Neurological manifestations in COVID-19: A narrative review

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Abstract
COVID-19, a respiratory viral infection, has affected more than 10 million individuals worldwide. Common symptoms include fever, dry cough, fatigue and shortness of breath. Some patients show neurological manifestations such as headache, dizziness, cerebrovascular disease, peripheral nerve and muscle symptoms and smell and taste impairment. In previous studies, SARS-CoV-1 and MERS-CoV were found to affect the nervous system. Given the high similarity between SARS-CoV-1 and SARS-CoV-2, effects on the nervous system by SARS-CoV-2 are a possibility. We have outlined the common neurological manifestations in COVID-19 (information are up-to-date as of June 2020) and discussed the possible pathogenetic mechanisms and management options.

Keywords
COVID-19, SARS-CoV-2, neurological manifestations, cerebrovascular disease, taste and smell impairments, Guillain-Barré syndrome

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Introduction
Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus originated in Wuhan, China, in December 2019. It is currently pandemic, and as of 28 June 2020, there have been more than 10 million cases worldwide and over 500,000 deaths. The common symptoms in COVID-19 include fever, dry cough, fatigue and shortness of breath. Respiratory distress/failure is seen in severe/critically ill COVID-19 patients. The SARS-CoV-2 primarily affects the respiratory system, but increasing numbers of publications point to the involvement of the nervous system in a significant group of patients. This article outlines the common neurological manifestations of COVID-19 and discusses the possible pathogenetic mechanisms.

Literature search
A literature search was performed in PubMed and Google Scholar to identify studies published on the neurological manifestations of COVID-19. The keywords used in the search were SARS-CoV-2, Neurological manifestations, COVID-19, stroke, loss of smell and taste, nervous system, encephalitis, coronavirus. Articles published from January to June 2020 were included. The initial selection was based on the article title and abstract, following which the full-text article was read. The reference lists in the full-text articles were scanned to obtain additional citations. After removing duplicates, the findings from 97 articles (primary research papers, case reports and case series) are summarized and discussed.

Coronaviruses and the nervous system
Previous studies suggest that four of the human coronaviruses—HCoV-229E, HCoV-OC43, severe acute respiratory

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syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV)—may involve the nervous system. For instance, in a postmortem study of the brains of patients with multiple sclerosis (MS), HCoV-229E and HCoV-OC43 were detected in some, suggesting neuroinvasion by these viruses. However, this could also be due to a disturbance in the blood–brain barrier; further studies would be required to distinguish between opportunistic and disease-associated viral presence. In cell-based studies, astrocytes, oligodendrocytes, neurons and microglia were susceptible to infection by HCoV-OC43. Polyneuropathy, myopathy, rhabdomyolysis and large artery ischemic stroke have also been reported in a few patients with SARS-CoV-1. The SARS-CoV-1 was detected in the cerebrospinal fluid (CSF) of some patients, and an autopsy study found SARS-CoV-1 in the brain. Arabi and colleagues reported the presence of MERS-CoV in three patients with encephalitis. Compared with MERS-CoV, there are more reports of neurological manifestations with SARS-CoV-1. There is high similarity between the genomes and cell entry mechanisms of SARS-CoV-1 and SARS-CoV-2, thus raising the possibility of neurological involvement in COVID-19.

Neurological manifestations by SARS-CoV-2

Two large cohort-based studies on neurological manifestations of COVID-19 have been reported so far. In a study done in Wuhan, China, Mao et al. noted neurological manifestations in 36.4% of 214 COVID-19 patients and these were significantly more common in patients with severe disease. Central nervous system (CNS) and peripheral nervous system manifestations were seen in 24.8% and 8.9%, respectively. In a study conducted in France, Helms et al. reported 84% of 58 patients admitted to the intensive care unit because of acute respiratory distress syndrome due to COVID-19 to have neurological signs. The differences in percentage between the two studies may be because the second study focused on more severely affected COVID-19 patients. Table 1 summarizes the common neurological manifestations in COVID-19.

**CNS manifestations**

The main CNS manifestations observed are headache, dizziness, cerebrovascular disease (CVD), encephalopathy, delirium and other related manifestations as discussed below.

**Headache and dizziness**

Headache and dizziness are the most common neurological manifestations recorded in several studies (Table 1). It is uncertain whether these two manifestations were caused by a direct effect of the infection on the nervous system or due to other factors such as stress, fear or anxiety.

**Cerebrovascular disease**

Li et al., who analyzed the cohort of patients described by Mao et al. and seven more, found 5% to have acute ischemic stroke. Stroke was also reported in five patients younger than 50 years from New York. Based on brain magnetic resonance imaging (MRI) findings from 13 of their 58 patients, Helms et al. reported two to have acute cerebral ischemic stroke and one to have subacute cerebral ischemic stroke. In a retrospective cohort-based study from New York, 0.9% had imaging-proven acute ischemic stroke and most (65%) strokes were cryptogenic, possibly related to an acquired hypercoagulability. A recent systematic review showed the incidence of acute ischemic stroke in COVID-19 to be 0.9% to 2.7% with a mortality rate of 38%. In addition, several case reports of stroke in patients with COVID-19 have been published (Table 2). The CVD in COVID-19 may be due to high levels of inflammation and/or a hypercoagulable state. Raised serum interleukin and C-reactive protein concentration have been reported, and coagulation abnormalities are increasingly noted with raised D-dimer concentration pointing to a poorer prognosis. Awareness by clinicians of the possibility of CVD in COVID-19 patients may lead to more timely management decisions and thus a reduction in both morbidity and mortality.

### Table 1. Cohort studies on neurological manifestations in COVID-19.

| Study       | N     | Headache (%) | Dizziness (%) | Impaired consciousness (%) | Acute cerebrovascular disease (%) | Skeletal muscle injury (%) | Ataxia (%) | Seizure |
|-------------|-------|--------------|---------------|---------------------------|-----------------------------------|--------------------------|-------------|---------|
| Li et al.⁸  | 221   | NA           | NA            | NA                        | 5.8                               | NA                       | NA          | NA      |
| Mao et al.⁶ | 214   | 13.1         | 16.8          | 7.5                       | 2.8                               | 10.7                     | 0.5         | 0.5     |
| Qin et al.² | 452   | 11.4         | 8.1           | NA                        | NA                                | NA                       | NA          | NA      |
| Helms et al.⁷ | 58    | NA           | NA            | NA                        | 23 (3/13)⁸                       | NA                       | NA          | NA      |
| Wang et al.¹⁰ | 138   | 6.5          | 9.4           | NA                        | NA                                | 34.5⁹                    | NA          | NA      |

COVID-19: coronavirus disease 2019; N: number of patients; NA: not analyzed (all studies were conducted in 2020); MRI: magnetic resonance imaging.

⁸Brain MRI scans were done in 13 patients and cerebral ischemic stroke was identified in three.

⁹Only myalgia was considered.
| First author          | Number of patients | Neurological manifestation | Findings                                                                                           |
|----------------------|--------------------|---------------------------|----------------------------------------------------------------------------------------------------|
| Ercoli et al.         | 2                  | Encephalopathy            | Two patients diagnosed with encephalopathy after infection with SARS-CoV-2. Viral antibodies were present in the CSF in both patients. |
| Buckley et al.        | 4                  | Delirium                  | Four cases of older patients having delirium presenting with a change in mental status. Three of the four cases did not show respiratory symptoms. |
| Dixon et al.          | 1                  | Acute encephalopathy     | A 59-year-old female patient with aplastic anemia reported seizures and reduced consciousness 10 days after fever. CT and MRI showed swelling of the brain. Patient did not respond to steroid treatment and died on the 8th day after hospitalization. |
| Filatov et al.        | 1                  | Encephalopathy            | A 76-year-old female patient presented with encephalopathy and tested positive for COVID-19. CSF tested negative for virus. |
| Pilotto et al.        | 1                  | Encephalopathy            | A 60-year-old female with COVID-19 who progressively developed severe encephalopathy. Improved with high doses of steroid treatment. |
| Poyiadji et al.       | 1                  | Acute encephalopathy     | A female patient in her late 50s presented with acute encephalopathy and later tested positive for COVID-19. The CSF was not tested for SARS-CoV-2 virus. |
| Zayet et al.          | 2                  | Encephalopathy            | Two cases having symptoms of encephalopathy followed by being positive for COVID-19. CSF was tested negative for SARS-CoV-2 virus, and MRI showed no signs of inflammation. |
| Cerebrovascular disease |                   |                           |                                                                                                    |
| Avula et al.          | 4                  | Acute stroke              | A series of four patients presenting with radiographic evidence of acute stroke.                    |
| Beyrouti et al.       | 6                  | Acute ischemic stroke     | A series of six COVID-19 patients with acute ischemic stroke.                                      |
| Co et al.             | 1                  | Stroke                    | A 62-year-old female patient with a past history of stroke presented typical symptoms of COVID-19 initially. Developed right upper and lower extremity weakness and severe dysarthria. |
| Fara et al.           | 3                  | Stroke                    | A series of three patients presenting with stroke-like symptoms. The patients were found to have subocclusive severe stenosis of the common carotid artery. None had severe respiratory symptoms. |
| Gunasekaran et al.    | 1                  | Stroke                    | A 40-year-old female patient presenting with typical symptoms initially, developed stroke during hospitalization. |
| Immovilli et al.      | 19                 | Stroke                    | A series of 19 patients having stroke; two cases of hemorrhagic stroke and 17 cases of ischemic stroke. Reports an association between stroke and pneumonia severity in COVID-19 patients. |
| Morassi et al.        | 6                  | Acute ischemic and hemorrhagic stroke | A series of six patients who developed stroke. Mainly presented severe pneumonia and multiorgan failure. |
| Oxley et al.          | 5                  | Large vessel stroke       | A series of five patients younger than 50 years of age presented with large vessel stroke.         |
| Al Saleh et al.       | 2                  | Stroke                    | One patient showing Hunt and Hess (H&H) grade 3 aneurysmal subarachnoid hemorrhage, and the second patient having had an ischemic stroke with massive hemorrhagic conversion. CSF tested negative for SARS-CoV-2 virus. |
| Valderrama et al.     | 1                  | Ischemic stroke           | A 52-year-old male patient with hypertension who tested positive for COVID-19. The patient presented to the hospital with symptoms of a stroke 7 days later. |
| Zhai et al.           | 1                  | Acute ischemic stroke     | A 79-year-old male patient showing symptoms of a stroke and diagnosed with COVID-19.              |
| Other CNS manifestations |                   |                           |                                                                                                    |
| Bernard-Valnet et al. | 2                  | Acute meningencephalitis  | Both patients developed meningencephalitis a few days after diagnosis of COVID-19 having mild respiratory and general symptoms. CSF was tested negative for SARS-CoV-2 virus. |
| Chaumont et al.       | 3                  | Meningoencephalitis       | A 69-year-old patient developed meningencephalitis 1 week after infection. CSF was tested negative for SARS-CoV-2 virus but the virus was detected in bronchoalveolar lavage. |
| First author | Number of patients | Neurological manifestation | Findings |
|--------------|--------------------|----------------------------|----------|
| Huang et al. | 34                 | Encephalitis                | A 40-year-old female patient admitted for encephalitis. The virus was not detected in the CSF initially, but detected later. |
| McAbee et al. | 35                 | Encephalitis                | A 11-year-old who presented with status epilepticus and CSF evidence for encephalitis. |
| Moriguchi et al. | 36               | Meningitis/Encephalitis     | A 24-year-old male patient having encephalitis based on MRI reports. CSF tested positive for virus. |
| Munz et al.  | 37                 | Acute transverse myelitis   | The patient had typical respiratory symptoms of COVID-19 and was discharged from the hospital. Admitted back and diagnosed with multifocal myelitis. CSF was negative for SARS-CoV-2 virus. |
| Al-Ofama et al.  | 38                | Meningoencephalitis         | A 36-year-old male patient initially with typical COVID-19 symptoms developed meningoencephalitis with intracerebral subdural hematomas. Fluid from chronic subdural hematoma tested positive for SARS-CoV-2 RNA. |
| Sharifi-Razavi et al. | 39     | Intracerebral hemorrhage    | A 79-year-old with a history of fever and cough who tested positive for COVID-19. The patient presented with intracerebral hemorrhage after few days. |
| Reichard et al. | 40                | Acute disseminated encephalitis like pathology | A patient was admitted due to coronary heart disease and underwent surgery. Subsequently developed COVID-19. The patient died after 2 weeks in hospital and autopsy revealed neuropathological lesions. |
| Sarma and Bilello | 41            | Acute transverse myelitis   | A 28-year-old female patient with SARS-CoV-2 presenting lower back pain, bilateral symmetric upper, and lower extremity numbness. Diagnosed with acute transverse myelitis. |
| Valiuddin et al. | 42               | Acute transverse myelitis   | The patient first presented with generalized weakness, following bilateral lower and upper extremity weakness. The CSF tested negative for SARS-CoV-2 virus. |
| Vollono et al. | 43                | Focal status epilepticus    | A 78-year-old female patient whose primary presentation was focal status epilepticus. CSF analysis was not carried out. |
| Wong et al.   | 44                 | Rhombencephalitis           | A 40-year-old male patient who initially had fever developed with acute brainstem dysfunction. MRI showed changes in inflammation of the brainstem and upper cervical cord. |
| Ye et al.     | 45                 | Encephalitis                | Patient first presented with typical symptoms of COVID-19, followed by deteriorated consciousness. CSF tested negative for virus. The condition gradually improved with the clearance of the virus and treatment. |
| Zanin et al.  | 46                 | Seizure/brain and spine demyelinating lesions | A 54-year-old female patient who was found unconscious at home tested positive for COVID-19. The MRI revealed demyelinating lesion in the brain and spine. CSF tested negative for SARS-CoV-2. |
| Zhang et al.  | 47                 | ADEM                        | First described case of ADEM with COVID-19. The MRI showed patchy areas of abnormal signals in certain areas of the brain. |
| Zhao et al.   | 48                 | Acute myelitis              | A 66-year-old male patient with post-infectious acute myelitis. |

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CSF: cerebrospinal fluid; CT: computed tomography; MRI: magnetic resonance imaging; CNS: central nervous system; ADEM: acute disseminated encephalomyelitis.
Encephalopathy and delirium

There are reports of encephalopathy in COVID-19 (Table 2), and healthcare workers need to consider testing for SARS-CoV-2 in such patients.\textsuperscript{18,21} Delirium has been reported to occur in COVID-19, especially among older persons.\textsuperscript{7} Beach et al. presented a case series, where three of the four COVID-19 patients had delirium, without the presence of significant respiratory symptoms.\textsuperscript{18} At present, in most reported studies, CSF had not been tested for SARS-CoV-2. In the patient described by Filatov et al.,\textsuperscript{18} CSF was tested and found to be negative. Encephalopathy and delirium may be due to direct invasion of the CNS by SARS-CoV-2, inflammation secondary to a cytokine storm or as a result of septic encephalopathy.

Other CNS manifestations

There are reports of encephalitis and meningitis in COVID-19. For instance, the SARS-CoV-2 virus has been detected in the CSF of two patients with encephalitis,\textsuperscript{34,36} raising the possibility of direct cerebral effects of the virus. Mao et al.\textsuperscript{6} reported seizures and hemiplegia in one and two patients, respectively, prior to the onset of respiratory symptoms. However, in a retrospective study, Lu et al.\textsuperscript{49} did not find an increased risk of symptomatic seizures in COVID-19 patients. At present, it is uncertain whether the seizures are coincidental or due to SARS-CoV-2 viral effects or the drugs used in treatment.

Peripheral nervous system manifestations

In the study by Mao et al.\textsuperscript{6} 8.9% of patients had peripheral nervous system manifestations. The common manifestations include Guillain-Barré syndrome (GBS) and other related variants and loss of the sense of taste and smell.

GBS and other variants

Currently, a total of 27 reports on GBS and its variants in COVID-19 have been reported. Pathogen-associated antibodies that attack peripheral nerves due to molecular mimicry have been previously put forward as a disease mechanism in GBS. COVID-19-related GBS is mainly seen in the elderly while typical GBS can occur in all age groups.\textsuperscript{50} None of the patients with post-COVID-19 GBS tested positive for SARS-CoV-2 in the CSF,\textsuperscript{51} pointing to an immune mechanism such as inflammation secondary to a cytokine storm as a possible cause. Some variants of GBS such as Miller Fisher syndrome and polyneuritis cranialis have been reported in two COVID-19 patients from Italy; both recovered fully within 2 weeks.\textsuperscript{52}

Loss of the sense of taste and smell

Twenty cohort studies have reported on loss of smell (anosmia) and taste (ageusia) as early symptoms of COVID-19 (Table 3). These symptoms may appear early in the course of the disease or in otherwise asymptomatic individuals. A European study of 417 COVID-19 patients, conducted across four counties, found 85.6% and 88% to have impairment of the sense of smell and taste, respectively.\textsuperscript{53} At present, there have been only a few studies on this aspect from the Asia-Pacific region. For instance, Mao et al.\textsuperscript{6} found 5.6% and 5.1% of their cohort to have taste and smell impairment, respectively. Compared with the European studies, the frequency of smell and taste impairment in the Chinese study was low, which may be because the latter study was not specifically designed to assess this aspect. Smell and taste impairment may also vary across different populations; individuals with a strong preference for spicy foods may have a reduced taste sensitivity than those with a lower preference. The variations may also be attributed to the method of testing, as most of the studies were questionnaire based. For instance, in a study by Lechien et al.,\textsuperscript{45} of the 61.4% of patients self-reporting olfactory disorders, 38.3% were subsequently found to be normal on objective testing. A standard quantifiable test needs to be developed to validate the variations of smell and taste impairment. Increased awareness that olfactory and gustatory dysfunction is common and early symptoms in COVID-19 would allow earlier diagnosis and thus effective self-isolation. Currently, although complete recovery has been reported in the majority of patients, it may be too early to comment on the longer-term implications.

It is still uncertain whether the taste and smell alterations are due to inflammation of the nasal tract or damage to the sensory neurons in the olfactory bulb. A large number of cells in the nasal epithelium express the angiotensin-converting enzyme 2 (ACE2) receptor which is the cell entry receptor for SARS-CoV-2.\textsuperscript{73} However, Brann et al.\textsuperscript{74} noted an absence of ACE2 receptors in the olfactory sensory neurons and suggested inflammation may be the primary cause for small impairment. A previous mouse study found SARS-CoV-1 to be able to enter the brain through the olfactory bulb.\textsuperscript{75} ACE2 receptors are found to be expressed in olfactory sustentacular cells and other non-neuronal cells in the olfactory epithelium.\textsuperscript{76} These cells maintain the integrity of the sensory neurons and damage to these may lead to alterations in smell and taste.

Skeletal muscle injury

Skeletal muscle injury was recorded in 10.7% of the COVID-19 patients studied by Mao et al. Creatine kinase (CK), D-dimer, C-reactive protein and lactate dehydrogenase levels were found to be elevated in patients with skeletal muscle injury. In another report, myalgia was noted in 34.8% of the studied COVID-19 patients.\textsuperscript{10}

Clinicians should be aware of the range of neurological manifestations in COVID-19, as this would facilitate early recognition and appropriate management. Further studies from different regions of the world, using appropriate brain
imaging, electroencephalography (EEG) and CSF analysis, could provide evidence for the neuro-invasive potential of SARS-CoV-2. Such studies would also shed further light on why many neurological manifestations are more common in the elderly with severe COVID-19.

**Possible pathogenic mechanisms**

Neurological involvement in COVID-19 may be due to direct SARS-CoV-2 viral damage to the nervous system or through indirect means. ACE2 receptors are highly concentrated in the substantia nigra and ventricles of the brain. It is also found in many neurons, astrocytes, oligodendrocytes, middle temporal gyrus and posterior cingulate cortex.77 A mouse cell culture study found ACE2 receptor expression on astrocytes.78 ACE2 receptors are also expressed on endothelial and arterial smooth muscle cells of blood vessels in the brain. These studies suggest that major CNS manifestations are possible if the virus invades the brain. A recent autopsy study found SARS-CoV-2 viral particles, on electron microscopic examination, in the frontal lobe of the brain. Virus-like particles were observed budding out of endothelial cells in the blood vessels of the frontal lobe, thus pointing to a hematogenous pathway of spread through the blood–brain barrier.79

In a study by Ding et al.,4 SARS-CoV-1 virus was detected exclusively in the neurons of the brain. The SARS-CoV-1 virus has also been found in the CSF. A transgenic-mouse study found SARS-CoV-1 entry into the brain via the olfactory bulb,75 and a similar pathway has been postulated in humans. The entry of SARS-CoV-2 to the olfactory bulb through the cribriform plate might explain smell impairment in COVID-19.

Li et al.80 suggest the SARS-CoV-2 virus may spread to the medullary cardiorespiratory center in the brainstem via chemosensory and mechanoreceptors in the lung, as has been observed with some other respiratory viruses. This raises the possibility of a neurological mechanism for respiratory failure in some COVID-19 patients. While ACE-2 receptors are found in the alveolar epithelium of the lung, the mechanism of viral movement from the lungs to the nervous system remains unclear. The detection of the SARS-CoV-2 in CSF or brain biopsies would further clarify this potential pathway. No previous studies have been published of such a mechanism in either SARS-CoV-1 or MERS-CoV infections. In addition to inflammatory effects in the brain, neurological manifestations may also be caused by hypoxia-related injuries, as alveolar and interstitial lung inflammation may lead to CNS hypoxia. This in turn may cause cerebral vasodilation and cerebral edema.

### Table 3. Studies on taste and smell impairment of patients with COVID-19.

| First author (country) | N   | Method of testing                  | Taste impairments* (%) | Smell impairmentsb (%) |
|-----------------------|-----|-----------------------------------|------------------------|------------------------|
| Beltrán-Corbellini (Spain)55 | 79  | Questionnaire                     | 35.4                   | 31.6                   |
| Bénézit (France)56     | 68  | Questionnaire                     | 62                     | 45                     |
| Boscolo-Rizzo (Italy)57 | 54  | Telephone surveys                 | 64                     |                         |
| Giacomelli (Italy)58    | 59  | Questionnaire                     | 33.9                   |                         |
| Hornuss (Germany)59     | 45  | Burghart Sniffin’ Sticks          | NA                     | 40                     |
| Kaye (USA, Mexico, Italy, UK, Other)60 | 237 | Validated survey                  | NA                     | 73                     |
| Klopfenstein (France)61 | 114 | Medical records/physical examination | NA                     | 47                     |
| Lee (Korea)62           | 3191| Telephone survey                  | 15.3                   |                         |
| Lechien (Belgium, France, Spain, Italy)53 | 417 | Questionnaire                     | 88                     | 85.6                   |
| Levinson (Israel)63     | 42  | Questionnaire and interview        | 33.3                   | 35.7                   |
| Luers (Germany)64       | 72  | Questionnaire                     | 69                     | 74                     |
| Mao (China)65           | 214 | Reported by patients              | 5.6                    | 5.1                    |
| Menni (USA, UK)65       | 6452 (UK) | Self-reported                  | 64.76 (UK)             | 67.49 (USA)           |
| Moein (Iran)66          | 60  | Odorant test                      | NA                     | 98                     |
| Sayin (Turkey)67        | 64  | Questionnaire                     | 71.9                   | 67.2                   |
| Speth (Switzerland)68   | 103 | Questionnaire                     | 65                     | 61.2                   |
| Spinato (Italy)69       | 202 | Sino-Nasal Outcome Test 22 (SNOT-22) Questionnaire | 64.4                   |                       |
| Vaira (Italy)70         | 72  | CCCRC and validated taste test    | 48.6                   | 83.4                   |
| Wee (Singapore)71       | 154 | Self-reported                     | 22.7                   |                         |
| Yan (USA)72             | 59  | Questionnaire                     | 71                     | 68                     |

COVID-19: coronavirus disease 2019; N: number of patients positive for COVID-19; NA: not analyzed (all studies were conducted in 2020); CCCRC: Connecticut Chemosensory Clinical Research Center orthonasal olfaction test.

*Taste impairments include ageusia and mild to severe hypogeusia.

*Smell impairments include anosmia and mild to severe hyposmia.
The possibility that medications used to treat COVID-19 may cause neurological manifestations should be remembered. For instance, other neurological infections that may occur due to the immunosuppressive effect of the medications or seizure thresholds may be reduced. Headache is a common side effect of the monoclonal antibody Tocilizumab and Chloroquine. Cases of Tocilizumab-associated multifocal cerebral thrombotic microangiopathy and Tocilizumab-related demyelinating disorders have been reported. Chloroquine and hydroxychloroquine are also known to have certain neurological side effects such as seizure, balance disorder, peripheral neuropathy, parasthesia and hypaesthesia.

Considering the high transmission rate of the SARS-CoV-2 virus, carrying out autopsy studies are challenging. However, the findings from such studies would contribute to and shed light on the potential neurological mechanisms and prognosis in COVID-19 and direct more evidence-based treatment plans.

**COVID-19 in patients with diagnosed neurological disorders**

Individuals with MS and neuromuscular disorders may be prescribed medications which suppress the immune system and thus are at a higher risk of developing severe COVID-19. However, guidelines specifically recommend having discussions with neurologists prior to modifying any courses of medication. Patients who suffer with CVD have a 2.5-fold higher risk of getting severe COVID-19. COVID-19 seems to have a worsening effect on patients with Parkinson’s disease too. Hainque and Grabli report two patients with Parkinson’s disease where early diagnosis of COVID-19 was challenging and thus associated with poorer outcomes. Currently, there is no evidence that individuals with epilepsy are at a higher risk of developing COVID-19.

Limitations of this review include the small number of studies reporting on certain neurological manifestations, thus making it difficult to provide more definitive conclusions on these aspects. It is possible that subtle neurological findings were not documented (and thus underestimated) due to the high workload during the early part of the pandemic. Further well-conducted studies from different regions of the world in the coming months would help expand this evidence base and thus provide better answers to the many questions at hand. Ours is a broad overview on the main reported neurological manifestations in COVID-19 and a more comprehensive clinical picture would emerge in the coming months.

**Future recommendations**

During the COVID-19 pandemic, if a patient has neurological symptoms such as loss of the sense of smell and taste or delirium, testing for SARS-CoV-2 should be considered irrespective of them not having the other typical symptoms. At present, the long-term effects of neurological manifestations are still uncertain but should become better defined as more studies using brain imaging, EEG and CSF findings become available. Detailed and systematically conducted histopathology and autopsy studies should shed light on aspects of pathogenesis and pathology that are still undefined and uncertain.

**Conclusion**

Neurological manifestations have been reported in some COVID-19 patients. The detection of SARS-CoV-2 in the CSF of two patients and in endothelial cells of blood vessels of the frontal lobe of another provides evidence for a neurotropic potential of this virus. The nervous system may also be affected via indirect methods such as hypoxia, inflammation or an immune-mediated damage. Future studies using brain imaging, EEGs, CSF analysis and histopathology would provide a clearer understanding of the effect of SARS-CoV-2 on the nervous system.

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