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DOI:
10.1212/CPJ.0000000000000897

Document Version
Accepted author manuscript

Neurology®
Clinical Practice

A peer-reviewed clinical neurology journal for the practicing neurologist
An Official Journal of the American Academy of Neurology

NEURCLINPRACT

DOI: 10.1212/CPJ.0000000000000897

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Neurology® Clinical Practice Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes. Videos ,if applicable, will be available when the article is published in its final form.

Submission Type: Article

Title Character count: 49

Number of Tables: 5

Number of Figures: 0

Word count of Abstract: 205

Word count of Paper: 3487

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A. Nordvig reports no disclosures relevant to the manuscript.

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K. Thakur reports no disclosures relevant to the manuscript.

A. Boehme reports no disclosures relevant to the manuscript.

W. Vargas reports no disclosures relevant to the manuscript.

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M. Elkind reports no disclosures relevant to the manuscript.

Study Funding:

Anna S. Nordvig is supported by NINDS 5T32 NS007153 (PI Elkind), and the Charles and Ann Lee Brown Fellowship.

Kiran T. Thakur is supported by NIH 1K23NS105935-01.

Amelia K. Boehme is supported by NINDS NIH R03 NS101417 and NINDS NIMHD R21 MD012451.

Craig J. Smith is supported by the University of Manchester and Salford Royal NHS Foundation Trust, and has received funding from NIHR, MRC and the Leducq Foundation.

Mitchell Elkind is supported by the National Institute of Neurological Disorders and Stroke and the Leducq Foundation.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsoring institutions.

Abstract

Purpose of review: Neurological 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 neurological symptoms. These symptoms raise the question of a neuroinvasive potential of SARS-CoV-2.

Recent findings: Potential neurological 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. Additionally, we discuss neurological effects of other coronaviruses, special considerations for management of neurological patients, and possible long-term neurological and public health sequelae.

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

Summary box: Take-home points

- Diverse neurological manifestations and long-term neuropsychiatric sequelae have been reported in infections with numerous previously-known coronaviruses.
- Potential neurological 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 neurological 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 neurological 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 post-infectious effects.
- In neurological patients, special consideration is needed for compliance with hygiene and social distancing, COVID-19 symptom identification, stroke management, and comorbidity management.

Introduction

Coronavirus disease 2019 (COVID-19) is the first coronavirus to cause a global pandemic,[1] and neurological 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 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Middle East respiratory syndrome coronavirus (MERS-Co) belongs to a related family of betacoronaviruses.[4]

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

Methods

A literature review was conducted on PubMed and LitCOVID. Search terms included all combinations of "COVID-19," "SARS-CoV-2," and "coronavirus" with "neurology," "neurological," and "nervous system." There were 233 papers published before May 8, 2020 that were identified and reviewed for pertinence and validity. The first author reviewed all papers. Other authors provided critical feedback. A formal systematic review, including review of each paper 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, 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 is 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]

Neurological involvement in other coronaviruses

While acute and chronic neurological diseases in animals have been described in relation to non-human strains of coronavirus,[10] reports of neurological manifestations from human coronaviruses are infrequent (Table 2).[11-18] There are numerous proposed mechanisms for neurological involvement by coronaviruses in animals and humans.[19] Among the seven strains of human coronavirus known to be pathogenic, three strains have been detected in the central nervous system (CNS): two 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 two 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 cardio-respiratory 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* 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 hypertension [30] and a pro-inflammatory 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%) multiple sclerosis (MS) patients, and in 7 of 51 (14%) controls (25 normal controls, 26 patients with other neurological diseases).[6]

In the pediatric population, HCoVs have been associated with clinical neurological disease. In a single-center Chinese study, IgM antibodies to HCoV were found in the cerebrospinal fluid (CSF) of 12% of hospitalized children with encephalitis over a one-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 neurological 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 post-mortem brain specimens among approximately 2500 laboratory-confirmed cases, but there are 6 patients described with neurological 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 six of the eight confirmed cases of SARS. SARS viral sequences and pathological 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 neurological symptoms during their acute illness. Importantly, edema and acidophilic neuronal degeneration are nonspecific markers of acute neuronal injury[39] – there was no reported evidence of direct pathological 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 neurological 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? Additionally, 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 three pathways for direct viral entry into the CNS[15] – some of these may be relevant to SARS-CoV-2 (See 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,ref 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) upon 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.[ref e-1,2,3] 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 neurological 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.[ref e-4]

In a 2015 study of MHV, 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.[ref e-5] When MHV 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 two weeks post-infection, 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.[ref e-6,7,8] Although SARS-CoV-2 has not yet been identified in CNS endothelium, viral particles were found on electron

microscopy in renal endothelial cells of one patient with a remote history of renal transplant; the two others in the series had systemic endotheliitis but no viral particles.[ref e-9]

Acute infections may be a trigger for stroke due to increased inflammation and consequent thrombosis.[ref e-10,11,12] In analyses from the Cardiovascular Health Study and the Atherosclerosis Risk in Communities study, recent hospitalization for infection was associated with an increased risk of stroke.[ref 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 (OR) 7.3, 95% CI 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 to 15 days post infection.[ref e-14] Even influenza and minor respiratory and urinary tract infections are associated with increased stroke risk, and vaccinations may help prevent stroke.[ref e-12,15] A Cochrane review of eight 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.[ref e-16] Research with administrative data has also identified sepsis as a stroke trigger, though the absolute risk is low.[ref e-12]

Some critically ill COVID-19 patients experience a systemic inflammatory response syndrome ("cytokine storm") that may lead to endothelial dysfunction[ref e-17]– a known risk factor for thromboembolic events.[ref e-18] Many systemic markers of pro-inflammatory activation are elevated, including multiple cytokines. For example, peripheral tumor necrosis factor (TNF)-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,ref e-19]

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

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

In summary, neurological 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 neurological findings in COVID-19

Reports of early and mild neurological 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 (See Table 4). Many of these reported symptoms are non-specific, 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,[ref e-24] as data emerges.[ref e-25,26] In contrast to low rates of anosmia and ageusia in hospitalized or critically ill patients, two retrospective studies of only mild to moderate COVID-19 patients report high rates of olfactory and gustatory impairment of over 68-80%.[ref e-1,2] While 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 neurological complications including ischemic stroke, intracerebral hemorrhage, encephalopathy, Guillain-Barré Syndrome, meningoencephalitis, syncope, seizures, possible demyelination, and recrudescence of prior strokes and seizure syndromes (Table 4).

In a series of 214 from Wuhan, China, ~40% of patients had at least one co-morbidity that increased 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 non-severe CNS symptoms. While milder neurological symptoms occurred within 1-2 days of symptom onset, mean onset of stroke and impaired consciousness was 8-10 days into the illness.[ref e-27] Other case series have reported stroke onset within 0-4 days (Table 4).

Among thirteen stroke patients 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.[ref e-28] This suggests that the mechanism of stroke is likely not specific to a particular pathophysiological feature of the SARS-CoV-2 virus, but rather the result of non-specific effects of inflammation, and endothelial and coagulation dysfunction, likely superimposed on pre-existing risk factors.

While 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 time period of 45 days.[ref e-12] In 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.[ref e-29]

The causes of common neurological symptoms in critical illness may include drug-induced paralysis, hypotension, ECMO, concomitant super-infections, profound changes in systemic thrombo-inflammation/ immune cellular function and extended immobility. Profound multi-organ involvement of COVID-19 may multiply intensive care issues contributing to delirium.[ref e-30] Of 113 deceased COVID-19 patients in one series, 23 (20%) suffered hypoxic encephalopathy.[ref e-31] Chinese brain autopsies show endovasculitis, endothelial damage, cerebral edema, hyperemia, and neurodegeneration with SARS-CoV-2[ref e-32] — many of these findings could also be attributed to critical illness as discussed earlier. To understand the neurological role of SARS-CoV-2 in critically ill COVID-19 patients, further data is needed on the frequency of

neurological 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 neurological effects of COVID-19.[ref e-33]

At-risk neurological patients

As suggested by coronavirus mechanisms of neurological injury, there is potential for some neurological patients to be at increased risk for further morbidity (see 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[ref 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).[ref e-35]

Given the susceptibility of patients with respiratory comorbidities to COVID-19, some neurological patients may be more susceptible to COVID-19-related morbidity due to underlying respiratory compromise in pre-existing neuromuscular disease,[ref e-36] major stroke,[ref e-18] and advanced neurodegeneration. For example, in hemispheric stroke, cough, expiratory muscle function and functional residual capacity are impaired.[ref e-37,38] Other neurological patients with frequent cardiac comorbidities, such as Parkinson's disease patients, may also be at higher-risk, although there is no evidence that Parkinson's disease or other movement disorders decrease chance of survival when compared with otherwise similar patients.[ref e-39] As seen with other

infections, patients with chronic deficits suffering COVID-19 may have recrudescence or worsening of their neurological symptoms, including seizure or residua from stroke.[ref e-40]

Immunosuppressed patients have been specifically cautioned about COVID-19,[ref e-41] although clear data regarding their risk is not yet available. Clinicians and patients are already weighing these advisories when deciding on standard of care treatments;[ref e-42] the data remains controversial.[ref e-43,44,45,46]

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.[ref e-47] Traditional contraindications to anticoagulant therapy, such as a prolonged activated partial-thromboplastin time (aPTT), may not be as helpful in COVID-19 patients, in whom prolonged aPTT and lupus anticoagulant, may be seen.[ref e-48] Neurologists and intensivists will need to carefully weigh the benefits of antithrombotic therapies against the risks of intracerebral hemorrhage.

While staging models of clinical COVID-19 disease progression warrant consideration of neurological involvement,[ref e-49] the realities of sterilization and staffing of head imaging studies during a pandemic are restrictive, and may limit neurological investigations in COVID-19 patients with severe cardiopulmonary complications.

Finally, national social isolation policies may be restricting neurological patient access to specialist care, with widespread closures of outpatient neurology offices. As the case fatality rate

of COVID-19 for elderly dementia patients is 3-11x that of patients in their 50s[ref e-50], dementia patients may be disproportionately affected by stringent restrictions aimed at protecting the highest COVID-19 risk group.

Longer-term neurological implications of COVID-19

It remains unknown whether SARS-CoV-2 will cause longer-term neurological morbidity. It is important to consider whether widespread recovered COVID-19 in our population will be a risk factor for additional neurological 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 1994 diagnostic criteria for Chronic Fatigue Syndrome. In another small study of 22 SARS survivors who were unable to return to work mainly as healthcare 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.[ref 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, BMI 24), 68% vs. 40% reported hyperlipidemia, 60% vs. 16% reported glucose metabolism disorder and 44% vs. 0% reported cardiovascular system abnormalities.[ref 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.[ref 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.[ref e-53-61] Sepsis survivors showed not only cognitive deficits in verbal learning and memory, but had reduction of left hippocampal volume compared to healthy controls.[ref e-62] Seventy to 100% of ARDS survivors had cognitive impairment at discharge – 46-80% one year later – and worse impairment correlated with ARDS severity.[ref 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 neurological 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 two case reports suggest COVID-19-associated paroxysmal events in infants (Table 4).[ref e-64] Other 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 multiple sclerosis, there is insufficient evidence to make the same

assertion about coronaviruses.[7, 17,ref e-65] Rare neurological complications of medium-vessel vasculitis have also occurred in the past[ref e-66], and now a case of Kawasaki disease after COVID-19 has been reported.[ref e-67] Since 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.

Conclusion

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

Appendix 1: Authors			
Name	Location	Role	Contribution
Anna S. Nordvig MD	Columbia University, The New York Presbyterian Hospital, NY	Author	Design and conceptualized article; interpreted the data; drafted the manuscript for intellectual content
Kathryn T. Rimmer MD	Columbia University, The New York Presbyterian Hospital, NY	Author	Interpreted the data; significant role in revising the manuscript for intellectual content
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Acknowledgements: The authors thank Dr. Richard Mayeux for his helpful review of a draft of this manuscript.

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Table 1: Neurologically-notable coronaviruses in humans and animals[ref e-68]

Coronavirus	Host	Host Entry	Reservoir	Site of discovery	Major Geographic Distribution	Systemic Features	Associated Neurological Features
SARS-CoV	Human	ACE2	Bats, civets	China	China, Taiwan, Singapore, Vietnam	Mild to severe respiratory illness	Encephalopathy, seizure, stroke, polyneuropathy, myopathy
MERS-CoV (50% identity with SARS-CoV-2)[ref e-69]	Human	DPP4	Bats, camels	Saudi Arabia	Egypt, Oman, Qater, Saudi Arabia	Moderate to SARS, fever	Encephalopathy, ischemic stroke, intracerebral hemorrhage
HCoV-OC43	Human	Unknown	Bats, rodents		Global	Mild respiratory illness	ADEM (case report), acute encephalitis (possible)
HCoV-229E	Human	APN	Bats, camelids		Global	Mild respiratory illness	Encephalitis (possible)
HCoV-NL63[ref e-70]	Human	ACE2			Global	Mild respiratory illness	None reported
Mouse hepatitis virus	Mouse					Severe pneumonitis, SARS	Acute encephalitis or chronic demyelinating disease[ref e-7]
Sialodacryoadenitis coronavirus	Rat						Neurologic infection[ref e-71]
Hemagglutinating encephalomyocarditis virus	Pig						Neurologic infection[ref e-71]

ACE2 = angiotensin converting enzyme 2, APN = aminopeptidase N, DPP4 = dipeptidyl peptidase 4

Table 2: Neurological findings in case reports of SARS-CoV, MERS-CoV, and HCoV-OC43

Demographic	Clinical presentation	Neurological presentation	CSF findings	Neurological clinical studies	Autopsy findings
SARS-CoV					
32 yo W, 26 weeks 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 non-inflammatory with 20 RBC per mm^3	Normal MRI day 46 Normal EEG day 39	Survived
59 yo W, IgA nephropathy on peritoneal dialysis[14]	Fever, chills, cough, diarrhea, respiratory distress	Vomiting and appendicular twitching on hospital day 5	+ SARS-CoV RNA 6884 copies/mL*, otherwise non-inflammatory	Normal HCT No MRI or EEG available	Outcome not provided
39 yo M[18]	Fever, chills, headaches, dizziness, myalgias, treated with ribavirin/ steroids for 1 month, bacterial pneumonia, ARDS	Obscured monocular vision, dysphoria, delirium, vomiting after 1 month	NA	CT showed abnormalities consistent with ischemia or brain edema on day 33, brain herniation day 35	Viral N protein in glial cells and neurons. Enveloped viral particles compatible with coronavirus in suspended tissue**
51yo W[36]	Fever, dyspnea, cough, diarrhea progressed to multiple organ failure & intubation	Distal-predominant 4-limb weakness and leg numbness on day 21	NA	EMG polyradiculo-neuropathy	Survived
48yo W[36]	Fever, dyspnea, myalgia progressed to multiple organ failure & 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
42yo W[36]	Fever, dyspnea progressed to multiple organ failure & 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
31yo M[36]	Fever, cough, soft stool	Proximal leg weakness on day 22	NA	EMG myopathy, complete recovery by day 94	Survived
MERS-CoV					
74 yo M with HTN, DM, and	Unclear initial presentation; fever, later	Confusion, ataxia, vomiting	non-inflammatory with negative	MRI multifocal non-enhancing T1 hypo-, T2	No autopsy

dyslipidemia[ref e-72]	had lymphopenia with critically low absolute CD4 and CD8 counts		MERS-CoV RT-PCR	hyperintensities, restriction, subcortical gray and white matter.	
57 yo M with HTN and DM[ref e-73]	Flu-like illness, myocardial ischemia, pulmonary edema, gangrenous toe	Bilateral multifocal anterior circulation stroke	NA	CT angiography near occlusion at origin of both internal carotid arteries, middle cerebral artery narrowing, no vasculitis.	No autopsy
45 yo M with HTN, chronic kidney disease, and ischemic heart disease[ref e-73]	Fever, respiratory symptoms, diarrhea, pneumonia, 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 & corticospinal tracts, no enhancement or restriction	Survived, discharged home day 107
42 yo W with obesity and DM[ref e-74]	ARDS, lymphopenia, leukopenia, 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 yo W with DM[ref e-73]	ARDS, lymphopenia, inflammation, DIC	Intracranial hemorrhage on day 14	NA	CT head with ICH, massive edema, midline shift	No autopsy
28 yo M[ref e-73]	Fever, ARDS, bacterial pneumonia	Myalgias then paraparesis/paresthesia (critical illness)	NA	EMG: Length dependent axonal polyneuropathy MRI spine normal	Survived
HCoV-OC43					
9 month-old with acute leukemia[ref e-75]	Fever, upper airway symptoms	Altered consciousness, myoclonic seizures	Negative CSF	CT head normal, Abnormal brain MRI	Brain tissue positive for HCoV-OC43
11-month-old with combined immunodeficiency[8]	Respiratory infection	Encephalitis	NA		Brain tissue positive for HCoV-OC43
15yo M[ref e-76]	Upper respiratory symptoms	Ascending numbness, gait difficulty 5 days prior to hospitalization	+ HCoV-OC43 RNA	MRI brain and spine: acute disseminated encephalomyelitis	Survived

*SARS-CoV RNA was isolated in both CSF and serum at 6884 and 6750 copies/mL respectively.
**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.
Abbreviations: W=Woman, M=Man, DM=Diabetes mellitus type 2, HTN=Hypertension, ARDS=Acute respiratory distress syndrome, ICH=Intracerebral hemorrhage, DIC = Disseminated intravascular coagulation, SAH=Subarachnoid hemorrhage, CTA=Computer tomography angiogram; NA= Not available

Table 3: Potential mechanisms for neurological injury in COVID-19

Routes of direct CNS viral invasion[32,ref 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 peripheral nerve
Direct central nervous system 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

Possible neurological symptom	N	% of cohort	Comment	Region
Early and mild neurologic symptoms				
Hyposmia/	357	85.6	Mild-to-moderate patients, questionnaire response, ~10 days post-onset	West. Europe[ref e-2]
anosmia	44	61.1	25% hospitalized, 75% outpatients	Italy[ref e-78]
	11	5.1	Hospitalized patients	China[ref e-27]
	1	~40yoW with anosmia, cough, headache, without ageusia; MRI: inflammation of olfactory clefts		France[ref e-79]
	12	5.6	Hospitalized patients	China[ref e-27]
Hypogeusia/	342	88.8	Mild-to-moderate patients, questionnaire response	West. Europe[ref e-2]
ageusia	39	54.2	25% hospitalized, 75% outpatients	Italy[ref e-78]
Fatigue/	418	38.0	Hospitalized patients	China[ref e-80]
Malaise/asthenia	69	26.3	Hospitalized, mainly mildly-ill patients	China[ref e-81]
	48	66.7	25% hospitalized, 75% outpatients, ~19 days post-onset	Italy[ref e-78]
	18	34.6	Critically-ill hospitalized patients	China[ref e-82]
Headache	150	13.6	Hospitalized patients	China[ref e-80]
	30	41.7	25% hospitalized, 75% outpatients, ~19 days post-onset	Italy[ref e-78]
	28	13.1	Hospitalized patients	China[ref e-27]
	17	6.5	Hospitalized, mainly mildly-ill patients	China[ref e-81]
	9	6.5	Hospitalized patients	China[ref e-83]
	3	7.9	Hospitalized patients	China[22]
	3	5.8	Critically-ill hospitalized patients	China[ref e-82]
Anorexia	55	39.9	Hospitalized patients	China[ref e-83]*
Dizziness	36	16.8	Hospitalized patients	China[ref e-27]
	13	9.4	Hospitalized patients	China[ref e-83]
Myalgia	48	34.8	Hospitalized patients	China[ref e-83]
	6	11.5	Critically-ill hospitalized patients	China[ref e-82]
+ fatigue	18	43.9	Hospitalized patients	China[22]
+ arthralgia	164	14.9	Hospitalized patients	China[ref e-80]
Nerve pain	5	2.3	Hospitalized patients	China[ref e-27]

More severe neurologic symptoms (partial table, see Supplemental Online Appendix for remainder of table)

Post-ARDS Encephalopathy	26	65.0	MRI: 11/13 bifrontotemporal perfusion abnormalities, 8/13 leptomeningeal enhancement; CSF: 2/7 OCB, 1/7 elevated immunoglobulins and protein, no SARS-CoV-2; EEG: only 1/8 diffuse bifrontal slowing	France[ref e-84]
Impaired consciousness	16	7.5	Hospitalized patients	China[ref e-27]
Muscle injury	23	10.7	Hospitalized patients	China[ref 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 days)	China[ref e-28]
	6	2.8	Hospitalized patients (5.7% in severe infections vs. 0.8% in non-severe infections)	China[ref e-27]
	3	3.7	Arterial ischemic strokes (cumulative incidence)	Netherlands[ref e-47]
	6	53-85yo, 6/6 large vessel occlusions (3 multiterritory infarcts, 2 concurrent venous thromboses, 2 ischemic strokes despite therapeutic anticoagulation), D-dimer levels ≥1000µg/L (onset 0-24 days)		U.K.[ref e-85]
	5	33-49yo, 5/5 large vessel occlusions, 3/5 with elevated fibrinogen, D-dimer and ferritin (onset 0-ys)		New York[ref e-86]
	4	73-88yo, 1 embolic, 2 large vessel stenosis, 1 internal carotid occlusion (onset 0-2 days)		New York[ref e-87]
	4	45-77yo, 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 days)		Turkey[ref e-88]
	3	65-70yo, multiple bilateral cerebral infarcts and ARDS (onset 10-33 days)**		China[ref e-89]
Guillain-Barré Syndrome (partial list, continued in Supplemental Online Appendix)	5	23-77yo, 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[ref e-90]
	1	61yoW, EMG: demyelinating neuropathy, CSF: protein 124mg/dL, 5 cells/uL (presenting symptom, 4 days after visiting endemic region)		China[ref e-91]
	1	65yoM, EMG: motor-sensory axonal neuropathy, MRI: negative (onset ~2+ weeks)		Iran[ref e-92]
	1	71yoM, EMG: acute polyradiculoneuritis with prominent demyelination; CSF: protein 54mg/dL, 9 cells/uL, no SARS-CoV-2 (onset day 8)		Italy[ref e-93]

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 the Supplemental Online Appendix

* Anorexia was reported in 55 (39.9%) of which 66.7% required ICU care vs. 30.4% non-ICU care. 19 patients with nausea and vomiting (13.7%), without the skew in distribution of those requiring ICU care vs. non-ICU care.
**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.

Table 4: Neurological findings in case reports and case series of systemic SARS-CoV-2 infection (COVID-19)

Supplemental Online Appendix Table 4: Neurological findings in case reports and case series of systemic SARS-CoV-2 infection (COVID-19)

More severe neurologic symptoms (continued from print version)			
Guillain-Barré Syndrome	1	70yoW, EMG: sensorimotor polyradiculoneuropathy with predominant demyelination; CSF: protein 48mg/dL, 1 cells/uL, no SARS-CoV-2 (20 days post respiratory symptom resolution)	Italy[ref e-94]
	1	64yoM, EMG: demyelinating, no antiganglioside Ab, CSF: albuminocytologic dissociation, no SARS-CoV-2 (onset day 11)	France[ref e-95]
	1	~70yoM, EMG: sensorimotor demyelinating polyneuropathy, CSF: albuminocytologic dissociation, no antiganglioside Ab, no IgG (onset day 11)	Switzerland[ref e-96]
	1	54yoM, clinical diagnosis (onset day 8)	Italy[ref e-97]
Miller Fisher Syndrome	1	50yoM, anosmia, ageusia, internuclear ophthalmoparesis, oculomotor palsy, ataxia, areflexia, 2 positive GD1b-IgG Ab, CSF: albuminocytologic dissociation, no SARS-CoV-2 (onset day 6)	Spain[ref e-98]
	1	36yoM, oculomotor & bilateral abducens palsy, ataxia, hyporeflexia, hypoesthesia, no antiganglioside Ab, MRI: enhancement oculomotor nerve (onset day 5)	New York[ref e-99]
	1	71yoW, abducens palsy, CSF: normal, MRI: enhancement of the optic nerve sheaths and posterior Tenon capsules (onset day ~3)	New York[ref e-99]
Polyneuritis Cranialis	1	49yoM, ageusia, bilateral abducens palsy, areflexia, CSF: albuminocytologic dissociation, no SARS-CoV-2 (onset day 4)	Spain[ref e-98]
Syncope	5	65-70yo, syncope, with AICD or PPM showing no events, all preceded by lightheadedness, some with diaphoresis and nausea	Italy[ref e-100]
	1	79yoW, with vasovagal vs. orthostatic symptoms	Rhode Island[ref e-101]
Recrudescence	1	74yoM, encephalopathy, known large MCA stroke, likely recrudescent stroke vs. seizure	Florida[ref e-40]
Seizure	1	1/214 adult patients, no further information provided	China[ref e-27]
	1	72yoM, new focal temporal seizures after hypoxia; no MRI or LP	New York[ref-e106]
	1	6-week-old M infant, sustained upward gaze twice, b/l leg stiffening, less responsive; EEG: excess of temporal sharp transients and intermittent vertex delta slowing; CSF: normal, no SARS-CoV-2	New York[ref e-102]
Paroxysm	1	26-day-old male infant, 2 paroxysms with minutes of hypertonia and cyanosis, fever	Spain[ref e-64]
Ataxia	1	Hospitalized patient, no further information provided (part of 214 person case series)	China[ref e-27]
Meningo-	1	24yoM, CSF: SARS-CoV-2 RNA, Nasal swab: negative; MRI temporal & hippocampal FLAIR	Japan[ref e-103]

encephalitis		hyperintensities & DWI restriction (onset headache & fatigue; day 9 seizures & nuchal rigidity)***	
	1	56yoM, SARS-CoV-2 in CSF (little other information provided)	China[ref e-104]
	1	41yoW with diabetes mellitus I and obesity, meningismus, SARS-CoV-2 in CSF, CSF also with WBC 70, RBC 65, protein 100; no MRI	Los Angeles[ref e-107]
	2	64yoW, psychosis, focal status epilepticus and 67yoW, decreased alertness and focal deficits Both cases had normal MRI, CSF with lymphocytic pleiocytosis but no SARS-CoV-2 RNA.	Switzerland[ref e-108]
Hemorrhage	1	~50sW, MRI FLAIR & SWI cortical changes of AHNE (onset with altered mental status)****	Detroit[ref e-105]
Possible demyelination	1	54yoW, found unconscious, new seizures, nonenhancing, nonrestricting demyelinating lesions in brain and spinal cord (onset unclear, but new from prior MRI), CSF normal	Italy[ref e-106]

*** Lumbar puncture revealed an opening pressure of 320mm H2O (normal range 100-180mm H2O), 10 mononuclear cells, 2 polymorphonuclear cells, without red cells.
**** MRI showed hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. CSF bacterial culture and select other viral studies were negative but basic studies and SARS-CoV-2 CSF viral analysis could not be done because of a traumatic lumbar puncture. AHNE may be caused by cytokine storm, and may be another non-specific manifestation of critical illness.
Notes: Brain autopsy information on COVID-19 case reports and case series is very limited and is not discussed in this table. We do not include numerous COVID-19 case series that do not specifically report neurological symptoms. Larger case series reported multiple symptoms; to report by symptoms, those series were referenced several times. Critical illness myoneuropathy was not specifically queried for case report. CSF = cerebrospinal fluid, EMG = electromyography, MRI = magnetic resonance imaging (brain), OCB = oligoclonal bands, b/l=bilateral, AHNE = acute hemorrhagic necrotizing encephalopathy

Table 5: COVID-19 considerations for specific neurological patients

Preexisting neurological 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 pro-thrombotic state of COVID-19
Dementia	Possible increased risk of infection (e.g. difficulty following strict hand hygiene) Susceptibility to post-infectious delirium

Potential neurological manifestations of COVID-19

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Neurol Clin Pract published online June 30, 2020
DOI 10.1212/CPJ.0000000000000897