoV-2 infected patient presented with a variant of GBS, i.e., Miller Fisher Syndrome, which is a rare and acquired nerve disease. He had a history of fever, cough, malaise, headache, low back pain, altered sensations of smell and taste, double vision, perioral numbness, ataxia and right internuclear ophthalmoparesis, as well as right fascicular oculomotor palsy which lasted for five days. However, his CSF analysis, CT head and chest X-ray were normal (Gutiérrez-Ortiz et al. 2020).

Therefore, clinicians should be very alert in this era of COVID-19 pandemic because the patient can only have neurological findings at presentation because the symptoms of COVID-19 may be neglected and speed the spread of the infection. Overall, most patients presented with progressive paresthesia, and right internuclear ophthalmoparesis, as well as right fascicular oculomotor palsy which lasted for five days. Nevertheless, his CSF analysis, CT head and chest X-ray were normal (Gutiérrez-Ortiz et al. 2020).

Skeletal muscle damage

Patients with other neurological disorders are also at risk for multiple complications associated with COVID-19. Generally, the skeletal muscle dysfunctions can follow sensorimotor peripheral nerve disorders or secondary to sedentary conditions in ICU (Iida and Sakuma 2017). In a case report, three of four patients with acute neuromuscular disorders and SARS infection developed weakness, sensorimotor peripheral nerve symptoms and decreased deep tendon reflexes (Tsai et al. 2005).

In addition to the previously mentioned neurological manifestations, corona virus infection can cause some neuromuscular disorders, i.e., myalgia and myopathy (Tsai et al. 2004). However, there is usually at least one underlying comorbid disorder, such as hypertension, diabetes, cardiovascular/cerebrovascular disease or cancer in patients (Gammill et al. 2020).

Among 214 patients with COVID-19 hospitalized in Wuhan with neurological manifestations, 10.7% of patients had skeletal muscle injuries (Gammill et al. 2020). In this regards, Mao et al. observational study reported COVID-19 patients in the ICU were exposed to more severe lethargy, muscle atrophy, and weakness than patients in the critical care setting (Mao et al. 2020). The patients with severe COVID-19 showed symptoms of evident muscle injury (Mao et al. 2020), similar to those found in COVID-19 patients in the ICU (Bhatraju et al. 2020). Nevertheless, ICU-admitted patients receiving sedating drugs and paralyzing treatment can also be weak and unable to stand or walk. However, the severe muscle inability in COVID-19 patients refers to the involvement of vasculitis or myositis of varying etiologies (Guidon and Amato 2020). Similar evidences have shown myocarditis and myocardial infarction due to cytokine storm, hypercoagulability, and ischemia coincidence in SARS-Cov2 infected subjects (Basu-Ray and Soos 2020). Moreover, skeletal muscle injury defined as the existence of myalgia and high levels of creatine kinase (above 200 U/L), was observed in severely (19.3%) and non-severely (4.8%) ill patients (Mao et al. 2020). Patients with neuromuscular disorder, i.e., myasthenia gravis may experience a relapse or even an increase in their symptoms during the COVID-19 pandemic, but it was not clear whether muscular involvement was due to the direct effect of the virus on muscle tissue or not (Guidon and Amato 2020).

Another proposed mechanism for skeletal muscle damage is related to infection-mediated immune response with high pro-inflammatory cytokines in serum (Mao et al. 2020). It is noteworthy that patients with severe illness had high muscle enzymes, elevated liver enzymes and disturbed renal functions (Ahmad and Rathore 2020). However, no specific diagnostic test or muscle histopathology was used to determine myopathy and neuropathy in addition to skeletal muscle damage in these patients.

MS and COV

Acute transverse myelitis (ATM) or transverse myelitis, is an inflammatory myelitis with demyelination disorders manifestations, such as multiple sclerosis (MS), neuromyelitis optica (NMO), idiopathic transverse myelitis, herpes zoster
and herpes simplex virus infections, and other inflammatory disorders like systemic lupus erythematosus (SLE) and neurosarcoidosis (Jacob and Weinschenker 2008).

A 66-year-old male from Wuhan presented with fever and body aches, acute flaccid paralysis of bilateral lower limbs, as well as urinary and bowel incontinence and acute myelitis diagnosis. His chest CT scan revealed patchy pneumonia and his nasopharyngeal swab test for SARS-CoV-2 was positive (Chow et al. 2020). The acute myelitis most probably resulted from cytokine storm and overactive inflammatory response, yet this case report did not include CSF PCR for coronavirus or MRI of the spine (Ahmad and Rathore 2020). Of course, evidence supports a possible relationship between viral infections, such as coronavirus and the development of demyelinating-related diseases. It has been postulated that viruses are recognized by toll-like receptors, and they modulate the immune response of the patients with developing MS (Duffy and O’Reilly 2016). Indeed, toll-like receptors are involved in viral clearance and the development of ARDS in severe COVID-19 (O’Reilly and Duffy 2016).

An observational study was conducted to detect human corona virus RNA in human brain autopsies (Arbour et al. 2000). Samples from 39 patients with MS and 51 patients with other neurological diseases or healthy people were examined. The results showed higher prevalence of the OC43 strain of human coronavirus in MS patients (35.9% or 14 of 39 cases). Another similar study reported the detection of murine-like coronaviruses in 12 out of 22 MS brains (Arbour et al. 2000). These evidences are supported by discovering some traces of coronavirus-like particles in the perivascular of an MS patient and the detection of human corona virus in the brains of MS patients (Murray et al. 1992). Also, studies on animals showed that mice, infected with the coronavirus JHMV strain, caused an acute encephalomyelitis followed by a chronic demyelinating disease (Libbey et al. 2014).

In this regard, HCoV-OC43 viral proteins were shown to be expressed in microglia, astrocytes, oligodendrocytes, as well as neurons (Jacomy et al. 2006). The proposed mechanism including a prolonged infection of oligodendrocytes, astrocytes, or autoimmune responses (Boucher et al. 2007). Despite the existence of some connections between alpha and beta coronaviruses and demyelinating diseases, no association was confirmed between SARS-CoV-2 and MS; however, some associations can be expected.

**Psychological impairment**

Severe neurological and neuropsychiatric presentations associated with COVID-19 have become increasingly apparent. Cognitive disorders or “neurocognitive disorders” are known as mental health disorders that affect cognitive abilities, such as learning, memory, perception, problem solving, perceptual-motor function, language, complex attention and social cognition (Gottfredson 1997; Hosseini et al. 2017). In fact, dementia, developmental disorders, motor skill disorders, amnesia and substance-induced cognitive impairment are some common cognitive disorders leading to confusion, poor motor coordination, and loss of short-term or long-term memory, identity confusion and impaired judgment (Hugo and Ganguli 2014; Hosseini et al. 2013, 2017). Cognitive impairment may also be related to hypoxemia, hypoperfusion, inflammatory response infection, sedating and anesthetic drugs and mechanical ventilation (Waterman 2020).

Some diseases including depression, obsessive compulsive disorder, psychosis, Parkinson’s disease and AD can cause neuropsychiatric and neurocognitive conditions. On the other hand, the presence of dementia, mild cognitive impairment or other mental disorders can affect brain functions in patients with central or systemic diseases (Hosseini et al. 2017; Troyer et al. 2020).

Hypoxia, cardiac dysfunction, blood clots, strokes, and similar conditions, observed in COVID-19 have long-term effects on brain functions and cognition. The oxygen supplement is critical for the function of the brain (Kim et al. 2013). Studies support the vulnerability of MS patients to neuropsychiatric impacts of the COVID-19 pandemic due to some degrees of cognitive and neuropsychiatric disorders, i.e., anxiety and depression even in the early stages of the disease (Akhoundi et al. 2020). On the other hand, depression has deleterious effects on cognitive reserve through direct and indirect mechanisms influencing information-processing speed and cognition, respectively (Lester et al. 2007).

The combination of pathophysiological events, medical complications and interventions, and also preexisting conditions are several risk factors for long-term cognitive weakness after recovery from ARDS. Early reports suggested that the development of neurological symptoms would most probably occur in critically ill COVID-19 patients, and also pre-existing risk factors included dementia, subarachnoid hemorrhage and epilepsy similar to ARDS (Lleó and Alcolea 2020; Waterman 2020). A cross-sectional study in China showed that 53.8% of 1210 SARS-CoV-2 infected patients suffered from moderate to severe psychological problems (Wang et al. 2020a).

A study on 39 patients with new outbreak psychosis, neurocognitive decline, or other conditions demonstrated mental state alteration as the second most common neurological problem (Romero-Sánchez et al. 2020).
The results of a study on available data from 125 (82%) of 153 patients in the UK showed that 39 (31%) of 125 patients developed altered mental status. In addition, 23 of 125 patients suffered from neuropsychiatric disorders and 10 (43%) presented with new-onset of psychosis, six (26%) were reported with neurocognitive syndrome like dementia and four (17%) had affective disorder, including catatonia and mania. Some patients suffer from polyopathy and weakness, so their physical and mental health should be monitored to preserve their physical and psychological abilities (Varatharaj et al. 2020). However, it seems that age and underling cerebrovascular disorders are the most important factors influencing patients' physical and mental health. The psychological symptoms are believed to affect cognitive functioning, especially attention and executive function (Lahiri et al. 2020). For example, delirium can be followed by long-term cognitive deficits such as memory impairments due to which some patients experienced difficulty in choosing the right words, developed retrograde amnesia (Gerstein 2011), and did not remember events related to the onset of the COVID-19 pandemic (Fotuhi et al. 2020). Some patients showed personality instability, for instance they became aggressive, impulsive, depressed, slower at information processing, and showed a tendency towards drugs or alcohol (Schmidt and Freyberger 2001).

ICU hospitalized patients, who recovered from respiratory symptoms, were potentially at a higher risk for neuropsychiatric and neurocognitive conditions (Nath 2020; Troyer et al. 2020). Making matters worse, doctors commonly use sedation to repress drastic coughing and help patients tolerate the distress and disturbance of a breathing tube; however, these drugs can increase the risk for delirium (Servick 2020). According to a study, 20–40% of intensive care unit patients, and 80% of ICU patients who needed mechanical ventilation were at a higher risk for delirium (Pandharipande et al. 2017). Remarkably, even some patients in the rehabilitation stages experienced hallucinations or delusions (Huff 2020). Acute respiratory distress syndrome was usually accompanied by mild cognitive impairment in attention, memory and executive function which may continue for approximately one year in about one quarter of patients with viral pneumonia (England 2020).

Patients in ICU settings with multiple medical conditions, and on a long list of medications, can develop memory loss and delirium, show slow processing speed, or even lapse into coma (Kotis et al. 2020). As such, a decline in mental activity in severe COVID-19 may not necessarily represent a direct brain injury caused by SARS-Cov2. However, it seems that the rate of encephalopathy and delirium is higher in COVID-19 patients compared to other ICU patients (Mao et al. 2020; Zambrelli et al. 2020).

Some complications of SARS-Cov2 can appear a long time after infection; therefore, it is necessary to regularly follow-up patients. Monitoring of COVID-19 patients with neurological deficits may help us to manage aging-associated and neurodegenerative disorders, such as AD and Parkinson’s disease and MS has been previously proposed. Accordingly, a link between SARS-Cov1 and Parkinson’s disease (Fazzini et al. 1992) and MS has been previously proposed (Murray et al. 1994).

Notably, individuals recovering from acute ARDS showed executive functions deficit and short-term memory impairment with increased rates of anxiety, depression and post-traumatic stress disorder (PTSD) (Bienvenu et al. 2015), while up to 20% of them had long-term deficits (Sasannejad et al. 2019). However, new onset of anxiety and depression without any evidence of direct infection of the CNS are related to fear of virus infection in the COVID-19 pandemic (Lleó and Alcolea 2020). In this context, researchers introduced verbal fluency and inhibition as executive functions that are vulnerable in depression (Zakzanis et al. 1998), while major depression is associated with impairment of all aspects of the executive function (Snyder 2013). Thus, ICU-hospitalized patients who recovered from ARDS are potentially at higher risk for psychological disorders, i.e., depression, obsessive compulsive disorder, psychosis, Parkinson’s disease and AD (Nath 2020; Troyer et al. 2020).

Evidence suspected that hallucinations or delusions may continue in some patients even after recovery and during rehabilitation (Huff 2020). Of course, it is not also confirmed whether delirium is due to the virus attack or the experience of hospitalization, stressful conditions, and the healthcare workers’ protective equipment. The results of a study in France were stressed on neurologic problems in severe COVID-19 patients after being discharged from hospitals (Gammill et al. 2020). It was found that about 26 of 40 patients were confused, 39 of 58 patients (67%) had corticospinal tract signs, such as strengthened reflexes and clonus, and four of 39 patients (36%) presented with dys-executive syndrome (Gammill et al. 2020).

Patients with dysexecutive syndromes are unable to attend to thoughts, memories or environmental cues (Shimamura 2020). According to previous studies, critically ill patients wished for sleep and suffered from insomnia six to 12 months after recovery (Altman et al. 2017). Based on the results, sleep disturbances may reduce over time. Therefore, patients need to be examined by neurologists who should recommend neurocognitive testing for those with some cognitive disorders, even 6–8 months after hospital discharge, to reduce their risk for age-related cognitive decline in the future (Fotuhi et al. 2012, 2009). It is believed that current neuropsychological assessment and biochemical
or neuroimaging evaluation could help estimate the extent and progression of neurological symptoms in COVID-19. These studies increased awareness of the requirements for earlier monitoring of cognition in patients with COVID-19 as well as the need for prompt medical care if confusion is observed on hospital admission.

It is important to notice that populations with different cultures have different executive function requirement; therefore, the disease effects on this cognitive attribute can be varied. The final point is that few aspects of COVID-19 are known, and so far it is not clearly determined whether SARS-CoV-2 targets cognitive functions directly or indirectly.

Alzheimer disease (AD)

AD is known as a neurodegenerative disease with a wide spectrum of cognitive problems from learning and memory to personality disorders and so on (Tarawneh and Holtzman 2012). Hence, patients with AD may be at a higher risk for developing COVID-19. Patients who live alone without a caregiver, may not be able to follow guidelines for the prevention of COVID-19, such as hand washing, using mask, covering mouth and nose when coughing or sneezing, physical distancing, or staying at home.

Depression, dysphoria, sedentary states, and apathy can result in unpleasant outcome in patients with AD (Fotuhi et al. 2020). Patients with depression, malaise, reduce mobility, and apathy may not be able to handle their tasks. In addition, patients with psychiatric symptoms, including agitation, wandering, or psychosis may have some problems with isolation and put them at risk for developing dementia. Therefore, in AD patients, who are usually old, SARS-CoV2 infection can impose major challenges on caregivers, medical teams and nurses (Fotuhi et al. 2020).

Cerebrovascular disease

Although COVID-19 initially appeared with ARDS, physicians encountered a wide range of medical problems like cerebrovascular disease and other forms of vascular disease (Avula et al. 2020; Lodigiani et al. 2020; Oxley et al. 2020). Based on the evidence regarding COVID-19 patients, young people and healthy people with no risk factors were at a high risk for stroke; however, based on a subsequent case series, stroke occurred in elderly patients with vascular comorbidities (Oxley et al. 2020). Therefore, it is unclear whether SARS-CoV-2 is responsible for the stroke or it occurs in high-risk patients affected by SARS-CoV-2.

In a notable proportion of critically ill patients with COVID-19, secondary bacteremia may follow the primary viral infection (Goyal et al. 2020). According to the results of a case series, bacteremia increases the risk for stroke by over 20-fold (Dalager-Pedersen et al. 2014). Also, septic emboli to the brain often results in hemorrhage (Coolen et al. 2020).

Some cerebrovascular manifestations include ischemic stroke, hemorrhagic stroke, intracerebral hemorrhage and cerebral venous sinus thrombosis. The results of a study demonstrated that 13 (6%) of 221 SARS-CoV-2 patients developed ischemic stroke, one patient had intracerebral hemorrhage, and one had cerebral venous sinus thrombosis (Li et al. 2020b). A similar report in the UK showed the existence of a wide clinical syndrome of cerebrovascular complications in 77 (62%) of 125 patients, 57 (74%) of whom presented with ischemic stroke and nine (12%) with intracerebral hemorrhage (Varatharaj et al. 2020). Besides, over 30% of ischemic strokes were related to posterior arterial territories (Romero-Sánchez et al. 2020). Intracranial dissections are usually associated with severe neurological deficits or subarachnoid hemorrhage with a poor prognosis (Bond et al. 2020). Some cases of SARS-CoV-2 infected patients showed unexplained vertebro–basilar dissection and one case of multiple cortical hemorrhages also was associated with posterior reversible encephalopathy syndrome signs in brain MRI report (Romero-Sánchez et al. 2020). The researchers believe that SARS-CoV-2 probably involves posterior circulation and endotheiopathy.

Intracranial hemorrhage and ischemic stroke were also reported in three (0.4%) and 11 (1.3%) of 841 hospitalized COVID-19 patients, respectively (Romero-Sánchez et al. 2020). The MRI reports indicated ischemic stroke, bilateral frontotemporal hypoperfusion, acute small strokes, and acute ischemic stroke in the cerebellum in 13, 11, two, and one patient, respectively; however none of the patients were aware of their problems since they were asymptomatic (Helms et al. 2020). A clinical diagnosis of CNS vasculitis was reported in one patient with an unusual and otherwise unexplained infarct of the corpus callosum. The patient's imaging appearances were indicative of vasculitis, but the full angiographic report and pathological confirmation were not provided (Varatharaj et al. 2020). The patient’s imaging appearances were indicative of vasculitis, but the full angiographic report and pathological confirmation were not provided.

A report from Italy showed that 43 (77%) of 56 COVID-19 patients had cerebrovascular disease (Benussi et al. 2020) and many had some known risk factors for cerebrovascular disease like hypertension, diabetes, and hyperlipidemia (Avula et al. 2020; Li et al. 2020b; Zhai et al. 2020; Zhang...
et al. 2020b). Vascular diseases and severity of COVID-19 were directly related to the presence of these cardiovascular co-morbidities. According to a meta-analysis of eight studies, including 46,248 infected Chinese patients, the most prevalent co-morbidities included HTN (17%) and DM (8%), followed by cardiovascular diseases (5%) (Yang et al. 2020). In addition, acute cardiac injury and arrhythmias have been reported in about 10% of COVID-19 patients (Wang et al. 2020e). However, based on the evidences, myocarditis and heart failure are rare in COVID-19 patients without pulmonary involvement (Halushka and Vander Heide 2020). Myocardial injury and arrhythmia along with severe infection may result in cardiac embolism and brain infarction. Hence, patients with COVID-19 may be at a risk for cardioembolic stroke (Ranard et al. 2020). The most important mechanism of cerebrovascular disease in COVID-19 patients without vascular risk factors may be associated with hypercoagulability (Yang et al. 2020; Zhou et al. 2020) that causes cerebrovascular events. Meanwhile, patients at a risk for vascular diseases may have a high risk for stroke by prior complications, i.e., hypotension, shock, cardiomyopathy, heart failure, and DIC that can lead to hypoperfusion, embolism and large vessel occlusion (Avula et al. 2020; Panggada et al. 2020). Moreover, evidences of the small or large blood clots in the brain and in multiple other organs were reported in SARS-CoV-2 infection (Fotuhi et al. 2020; Tsai et al. 2004), which can lead to many cerebrovascular diseases with direct or indirect effects of the virus.

A report by Li et al. showed the majority of COVID-19 patients with cerebrovascular disease had ischemic infarcts in both small and large arterial vessels (Li et al. 2020b). In their study on 214 COVID-19 patients, Mao et al. identified ischemic strokes in five patients and intracranial hemorrhage in another patient (Mao et al. 2020). Most of the patients with cerebrovascular disease in this study had severe COVID-19 symptoms with a poor outcome. In another study in Singapore, five of 206 SARS-CoV2 patients had large vessel strokes, four of whom were severely ill and three eventually lost their lives (Umapathi et al. 2004). Also, venous thromboembolisms increased in sever COVID-19 patients (Lew et al. 2003).

It was found that 8.7% of 138 hospitalized patients with COVID-19 suffered from shock, 7.2% had acute cardiac injury, and 16.7% had arrhythmia, all of which are risk factor for stroke (Wang et al. 2020b). Yet, it is not clear if hypercoagulability, arteritis and endothelial dysfunction contribute to ischemic stroke or of intracranial hemorrhage is due to specific viral factors; thus it requires clarification in further research (Montalvan et al. 2020).

Notably, younger stroke patients have also been reported with large vessel ischemic strokes (Al Saiegh et al. 2020; Beyrouti et al. 2020; Lodigiani et al. 2020; Oxley et al. 2020). Unfortunately, vertebral artery dissection can lead to stroke in young and healthy men after age 50 (Park et al. 2008), and young healthy individuals can be afflicted by large strokes, with or without apparent COVID-19 symptoms such as cough or fever (Oxley et al. 2020). The researchers found large vessel stroke in five patients under age 50, while four of them had no previous history of cerebrovascular complications. Similarly, Al Saiegh et al. reported two COVID-19 cases with acute cerebrovascular disease (Al Saiegh et al. 2020). A young male patient was diagnosed with acute subarachnoid hemorrhage secondary to COVID-19, while he had no previous history of hypertension or other chronic illness. Finally, three of five younger cases of COVID-19, had vascular risk factors including diabetes, dyslipidemia and hypertension. They had evidence of previous large vessel occlusion and endovascular therapy. The close connection of COVID-19 and stroke is likely due to existence of similar risk factors (Montalvan et al. 2020).

Further evidence proposed that the emergence of cerebrovascular symptoms ranged from 0–33 days, an average of 10 days after the onset of respiratory disease, although some of the patients had only cerebrovascular symptoms (Al Saiegh et al. 2020; Avula et al. 2020; Oxley et al. 2020), which were associated with thrombus in the aorta (González-Pinto et al. 2020; Lushina et al. 2020), limb ischemia (Moshayedi et al. 2020; Zhang et al. 2020b), deep vein thrombosis and pulmonary embolism (Beyrouti et al. 2020; González-Pinto et al. 2020).

The underlying mechanism may be related to virus attachment to ACE2 receptors and clot coupling throughout the body making the patients vulnerable to stroke (Rutkowski 2020). Overall, these clinical findings suggest that moving or stationary blood clots in the lungs, heart, kidney and brain showed the close relation with morbidity and mortality in COVID-19 patients, and it may be necessary to start anti-platelet or anticoagulant therapy, such as aspirin or heparin to prevent vascular events, pulmonary embolism, heart attacks, kidney failure and embolic strokes (Fotuhi et al. 2020).

**Pathophysiology of neurological abnormalities in COVID-19**

Evidently, neurons are the target cells for SARS-Cov2 virus. In vitro and in vivo studies showed that the neuroinvasive and neurotropic action of SARS-CoV can be due to the virus’s direct effect on the nervous system or the two
indirect major mechanisms, i.e., hypoxic brain injury and an immune-mediated damage to the CNS (Ahmad and Rathore 2020). The direct effect may be due to virus entry into neurons (Paniz-Mondolfi et al. 2020), neuronal infection, apoptosis development (Varga et al. 2020), demyelination or neuronal death during the acute phase of disease (Jacomy et al. 2006). The direct viral infection of neurons can because seizures as well (Fotuhi et al. 2020). Neuron infection may be the result of a retrograde transport of the virus from nasal mucosa to the brain, in the same way that has been described for SARS-CoV1 (Baig et al. 2020; Conde et al. 2020). As such, it is conceivable that SARS-CoV2 can also cross the cribriform plate and bind to neurons in the olfactory bulb (the only part of the CNS not protected by dura) (Butowt and Bilinska 2020). Similarly, the mouth is a different route that can conduct the virus directly to the brain stem (Rutkowski 2020). A retrograde transport of virus from mouth to the gustatory receptor cells in the tongue can damage the neurons in the nucleus solitarius in medulla, and lead to ageusia sensation in COVID-19 (Vaira et al. 2020a). The virus spreads either across the blood–brain barrier (BBB) or by means of leukocytes (Desforges et al. 2020).

ACE, NRP1 and BSG are putative receptors for SARS-CoV-2 to cross BBB (Cantuti-Castelvetri et al. 2020), while cytokines such as interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF) and IL-17 can penetrate BBB and facilitate the virus entrance (Erickson and Banks 2018).

BBB becomes leaky in some areas of the brain through fenestrae in the capillary walls in the median eminence of the hypothalamus and other circumventricular organs (Kaur and Ling 2017). The size of SARS-CoV-2 is approximately 80–120 nm which is larger than that of the capillary fenestrate (Sarin 2010), hence the virus can enter the hypothalamus and brain through ACE2 and TMRPRSS (Nampoothiri et al. 2020).

Another mechanism, by which the coronaviruses can reach the CNS, is the sensory and motor nerve endings of the vagus nerve from the lungs (Li et al. 2020c). Exosomal cellular transport is another pathway for SARS-CoV-2 systemic dissemination and CNS entry (Alenquer and Amorim 2015). The blood circulation pathway is another proposed route for SARS-CoV-2 dissemination (Ahmed et al. 2020). Neurons, glial tissues and brain vasculature contain significant levels of angiotensin converting enzyme 2 (ACE2) receptors (Turner et al. 2004). An increase in angiotensin II leads to vasoconstriction, kidney failure, heart disease, apoptosis and oxidative stress that proceed aging and accelerate brain degeneration (Kai and Kai 2020). The binding of corona virus to ACE2 is a main step in the pathophysiology of clinical manifestations in patients with COVID-19 (Verdecchia et al. 2020). The ACE2 protein in the cell membranes of neurons and other cells can bound to SARS-CoV2 through the S spike protein (Netland et al. 2008). Then the virus penetrates the cells and interrupts energy produced by mitochondria and protein folding. However, SARS-CoV 2 and other CoVs can reside in some neurons without any toxic effects (Nath 2020). ACE2 deficiency reduces the effects of SARS-CoV2 infection (Verdecchia et al. 2020) because it acts as a protecting factor for cardio–cerebral vascular systems (Turner et al. 2004); so it is important to notice that the endothelial damage in cerebral capillaries can result in bleeding and have serious and fatal outcomes in COVID-19 patients (Ahmed et al. 2020). ACE2 is a part of the renin angiotensin system, which modulates blood pressure and essentially balances angiotensin II, a powerful blood vessel constrictor and inflammation promoter (Rutkowski 2020). Immune-mediated injury is largely due to huge levels of cytokines and activation of immune cells, including lymphocytes, macrophages and endothelial cells (Mehta et al. 2020; Tveito 2020). The binding of ACE2 to respiratory and blood vessels, and epithelial cells causes SARS-CoV2 to launch the cytokine storm and elevation in the levels of interleukin-1, interleukin-6 and TNFs (Mehta et al. 2020; Xiong et al. 2020).

In addition, high levels of IL-6, IL-1β, TNF, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1 and MIP1α have been reported in more COVID-19 patients (Diao et al. 2020).

Immunohistochemical staining revealed that SARS-CoV in the brain was associated with both the increased expression of the cytokine and monokine induced by gamma interferon, and with the infiltration of monocytes, macrophages and T cells which contribute to tissue damage (Ellul et al. 2020). High levels of these cytokines result in increased vascular permeability and leakage, edema, activation of complement and coagulation cascade, disseminated intravascular coagulation and widespread inflammation with consequent damage in multiple organs (Mehta et al. 2020; Tveito 2020). The cytokine storm is important in the formation of blood clots. The mobilization of high inflammatory markers, vascular injury, and coagulation factors contribute to ARDS, kidney failure, liver injury, heart failure, myocardial infarction and multiple neurological conditions (Wu et al. 2020; Xiong et al. 2020). Some inflammatory agents like C-reactive protein, ferritin, interleukin-1, interleukin-6, TNFα, and d-dimer have an important role in hypercoagulable state in COVID-19 (Jose and Manuel 2020). The mechanism of cytokine storm and the secondary hypercoagulation after the binding of SARS-CoV2 to ACE2, which contributes to a major morbidity and mortality in COVID-19 patients, has not yet been fully understood (Fotuhi et al. 2020) and more research is needed. Ischemic events have
been introduced as the main cause of strokes in patients with COVID-19 although few cases of intracranial hemorrhage have been also reported (Li et al. 2020b; Wang et al. 2020c; Wu et al. 2020). One proposed mechanism is related to the binding and downregulation of ACE that reduce the conversion of angiotensin II to angiotensin (I-7) (Kai and Kai 2020), while the exact mechanism is not clearly understood. High levels of angiotensin II with suppressing ACE2 can lead to vasoconstriction and peripheral vascular resistance that ruptures blood vessels in the brain. Another capability is related to polymorphism of ACE, which is associated with an increased risk of intracranial hemorrhage, especially in Asian population (Li et al. 2005). A noticeable variation between patients with COVID-19 in Asia and Europe is smell and taste disturbances that can be explained by the ACE2 polymorphism. Based on the studies, East-Asian populations may show various allele frequencies of ACE2, and some ACE2 variants may have low capacity to bind SARS-Cov1 (Cao et al. 2020; Li et al. 2005). Furthermore, symptoms and prognosis of COVID-19 may differ depending on the type of ACE2 variant in tissues. This issue is of great importance for clinical implications; therefore it needs to be more investigated (Fotuhi et al. 2020).

Moreover, high levels of IL-6, IL-1α, IL-1β cytokines and TNF-α are likely to induce neurotoxicity, for example sickness behavior syndrome with impaired concentration, reduced motivation, bradykinesia and depressive symptoms (Dantzer et al. 2008). The increase of interleukin-1, interleukin-6, interleukin-8 (Bell et al. 1996), interleukin-16 and TNFα contribute to the BBB injury in COVID-19 (Wu et al. 2020). Cytokines penetrate the brain parenchyma, especially in temporal lobes, where BBB is weaker (Sweeney et al. 2018; Van Vliet et al. 2007). Intensive inflammatory reactions and entry of blood contents into the brain can lead to seizures and encephalopathy (Wu et al. 2020). Pregnant mice infected by Corona virus-2 had elevated levels of the cytokines (Liu et al. 2020), which may directly influence fetal brain property and development and cause autism-like behavioral symptoms (Choi et al. 2016).

On the other hand, apoptosis induced by coronavirus infection could be associated with HCoV-mediated neuropathogenesis by killing cells or by disseminating virus, while inflammatory responses become limited (DeBiasi et al. 2002). Indeed, neuronal apoptosis seems to be an important contributing factor in acute CNS injury in humans after viral infection (DeBiasi et al. 2002; Nakai et al. 2003), and they were positive for activated caspase-3 (Jacomy et al. 2006).

In addition, both neuronal and non-neuronal cells seem to be susceptible to viral infection in different ways; glial cells become infected in a nonproductive way, whereas neurons are considered as viral targets and are productively infected (Jacomy et al. 2006). Based on evidence, neuronal cell death induced by coronavirus was associated with viral persistence and activation of microglial cells which can induce CNS impairment in surviving virus infection. Apoptosis may be a major contributor to cytotoxicity (Jacomy et al. 2006). TNF-α, which is mainly produced by activated microglial cells, can also lead to apoptosis (Guidotti and Chisari 2001; Robertson et al. 2001).

The synergistic effects of astrocytes, microglia and fibroblasts can release cytokines or chemokines that may induce some alterations in cell-surface receptors and transcription factors and create a favorable environment for virus entry and replication (Jacomy et al. 2006). Moreover, infected neurons present aggregated appearance with less density of axonal neurites (Jacomy et al. 2006). The brain produces proinflammatory cytokines through microglia in response to peripheral innate immune reactions by some parallel acting pathways (Lleó and Alcolea 2020). Some intermediators, such as prostaglandins E2 are also involved (Lleó and Alcolea 2020). The psychological stress that occurs in COVID-19 is associated with high levels of cortisol and steroid (Steenblock et al. 2020).

High stress also can raise cytokine levels in addition to cytokine storm that occurs in COVID-19 patients and contribute to secondary medical complications (Heffner 2011) and a variety of neuropsychiatric and neurocognitive symptoms in the long term (Rogers et al. 2020). Similar to other conditions, it is not clear whether SARS-Cov2 itself causes neurological complications or is triggered by other reasons, such as exaggerated cytokine responses and/or formation of blood clots in the central or peripheral blood vessels.

Overall, COVID-19 patients with neurological diseases might be infected coincidentally through nosocomial transmission in the hospital (Ellul et al. 2020). Therefore, a broad investigation is needed to specify other causes of brain infections before attributing a disease to COVID-19.

**Conclusion**

Unfortunately, COVID-19 continues to spread globally, and 50–80% of the world’s population will probably be infected prior to herd immunity. COVID-19 causes a broad range of problems from asymptomatic infections to severe respiratory failure, cardiovascular complications and neurological disorders in adults. Therefore, due to the increasing incidence of neurological symptoms, it is necessary to pay...
special attention to the disease. The possible mechanisms for neurological manifestations of COVID-19 are related to both direct and indirect effects of the virus on the CNS or PNS. Alternatively, the neurological symptoms may be part of the systemic autoinflammatory leading to an increase in systemic inflammatory response. ACE2 is considered as the host-cell receptor of SARS-CoV-2. The virus affects the nervous system through cytokine storm and damages to the brain via small or large strokes, BBB disturbance, and high levels of inflammation inside the brain that results in long term neuropsychiatric consequences. Currently, cerebrovascular complications and hypercoagulable states are important neurological complications of COVID-19, but they are rarely associated with some acute viral infections.

Regarding the prevalence of the disease, health care systems must expect and beware of increased patients with depression, PTSD, anxiety, insomnia, psychosis and cognitive impairment. However, patients discharged from hospitals may not fully return to their baseline emotional and neurocognitive functioning. For this reason, more investigations are required, such as clinical trials and documentation of chronic onset of neurological symptoms, detailed neurological test results, progression, and long-term recovery of symptoms in patients with COVID-19. Therefore, physicians and medical staff are recommended to use a screening questionnaire for common symptoms of COVID-19 like anosmia, ageusia, fever, cough, shortness of breath, family history of SARS-CoV2 infection, or even for some clinical and para clinical examinations. Even though a patient with an onset of some neurological symptoms, including unilateral weakness, seizure, or diplopia may have a non-COVID-19 etiology, he/she may have recently been involved in SARS-CoV2 infection. Future studies are necessary to identify the specific risk factors or protective determinants concerning neurological and neurocognitive events to minimize the risk for these complications and manage them during the COVID-19 pandemic.

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