

REVIEW ARTICLE

Neurological complications of coronavirus disease 2019 and the underlying mechanisms

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Huahong Zhu⁴ and Yun Xu^{1,5,6,7*}¹Department of Neurology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China²Department of Neurology, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China³Department of Neurology, Nanjing Drum Tower Hospital Clinical College of Jiangsu University, Nanjing, China⁴Department of Neurology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China⁵The State Key Laboratory of Pharmaceutical Biotechnology, Institute of Brain Science, Nanjing University, Nanjing, China⁶Jiangsu Key Laboratory for Molecular Medicine, Medical School of Nanjing University, Nanjing, China⁷Jiangsu Province Stroke Center for Diagnosis and Therapy, China Nanjing Neurology Clinic Medical Center, Nanjing, China**Abstract**

The recent global pandemic of coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although respiratory symptoms are the primary manifestation of the majority of COVID-19 patients, an increasing number of neurological symptoms and manifestations of COVID-19 have been observed. In this review, we detail the neurological complications of COVID-19, such as gustatory and olfactory dysfunctions, stroke, memory decline, muscle injury, and seizures. Furthermore, we introduce neural invasion mechanism underlying SARS-CoV-2 infection and, further, explain the occurrence of these complications. This review offers insights into the neurological signs and symptoms of COVID-19, which may help improve the prognosis of the infected patients.

Keywords: COVID-19; Neurological complications; Clinic characteristics; Neural invasion

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic^[1]. At present, there are over 100 million confirmed cases of COVID-19 worldwide, with more than 6 million deaths. Most patients with COVID-19 present with respiratory symptoms, such as cough and dyspnea^[2]. COVID-19 patients also exhibit manifestations of other systems, which do not receive much attention despite their clinical significance. With further investigations, neurological manifestations are found to be instrumental in the diagnosis, treatment, and prognosis of COVID-19 patients; these manifestations include

headache, memory decline, cerebrovascular event, and taste and smell disorders. In this review, we summarize the neurological complications in COVID-19 patients and the underlying mechanisms, which might help facilitate early diagnosis and early treatment so as to improve prognosis of COVID-19 patients.

2. Neurological complication of COVID-19

2.1. Alterations in taste and smell

The loss or diminished senses of taste (ageusia) or smell (anosmia) are the frequent symptoms and the early neurologic manifestations in COVID-19 patients^[3]. The occurrence rate of these symptoms is reported to range between 38% and 74% across different cohorts^[4-8]. In addition, in a multicenter study, around 38% and 41% of mildly infected patients have been reported to show gustatory and olfactory impairment, respectively^[7]. Further, a meta-analysis of 15 studies consisting of a total of 3739 participants with confirmed COVID-19 reported that around 1354 and 1729 of infected patients showed symptoms of taste and smell impairment, respectively^[9]. The similar study also demonstrated that the loss of taste and smell occurred in 49.0% (95% confidence interval [CI] 34.0–64.0) and 61.0% (95% CI 44.0–75.0) of the COVID-19 patients, respectively. Another meta-analysis on patients in North America reported that the rate of taste disorder was 38.6% (95% CI 7.9–75.3), while the rate of smell disorder was 54.5% (95% CI 39.3–69.3), and around 5977 patients manifested symptoms of both smell and taste disorders, accounting for 31.3% of the patients (95% CI 13.6–52.2)^[10]. Taken together, the loss of smell and/or taste is a common neurologic symptom of COVID-19 patients.

However, the occurrence rate of smell and taste disorders in COVID-19 patients varies among different populations as well as gender and age groups. Compared with male COVID-19 patients, female patients were more likely to have trouble in smelling and tasting^[11]. On the contrary, another study reported that gender did not significantly influence the olfactory and gustatory function in patients^[12]. In addition, younger people have been reported to have more severe smell disorders and take longer time to recover^[8]. It is worth noting that in a study on 841 COVID-19 patients, olfactory and gustatory disorders were more common in patients with mild COVID-19^[13], suggesting that olfactory and gustatory changes may be an important marker for the early disease diagnosis.

The recovery of smell and taste disorders in the infected patients is another concerning topic. The recovery time of the olfactory and gustatory disorder depends on the severity of COVID-19 and the disorders themselves^[14]. A follow-up study reported that after 4 weeks of infection, patients with

mild COVID-19 (89%) underwent a complete resolution or improvement of olfactory and gustatory functions^[4]. According to another study, the recovery time of infected adolescents aged 10–19 years varied from 2 days to 2 weeks, with an average of 5.7 days^[15]. Besides, it has been reported that 12% of smell disorders preceded the onset of other symptoms, 22% of these disorders occurred in conjunction with other symptoms, and 65% occurred after other symptoms^[16].

However, at present, the mechanism of smell and taste disorders in patients with COVID-19 is still not clearly defined. Angiotensin-converting enzyme 2 (ACE2) receptors are functional receptors of SARS-CoV-2^[17]; therefore, the olfactory epithelium cells, which have high ACE2 expression, become easily infected by SARS-CoV-2^[18]. Anosmia is caused by the injury of olfactory epithelium, instead of sensory neurons. Furthermore, there is a positive correlation between olfactory and gustatory disorders^[19]. Most COVID-19 patients gradually recover from olfactory and gustatory disorders, and some interventions such as olfactory training may be helpful during the recovery process^[20]. The interventions for loss of taste are less common and deserve more investigations.

2.2. Brain function decline

The COVID-19 affects the brain functions, such as cognitive ability and consciousness, in a variety of ways, which result in acute and long-term effects on the infected individuals. Acute brain dysfunctions include delirium, coma, confusion, and somnolence. It has been reported that delirium was present in 81.7% of COVID-19 patients admitted to intensive care units^[21]. In addition, these acute symptoms are associated with higher risk of long-term cognitive decline^[22], which explains why longitudinal studies on long-term changes in cognitive function have attracted much attention. In a longitudinal study of 3232 COVID-19 patients in China, it was found that the occurrence rate of cognitive impairment in COVID-19 survivors was 12.45% after 12 months. The cognitive function of severe patients was lower than that of non-severe patients and control group^[23]. High risk of the early-onset (95% CI 3.30–7.20) and late-onset (95% CI 3.58–16.03) cognitive impairment was associated with severe COVID-19. Another follow-up study on home-isolated COVID-19 patients reported that around 44% of young patients had cognition impairments, such as memory problems and impaired concentration, 6 months after infection, which were associated with increased convalescent antibody titers, indicating the severity of underlying disease^[24].

The reduction in brain function caused by COVID-19 is governed by a number of factors, such as lung damage and the resulting hypoxemia caused by COVID-19. It has been

reported that patients with chronic hypoxemia, such as obstructive sleep apnea and chronic obstructive pulmonary disease, often experience cognitive decline, and chronic hypoxemia is also common in patients with COVID-19^[25]. To fight against chronic hypoxemia, sedatives are often used to facilitate invasive mechanical ventilation; however, the use of sedatives is commonly associated with high risk of acute phase brain decline. A multi-center study found that excessive sedation in response to COVID-19 was associated with an increase in incidence of delirium in the infected patients^[21].

Inflammation often leads to brain dysfunction with the aid of pro-inflammatory cytokines and inflammatory mediators, which are abundant in the blood and brain^[26]. The pro-inflammatory cytokines disrupt the blood-brain barrier permeability by increasing the cyclooxygenase-2 expression and activating matrix metalloproteinase^[27]. In addition, the microglial activation and oxidative stress caused by the pro-inflammatory cytokines lead to short-term delirium and severe long-term cognitive impairment. An electroencephalogram (EEG) study found that higher regional current density at delta band was correlated with worse executive performances in COVID-19 patients^[28]. A follow-up study also found that lower EEG delta band at baseline predicted worse cognitive performance. Further, a neuroimaging study found that COVID-19 patients showed poorer hypometabolism predominantly in the frontoparietal network, and this neuroimaging patterns showed a high correlation ($R^2 = 0.62$) with the Montreal Cognitive Assessment performance^[29].

2.3. Muscle injury and movement disorders

Muscle injury and movement disorders are among the complications associated with COVID-19. Some patients showed fatigue, muscle soreness, and elevated muscle enzyme levels^[30]. Another study also reported that the creatine kinase level in 15.7% of hospitalized COVID-19 patients increased dramatically^[31]. In addition, a meta-analysis on 1100 studies found that around 34.7% of COVID-19 patients showed symptoms of myalgia or fatigue (95% CI 26.0–44.4)^[32]. In addition, a meta-analysis involving 3062 hospitalized COVID-19 patients reported that the patients suffered from muscle soreness, which was the third most common symptom after fever and cough^[33]. Besides, the associated symptoms in discharged patients are also noteworthy. In a longitudinal follow-up study, fatigue and muscle weakness were the most common sequelae (63%, 1038 of 1655)^[34]. Furthermore, a comprehensive health assessment after 3 months of rehabilitation found that 22% and 64% of COVID-19 survivors had poor exercise capacity and muscle fatigue, respectively^[35].

A number of possible mechanisms underlying muscle injury in COVID-19 patients have been proposed, such as: (i) increased oxidative stress caused by COVID-19; (ii) the abuse of medications; and (iii) being bedridden and lack of exercises. Malnutrition or inflammation is the main cause of increased secretion of cytokine in COVID-19 patients, and excessive cytokines can lead to skeletal muscle damage and rhabdomyolysis^[36,37]. These cytokines can also reduce the production of testosterone, a hormone which promotes muscular integrity^[38]. Some antiviral drugs such as hydroxychloroquine and medications, which are used to treat critical patients with COVID-19, were also found to damage muscles^[39], and this effect was more pronounced in inactive patients. In addition, intubation and mechanical ventilation used in the treatment of COVID-19 patients as well as long hours of bed rest could contribute to significant muscle loss^[40]. A few reports have suggested that SARS-CoV-2 can directly induce muscle toxicity in the infected patients^[39]. A Chinese study on 1014 hospitalized COVID-19 patients showed that those with rhabdomyolysis were susceptible to a higher risk of deterioration and had a higher mortality rate than those without rhabdomyolysis^[41]. COVID-19 is believed to exacerbate pre-existing motor impairments, such as those in infected patients with Parkinson's disease. In a study on 694 COVID-19 patients, it is found that patients with Parkinson's disease have a higher mortality rate than patients without the disease (95% CI 1.04–1.53)^[42]. Therefore, early diagnosis and intervention are necessary in patients with poor baseline underlying conditions.

2.4. Cerebrovascular diseases

Acute ischemic stroke is a dangerous complication of COVID-19. The coincidences of ischemic stroke reported in hospitalized COVID-19 patients range from 1% to 5%, and patients with more severe infection had a higher risk of stroke^[43,44]; however, the occurrence rate of hemorrhagic cerebrovascular disease was lower than 1%. A meta-analysis reported that ischemic stroke occurred in 1.5% of COVID-19 patients (95% CI 0.9–3.7%), and the in-hospital mortality rate was 34.4% (95% CI 27.2–42.4%)^[45]. Furthermore, a study on influenza ($n = 1486$) or COVID-19 ($n = 1916$) patients found that COVID-19 patients had a higher risk of stroke (95% CI 2.3–25.2) compared to influenza patients^[46]. The pathogenic pathways underlying the development of ischemic stroke vary between patients with and without COVID-19, and COVID-19 patients had worse prognosis. Another report also showed that stroke patients with COVID-19 took longer time for recovery and were more likely to have higher mortality rate and worse baseline neurological test scores^[47]. It is noteworthy that the risk factors of ischemic stroke in COVID-19 patients

may be associated with hypercoagulability under hypoxia state. In concordance with the above, a study demonstrated that a considerable part of COVID-19 patients have abnormal coagulation parameters, such as elevated levels of d-dimer and C-reactive protein as well as positive lupus anticoagulant test^[48]. Elevations in these factors may be a sign of COVID-19-mediated damage to the nervous system. This suggests that COVID-19 may directly increase the risk of stroke through cerebral vasculitis. It has been found in another cohort that the patients were negative for lupus anticoagulant but positive for anti-cardiolipin and anti-B2-glycoprotein antibodies^[49]. These abnormal coagulation parameters may predict the risk of cerebrovascular disease in COVID-19 patients, but, further, investigations on the mechanisms underlying these abnormalities are warranted.

The treatment with prophylactic anticoagulation may be beneficial to patients with COVID-19. According to the recommendation of The American Society of Hematology, hospitalized COVID-19 patients should be treated with standard thromboprophylaxis^[50]. Based on the findings of randomized clinical trials, a full-dose anticoagulant therapy may benefit the critically ill patients with COVID-19, but at the same time, this treatment may increase the risk of other complications^[51]. Thus, the prophylactic use of anticoagulants as a treatment for critically ill patients is still up for debate. Of note, the occurrence rate of arterial or venous thromboembolism in hospitalized COVID-19 patients has been reported to be between 8% and 31% despite the fact that prophylactic anticoagulant therapy was adopted^[52,53]. A multicenter study conducted in Italy has reported that COVID-19 patients to whom stroke occurred despite the use of anticoagulant therapy had a worse clinical outcome, along with 64.7% of fatality rate^[54]. The treatment for stroke is similarly administered to patients with or without COVID-19; however, there are few studies about the safety and feasibility of thrombectomy treatment in COVID-19 patients with acute ischemic stroke.

Despite its rarity, cerebral venous thrombosis is also a complication of COVID-19. Most patients with cerebral venous thrombosis present with only nonspecific symptoms, such as headache, fever, and visual problems, which implies elevated intracranial pressure^[55]. A study found that the median duration of onset in hospitalized COVID-19 patients across different countries was three days from COVID-19 diagnosis, and the superior sagittal sinus is the most common site of thrombosis^[56]. The diagnosis of cerebral venous sinus thrombosis is based on clinical and radiological findings obtained from magnetic resonance imaging (MRI) and venography. Heparin anticoagulant therapy, either at therapeutic doses

of low molecular weight heparin or unitary heparin, is preferred for patients suffering from this complication^[57]. It is important to note that RNA vaccination may increase the risk of cerebral venous sinus thrombosis. Moreover, a German study has reported that the occurrence rate of cerebral venous sinus thrombosis was 0.55 (95% CI = 0.38–0.78) per 100,000 person-months, which was higher than that in the general population^[58]. Therefore, the vaccination against COVID-19 is essential, given that it can reduce the risk of serious complications of COVID-19.

2.5. Other neurological complications

In addition to the neurological complications mentioned above, there are many other complications associated with COVID-19, such as epilepsy, meningitis, and demyelinating diseases.

A growing number of case reports point out that COVID-19 could exacerbate epilepsy in patients who already have the nervous disorder and, unfortunately, trigger epilepsy in patients who do not at the same time suffer from the disorder^[59,60]. Metabolic disorders, high fever, or electrolyte disarrangements caused by COVID-19 may be the cause of epilepsy^[61]. Therefore, electroencephalography monitoring of severe COVID-19 patients is helpful for early diagnosis and prevention of epilepsy, and early monitoring of patients with symptoms of encephalopathy is also beneficial^[62]. COVID-19 patients may develop symptoms of epilepsy before the onset of respiratory symptoms, and the symptoms may include both generalized tonic-clonic seizures and focal seizures^[63]. It is important to note that cases of epilepsy in pediatric COVID-19 patients have been reported, although the exact cause of epilepsy is unknown^[64]. In short, epilepsy and seizures should be considered the underlying manifestations of COVID-19 in the pediatric patients.

Symptoms of encephalitis have also been reported in COVID-19 patients. SARS-CoV-2 has been found in the cerebrospinal fluid (CSF) of COVID-19 patients^[65,66]; however, CSF of some COVID-19 patients with acute meningoencephalitis was found to be free from SARS-CoV-2 or other viral pathogens^[67]. This indicates that meningitis in the COVID-19 patients is not caused directly by brain infection, but by other factors, such as inflammation during acute COVID-19 phase. Encephalitis can be complicated by intracerebral and subdural hematoma, and it is either severely disabling or life-threatening; therefore, infected individuals should be wary of this possible complication following COVID-19.

Besides, the rare connection of COVID-19 with temporary visual impairment has been reported, and the visual loss may be associated with cerebral vasculitis^[68]. In addition, demyelinating diseases such as Guillain-Barré syndrome

(GBS) are also increasingly well-recognized as one of the complications of COVID-19. Recently, a study described the development of GBS in COVID-19 patients, who first developed weakness in the lower limbs and then progressive quadriplegia on the 5–10 days after the onset of COVID-19 symptoms^[69]. However, no SARS-CoV-2 was detected in the CSF of these patients, and the CSF protein levels were normal in 40% of infected patients. However, another study reported the isolation of conalbumin from CSF in COVID-19 patients with GBS, and CSF analysis showed normal white blood cell counts and elevated protein levels^[70]. In general, GBS responds well to intravenous immunoglobulin therapy, which brings about significant improvement in nervous system, suggesting that neuropathy is immune-mediated^[71], but the long-term outcomes are still unclear.

3. Mechanisms underlying the neurologic complications of COVID-19

In this section, we summarize the underlying mechanisms of how COVID-19 affects the nervous system (Figure 1). Early in the outbreak of COVID, researchers had attempted to detect the SARS-CoV-2 RNA in the CSF of infected patients with neurological symptoms^[65]. However, the virus has never been successfully detected in most COVID-

19 patients^[72], most likely due to the insufficient viral load in the CSF or the fact that the virus does not enter the CSF.

The COVID-19-related neurological complications are mainly observed in the central nervous system (CNS), the peripheral nervous system (PNS), and the musculoskeletal system. Possibly, different mechanisms, such as neuronal retrograde dissemination and systemic hematogenous spread, are in place to allow viral entry and damage to the nervous system. Although the exact mechanism of SARS-CoV-2 invasion remains unclear, multiple lines of evidence showed that the virus can destroy the neurons by either of the two mechanisms^[73]. In addition to destroying the blood-brain barrier and causing central neuron death through viremia, SARS-CoV-2 can also infect olfactory bulb (OB) and subsequent transport to neurons^[74].

SARS-CoV-2 could cause viremia to destroy neurons by binding to ACE2. ACE2 receptors are widely expressed in the CNS systems, including neurons, astrocytes, oligodendrocytes, and OB^[17]. Binding of the transmembrane protease serine 2 to the ACE2 receptor results in protein cleavage and activation of the spike protein, therefore allowing the virus to enter the host cell^[75]. Thus, SARS-CoV-2 has the potential to infect neurons and glial cells throughout the CNS.

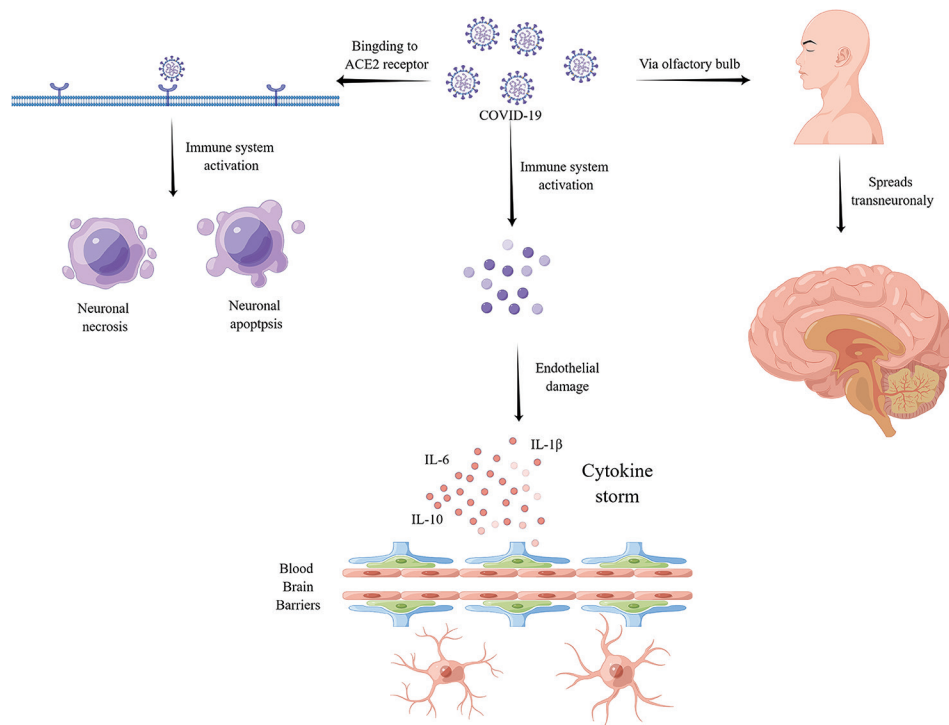


Figure 1. Mechanisms underlying the damages to the central nervous system mediated by SARS-CoV-2. The binding of SARS-CoV-2 to the ACE2 receptor leads to neuronal apoptosis or death. In addition, SARS-CoV-2 not only disrupts the blood-brain barrier by triggering cytokine storm, but also spreads retrograde through neurons by infecting the olfactory bulb, thus disrupting the normal function of the central nervous system. The schematic is illustrated with Figdraw (www.figdraw.com).

Table 1. Neurological complications associated with COVID-19 and their prevalence

Neurological complications	Occurrence rate
Gustatory dysfunctions ^[9]	49% of COVID-19 patients
Olfactory dysfunctions ^[9]	65% of COVID-19 patients
Stroke ^[45]	1.5% of COVID-19 patients
Memory impairment ^[23]	12.5% of COVID-19 patients
Muscle injury ^[13]	16% of COVID-19 patients
Epilepsy ^[51]	<1% of COVID-19 patients
Headache ^[13]	15% of COVID-19 patients
Dizziness ^[85]	9% of COVID-19 patients
Nausea and vomiting ^[86]	5% of COVID-19 patients

On the one hand, after infecting the respiratory system, SARS-CoV-2 can enter the bloodstream by infecting endothelial cells in the choroid plexus blood-brain barrier or blood-CSF barrier in the choroid plexus. Furthermore, SARS-CoV-2 can infect leukocyte and cross the barriers to invade the CNS so as to spread throughout the body with leukocyte^[76]. In this process, leukocytes release pro-inflammatory factors, such as tumor necrosis factor, interleukin (IL)-1 β , IL-6, IL-12, and even cause cytokine storm, which can destroy oligodendrocytes and neurons^[77]. The integrity of the blood-brain barrier may be compromised by cytokine-driven damage and immune-mediated toxicity^[78]. Taken together, SARS-CoV-2 binds to the ACE2 receptor, which, in turn, induces an inflammatory cascade that ultimately destroys the neurons.

On the other hand, SARS-CoV-2 could also enter the CNS through OB. OB is often considered an immune organ that can prevent viruses from entering the CNS, but its dysfunction may lead to an infection of the CNS^[79]. A previous study has confirmed that virus can penetrate the olfactory epithelium into the brain and cause death in the mice^[80]. Meanwhile, a recent study showed that olfactory epithelial cells express ACE2, allowing viruses to infect the cells through a replacement receptor^[18]. OB MRI studies showed that MRI signal changes were consistent with virus invasion of OB and cortical regions^[80], suggesting that SARS-CoV-2 may invade human CNS from the external environment through OB.

Fecal-oral route is hypothesized as a potential route of transmission for SARS-CoV-2 on the grounds of the high expression of ACE2 in gastrointestinal system^[81], and the nervous system injury caused by indirect immune-mediated cytokine storm could be another possible mechanism of nervous system complications^[82]. Further and more detailed research is needed to investigate the mechanism of how SARS-CoV-2 affects the nervous system and causes neurological complications. It is worth noting that there are

many subtypes of COVID-19, and these subtypes differ in many aspects, such as virulence and transmissibility, which explain the variability in the mechanisms. A study found that convulsions could be a sign of the Omicron variant in children with COVID-19^[83]. Another study on children with COVID-19 found that the Omicron variant is more likely to be associated with neurologic manifestations such as seizures compared with other COVID-19 virus variants^[84]. However, there is still a lack of multicenter and forward-looking research on the neurological complications caused by specific COVID-19 virus variants.

4. Conclusion

Despite being a disease primarily affecting the respiratory system, COVID-19 has gradually attracted attention as a disease accompanied by the unexpected neurological complications, evidenced by a growing number of studies (Table 1). In this review, we summarize the symptoms, characteristics, and mechanisms underlying the neurological complications of COVID-19. The neurological complications of COVID-19 patients include CNS complications, such as brain function decline, cerebrovascular disease and dysgeusia, as well as PNS complications. Some of these complications are reversible, but others could be life-threatening. The SARS-CoV-2 infection in the nervous system is mediated by the binding of the virus to the ACE2 receptor or its replacement receptor, which leads to a chain of inflammatory responses. This review provides reference contents for understanding the heterogeneous neurological symptoms and manifestations as well as potential neurological complications of COVID-19. A deeper understanding of these manifestations and complications can help make appropriate treatment decisions that would directly reduce morbidity and mortality among the patients. Finally, more investigations should be carried out to determine the broad spectrum of neurological symptoms and the underlying pathophysiological mechanisms of COVID-19.

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Conflict of interest

The authors have no competing interest to declare.

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