

Potential Neurologic Manifestations of COVID-19

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Abstract

Purpose of Review

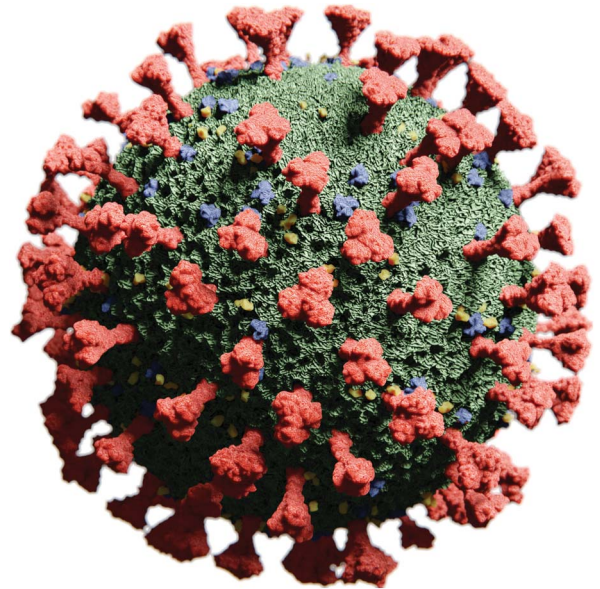
Neurologic complications are increasingly recognized in the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This coronavirus is related to severe acute respiratory syndrome coronavirus (SARS-CoV) and other human coronavirus-related illnesses that are associated with neurologic symptoms. These symptoms raise the question of a neuroinvasive potential of SARS-CoV-2.

Recent Findings

Potential neurologic symptoms and syndromes of SARS-CoV-2 include headache, fatigue, dizziness, anosmia, ageusia, anorexia, myalgias, meningoencephalitis, hemorrhage, altered consciousness, Guillain-Barré syndrome, syncope, seizure, and stroke. In addition, we discuss neurologic effects of other coronaviruses, special considerations for management of neurologic patients, and possible long-term neurologic and public health sequelae.

Summary

As SARS-CoV-2 is projected to infect a large part of the world's population, understanding the potential neurologic implications of COVID-19 will help neurologists and others recognize and intervene in neurologic morbidity during and after the pandemic of 2020.



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Coronavirus disease 2019 (COVID-19) is the first coronavirus to cause a global pandemic,¹ and neurologic problems are increasingly recognized among its complications. The United States now has the highest number of cases worldwide.² Spread of the virus is projected to continue for months.³ COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus that belongs to the sarbecovirus family of betacoronaviruses, together with SARS-CoV. Middle East respiratory syndrome coronavirus (MERS-CoV) belongs to a related family of betacoronaviruses.⁴

Neurologic involvement is documented in SARS-CoV, MERS-CoV, and other coronavirus-related illnesses.⁵⁻⁸ Now as SARS-CoV-2 is projected to infect a large part of the world's population within a short period,³ neurologists should be aware of the neurotropic mechanisms and clinical presentations known in other coronaviruses, the potential short-term neurologic

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effects of COVID-19, the special considerations for management of neurologic patients during the 2020 crisis, and the possible long-term medical and public health sequelae.

Methods

A literature review was conducted on PubMed and Lit-COVID. Search terms included all combinations of “COVID-19,” “SARS-CoV-2,” and “coronavirus” with “neurology,” “neurologic,” and “nervous system.” There were 233 articles published before May 8, 2020, that were identified and reviewed for pertinence and validity. The first author reviewed all articles. Other authors provided critical feedback. A formal systematic review, including review of each article by multiple authors, was not pursued, given the exigencies of the pandemic.

Phylogenetic Review of SARS-CoV-2 and Related Coronaviruses

Coronaviruses are divided into genera by serologic cross-reactivity and then further delineated into lineages. SARS-CoV-2 is a member of the betacoronavirus (group 2 genus) and sarbecovirus lineage (lineage 2). The only other human coronavirus in this lineage is SARS-CoV, which shares 79% genetic sequence identity with SARS-CoV-2.⁹ Features of other betacoronaviruses are listed in table 1. Because the genomic sequence identity in conserved replicase domains (ORF 1ab) is less than 90% between SARS-CoV-2 and all other members of the

betacoronavirus family, SARS-CoV-2 has been denoted as a novel betacoronavirus.⁹

Neurologic Involvement in Other Coronaviruses

Although acute and chronic neurologic diseases in animals have been described in relation to nonhuman strains of coronavirus,¹⁰ reports of neurologic manifestations from human coronaviruses are infrequent (table 2).^{11–18} There are numerous proposed mechanisms for neurologic involvement by coronaviruses in animals and humans.¹⁹ Among the 7 strains of human coronavirus known to be pathogenic, 3 strains have been detected in the CNS: 2 strains responsible for up to 30% of common colds, HCoV-229E, and HCoV-OC43,^{6,20} as well as SARS-CoV.²¹

The clinical respiratory illness in COVID-19 is similar to SARS, and involvement of other organs may also be similar between the 2 diseases.²² The angiotensin-converting enzyme 2 (ACE2) is the portal of entry for both SARS-CoV and SARS-CoV-2.²² ACE2 on neurons was implicated as the entry point of CNS infection by SARS-CoV.²³

In a 2008 mouse study using a selective antibody, ACE2 was found to be widespread on the cardiorespiratory neurons of the brainstem (raphe nuclei, nucleus of the tractus solitarius, and rostral ventrolateral medulla), hypothalamus (paraventricular nucleus), and the subfornical organ, as well as the motor cortex.^{24–26} Human studies using quantitative *in vitro*

Table 1 Neurologically Notable Coronaviruses in Humans and Animals^{e-68}

Coronavirus	Host	Host entry	Reservoir	Site of discovery	Major geographic distribution	Systemic features	Associated neurologic features
SARS-CoV	Human	ACE2	Bats and civets	China	China, Taiwan, Singapore, and Vietnam	Mild to severe respiratory illness	Encephalopathy, seizure, stroke, polyneuropathy, and myopathy
MERS-CoV^{e-69}	Human	DPP4	Bats and camels	Saudi Arabia	Egypt, Oman, Qatar, and Saudi Arabia	Moderate to severe respiratory illness	Encephalopathy, ischemic stroke, and intracerebral hemorrhage
HCoV-OC43	Human	Unknown	Bats and rodents		Global	Mild respiratory illness	ADEM (case report) and acute encephalitis (possible)
HCoV-229E	Human	APN	Bats and camelids		Global	Mild respiratory illness	Encephalitis (possible)
HCoV-NL63^{e-70}	Human	ACE2			Global	Mild respiratory illness	None reported
Mouse hepatitis virus	Mouse					Severe pneumonitis and SARS	Acute encephalitis or chronic demyelinating disease ^{e-7}
Sialodacryoadenitis coronavirus	Rat						Neurologic infection ^{e-71}
Hemagglutinating encephalomyocarditis virus	Pig						Neurologic infection ^{e-71}

Abbreviations: ACE2 = angiotensin-converting enzyme 2; ADEM = acute disseminated encephalomyelitis; APN = aminopeptidase N; DPP4 = dipeptidyl peptidase 4.
MERS-CoV (50% identity with SARS-CoV-2).

Table 2 Neurologic Findings in Case Reports of SARS-CoV, MERS-CoV, and HCoV-OC43

Demographic	Clinical presentation	Neurologic presentation	CSF findings	Neurologic clinical studies	Autopsy findings
SARS-CoV					
32-y-old woman, 26 wk pregnant ³⁸	Fever, myalgias, dry cough, progressed to respiratory and renal failure, extubated day 27	Generalized tonic-clonic convulsions on day 22	+ SARS-CoV RNA, otherwise noninflammatory with 20 RBCs per mm ³	Normal MRI day 46 Normal EEG day 39	Survived
59-y-old woman, IgA nephropathy on peritoneal dialysis ¹⁴	Fever, chills, cough, diarrhea, and respiratory distress	Vomiting and appendicular twitching on hospital day 5	+ SARS-CoV RNA 6,884 copies/mL, ^a otherwise noninflammatory	Normal HCT No MRI or EEG available	Outcome not provided
39-y-old man ¹⁸	Fever, chills, headaches, dizziness, myalgias, treated with ribavirin/steroids for 1 mo, bacterial pneumonia, and ARDS	Obscured monocular vision, dysphoria, delirium, and vomiting after 1 mo	NA	CT showed abnormalities consistent with ischemia or brain edema on day 33 and brain herniation day 35	Viral N protein in glial cells and neurons. Enveloped viral particles compatible with coronavirus in suspended tissue ^b
51-y-old woman ³⁶	Fever, dyspnea, cough, and diarrhea progressed to multiple organ failure and intubation	Distal-predominant 4-limb weakness and leg numbness on day 21	NA	EMG polyradiculoneuropathy	Survived
48-y-old woman ³⁶	Fever, dyspnea, and myalgia progressed to multiple organ failure and intubation	Distal-predominant 4-limb weakness and bilateral finger numbness on day 24	Protein 46 mg/dL, negative SARS-CoV	EMG axonopathic sensorimotor polyneuropathy, recovery by day 92	Survived
42-y-old woman ³⁶	Fever and dyspnea progressed to multiple organ failure and intubation	Distal-predominant 4-limb weakness and left foot numbness on day 25	Protein 15 mg/dL, 0 cells, negative SARS-CoV	CPK 9050; EMG myopathy with asymmetric sensorimotor polyneuropathy (axonopathic); recovery day 87	Survived
31-y-old man ³⁶	Fever, cough, and soft stool	Proximal leg weakness on day 22	NA	EMG myopathy, complete recovery by day 94	Survived
MERS-CoV					
74-y-old man with HTN, DM, and dyslipidemia ^{e-72}	Unclear initial presentation; fever, later had lymphopenia with critically low absolute CD4 and CD8 counts	Confusion, ataxia, and vomiting	Noninflammatory with negative MERS-CoV RT-PCR	MRI multifocal nonenhancing T1 hypo-, T2 hyperintensities, restriction, subcortical gray and white matter	No autopsy
57-y-old man with HTN and DM ^{e-73}	Flu-like illness, myocardial ischemia, pulmonary edema, and gangrenous toe	Bilateral multifocal anterior circulation stroke	NA	CTA near occlusion at origin of both internal carotid arteries, middle cerebral artery narrowing, and no vasculitis	No autopsy
45-y-old man with HTN, chronic kidney disease, and ischemic heart disease ^{e-73}	Fever, respiratory symptoms, diarrhea, pneumonia, and kidney injury	After tracheostomy on hospital day 24, impaired consciousness	Elevated protein, negative MERS-CoV RT-PCR	MRI confluent T2 hyperintensities in bilateral white matter and corticospinal tracts, no enhancement, or restriction	Survived, discharged home day 107

Continued

Table 2 Neurologic Findings in Case Reports of SARS-CoV, MERS-CoV, and HCoV-OC43 (continued)

Demographic	Clinical presentation	Neurologic presentation	CSF findings	Neurologic clinical studies	Autopsy findings
42-y-old woman with obesity and DM^{e-74}	ARDS, lymphopenia, leukopenia, and treated with steroids and antivirals	Diabetes insipidus, then massive intraparenchymal hemorrhage with SAH	Unable due to tonsillar herniation	No aneurysm visualized on CTA	No autopsy
34-y-old woman with DM^{e-73}	ARDS, lymphopenia, inflammation, and DIC	Intracranial hemorrhage on day 14	NA	Head CT with ICH, massive edema, and midline shift	No autopsy
28-y-old man^{e-73}	Fever, ARDS, and bacterial pneumonia	Myalgias, then paraparesis/paresthesia (critical illness)	NA	EMG: length-dependent axonal polyneuropathy Normal spine MRI	Survived
HCoV-OC43					
9 mo old with acute leukemia^{e-75}	Fever and upper airway symptoms	Altered consciousness and myoclonic seizures	Negative CSF	Normal head CT and abnormal brain MRI	Brain tissue positive for HCoV-OC43
11 mo old with combined immunodeficiency⁸	Respiratory infection	Encephalitis	NA		Brain tissue positive for HCoV-OC43
15-y-old man^{e-76}	Upper respiratory symptoms	Ascending numbness and gait difficulty 5 d before hospitalization	+ HCoV-OC43 RNA	MRI of the brain and spine: acute disseminated encephalomyelitis	Survived

Abbreviations: ARDS = acute respiratory distress syndrome; CTA = computed tomography angiogram; DIC = disseminated intravascular coagulation; DM = diabetes mellitus type 2; HTN = hypertension; ICH = intracerebral hemorrhage; NA = not available; SAH = subarachnoid hemorrhage.

^a SARS-CoV RNA was isolated in both CSF and serum at 6,884 and 6,750 copies/mL, respectively.

^b Full autopsy revealed aspergillus pneumonia, neuronal denaturation and necrosis, broad glial cell hyperplasia with gliosome formation, and edema. Immunohistochemistry staining of glial cells and neurons revealed the presence of viral N protein, which was absent in a control specimen. An inflammatory infiltrate of CD68⁺ monocytes/macrophages and CD3⁺ T lymphocytes were also seen by immunohistochemistry. There was no report of electron microscopic examination or the identification of viral particles in brain tissue. A suspension of brain tissue was prepared and inoculated into cell culture, which produced enveloped viral particles compatible with coronavirus when examined by transmission electron microscopy.

autoradiography have shown ACE2 on neurons and glia in the hypothalamus, midbrain, pons, cerebellum, medulla oblongata, and basal ganglia,²⁷ although the enzyme's distribution in the human CNS is not as well characterized as in mice.²⁸

ACE2 is also found on endothelial cells.²⁹ Endothelial involvement in the brain could theoretically also lead to blood-brain barrier (BBB) disruption, such as that found in hypertension³⁰ and a proinflammatory state.³¹

In mouse models, there is immunohistochemical evidence of SARS-CoV and MERS-CoV CNS invasion, especially in the brainstem.^{32–34} In an underpowered human autopsy study, in situ hybridization confirmed the presence of viral RNA of HCoV-229E and HCoV-OC43 strains in brain bank samples of 14 of 39 (36%) patients with multiple sclerosis (MS) and in 7 of 51 (14%) controls (25 normal controls and 26 patients with other neurologic diseases).⁶

In the pediatric population, HCoVs have been associated with clinical neurologic disease. In a single-center Chinese study, IgM antibodies to HCoV were found in the CSF of 12% of hospitalized children with encephalitis over a 1-month period.¹⁷ Rare case reports suggest a link to fatal encephalitis and acute disseminated encephalomyelitis (table 2).

The SARS-CoV epidemic in 2003 tallied over 8,000 infections and 700 deaths. Case reports of neurologic illness in SARS-CoV (table 2) include central and peripheral nervous system manifestations—delirium, reduced level of consciousness,^{14,18} seizures,^{12,18} stroke, myopathy,^{11,35} neuropathy,³⁶ and striated muscle vasculitis.³⁷

MERS-CoV has not been isolated from CSF or postmortem brain specimens among approximately 2,500 laboratory-confirmed cases, but there are 6 patients described with neurologic illness following an intensive care unit (ICU) course (table 2).

Another autopsy study from 8 confirmed SARS cases found evidence of SARS-CoV genetic material in the brain by in situ hybridization, electron microscopy, and RT-PCR.³⁸ The signals were confined to the cytoplasm of numerous neurons in the hypothalamus and cortex. Edema and scattered red degeneration of the neurons were present in the brains of 6 of the 8 confirmed cases of SARS. SARS viral sequences and pathologic changes were not present in the brains of unconfirmed cases or 6 age-matched head trauma control cases. The report does not specify if any of the 8 SARS cases manifested neurologic symptoms during their acute illness. Importantly, edema and acidophilic neuronal degeneration are nonspecific markers of acute neuronal injury³⁹—there was no reported evidence of direct pathologic effects of SARS-CoV. This study, therefore, does not confirm whether the genomic sequences detected are indicative of direct viral invasion, virus-related brain injury, or an incidental secondary phenomenon.

Weaknesses of these studies include limited or inconsistent information about autopsy, inconsistent neuroimaging evidence of cerebral injury, comorbid conditions, and morbidities of intensive care treatment that are known to cause neurologic events. Many questions arise about the role of immunosuppression in these cases: did steroids alone or in combination with SARS-associated lymphopenia facilitate neuroinvasion? Was the patient with autoimmune history receiving immunosuppressive treatment? In addition, end-stage renal disease requiring dialysis may have contributed to an underlying immunosuppressed state.

Mechanisms of CNS Injury by Coronaviruses and Other Infections and Implications for SARS-CoV-2

HCoVs have proven capable of using at least 3 pathways for direct viral entry into the CNS¹⁵—some of these may be relevant to SARS-CoV-2 (table 3).

First, direct inoculation of the olfactory bulb through the cribriform plate may be one mechanism for the introduction of the virus into the CNS.^{32,e-8} Direct intranasal inoculation of SARS-CoV in mice induced widespread SARS-CoV neuronal infection in areas with first- or second-order connections with the olfactory bulb within 7 days. After inoculation, transneuronal spread was the likely mechanism for further viral infection.³² In a 1990 study, ablation of the olfactory bulb prevented the spread of the mouse hepatitis virus type 3 coronavirus (MHV) on nasal inoculation.⁴⁰ Moreover, low doses of MERS-CoV introduced intranasally in mice resulted only in CNS infection, and spared other organs in mice, providing indirect evidence for neurotropism.³⁴

In COVID-19, small studies are showing high rates of self-reported anosmia, and also ageusia (perhaps due to involvement of gustatory receptors), often without rhinorrhea or nasal congestion.^{e-1–e-3} Olfactory and gustatory dysfunction may be independent and persistent symptoms even as they are highly correlated in incidence (table 4). Whether the presence of these symptoms indicates transnasal spread and portends a mechanism that causes greater neurologic disease requires further study.

Second, in pigs and birds, after infection of peripheral nerve terminals through oronasal inoculation, CNS invasion may also occur by retrograde synaptic transmission through sensory nerves and ganglia. Trans-synaptic transfer has been documented in other coronavirus animal models such as swine hemagglutinating encephalomyelitis virus (where eventual brainstem infection was first detected in the trigeminal and vagal sensory nuclei) and avian bronchitis virus.^{e-4}

In a 2015 study of MHV in mice, BBB invasion by coronaviruses correlated with virus-induced disruption of tight junctions on brain microvascular endothelial cells. This led to BBB dysfunction and enhanced permeability.^{e-5} When MHV

Table 3 Potential Mechanisms for Neurologic Injury in COVID-19

Routes of direct CNS viral invasion ^{32,e-77}
Peripheral nerve infection (e.g., direct intranasal inoculation, mechanoreceptors and chemoreceptors in the lung and lower respiratory airways, perhaps oropharyngeal)
Olfactory receptor neuron infection through direct inoculation
Retrograde trans-synaptic transmission after infection of the peripheral nerve
Direct CNS neuronal entry
BBB disruption and infection of microvascular endothelial cells following viremia
Infection of circulating leukocytes ³⁸ that traffic the virus across the BBB (Trojan horse entry)
Indirect mechanisms for neuronal injury
Systemic inflammation (includes hypercoagulable state and cytokine storm)
Endothelial invasion, injury, and thrombosis
Hypoxic-anoxic brain injury after cardiorespiratory failure
CNS demyelination

Abbreviation: BBB = blood-brain barrier.

is directly inoculated into the CNS, proinflammatory cytokines and chemokines surge. Neutrophils, natural killer cells, and monocyte/macrophages rapidly migrate to the CNS, secreting matrix metalloproteinases to permeate the BBB. Virus-specific T cells infiltrate the CNS; oligodendroglia are primary targets of infection. Importantly, the virus becomes undetectable in the CSF 2 weeks postinfection, but persists mainly in white matter tracts. As a result of this largely immune-mediated response, animals develop demyelinating lesions within the brain and spinal cord that are associated with clinical manifestations, including awkward gait and hindlimb paralysis.^{e-6-e-8} Although SARS-CoV-2 has not yet been identified in CNS endothelium, viral particles were found on electron microscopy in renal endothelial cells of 1 patient with a remote history of renal transplant; the 2 others in the series had systemic endotheliitis but no viral particles.^{e-9}

Acute infections may be a trigger for stroke due to increased inflammation and consequent thrombosis.^{e-10-e-12} In analyses from the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities study, recent hospitalization for infection was associated with an increased risk of stroke.^{e-13} In CHS, among 669 participants who experienced a stroke, the risk of stroke increased following hospitalization for infection within the previous 30 days (odds ratio 7.3, 95% confidence interval 1.9–40.9). A population-based cohort study from Denmark showed that ~80% of cardiovascular events after exposure to bacteremia occurred

during the index hospitalization, with the risk of stroke highest in the first 3–15 days postinfection.^{e-14} Even influenza and minor respiratory and urinary tract infections are associated with increased stroke risk, and vaccinations may help prevent stroke.^{e-12,e-15} A Cochrane review of 8 randomized controlled trials (12,029 participants) provides evidence that influenza vaccination decreased cardiovascular outcomes, and a case series study found that the risk of stroke was increased after respiratory tract infection and was reduced after vaccination against influenza, pneumococcal infection, and tetanus.^{e-16} Research with administrative data has also identified sepsis as a stroke trigger, although the absolute risk is low.^{e-12}

Some critically ill patients with COVID-19 experience a systemic inflammatory response syndrome (cytokine storm) that may lead to endothelial dysfunction^{e-17}—a known risk factor for thromboembolic events.^{e-18} Many systemic markers of proinflammatory activation are elevated, including multiple cytokines. For example, peripheral tumor necrosis factor- α , a key upstream mediator of the systemic inflammatory response, and interleukin-6 (IL-6), a key driver of the acute-phase response, are higher in more severe COVID-19.^{22,e-19}

IL-6 is critically involved in thromboinflammatory activation, and elevated concentrations may therefore drive a prothrombotic state. Perturbations to the thrombosis-coagulation pathways have also been reported. Disruption to both anticoagulant (e.g., reduced antithrombin and elevated lupus anticoagulant) and procoagulant/thrombotic (increased fibrinogen, D-dimer, and increased prothrombin time) pathways is reminiscent of disseminated intravascular coagulation (table 4).^{e-20} In a case series of 5 COVID-19 skin and lung biopsies, thrombotic microvascular injury was associated with extensive complement activation.^{e-21}

There have been several reports of acute myopericarditis and other cardiac complications with SARS-CoV-2^{e-22} and SARS-CoV,^{e-23} which, combined with hypercoagulability, could also lead to stroke as a consequence of cardiac arrhythmia and dysfunction causing cardiac embolism.

In summary, neurologic effects of coronaviruses including SARS-CoV-2 may be triggered by direct cytopathic effects of the virus, secondary effects of severe pulmonary infection, the systemic inflammatory response (cytokine storm), or a combination of these.

Clinical Neurologic Findings in COVID-19

Reports of early and mild neurologic symptoms of COVID-19 differ in both symptom classification and incidence despite most of them being reported from hospitalized cohorts; the most commonly reported symptoms are headache, mild confusion, dizziness, myalgias, fatigue, anorexia, anosmia, and ageusia (table 4). Many of these reported symptoms are

Table 4 Neurologic Findings in Case Reports and Case Series of Systemic SARS-CoV-2 Infection (COVID-19)

Possible neurologic symptom	N	% of cohort	Comment	Region
Early and mild neurologic symptoms				
Hyposmia/anosmia	357	85.6	Mild-to-moderate patients, questionnaire response, ~10 d postonset	Western Europe ^{e-2}
	44	61.1	25% hospitalized, 75% outpatients	Italy ^{e-78}
	11	5.1	Hospitalized patients	China ^{e-27}
	1	~40-y-old woman with	anosmia, cough, headache, and without ageusia; MRI: inflammation of olfactory clefts	France ^{e-79}
	12	5.6	Hospitalized patients	China ^{e-27}
Hypogeusia/ageusia	342	88.8	Mild-to-moderate patients, questionnaire response	Western Europe ^{e-2}
	39	54.2	25% hospitalized, 75% outpatients	Italy ^{e-78}
Fatigue/malaise/asthenia	418	38.0	Hospitalized patients	China ^{e-80}
	69	26.3	Hospitalized, mainly mildly ill patients	China ^{e-81}
	48	66.7	25% hospitalized, 75% outpatients, ~19 d postonset	Italy ^{e-78}
	18	34.6	Critically ill hospitalized patients	China ^{e-82}
Headache	150	13.6	Hospitalized patients	China ^{e-80}
	30	41.7	25% hospitalized, 75% outpatients, ~19 d postonset	Italy ^{e-78}
	28	13.1	Hospitalized patients	China ^{e-27}
	17	6.5	Hospitalized, mainly mildly ill patients	China ^{e-81}
	9	6.5	Hospitalized patients	China ^{e-83}
	3	7.9	Hospitalized patients	China ²²
	3	5.8	Critically ill hospitalized patients	China ^{e-82}
Anorexia	55	39.9	Hospitalized patients	China ^{e-83,a}
Dizziness	36	16.8	Hospitalized patients	China ^{e-27}
	13	9.4	Hospitalized patients	China ^{e-83}
Myalgia + fatigue + arthralgia	48	34.8	Hospitalized patients	China ^{e-83}
	6	11.5	Critically ill hospitalized patients	China ^{e-82}
	18	43.9	Hospitalized patients	China ²²
	164	14.9	Hospitalized patients	China ^{e-80}
Nerve pain	5	2.3	Hospitalized patients	China ^{e-27}
More severe neurologic symptoms (partial table, see appendix e-1)				
Post-ARDS encephalopathy	26	65.0	MRI: 11/13 bifrontotemporal perfusion abnormalities, 8/13 leptomeningeal enhancement; CSF: 2/7 OCBs, 1/7 elevated immunoglobulins and protein, no SARS-CoV-2; EEG: only 1/8 diffuse bifrontal slowing	France ^{e-84}
Impaired consciousness	16	7.5	Hospitalized patients	China ^{e-27}
Muscle injury	23	10.7	Hospitalized patients	China ^{e-27}
Stroke	13	5.9	3 small vessel occlusions, 5 large vessel stenosis, and 3 cardioembolic, 1 cerebral venous thrombosis, 1 hemorrhage (onset ~10 d)	China ^{e-28}
	6	2.8	Hospitalized patients (5.7% in severe infections vs 0.8% in nonsevere infections)	China ^{e-27}
	3	3.7	Arterial ischemic strokes (cumulative incidence)	The Netherlands ^{e-47}

Continued

Table 4 Neurologic Findings in Case Reports and Case Series of Systemic SARS-CoV-2 Infection (COVID-19) (continued)

Possible neurologic symptom	N	% of cohort	Comment	Region
	6	53–85 y old, 6/6 large vessel occlusions (3 multiterritory infarcts, 2 concurrent venous thromboses, 2 ischemic strokes despite therapeutic anticoagulation), D-dimer levels $\geq 1,000$ $\mu\text{g/L}$ (onset 0–24 d)		United Kingdom ^{e-85}
	5	33–49 y old, 5/5 large vessel occlusions, 3/5 with elevated fibrinogen, D-dimer, and ferritin (onset 0 y)		New York ^{e-86}
	4	73–88 y old, 1 embolic, 2 large vessel stenosis, 1 internal carotid occlusion (onset 0–2 d)		New York ^{e-87}
	4	45–77 y old, 2 suspected large vessel stenosis and 2 small vessel occlusions on MRI, 3/4 elevated D-dimer, 2/4 elevated CRP, 1/4 elevated ferritin, none critically ill (onset 1–4 d)		Turkey ^{e-88}
	3	65–70 y old, multiple bilateral cerebral infarcts and ARDS (onset 10–33 d) ^b		China ^{e-89}
Guillain-Barré syndrome (partial list, continued in appendix e-1)	5	23–77 y old, EMG: 3/5 axonal, 2/5 demyelinating; 2/5 antiganglioside Ab, CSF: 3/5 albuminocytologic dissociation, no SARS-CoV-2; MRI: 2 caudal and 1 facial nerve enhancement (onset 5–10 d)		Italy ^{e-90}
	1	61-y-old woman, EMG: demyelinating neuropathy; CSF: protein 124 mg/dL, 5 cells/ μL (presenting symptom, 4 d after visiting endemic region)		China ^{e-91}
	1	65-y-old man, EMG: motor-sensory axonal neuropathy; MRI: negative (onset ~2+ wk)		Iran ^{e-92}
	1	71-y-old man, EMG: acute polyradiculoneuritis with prominent demyelination; CSF: protein 54 mg/dL, 9 cells/ μL , no SARS-CoV-2 (onset day 8)		Italy ^{e-93}

Abbreviations: ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; ICU = intensive care unit; Ig = immunoglobulin; OCB = oligoclonal band. The remainder of the more severe neurologic symptoms (Miller-Fisher syndrome, polyneuritis cranialis, syncope, recrudescence, seizure, ataxia, meningoencephalitis, hemorrhage, and possible demyelination) are listed in appendix e-1 (links.lww.com/CPJ/A183).

e-References related to this article can be accessed at links.lww.com/CPJ/A184.

^a Anorexia was reported in 55 (39.9%), of which 66.7% required ICU care vs 30.4% non-ICU care. Nineteen patients with nausea and vomiting (13.7%), without the skew in distribution of those requiring ICU care vs non-ICU care.

^b All had elevated prothrombin time, fibrinogen concentrations, D-dimer, IgA anticardiolipin antibody, and IgA/G anti- β -glycoprotein I antibodies, but not lupus anticoagulant. The authors concluded that the multiple cerebral infarcts were related to secondary antiphospholipid syndrome, although all patients were older and had conventional vascular risk factors, and other potential explanations (e.g., findings of atrial fibrillation or cerebral vasculitis) were not reported.

nonspecific, found in many viral illnesses, and may or may not indicate CNS involvement.

For example, although robust evidence for anosmia and ageusia is lacking, the American Academy of Otolaryngology–Head and Neck Surgery has established a COVID-19 Anosmia Reporting Tool for Clinicians,^{e-24} as data emerge.^{e-25,e-26} In contrast to low rates of anosmia and ageusia in hospitalized or critically ill patients, 2 retrospective studies of only patients with mild-to-moderate COVID-19 report high rates of olfactory and gustatory impairment of over 68%–80%.^{e-1,e-2} Although there may be substantial selection bias in the questionnaire response, these symptoms may be more prominent or more acknowledged in milder disease.

SARS-CoV-2 is associated with more serious neurologic complications including ischemic stroke, intracerebral hemorrhage, encephalopathy, Guillain-Barré syndrome, meningoencephalitis, syncope, seizures, possible demyelination, and recrudescence of prior strokes, seizure syndromes, or MS pseudorelapse (table 4).

In a series of 214 from Wuhan, China, ~40% of patients had at least 1 comorbidity that increased the risk of stroke, such

as hypertension, cardiovascular disease, diabetes, or cancer. Patients with stroke had higher D-dimer levels compared with both those with severe non-CNS symptoms and those with nonsevere CNS symptoms. Although milder neurologic symptoms occurred within 1–2 days of symptom onset, the mean onset of stroke and impaired consciousness was 8–10 days into the illness.^{e-27} Other case series have reported stroke onset within 0–4 days (table 4).

Among 13 patients with stroke in a Wuhan series, there were 3 small vessel, 5 large vessel, and 3 cardioembolic strokes, as well as 1 cerebral venous thrombosis and 1 hemorrhage.^{e-28} This suggests that the mechanism of stroke is likely not specific to a particular pathophysiologic feature of the SARS-CoV-2 virus, but rather the result of nonspecific effects of inflammation, and endothelial and coagulation dysfunction, likely superimposed on preexisting risk factors.

Although systemic inflammation from infectious disease is a recognized stroke risk factor, as discussed above, large studies on other viruses such as influenza A show only a 1% incidence of stroke over a period of 45 days.^{e-12} In acute respiratory distress syndrome (ARDS) intensive care

patients, patients treated with standard-of-care mechanical ventilation (with referral to venovenous extracorporeal membrane oxygenation [ECMO] for refractory cases) developed only 5% ischemic stroke and 2%–4% hemorrhagic stroke events.^{e-29}

The causes of common neurologic symptoms in critical illness may include drug-induced paralysis, hypotension, ECMO, concomitant superinfections, profound changes in systemic thromboinflammation/immune cellular function, and extended immobility. Profound multiorgan involvement of COVID-19 may multiply intensive care issues contributing to delirium.^{e-30} Of 113 deceased patients with COVID-19 in 1 series, 23 (20%) had hypoxic encephalopathy.^{e-31} Chinese brain autopsies show endovasculitis, endothelial damage, cerebral edema, hyperemia, and neurodegeneration with SARS-CoV-2^{e-32}—many of these findings could also be attributed to critical illness as discussed earlier. To understand the neurologic role of SARS-CoV-2 in critically ill patients with COVID-19, further data are needed on the frequency of neurologic complications of critical illness, such as thrombosis, critical illness myoneuropathy, and cerebral hypoperfusion. For example, the American Heart Association’s Get With The Guidelines COVID-19 registry will add an urgent module designed to capture nation-wide data on the cardiovascular and neurologic effects of COVID-19.^{e-33}

At-risk Neurologic Patients

As suggested by coronavirus mechanisms of neurologic injury, there is potential for some neurologic patients to be at increased risk for further morbidity (table 5). Patients with preexisting BBB compromise may be at higher risk. Stroke-induced suppression of the innate and adaptive immune systems, mediated by dysregulation of the autonomic nervous system, is well described^{e-34} and may increase susceptibility to, and severity of, SARS-CoV-2 infection in the acute phase of stroke and therefore worsen clinical outcomes. Another potential risk of infection is the dementia-related behaviors that may make it difficult for patients to comply with key infection prevention measures (e.g., remembering to wash hands).^{e-35}

Given the susceptibility of patients with respiratory comorbidities to COVID-19, some neurologic patients may be more susceptible to COVID-19–related morbidity due to underlying respiratory compromise in preexisting neuromuscular disease,^{e-36} major stroke,^{e-18} and advanced neurodegeneration. For example, in hemispheric stroke, cough, expiratory muscle function and functional residual capacity are impaired.^{e-37,e-38} Other neurologic patients with frequent cardiac comorbidities, such as patients with Parkinson disease, may also be at higher risk, although there is no evidence that Parkinson disease or other movement disorders decrease chance of survival when compared with otherwise similar patients.^{e-39} As seen with other infections, patients with chronic deficits having COVID-19 may have recrudescence or worsening of their neurologic symptoms, including seizure, MS pseudorelapse, or residual from stroke.^{e-40}

Table 5 COVID-19 Considerations for Specific Neurologic Patients

Preexisting neurologic condition	Possible considerations to be addressed
Structural lesions	Decreased seizure threshold, recrudescence
Neuromuscular respiratory compromise, diaphragmatic weakness	Worse outcome with COVID-19 respiratory symptoms
Myasthenia gravis	Respiratory compromise with contraindicated medications (hydroxychloroquine/azithromycin)
Neuroinflammatory and autoimmune disorders	Discussions with patients about immunomodulatory medications
Acute stroke	Hospital shortages limiting staffing/ utilization of advanced interventional mechanisms
	Reluctance to present urgently to hospital during pandemic
	Recognizing prothrombotic state of COVID-19
Dementia	Possible increased risk of infection (e.g., difficulty following strict hand hygiene)
	Susceptibility to postinfectious delirium

Immunosuppressed patients have been specifically cautioned about COVID-19,^{e-41} although clear data regarding their risk are not yet available. Clinicians and patients are already weighing these advisories when deciding on standard-of-care treatments;^{e-42} the data remain controversial.^{e-43–e-46}

Thromboembolic disease is common in COVID-19. Deep venous thrombosis was confirmed in 27% of 184 COVID-19 ICU patients (of which pulmonary embolism was 81%), despite prophylaxis.^{e-47} Traditional contraindications to anticoagulant therapy, such as a prolonged activated partial thromboplastin time (aPTT), may not be as helpful in patients with COVID-19 in whom prolonged aPTT and lupus anticoagulant may be seen.^{e-48} Neurologists and intensivists will need to carefully weigh the benefits of antithrombotic therapies against the risks of intracerebral hemorrhage.

Although staging models of clinical COVID-19 disease progression warrant consideration of neurologic involvement,^{e-49} the realities of sterilization and staffing of head imaging studies during a pandemic are restrictive and may limit neurologic investigations in patients with COVID-19 who have severe cardiopulmonary complications.

Finally, widespread social isolation policies may be restricting neurologic patient access to specialist care, with widespread closures of outpatient neurology offices. As the case fatality rate of COVID-19 for elderly patients with dementia is 3-11x that of patients in their 50s,^{e-50} patients with dementia may

be disproportionately affected by stringent restrictions aimed at protecting the highest COVID-19 risk group.

Longer-term Neurologic Implications of COVID-19

It remains unknown whether SARS-CoV-2 will cause longer-term neurologic morbidity. It is important to consider whether widespread recovered COVID-19 in our population will be a risk factor for other neurologic sequelae.

Psychiatric disease and fatigue may occur in severe COVID-19 survivors, as was reported after SARS. For example, 63% of SARS survivors from a Hong Kong hospital responded to a survey a mean 41 months after recovery; over 40% had active psychiatric illness, 40% complained of chronic fatigue, and 27% met the 1994 diagnostic criteria for Chronic Fatigue Syndrome. In another small study of 22 SARS survivors who were unable to return to work mainly as health care workers, symptoms closely overlapped with chronic fibromyalgia (chronic fatigue, pain, weakness, depression, and sleep disturbance).¹³

Longer-term stroke risk factors may also be elevated after severe coronavirus infection.^{e-22} For example, in a 12-year follow-up study of 25 patients infected with SARS-CoV and treated with methylprednisolone vs 25 healthy controls (average age 47 years, body mass index 24 kg/m²), 68% vs 40% reported hyperlipidemia, 60% vs 16% reported glucose metabolism disorder, and 44% vs 0% reported cardiovascular system abnormalities.^{e-51} Mechanisms for these increased prevalences are uncertain.

Infection is a risk factor for decreased cognitive function, both acutely and over time. In addition, a dose response with severity of infection has been associated with accelerated cognitive decline.^{e-52} Common infections such as upper respiratory tract infections, pneumonia, periodontal infections/inflammation, and general infections, particularly concurrent infections, are also associated with an increased risk of Alzheimer disease and related dementias.^{e-53-e-61} Sepsis survivors showed not only cognitive deficits in verbal learning and memory but had reduction of left hippocampal volume compared with healthy controls.^{e-62} Seventy percent to 100% of ARDS survivors had cognitive impairment at discharge—46%–80% 1 year later—and worse impairment correlated with ARDS severity.^{e-63} Cognitive and behavioral impairment after COVID-19 may warrant study.

Finally, ongoing and planned critical trials of neurodegenerative and non-life-threatening chronic neurologic disorders are being paused to keep elderly and vulnerable patients away from hospitals, which could have implications for those trials as well as advances in neurodegeneration research.

Implications for Pediatric Neurology

Implications for pediatric neurology remain very uncertain; just 2 case reports suggest COVID-19–associated paroxysmal

events in infants (table 4).^{e-64} Coronavirus HCoV-OC43 was detected in the CSF of a child presenting with acute demyelinating encephalomyelitis.¹⁶ Although other pediatric viral infections were associated with a higher incidence of diseases such as MS, there is insufficient evidence to make the same assertion about coronaviruses.^{7,17,e-65} Rare neurologic complications of medium-vessel vasculitis have also occurred in the past,^{e-66} and now a case of Kawasaki disease after COVID-19 has been reported.^{e-67} Because the outcomes of COVID-19 seem to be more favorable in many children, it will be difficult to estimate the potential role of coronavirus infection in long-term pediatric neurologic health.

SARS-CoV-2 is associated with several neurologic symptoms and syndromes including headache, fatigue, anosmia, ageusia, anorexia, myalgias, asthenia, meningitis, Guillain-Barré syndrome, altered consciousness, syncope, and stroke. Understanding the potential neurologic implications of COVID-19, and lessons from previous experience with coronaviruses, will help neurologists and others recognize and intervene in neurologic morbidity during and after the pandemic of 2020. It is difficult to fully separate the direct neurologic effects of COVID-19 from the secondary neurologic complications of critical systemic illness, but both issues need to be considered, given the overwhelming spread of COVID-19.

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TAKE-HOME POINTS

- Diverse neurologic manifestations and long-term neuropsychiatric sequelae have been reported in infections with numerous previously known coronaviruses.
- Potential neurologic complications of COVID-19 include headache, fatigue, dizziness, anosmia, ageusia, anorexia, myalgias, meningoencephalitis, hemorrhage, altered consciousness, Guillain-Barré syndrome, syncope, seizure, and stroke.
- Mechanisms of neurologic disease may be similar to other coronaviruses, especially to SARS-CoV, which is phylogenetically most similar and enters cells through the same protein, angiotensin-converting enzyme 2.
- Postulated mechanisms of neurologic damage from other coronaviruses suggest the possibility of systemic disease sequelae (including inflammation, thrombosis, and hypoxia), direct neuroinvasiveness (although neurotropism has never been definitively shown), peripheral nervous system and muscle involvement, and possible immune-mediated para- and postinfectious effects.
- In neurologic patients, special consideration is needed for compliance with hygiene and social distancing, COVID-19 symptom identification, stroke management, and comorbidity management.

Appendix Authors

Name	Location	Contribution
Anna S. Nordvig, MD	Columbia University, The New York Presbyterian Hospital	Designed and conceptualized the article; interpreted the data; and drafted the manuscript for intellectual content
Kathryn T. Fong, MD	Columbia University, The New York Presbyterian Hospital	Interpreted the data and significant role in revising the manuscript for intellectual content
Joshua Z. Willey, MD, MS	Columbia University, The New York Presbyterian Hospital	Interpreted the data and revised the manuscript for intellectual content
Kiran T. Thakur, MD	Columbia University, The New York Presbyterian Hospital	Interpreted the data and revised the manuscript for intellectual content
Amelia K. Boehme, PhD, MSPH	Columbia University, The New York Presbyterian Hospital	Interpreted the data and revised the manuscript for intellectual content

Appendix (continued)

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Wendy S. Vargas, MD	Columbia University, The New York Presbyterian Hospital	Interpreted the data and revised the manuscript for intellectual content
Craig J. Smith, MBChB, MD, MRCP	University of Manchester, United Kingdom	Interpreted the data and revised the manuscript for intellectual content
Mitchell S.V. Elkind, MD, MS	Columbia University, The New York Presbyterian Hospital	Provided supervision and funding; interpreted the data; and major role in revising the manuscript for intellectual content

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