Review Article

# Neurological manifestations of COVID-19: a clinical approach

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**ABSTRACT**

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by SARS-CoV-2 which attacks the respiratory tract and has been declared a global pandemic by the World Health Organization. The disease has a very wide clinical spectrum which can be manifested as asymptomatic to critical conditions. SARS-CoV-2 shows a neurotropism proven by its identification in the cerebrospinal fluid and brain vascular endothelial. The complete mechanism of how the virus invades the human nervous system is yet to be identified. Thus, every neurologist needs to follow the progressivity of COVID-19 symptoms involving the nervous system.

**KEYWORDS** COVID-19, neurological manifestations, SARS-CoV-2

A new disease caused by a novel virus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally to 216 countries with approximately >70,000,000 confirmed cases. With the rapid spread of the disease, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020.[1]

COVID-19 is an acute new emerging disease caused by SARS-CoV-2, which mostly affects the respiratory tract. Coronavirus has caused three epidemics in the last 20 years, namely SARS-CoV in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2013, and recently COVID-19. The latest pandemic has changed the way of life by forcing unprecedented isolation measures, triggering anxiety, and causing devastation to the world economy.[2]

Major clinical manifestations of COVID-19 are respiratory tract infection symptoms, including fever, unproductive cough, and dyspnea. However, several studies from major hospitals in Wuhan highlighted other symptoms related to the cardiovascular, digestive, and nervous systems.[3–5] Neurological manifestations of COVID-19 are caused by the direct effect of the viral infection, parainfectious complication, or as part of a multiple organ failure in critically ill patients.[6,7] Neurological manifestation has been reported to occur in approximately one-third of mostly critically ill patients with COVID-19.[8] COVID-19 has become a

big challenge for physicians due to its wide spectrum of clinical manifestations, fast transmission, and absence of drugs or vaccines proven to be effective in countering the disease.[9] This review showed the related neurological manifestations of COVID-19 and its possible mechanisms in affecting both the central nervous system (CNS) and peripheral nervous system (PNS).

**Epidemiology of nervous system involvement in COVID-19**

COVID-19 pandemic is a public health emergency because of the fast transmission of SARS-CoV-2.[9] Cases grow exponentially, and the epidemic size rises 2-fold every 7.4 days.[10] The basic reproductive number of COVID-19 is 2.24–3.35, which is much higher than SARS.[9] Human transmission is mediated by droplets, respiratory secretions, and direct physical contact with patients or asymptomatic carriers.[11,12] Elderly and people with comorbidity such as hypertension, chronic obstructive pulmonary disease, diabetes, and heart diseases are at high risk for severe COVID-19.[9,11,13] Clinical spectrum of COVID-19 is very wide, ranging from an asymptomatic carrier to a critically ill patient with severe pneumonia, sepsis, and multiple organ failure which leads to death.[11,14–16] Common symptoms that have been reported include fever, cough, malaise, and dyspnea with an incubation period of 2–14 days and an average of 5 days.[11,17,18]

Neurological deficits either as an initial presentation or late symptoms of the disease have been reported (Tables 1 and 2).[5,8,19] Neurological manifestation as initial symptoms may cause undetected COVID-19 cases, mismanagement, and threat to the public health (virus spreader).[20] Neurological manifestation of COVID-19 is 36.4%, divided into 24.8% of the CNS, 8.9% of PNS, and

**Table 1.** Retrospective studies on reported clinical presentation in COVID-19 including neurological manifestations

| Study, country | Number of patients | Neurological manifestation | | |
|---|---|---|---|---|
| | | CNS | PNS | Musculoskeletal |
| Liu et al,[4] China | 137 | Headache (9.5%) | | Myalgia or fatigue (32.1%) |
| Mao et al,[8] China | 214 | Dizziness (16.8%)<br>Headache (13.1%)<br>Impaired consciousness (7.5%)<br>Acute cerebrovascular disease (2.8%)<br>Ataxia (0.5%)<br>Seizure (0.5%) | Ageusia (5.6%)<br>Anosmia (5.1%)<br>Impairment of vision (1.4%)<br>Nerve pain (2.3%) | Skeletal muscle injury (10.7%) |
| Chen et al,[12] China | 113 | Hypoxic encephalopathy (20%) | | |
| Chen et al,[15] China | 99 | Headache (8%) | | Myalgia (11%) |
| Guan et al,[16] China | 1,099 | Headache (13.6%) | | Fatigue (38.1%)<br>Myalgia or arthralgia (14.9%) |
| Lechien et al,[21] Europe | 1,420 | Headache (70.3%)<br>Decrease of consciousness<br>Cerebrovascular disease | Anosmia (70.2%)<br>Ageusia (54.2%)<br>Dysphonia (28.4%) | Myalgia (62.5%) |
| Helms et al,[22] France | 58 | Agitation (69%)<br>Corticospinal tract signs (67%)<br>Dysexecutive syndrome (36%) | | |
| Huang et al,[23] China | 41 | Headache (8%) | | Myalgia or fatigue (44%) |
| Jin et al,[27] China | 651 | Headache (62%) | | Myalgia (13.51%)<br>Fatigue (31.08%) |
| Lechien et al,[28] Europe | 417 | Headache (45%) | | Myalgia (58%) |
| Giacomelli et al,[29] Italy | 60 | Headache (3.4%) | Olfactory and taste disorders (33.9%) | |

CNS=central nervous system; COVID-19=coronavirus disease 2019; PNS=peripheral nervous system

10.7% of musculoskeletal system.[8] Anosmia (5.1%) and ageusia (5.6%) are the most reported PNS symptoms.[8] In Europe, headache, anosmia, ageusia, and myalgia are the most reported symptoms in mild to moderate cases,[21] while loss of consciousness, cerebrovascular accident (CVA), and muscle injury are the major neurological complications in critically ill patients.[8,22] Headache is identified in 8–13% of COVID-19 patients in China.[8,16,23] A similar report from Europe stated that headache is one of the dominant symptoms, which is identified in 70.3% of mild to moderate patients.[21] The most reported symptoms of CNS are vertigo (16.8%) and headache (13.1%).[8] CVA related to COVID-19 occurrs in 5.9% of the cases, and the majority are ischemic stroke, followed by cerebral venous thrombosis and hemorrhagic stroke.[24,25] Neuromuscular problems including myalgia and fatigue are reported in 15–44% of patients with COVID-19 and confirmed by an increase in creatine kinase and lactate-dehydrogenase.[8,16,23,26]

**Human coronavirus (HCoV) and the nervous system**

SARS-CoV-2 is a ribonucleic acid virus, which belongs to β-coronavirus group. This is an enveloped virus with three essential proteins, namely spike (S), envelope (E), and membrane (M), which enclose its genetic material. S protein is responsible for the virus, engagement to the host's receptor and undermining the host's immune system.[3,30,41] The virus was initially zoonotic, which was later on transmitted from bat to unknown intermediate host before infecting humans. This virus initiated an adaptive measure to enable a

**Table 2.** Case reports on neurological manifestation in COVID-19

| Study, country | Neurological disease | Clinical presentations | Important findings | Disease severity |
|---|---|---|---|---|
| Moriguchi et al,[19] Japan | Encephalitis | Unconsciousness, general seizure, and neck stiffness | CSF cell count 12/µl (MN dominant), RT-PCR CSF positive for SARS-CoV-2, MRI: medial temporal lobe encephalitis | Severe |
| Paniz-Mondolfi et al,[30] New York | Parkinson's disease | Fever and confusion | Viral particle in the frontal lobe sections of post mortem brain examination | Severe |
| Ye et al,[31] China | Encephalitis | Confusion, nuchal rigidity, Kernig sign, and Brudzinski sign | CSF WBC 0.001x$10^9$/l, protein 0.27 g/l, ADA 0.17 U/l, sugar 3.14 mmol/l | Severe |
| Oxley et al,[32] New York | Large vessel stroke | Neurological deficits according to affected vessels | High D-dimer | Mild–moderate |
| Alberti et al,[33] Italy | Guillain-Barré syndrome | Subacute paresthesia at the limbs followed by flaccid tetraparesis | CSF: protein 54 mg/dl and leukocytes 9 cells/µl, negative SARS-CoV-2 | Severe |
| Zhao et al,[34] China | Guillain-Barré syndrome | Acute weakness and severe fatigue | CSF: protein 124 mg/dl, normal cell | Moderate |
| Toscano et al,[35] Italy | Guillain-Barré syndrome | Two patients with paraplegia, one patient with tetraplegia and two patients with tetraparesis | CSF: two patients with normal level of protein, CSF RT-PCR negative for SARS-CoV-2 | Two patients moderate, three patients severe |
| Virani et al,[36] United States | Guillain-Barré syndrome | Numbness and weakness of the lower extremities | No CSF examination | Severe |
| Gutiérrez-Ortiz et al,[37] Spain | Miller Fisher syndrome | Anosmia, ageusia, internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, and areflexia | CSF: albuminocytologic dissociation, positive testing for GD1b-IgG antibodies | Moderate |
| Gutiérrez-Ortiz et al,[37] Spain | Polyneuritis cranialis | Ageusia, bilateral abducens palsy, and areflexia | CSF: albuminocytologic dissociation | Moderate |
| Barzegar et al,[38] Iran | Multiple sclerosis | Muscle aches, gait difficulty, sensory disturbances, and weakness on the right side | Decrease lymphocyte count 601.6/µl | Moderate |
| Delly et al,[39] United States | Myasthenia gravis | Dyspnea, fevers, rhinorrhea, and difuse myalgia | | Severe |

ADA=adenosine deaminase; COVID-19=coronavirus disease 2019; CSF=cerebrospinal fluid; IgG=immunoglobulin G; MN=mononuclear; MRI=magnetic resonance imaging; RT-PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WBC=white blood cell

human-to-human transmission.[2] Hence, SARS-CoV-2 infection has become a real threat from zoonotic to global public health.[42] Zoonotic viral infection in its natural host usually only causes mild disease. However, once it penetrates other hosts, it can be so virulent by inducing an uncontrolled immune response known as cytokine storm.[43]

Angiotensin-converting enzyme 2 (ACE2) is identified as the primary receptor of SARS-CoV-2. This enzyme is expressed abundantly in the lower respiratory tract.[2,11] This protein is also identified in the enterocyte, vascular endothelial, renal tubular epithelial, cardiac myocyte, and immune cells.[2,44,45] ACE2 receptors have also been identified in the brain, particularly in the subfornical organ, paraventricular nucleus, solitary tract nucleus, rostral ventrolateral medulla, motor cortex, and raphe neurons.[45]

SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-OC43 are types of β-coronavirus proven capable of invading the nervous system. SARS-CoV-2, which has a close similarity with SARS-CoV, is probably also capable to directly invade the nervous system. This view is supported by a report of the viral genome isolation from the cerebrospinal fluid (CSF) and brain tissue of patients with COVID-19.[8,14,19,30,44,46] Paniz-Mondolfi et al[30] identified viral particles in small vesicles in endothelial cells of the intracranial arteries and brain cells through electron microscope examination. These findings support the view of the hematogenous route of SARS-CoV-2 spreading to the nervous system.[30]

**COVID-19 manifestation on the CNS**

Headache is a common symptom of intracranial and systemic infection (Table 1). Infection-related headache is mostly a moderate to severe holocranial headache, which usually begins at the onset of the infection. The intensity and the frequency of the headache depend upon the disease progression and is related to systemic symptoms of fatigue and gastrointestinal.[15–18] Headache can occur episodically with coughing, usually in the temporoparietal area of the head, which is throbbing and pressuring. It may also be accompanied by photophobia, nausea, and neck stiffness.[20] Intensity of headaches can range from moderate to severe. It can also occur due to other factors such as anxiety and insomnia. Shortness of breath related to hypercapnia and hypoxia may also trigger the headache.[20,21] Headache in intracranial infection is part of the acute encephalitis syndrome.[19,22]

Encephalitis related to COVID-19 has also been reported (Table 2).[19,27] This condition is a neurological emergency characterized by acute alteration of consciousness and various neurological deficit including fever, seizure, and other focal neurological deficits. Pleocytosis of the CSF has been reported together with apparent pathological findings in imaging and electroencephalography.[47,48] The clinical differentiation of viral encephalitis and other types of unspecific and toxic encephalopathy is difficult; therefore, history taking to figure out the disease chronology is the key to its diagnosis.[23,48,49] COVID-19 is confirmed by positive findings in the polymerase chain reaction examination of CSF or nasopharyngeal swab.[19,27]

COVID-19 related encephalopathy is mostly reported as a complication of severe disease, without a direct invasion of the virus to the brain (Table 1). Multiple organ damage causes hypoxia, uremia, and other metabolic disturbances that increase the release of metabolites, which are toxic to the brain. The syndrome is complex, with altered consciousness and diffused corticospinal signs, including clonus hyperreflexia and bilateral Babinski sign.[22,31]

The onset of CVA was around 12 days after initial symptoms and was reported in the elderly with severe disease and those with cardiovascular comorbidities such as hypertension, diabetes, history of cardiovascular disease, immunocompromised, and hypercoagulation state.[50,51] However, large vessel stroke in young patients with COVID-19 has also been reported recently (Table 2).[52]

**COVID-19 manifestation in the PNS**

Smell and taste disorders are the most common neurological symptoms reported by mild to moderate patients with COVID-19 (Table 1).[53] Smell disorders include anosmia, hyposmia, phantosmia, and parosmia. It may present in the early or late stage of the disease regardless of rhinorrhea or nasal obstruction. Taste disorders affect all taste modalities (sweet, sour, salt, and bitter).[53–55] Symptoms are usually reversible within weeks after disease resolution.[53]

Guillain-Barré syndrome (GBS) is also reported in a patient with COVID-19 (Table 2). The clinical

manifestation includes progressive-symmetrical weakness of the limbs, albuminocytological dissociation, and electrophysiological features, confirming demyelination and axonal degeneration 5–10 days from the onset.[33–36] Similarly to Zika virus infection, GBS-related COVID-19 has a parainfectious pattern and does not follow the classical pattern.[34–36] The neurologist has to differentiate between GBS and neuropathy or myopathy that is commonly reported in the late stage of critically ill patients.[36] COVID-19 patients with classical Miller Fisher syndrome has also been reported presenting with ophthalmoplegia, areflexia, and ataxia with anosmia and ageusia, which appear on day-5 from the onset. In addition, a case with cranial polyneuritis with bilateral paralysis of abducens nerves and ageusia has been reported. This phenomenon is related to an immune dysregulation caused by the virus.[37]

Patients with the chronic neurological disease are very prone to SARS-CoV-2 infection due to the immune system disorder, long-term immunosuppressant treatment, comorbidities, or disabilities, which may impair the respiratory system.[56–58] Relapse in a patient with multiple sclerosis has been reported (Table 2)[38] as well as a patient with myasthenia gravis, which progressed into myasthenic crisis after SARS-CoV-2 infection.[39] During this pandemic, patients with neurologic problems who have organ function disorder are at greater risk of disease worsening due to the viral infection or stress related to the pandemic.[58]

**COVID-19 manifestation on the musculoskeletal system**

Clinical manifestations of muscle pain in COVID-19 are more common in adults than in children, which are also generally milder than in adults (Table 1).[59] Skeletal muscle damage is related to liver and renal problems, direct invasion of the virus through ACE2 receptors in skeletal muscles, and cytokine storm produced by the infection-mediated harmful immune response.[8] In severe disease, the occurrence of neuropathy and myopathy in critically ill patients are probably induced by neuromuscular block agent in intensive care.[8,26]

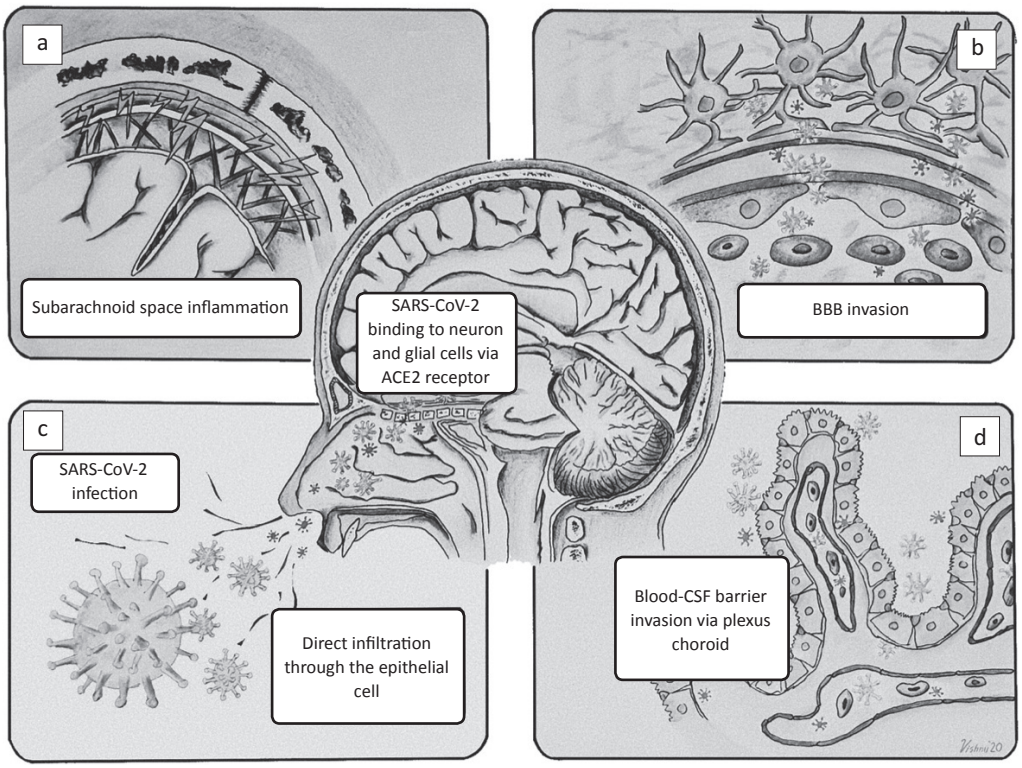


**Figure 1.** SARS-CoV-2 takes several routes to affect the CNS. The virus induces systemic inflammation and release of proinflammatory cytokines, which in turn causes endothelial dysfunction, disruption of the BBB, and inflammation of the subarachnoid space (a). It invades directly to the brain by infecting vascular endothelial cells of the BBB (b); and choroid epithelial cells of the blood-CSF barrier (d). It attacks directly through the olfactory system and affects the neuroepithelial of nasal mucous, mitral cells, olfactory nerve, olfactory bulb, and the brain in a retrograde manner (c). BBB=blood-brain barrier; CNS=central nervous system; CSF=cerebrospinal fluid; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

**Mechanisms of COVID-19 in affecting the nervous system**

The human CNS is protected by a complex barrier from viral infection;[60] however, several viruses are still able to trespass the barrier and invade the nervous system (neuroinvasion), infect neuron and glia (neurotropism), and induce neurological diseases (neurovirulence).[61] Viruses affect the nervous system through two pathways, namely hematogenous and peripheral pathways (Figure 1).[43,56,57,60]

Some respiratory viruses, including HCoV, have neuroinvasive properties. The virus causes disturbance in immune response, replication in neurons, and result in direct destruction of the nervous system in vulnerable people, especially those who are immunocompromised.[53] HCoV can infect the CNS through: (1) direct pathway, which can be through hematogenous and cranial nerves (the olfactory nerves) route and (2) indirect pathway as a secondary process of hypoxia, immune system disturbance, ACE2 receptor, and other probable unidentified mechanisms (Figure 1 and Table 3).[52,55,56,58]

The virus takes several routes in the hematogenous pathway to invade the CNS. Firstly, it destroys the epithelial cells of the respiratory tract, transmits the virus into the circulation, and spreads it to the lymphatic system and vital organs, including the brain. Secondly, it infects the immune cells in the circulation, especially the monocyte/macrophage. Thirdly, it infects the leucocyte, which in turn becomes the virus reservoir and invades the nervous system. In the brain, virus trespasses the blood-brain barrier (BBB) by infecting the vascular endothelial cells of the BBB, choroid epithelial cells of the blood-CSF barrier and uses Trojan horse strategy by infecting the immune system cells.[21,30,41,44]

Systemic inflammation in SARS-CoV-2 infection is related to high proinflammatory cytokines in the CSF. In turn, the BBB is disrupted and facilitated virus invasion which causes encephalitis.[44,62] However, toxic encephalopathy may be related to systemic toxemia, metabolic disturbance, hypoxia, and cytokine storm without viral confirmation in the CSF.[41,44,55]

In CVA-related COVID-19, the immune response is the contributing factor to the disease pathophysiology. The proinflammatory molecules induce the coagulation process.[5,24,55] The cytokine storm causes thrombosis that leads to ischemic stroke and coagulopathy that may cause hemorrhagic stroke.[5,63] The pathomechanism of hemorrhagic stroke may also be related to the downregulation of ACE2 receptor after viral invasion. ACE2 is an important agent in controlling blood pressure. Disturbance of its balance with ACE causes uncontrolled hypertension and induces a cerebral hemorrhage, especially in patients with comorbidity of CVA.[5,45,55]

Dysregulation of the adaptive immune system occurs in SARS-CoV-2 infection. The virus has a similar structure and phylogenetic with SARS-CoV that is capable to invade T cells and a macrophage in circulation by which is responsible for lymphopenia,[64] macrophage hyperactivity,[65] decrease in the cluster of differentiation (CD) 4+ and CD8+, increase in

**Table 3.** Neurological manifestations and related possible pathophysiology of SARS-CoV-2 infection in the human nervous system

| Route of Infection SARS-CoV-2 in the nervous system | | |
|---|---|---|
| Neural pathway via olfactory system | Mucosal neuroepithelial dysfunction | Smell and taste disorders |
| Hematogenous pathway | CNS involvement | Headache<br>Dizziness<br>Seizure<br>Encephalopathy<br>Encephalitis<br>Stroke<br>MS relapse<br>Neurodegenerative |
| | PNS involvement | Diplopia<br>GBS and variant<br>Myalgia and fatigue<br>Myasthenic crisis |

CNS=central nervous system; GBS=Guillain-Barré syndrome; MS=multiple sclerosis; PNS=peripheral nervous system; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

proinflammatory cytokine, and decrease in anti-inflammatory cytokine.[66] This immune response imbalance contributes to chronic inflammation, thus inducing post-infection autoimmune diseases and tissue destruction.[66] In the CNS, SARS-CoV-2 may also infect the microglia and astrocyte and induce an inflammatory response.[55] Immune cell activation damages the BBB and prolongs a proinflammatory state inducing neurodegenerative problems in individuals at risk;[6,55,58] therefore, a long-term study is necessary to evaluate COVID-19's impact on neurodegenerative diseases.[6,55,67] In the PNS, immune system disturbance can also cause GBS in COVID-19, most possibly due to its molecular mimicry between HCoV and myelin basic protein causing neural demyelination.[66]

Some viruses affect the PNS by binding to several receptors in the terminal axon of sensory nerves, autonomic nerves, neuromuscular junction, and olfactory epithelial lining.[43] HCoV has been known for its capability to invade the olfactory nerve receptor, which affects the neuroepithelial of the nasal mucous, mitral cells, olfactory nerve, olfactory bulb, and the brain in a retrograde manner.[61,68] The olfactory system is in proximity to the brain, only one synaptic; hence, it is a strategic route for the virus to infect the brain.[21,43] In an animal model on SARS-CoV infection, a viral antigen in the olfactory bulb was detected after 5–6 days post-infection and spread to the infralimbic and piriform cortex, ventral pallidum, lateral preoptic region of ganglia basal, and midbrain. Thus, it causes neuronal death.[21,69]

The exact mechanism of the COVID-19 affecting the nervous system has not been completely explained. Further studies are needed to identify the pathophysiology. Albeit the rarity the nervous system involvement in COVID-19 cases, clinicians have to increase the awareness of this probability.[50]

**Treatment implication and recommendations for neurologists in COVID-19 pandemic**

COVID-19 pandemic is a big challenge for neurologists. Growing evidence of nervous system involvement in COVID-19 may place neurologists as one of the health professional front-liners in the war to the virus. Neurologists must have a good understanding of the disease detection and prevention and control of infection. Some adaptive recommendations have been developed in the neurological clinical pathway, including the procedure of neurological examination, interventional measures, and a routine visit to the patients.[8,70,71]

The majority of neurological diseases are chronic diseases. No specific therapy recommendations during this pandemic have been reported. However, neurologists must take extra precautions in handling patients with immunosuppressive therapies. Strategies to minimize contact of those patients in high-risk environments, such as hospitals or clinics, should be developed. Telemedicine is a promising alternative to closely monitor these patients while at the same time reduces the risk for SARS-CoV-2 infection[63,70,72–74] including developing virtual neurologic examinations,[74] counseling, and education through the social media platform.[75]

The pandemic situation should not alter the current recommendation for acute inpatient treatment of neurological disease. Hyperacute stroke management must be performed according to the latest recommendation, with no exception for patients with COVID-19. However, clinicians should practice the general precautions procedure to minimize the risk of infection. Judgment must be made by prioritizing infection prevention in deciding treatment modality.[76]

In conclusion, patients with COVID-19 may present with various neurological manifestations. Some diseases of CNS, PNS, and musculoskeletal have been reported. The virus takes several routes to invade the CNS, including destroying the epithelial cells, infecting the immune cells in circulation, and infecting the leucocyte. In addition to direct invasion, the neurological manifestation can be caused by immunopathology in response to viral infection. During the pandemic, neurologists are recommended to adhere to recent recommendations or guidelines in managing COVID-19 patients with neurological symptoms while at the same time responsible for preventing the spread of the infection.

**Conflict of Interest**
The authors affirm no conflict of interest in this study.

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