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# Emerging Neurology of COVID-19

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**Abstract**

The virus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the current pandemic known as coronavirus disease 2019 (COVID-19) with severe respiratory illness as the predominant manifestation. Neurologic complications from COVID-19 were reported in the early stages of the pandemic and are now increasingly recognized. These include various symptoms like headache and anosmia as well as neurologic complications of severe COVID-19 like encephalopathy, seizures, and stroke. There are few reports of direct involvement of the central nervous system with SARS-CoV-2 causing meningoencephalitis. There is concern for higher incidence and severity of COVID-19 in patients with chronic neurologic conditions. Here, we review the emerging literature along with our anecdotal experience in regard to these neurologic manifestations in patients with COVID-19 and detail the putative pathophysiologic mechanisms for the same.

**Keywords**

COVID-19, SARS-CoV-2, encephalopathy, meningoencephalitis

## Introduction

An outbreak of a novel coronavirus disease starting in December 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has now taken over almost all countries of the world.[1] Infection with SARS-CoV-2, which has homologous sequences and pathogenesis similar to SARS-CoV-1, manifests primarily as respiratory illness.[2] However, various other systemic complications including that of gastrointestinal, renal, hematological, and rheumatological systems are increasingly recognized.[3] Here, we review the neurologic issues related to COVID-19 based on the evolving literature and our experience (Table 1).

## Neurologic Symptoms of COVID-19

Along with fever, cough, and respiratory symptoms, various neurologic symptoms like headache, dizziness, myalgias, hyposmia, and dysgeusia are commonly reported.[4-8] A detailed review of literature on these symptoms is reported in Table 2.

In a retrospective case series study out of Wuhan, China, of 214 patients, dizziness was reported to be the most common neurologic complaint (16.8%) followed by headache (13.1%).[4] Few other case series from China have reported 6% to 8% of patients presenting with headaches.[9,12] The true prevalence of these symptoms cannot be determined as most of the current reports are based on retrospective chart review and vary based on ambulatory or inpatient setting. These symptoms are thought to be common early manifestations of COVID-19 and sometimes the only presenting symptom. The duration of these symptoms is not well studied yet. Our anecdotal experience suggests that at least a subset of patients have headaches for weeks after initial diagnosis. The pathophysiology of these symptoms is not yet defined, but is thought to be due to initial cytokine release as is seen in various viral illnesses.[14] Our recommendation is that patients with severe headache and/or those with accompanying focal neurologic symptoms should undergo head imaging and cerebrospinal fluid (CSF) analysis to assess for stroke and for the rare possibility of meningoencephalitis due to direct invasion of the central nervous system (CNS) with SARS CoV-2. It is noteworthy that there are no clinically validated Food and Drug Administration–approved polymerase chain reaction (PCR) assays in CSF available at this time.

In a prospective European study of 417 patients, olfactory and gustatory dysfunction was quite common (85.6% and 88.0%, respectively). Of these, 25% of patients recovered both olfactory and gustatory functions in approximately 2 weeks after the resolution of upper respiratory symptoms.[6] Many studies have now found these to be early symptoms in the disease course, more frequent among patients with COVID-19 than patients with influenza and sometimes the

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**Table 1.** Neurologic Issues Related to COVID-19.

| | Symptoms or syndromes | Onset in relation to disease course | Frequency |
|---|---|---|---|
| Neurologic symptoms of COVID-19 | Anosmia, dysgeusia, headache, dizziness, paresthesias | Early (within 7 days of initial illness) | Common |
| Neurologic complications of severe COVID-19 | Encephalopathy, stroke, acute necrotizing encephalopathy | Late (after 7 days of initial illness) | Common in severe disease |
| Direct involvement of CNS with SARS CoV-2 | Meningoencephalitis | Unknown | Rare |
| Parainfectious and post-infectious complications of SARS Cov-2 | Guillain-Barré syndrome, Miller-Fisher syndrome, ADEM | 7 to 10 days after onset | Unknown |
| COVID-19 in patients with existing neurologic illness | Multiple sclerosis, myasthenia gravis, epilepsy, dementia, Parkinson disease | NA | Unknown |

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; COVID-19, coronavirus disease 2019; NA, not applicable; SARS Cov-2, severe acute respiratory syndrome coronavirus-2.

primary manifestation.[13] The mechanism for such prominent olfactory and gustatory dysfunction is unknown. This seems to be independent of the nasal tract inflammation as upper respiratory tract symptoms like rhinorrhea are not as pronounced with COVID-19. One hypothesis is dysfunction in olfactory bulb, secondary to the binding of SARS-CoV-2 to the human angiotensin-converting enzyme 2 (ACE2) receptors in olfactory bulb.[5,15]

Myalgias, neuralgias, and arthralgias are reported as well. However, detailed descriptions on these symptoms are not yet available.[10,11] Some reports of myalgia suggest that it may be associated with elevated levels of creatine kinase.[16] In the cohort from Wuhan, China, skeletal muscle injury was associated with severe COVID-19 disease.[4] It is unclear if these are early or late manifestations of the disease or what the underlying pathophysiologic mechanisms are.

## Neurologic Complications of Severe COVID-19

Severe COVID-19 is associated with acute respiratory distress syndrome as well as multi-organ dysfunction. Neurologic complications in severe disease include encephalopathy, ischemic stroke, hemorrhagic stroke, and seizures.

In a series of 58 patients with severe COVID-19 disease from France, 49 (84%) patients had some neurologic findings. Majority of these consisted of delirium or agitation.[17] The same is reported from other series from China in association with severe COVID-19.[18] Various factors likely contribute to encephalopathy, including hypoxia, critical illness–related encephalopathy, stroke, seizures, medication effects, and possibly immunologic mechanisms related to cytokine release.[19]

Cerebrovascular diseases including ischemic stroke, hemorrhagic stroke, and cerebral venous infarction have been identified.[20-22] In a series where 4 stroke patients were identified, they were more likely to be older and also more likely to have underlying cardiovascular risk factors.[23] A case series from New York, identified 5 young patients (<50 years old) with stroke. Two of them had diabetes, and 1 had hypertension and hyperlipidemia, with 2 having no vascular risk factors. Two of the 5 did not have any other symptoms of COVID-19. All of them had large vessel occlusions, with one receiving intravenous (IV) tissue plasminogen activator and 4 of the 5 undergoing clot retrieval.[24] Putative mechanisms for these cerebrovascular events include thrombogenesis secondary to cytokine storm, hypercoagulable state, endothelial dysfunction, and cardioembolism secondary to multi-organ failure.

A remarkable case of acute hemorrhagic necrotizing encephalopathy was described in a female airline worker in her 50s who presented with altered mental status. Magnetic resonance imaging (MRI) was significant for hemorrhagic, ring-enhancing lesions in bilateral thalami, medial temporal lobes, and subinsular regions.[25] Severe acute respiratory syndrome-CoV-2 testing in CSF could not be performed in this patient. Acute necrotizing encephalopathy is a rare but well-described complication of influenza, occurring more commonly in children or adolescents. It is typically associated with cytokine storm and does not reflect direct invasion of the brain from the virus.

Epilepsy was reported only in 1 of 214 patients from Wuhan, China.[5] Another study of 304 individuals did not identify any with new-onset seizures, except for 2 patients with provoked seizures secondary to metabolic abnormalities.[26] However, most of these centers were limited in their ability to obtain electroencephalography (EEG). In our experience, we have identified patients presenting with new-onset seizures as the initial manifestation of COVID-19. It is possible that nonconvulsive seizures may be contributing to encephalopathy that is widely recognized as a complication of severe COVID-19. The etiology of seizures is postulated to be secondary to metabolic dysfunction in severely ill patients, or secondary to strokes or meningoencephalitis.

## Direct Involvement of the CNS With SARS CoV-2

SARS-CoV-2 has been isolated in the CSF of patients presenting with clinical syndrome of meningoencephalitis. Currently, this seems to be a rare occurrence. The first case of

**Table 2.** Literature Review of Neurologic Symptoms in COVID-19.

| Neurologic symptom | Study | Location, setting | Method | Prevalence of symptom, total cases |
|---|---|---|---|---|
| Headache | Tao et al. *BMJ* 2020[14] | China, deceased patients | Retrospective chart review, single centered | 11%, 113 |
| | Xu et al. *BMJ* 2020[10] | China, inpatients not critically ill | Retrospective chart review, multicenter | 34%, 62 |
| | Yang et al. *Lancet* 2020[11] | China, inpatients critically ill | Retrospective chart review, single center | 6%, 52 |
| | Wang et al. *JAMA* 2020[12] | China, inpatients | Retrospective chart review, single center | 6.5%, 138 |
| | Chen et al. *Lancet* 2020[9] | China, inpatients | Retrospective chart review, single center | 8%, 99 |
| | Mao et al. *JAMA Neurology* 2020[4] | China, inpatients | Retrospective chart review, multicenter | 13.1%, 214 |
| | Lechien et al. *Eur Arch Otorhinolaryngol* 2020[6] | 12 European hospitals, inpatients and ambulatory with mild-to-moderate disease | Questionnaire based, multicenter | 45%, 417 |
| | Guan et al. *NEJM* 2020[8] | China, inpatient and ambulatory | Retrospective chart review, multicenter | 13.6%, 1099 |
| Dizziness | Tao et al. *BMJ* 2020[14] | China, deceased patients | Retrospective chart review, single centered | 8%, 113 |
| | Wang et al. *JAMA* 2020[12] | China, inpatients | Retrospective chart review, single center | 9.4%, 138 |
| | Mao et al. *JAMA Neurology* 2020[4] | China, inpatients | Retrospective chart review, multicenter | 16.8%, 214 |
| Myalgias | Zhou et al. *Lancet* 2020[3] | China, inpatients | Retrospective chart review, multicenter | 15%, 199 |
| | Tao et al. *BMJ* 2020[14] | China, deceased patients | Retrospective chart review, single centered | 22%, 113 |
| | Xu et al. *BMJ* 2020[10] | China, inpatients not critically ill | Retrospective chart review, multicenter | 52%, 62 |
| | Yang et al. *Lancet* 2020[11] | China, inpatients critically ill | Retrospective chart review, single center | 11.5%, 52 |
| | Wang et al. *JAMA* 2020[12] | China, inpatients | Retrospective chart review, single center | 34.8%, 138 |
| | Chen et al. *Lancet* 2020[9] | China, inpatients | Retrospective chart review, single center | 11%, 99 |
| | Mao et al. *JAMA Neurology* 2020[4] | China, inpatients | Retrospective chart review, multicenter | 10.7%, 214 |
| | Lechien et al. *Eur Arch Otorhinolaryngol* 2020[6] | Europe, inpatients and ambulatory with mild-to-moderate disease | Questionnaire-based, cross-sectional, multicenter | 58%, 417 |
| | Yan et al. *Int Forum Allergy Rhinol* 2020[7] | The United States, ambulatory | Online questionnaire, cross-sectional, single center | 63%, 59 |
| | Guan et al. *NEJM* 2020[8] | China, inpatient and ambulatory | Retrospective chart review, multicenter | 14.9%, 1099 |
| Hyposmia/ anosmia | Mao et al. *JAMA Neurology* 2020[4] | China, inpatients | Retrospective chart review, multicenter | 5.1%, 214 |
| | Lechien et al. *Eur Arch Otorhinolaryngol* 2020[6] | Europe, inpatients and ambulatory with mild-to-moderate disease | Questionnaire-based, cross-sectional, multicenter | 85.6%, 417 |
| | Yan et al. *Int Forum Allergy Rhinol* 2020[7] | The United States, ambulatory | Online questionnaire, cross-sectional, single center | 68%, 59 |
| | Beltrán-Corbellini et al. *Eur J Neurol* 2020[13] | Spain, mild-to-moderate severity | Questionnaire-based, case–control, multicenter | 31.6%, 79 |
| Hypogeusia/ ageusia | Mao et al. *JAMA Neurology* 2020[4] | China, inpatients | Retrospective chart review, multicenter | 5.6%, 214 |
| | Lechien et al. *Eur Arch Otorhinolaryngol* 2020[6] | Europe, inpatients and ambulatory with mild-to-moderate disease | Questionnaire-based, cross-sectional, multicenter | 88.8%, 417 |
| | Yan et al. *Int Forum Allergy Rhinol* 2020[7] | The United States, ambulatory | Online questionnaire, cross-sectional, single center | 71%, 59 |
| | Beltrán-Corbellini et al. *Eur J Neurol* 2020[13] | Spain, mild-to-moderate severity | Questionnaire-based, case–control, multicenter | 35.4%, 79 |

Abbreviation: COVID-19, coronavirus disease 2019.

encephalitis was reported in Japan of a 24-year-old man who had mild respiratory symptoms followed by transient generalized seizures. Surprisingly, nasopharyngeal swab testing was negative, but real-time PCR for SARS-CoV-2 on CSF returned positive along with CSF findings of pleocytosis.[27] Another case of encephalitis was reported in New York in an 11-year-old child who presented with refractory status epilepticus, with SARS CoV-2 detected in nasopharyngeal swab and CSF.[28] There are some other reports of meningoencephalitis in patients with confirmed SARS CoV-2 but with inability to analyze CSF for SARS-CoV-2.[29]

Identification of SARS-CoV-2 in the CSF suggests neuroinvasive potential of the virus. In an autopsy series of 27 patients, SARS-CoV-2 RNA was detected in the brain tissue, albeit in small quantities.[30] At least 2 theories are proposed based on testing in transgenic mice. The first one hypothesizes that the viral spread starts in the olfactory bulb and progressively invades subcortical and cortical regions with further spread along specific pathways (neurotransmitters, blood, or Virchow-Robin spaces).[31] The other theory suggests that coronavirus can enter the CNS primarily via a hematogenous route using dendritic or white blood cells as reservoirs.[32] Human ACE2 receptor has been confirmed to be the receptor for SARS-CoV-2.[33] The affinity of SARS-CoV-2 to the ACE2 receptors is greater compared to SARS-CoV-1.[34] Given the expression of this receptor in neurons and endothelial cells, there is concern for higher neuroinvasive potential with SARS-CoV-2 compared to previous coronaviruses.[35,36] There may be other entry proteins for SARS-CoV-2 and mechanisms of neuronal entry still remain to be defined.

## Parainfectious and Post-Infectious Complications of SARS-CoV-2

There are many reports of Guillain-Barré syndrome (GBS) in association with COVID-19. Most of these patients presented with typical symptoms of GBS after 5 to 10 days of symptom onset of COVID-19 had expected changes on the nerve conduction tests and were treated with IV immunoglobulin.[37-40] In one case report from Wuhan, the patient had presented with symptoms consistent with GBS and was identified to have COVID-19 later during the hospitalization.[41] These presentations may be suggestive of a parainfectious etiology of GBS rather than a post-infectious etiology. Although CSF analysis was available, none of these patients were found to have SARS-CoV-2 in the CSF.[30] Along similar lines, a patient from Spain with Miller-Fisher syndrome is described.[42] Although other post-infectious complications like acute disseminated encephalomyelitis are expected, none such have been reported yet in the literature. Similar to GBS secondary to other viral infections, pathophysiologic mechanism for GBS in these patients is thought to be secondary to molecular mimicry in a post-infectious presentation or a hyperacute immune response in a parainfectious setting.

## Coronavirus Disease 2019 in Patients With Existing Neurologic Disease

As COVID-19 continues to spread, we need to assess how it affects people with underlying chronic neurologic diseases. The data in this regard are emerging through various registries for these diseases. One major concern is susceptibility of individuals and risk for severe disease in those who are on immunosuppressive medications for their neurologic diseases such as multiple sclerosis, neuromyelitis optica spectrum disorders, and myasthenia gravis. On the contrary, the same medications may offer protection from the cytokine storm seen in severe COVID-19. Relapse of the disease in setting of COVID-19 is also a concern. At our institution, we have had patients with COVID-19 presenting as myasthenia gravis relapses. Older individuals with Alzheimer disease, Parkinson disease, and chronic strokes may be at higher risk of developing encephalopathy when infected with COVID-19. Breakthrough seizures may occur in individuals with epilepsy who contract SARS-CoV-2.

## Conclusion

An online survey for Italian physicians including both neurologists and non-neurologists reported some neurologic symptom in 82% of the respondents, with around 66.7% of the physicians considering them as probably correlated to COVID-19.[43] Although these data are not reflective of some of the above-reported retrospective studies, it is possible that neurological symptoms are under-reported in retrospective studies and/or obscured by the more prominent respiratory symptoms in severe COVID-19. A thorough academic study of these individuals with MRI or EEG is often limited due to risks of exposure to health care workers and other patients. On the other hand, with a disease that is so widespread, a possibility is that the neurologic syndromes being reported may be a coincidence and have no causative mechanism. Role of host factors in development and severity of neurologic manifestations needs to be studied. Whether neurologic complications are associated with mortality from COVID-19 is yet unknown. We await further data from the various national and international registries, biorepositories, and autopsy studies that have been set up to help answer these questions.

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