REVIEW

Neurology and the COVID-19 Pandemic

Gathering Data for an Informed Response

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Abstract

Purpose of Review

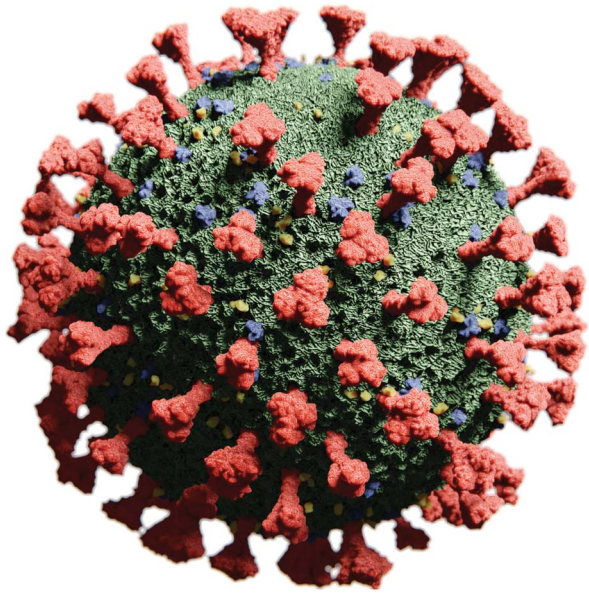
The current coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the greatest medical crises faced by our current generation of health care providers. Although much remains to be learned about the pathophysiology of SARS-CoV-2, there is both historical precedent from other coronaviruses and a growing number of case reports and series that point to neurologic consequences of COVID-19.

Recent Findings

Olfactory/taste disturbances and increased risk of strokes and encephalopathies have emerged as potential consequences of COVID-19 infection. Evidence regarding whether these sequelae result indirectly from systemic infection or directly from neuroinvasion by SARS-CoV-2 is emerging.

Summary

This review summarizes the current understanding of SARS-CoV-2 placed in context with our knowledge of other human coronaviruses. Evidence and data regarding neurologic sequelae of COVID-19 and the neuroinvasive potential of human coronaviruses are provided along with a summary of patient registries of interest to the Neurology community.



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Coronaviruses (CoVs) are ubiquitous pathogens and have been isolated from many animal species ranging from turkeys to bats to beluga whales.[1] CoVs belong within the taxonomic family Coronaviridae, which is further divided into 4 genera—α-, β-, γ-, and δ-CoVs.[2] There are 7 known species of human CoVs (HCoVs), and all are in the α- and β-CoV genera.[3,4] HCoVs consist of 2 α-CoVs, HCoV-NL63 and HCoV-229E, and 5 β-CoVs, HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome (SARS)-CoV-1, Middle East respiratory syndrome (MERS)-CoV, and now the recently identified SARS-CoV-2, which is responsible for the coronavirus disease 2019 (COVID-19) pandemic.[1–4]

Of the 7 HCoVs, the -NL63, -229E, -OC43, and -HKU1 species are endemic worldwide and are primarily associated with mild upper respiratory disease (the common cold).[1–4] In the past 30 years, the 3 other HCoV species have now emerged to infect humans and are most well known for causing severe respiratory disease: SARS-CoV-1, MERS-CoV, and SARS-CoV-2. The modern outbreaks of these HCoVs are thought to represent bat-to-human zoonotic transmissions with the involvement of an intermediate host. Although the SARS-CoV-2

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outbreak was first associated with workers at a live animal market in Wuhan, China, the exact origin and evolution of this virus remains to be fully delineated.[5,6]

Basic Virology

CoV virions are ~125 μm in diameter and are composed of a host-derived lipid envelope surrounding a helical nucleocapsid with a single strand of positive-sense RNA (+ssRNA) as the viral genome[4,7] (figure 1). CoV genome sizes range from 26 to 32 kb and are the largest known +ssRNA viral genome.[8] These genomes encode viral proteins that assist in different steps of the viral life cycle and thus are potential vaccine targets. CoVs are named for their distinctive crown-like appearance under electron microscopy resulting from a radiating array of spike (S) proteins projecting from the viral envelope.[1,7] The S protein is critical for CoV binding to cell receptors. In addition, the viral genome encodes other structural proteins including the membrane (M) protein, which helps to shape the viral envelope and disrupt host interferons, and envelope (E) protein, which participates in various stages of the viral life cycle and contributes to host cell death (figure 1).[1,9,10] The nucleocapsid (N) protein, which surrounds the RNA genome, acts as an RNA chaperone (figure 1).[1,7,9]

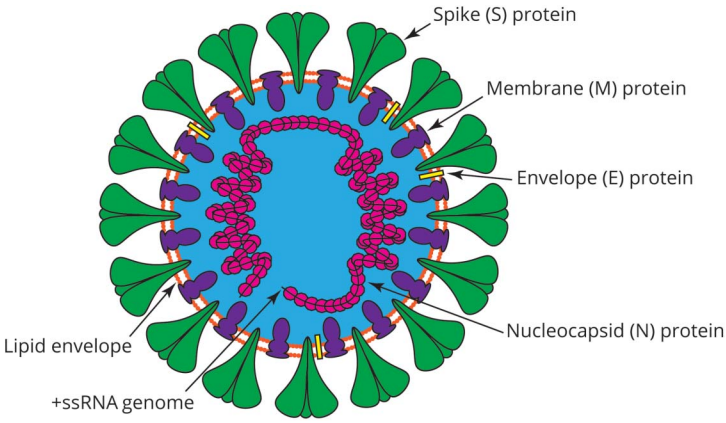
The significance of the genomic differences between SARS-CoV-2 and the other modern HCoVs and the implications for disease phenotype and tropism remains to be fully characterized. Following identification of the first case cluster in Wuhan, China, in late December 2019, the pathogen was isolated by January 7, 2020, and the whole-genome sequence was shared with the World Health Organization only 5 days later on January 12, 2020.[11] The available sequencing data indicate that the genome size is 29.8 kb with 14 open reading frames encoding 27 proteins.[8] SARS-CoV-2 appears more closely related to SARS-CoV-1 (~79% homology) and more distantly related to MERS-CoV (~50% homology).[6,8,12] Like SARS-CoV-1, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor and appears to have a 4- to 20-fold higher ACE-2 binding affinity than SARS-CoV-1.[13–15] SARS-CoV-2 also appears to have the ability to use a host protease, furin, to cleave the viral S protein. This furin cleavage site is not found in SARS-CoV-1, and its exact function in the SARS-CoV-2 life cycle has yet to be determined.[15] Acquisition of mutations allowing for furin cleavage has been seen in other viruses, such as influenza and MERS-CoV, and has been implicated in causing increased virulence and promoting cross-species transmission.[16,17] It may function in enhancing viral fusion following receptor binding or assist in viral exit from an infected cell.

Clinical Spectrum and Transmission of COVID-19

As of May 30, 2020, there have been over 5.9 million confirmed cases of COVID-19 worldwide with over 365,000 deaths.[18] The global case fatality rate is estimated to range from 2% to 5%, although testing variability between countries—including a lack of testing for mild and asymptomatic cases—likely overestimates this range.[19] In most instances, COVID-19 is less lethal than the disease caused by SARS-CoV-1, which had a case fatality rate of 11%. However, the higher rate of human-to-human transmission of SARS-CoV-2 has created a global pandemic with dire implications for health care capacity. SARS-CoV-2 is thought to be transmitted primarily through respiratory droplets when an infected person coughs or sneezes (figure 2A).[20] The virus can remain viable on various surfaces, thus allowing potential fomite transmission.[20] Finally, asymptomatic carriers, who tend to be younger and healthier than those with moderate or severe courses of disease, are increasingly being recognized as drivers of disease propagation. However, the exact prevalence of this group is unclear due to gaps in testing.[21,22]

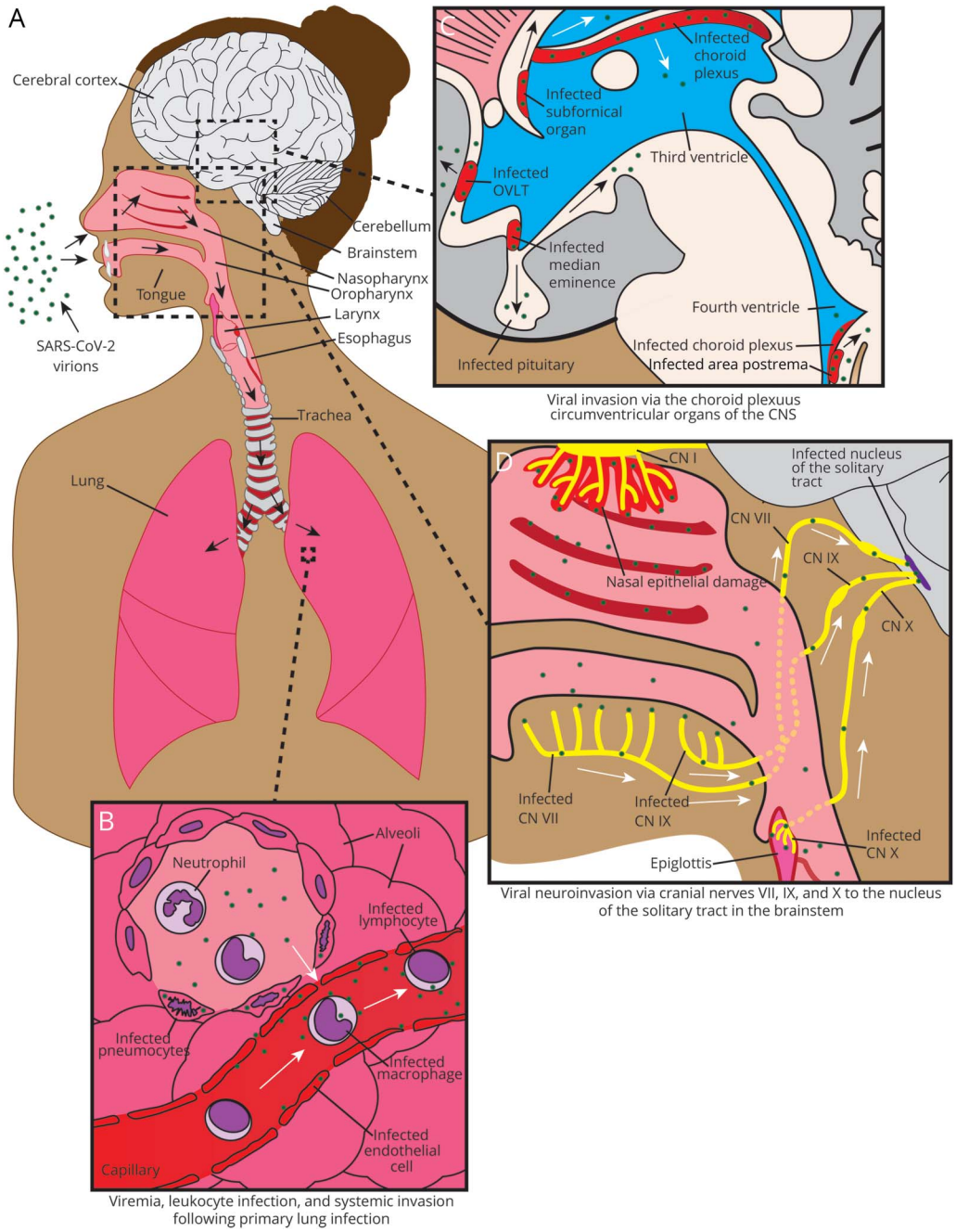
The incubation time to symptom onset following exposure can range from 2 to 14 days (mean: 5 days).[23,24] Typical COVID-19 presenting symptoms include fever, cough, and shortness of breath.[25] Chest CT abnormalities are observed in nearly all hospitalized patients with COVID-19 and consist of ground-

Figure 1 Schematic of a SARS-CoV-2 Virion



The image depicts the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virion with lipid bilayer membrane and shows the structural spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The virion contains a single-strand, positive-sense RNA (+ssRNA) genome surrounded by its N protein chaperone. The S, M, E, and N proteins are possible targets for vaccine development.

Figure 2 Proposed Pathways of SARS-CoV-2 Systemic Infection and Neuroinvasion



(A) Initial infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with viral entry into the nasopharynx, oropharynx, larynx, and lungs. (B) Magnified cross-section of a lung alveolus and capillary. SARS-CoV-2 is known to infect type II pneumocytes as well as endothelial cells, which express the angiotensin-converting enzyme 2 (ACE-2). From the lungs, the virus could enter the vasculature and circulate to other organs, resulting in multiorgan infection and sepsis. Inflammation of cells such as neutrophils, monocytes, and lymphocytes could contribute to viral access to the vasculature due capillary leakage and direct tissue damage. This may also be an initial site for viral infection of immune cells such as macrophages and lymphocytes, which have been shown to become infected by other coronaviruses, such as SARS-CoV-1, and express the ACE-2 receptor. (C) Sagittal cross-section of the brain at the level of the third and fourth ventricles with surrounding structures. Hematogenous spread could lead to direct viral infection of the CNS or infection of the CNS via the circumventricular organs (CVOs) including the subfornical organs, the vascular organ of the lamina terminalis (OVLT), the median eminence, and the area postrema, which do lack a blood-brain barrier and have been shown to express ACE-2. SARS-CoV-2 may also access the CNS via the choroid plexus, depicted on the roof of the third ventricle and in the fourth ventricle. Virus could infect the vasculature of these regions, which expresses ACE-2 or traffic into the CNS via infected lymphocytes. (D) Sagittal cross-section of the upper respiratory tract. SARS-CoV-2 infection has been associated with hyposmia and hypogeusia in a significant number of patients. ACE-2 has been found in the non-neuronal cells of the olfactory system, suggesting dysfunction damage to non-neuronal cells as a cause of anosmia. Hypogeusia could be caused by viral infection of gustatory neurons of cranial nerves VII (chorda tympani of the facial nerve), CN IX, and CN X, all of which project to the nucleus of the solitary tract in the brainstem and are known to express ACE-2. Gustatory pathways could contribute to viral CNS access to the brainstem that ultimately contributes to respiratory dysfunction. Infection of the brainstem could worsen respiratory distress in patients with severe COVID-19. For all panels, SARS-CoV-2 virions are depicted as green dots. Black or white arrows show possible directions of viral spread in each organ or tissue.

glass opacities with bilateral multiple lobular and subsegmental areas of consolidation.[25,26] Most symptomatic individuals have a mild course that resolves without the need for hospitalization, but infection can rapidly progress to severe disease with multiorgan failure and death.[24,27] Severe complications of COVID-19 include acute respiratory distress syndrome, acute kidney injury, acute cardiac disease, and disseminated intravascular coagulopathy, and laboratory findings can include leukopenia, lymphopenia, or lymphocytosis, abnormal liver enzymes, elevated D-dimer, and elevated inflammatory markers (e.g., interleukin [IL]-6, ferritin, and C-reactive protein).[19,24]

The risk of developing severe COVID-19 increases progressively with age. Individuals >65 years in age are more likely to experience hospitalization, intensive care unit admission, mechanical ventilation, and death compared with younger people.[25,28,29] These epidemiologic patterns of COVID-19 are similar to those seen with SARS-CoV-1 and MERS-CoV.[30,31] Although children tend to experience milder symptoms and a better prognosis compared with adults, there have been emerging reports from Europe and North America of multisystem inflammatory conditions like that of Kawasaki disease and hyperinflammatory shock syndrome in children and adolescents.[32,33] The association between SARS-CoV-2 and severe pediatric disease is likely a reflection the size of the global outbreak in diverse populations rather than increased virulence of the SARS-CoV-2 compared with other modern HCoVs.

For the 3 modern HCoVs—SARS-CoV-1, MERS, and SARS-CoV-2—a key feature of severe disease is a dysregulated immune response that damages the lungs and organs above and beyond the direct viral damage.[10,34] The exact mechanisms driving this hyperinflammatory immunopathology are not well understood and may be multifactorial.[10] Overall, individuals with severe disease appear to have rapid viral replication in the lungs with increases in alveolar macrophages and proinflammatory cytokines, including tumor necrosis factor-α, IL-1, IL-6, and ferritin.[34] Seemingly paradoxically, as many as 80% of patients with COVID-19 develop lymphopenia.[35] The exact cause of lymphopenia is unknown but could be due to tissue redistribution to areas of infection (lungs), direct viral infection of lymphocytes followed by cell death, or cytokine-induced lymphotoxicity.[10,34,36] Together, these factors promote massive inflammation and cytokine storm.

Health-related comorbidities also contribute to the development of severe disease, with 94% of deaths occurring in patients with at least 1 comorbidity.[37] Conditions increasing the risk of severe disease include diabetes, hypertension, Class III obesity (body mass index >40 kg/m^2), severe or chronic cardiac disease, chronic lung disease including moderate to severe asthma, and being male.[37] Members of racial minorities in the United States are at a higher risk of poor outcomes that are most likely due to inequalities in medical care and the higher prevalence of comorbidities in this population driven by health disparities.[38] The relationship between these comorbidities and development of cytokine storm could be driven by changes in receptor expression and dysregulation of innate immunity and inflammation that can occur in these disease states, among other hypotheses.

Neurologic Sequelae of SARS-CoV-2 and COVID-19

Although COVID-19 is primarily a disease of the respiratory tract, neurologic symptoms are increasingly being recognized.[39–50] With a rapid rise in severely ill patients, nervous system manifestations can be overlooked, masked by sedation during ventilation, or be of lower priority when severe respiratory and cardiac compromise occur. The neurologic sequelae that have been described to date are discussed with attention to available evidence for indirect, direct, or postinfectious mechanisms.

Olfactory and Taste Disturbances

The CDC recently expanded the COVID-19 symptom list from the typical fever, cough, and shortness of breath triad to include sudden onset of taste and/or smell loss.[37] Table 1 summarizes studies focusing on taste/smell dysfunction with COVID-19. The prevalence of these symptoms among patients with COVID-19 is estimated around 52.73% (95% confidence interval [CI] 29.64%–75.23%) for olfactory dysfunction and 43.93% (95% CI 20.46%–68.95%) for gustatory dysfunction in a meta-analysis of published reports before April 19, 2020.[51] The timing of onset of the olfactory/taste disorders presents particular interest because they may occur earlier than other hallmark features of COVID-19 (fever or cough), which opens the possibility of using them as initial screening measures.[52] In a cohort of hospitalized patients in Milan, Italy, 20% experienced smell and taste disturbance before admission, whereas the remainder reported these disturbances during their hospital stay.[39] Taste alterations were noted to be more prevalent before hospitalization (91%), whereas taste and smell changes were equally prevalent during hospitalization.[39] In other another report, symptoms of loss of taste, smell, or both have been noted to persist for up to several weeks.[41] Although olfactory disturbances are common in other upper respiratory illnesses of viral origin due to sinonasal symptoms (rhinorrhea and congestion), these are less commonly observed in patients with COVID-19.[51] The lack of sinonasal symptoms suggests viral-mediated dysfunction of gustatory and olfactory organs rather than inflammatory damage; however, the exact mechanisms remain to be determined.

Cerebrovascular Disease

A small but growing number of reports suggest an increased risk of stroke as a potential complication of COVID-19 infection (table 2).[42,53–56] Predisposition to stroke may be related to an infection-induced coagulopathy as indicated by elevated D-dimer, elevated fibrinogen, and thrombocytopenia common in patients with severe COVID-19 disease.[54]

Table 1 Summary of Current Reports on Acute Taste and Smell Sequelae of COVID-19

Study type	Location	Patient characteristics	Neurologic symptoms	Evaluation	Reference
Multicenter questionnaire	Belgium, France, Spain, and Italy	417 patients, mean age 36.9 y (range 19–77 y); female: 263 (63.1%), male: 154 (36.9%); all with mild COVID-19	Anosmia or hyposmia: 85.6%; dysgeusia: 88.0%	Online questionnaire of Olfactory Disorders—Negative Statements	Lechien et al., 2020[41]
Case report	Aarhus, Denmark	Female patient in early 30s with mild COVID-19	Anosmia and hypogeusia	Anosmia verified with Sniffin Sticks extended test (8/48); hypogeusia verified with taste spray screening (2/4), taste drop test (24/40), and taste strips (12/16)	Haldrup et al., 2020[40]
Single-center, cross-sectional survey	Milan, Italy	59 patients, median age 60 y (range 50–74 y); female: 29 (32.2%), male: 30 (67.8%); all were hospitalized with COVID-19 but capable of completing the survey	Sudden onset olfactory or taste disorder in 20 patients (33.9%)	Self-reported	Giacomelli et al., 2020[39]
Case series	Padua, Italy	6 patients, no further descriptions given	Sudden-onset hyposmia and hypogeusia as only or main COVID-19 symptom	Suprathreshold Odor Rating Test using six odors to confirm hyposmia	Marchese-Ragona et al., 2020[44] (note: non–peer-reviewed report)
Case control	Tehran, Iran	60 hospitalized patients with COVID-19 median age 46.55 ± 12.17 y; female: 40 (67%), male: 20 (33%); COVID-19 disease: mild (42%), moderate (48%), and severe (10%)	Mild microsmia (13%), moderate microsmia (27%), severe microsmia (33%), and anosmia (25%)	University of Pennsylvania Smell Identification Test of 40 odorants	Moein et al., 2020[45]
Retrospective observational	Mulhouse, France	54 (47%) of 114 examined and/or hospitalized patients with COVID-19 with reported anosmia; mean age 47 ± 16 y; female: 36 (67%), male 18 (33%)	Anosmia mean duration 8.9 ± 6.3 d, anosmia developed 4.4 ± 1.9 d after infection onset; dysgeusia in 85%	Self-reported	Klopfenstein et al., 2020[102]
Retrospective review	Tehran, Iran	8 patients with sudden-onset anosmia, 5 COVID-19+; age range 22–44 y; female: 6 (75%), male: 2 (25%)	Anosmia in 8/8 patients onset between 2 and 4 d after fever; ageusia in 2/8 patients	Self-reported	Gilani et al., 2020[103]
Case report	Madrid, Spain	40-y-old Venezuelan female radiologist caring for multiple symptomatic patients with COVID-19	Anosmia 3 d after symptom onset, anosmia resolved after 14 d	Self-reported	Ollarves-Carrero et al., 2020[104]
Case series	Washington DC	177 pediatric and young adult patients (25% hospitalized, 20% critically ill), male: 92 (52%), female: 85 (48%)	Loss of taste and smell in 15 (9%) patients	Methods not described	DeBaisi et al., 2020[105]

Abbreviation: COVID-19 = coronavirus disease 2019.

Table 2 Summary of Current Reports on Acute Neurologic Sequelae of COVID-19

Study type	Location	Patient characteristics	Neurologic symptoms	Imaging	Laboratory findings	Reference
3 centers, retrospective	Wuhan, Hubei, China	214 patients, mean age 52.7 ± 15.5 y; female: 127 (59.3%), male 87 (40.7%); severe COVID-19: 88 (41.1%)	Any neurologic signs or symptoms: 78 (36.4%); CNS signs or symptoms (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure): 53 (24.8%); PNS signs or symptoms (taste impairment, smell impairment, vision impairment, and nerve pain): 19 (8.9%)	None described	Patients with severe symptoms: ↑ CRP, D-dimer; ↓ lymphocytes, ↑ BUN/Cr	Mao et al., 2020[43]
Single-center, retrospective	Wuhan, Hubei, China	221 patients, mean age 53.3 ± 15.9 y; female: 90 (40·7%), male: 131 (59·3%); severe COVID-19: 94 (42·5%)	AIS: 11 (5%); CVST: 1 (0·5%); CH: 1 (0·5%)	Representative brain CTs showing new-onset AIS, CVST, and left basal ganglia CH	Blood from patients with AIS/CVST/CH showed ↑ WBCs, neutrophils, CRP, D-dimer ↓ lymphocytes	Li et al., 2020[42]
Case report	Shimokato, Chuo, Yamanashi, Japan	24-y-old man with headache, fatigue, and fever	Altered mental status, seizures, meningitis/encephalitis	Brain MRI: DWI showing hyperintensities along the right lateral ventricle; FLAIR showing hyperintense signals in the mesial temporal lobe and hippocampus; T2WI showing pan-paranasal sinusitis	CSF: ↑ opening pressure, ↑ WBCs, SARS-CoV-2+ by RT-PCR; blood: ↑ WBCs, ↑ CRP	Moriguchi et al., 2020[46]
Case report	Beijing, Hebei, China	56-y-old patient of unknown sex	Viral encephalitis	None	CSF: SARS-CoV-2+ by RT-PCR	Zhou et al., 2020[50] (note: non–peer-reviewed report)
Case report	Detroit, MI	Female patient, age in late 50s with 3 d of cough and fever with COVID-19 in nasal swab	Altered mental status and necrotizing hemorrhagic encephalopathy	Head CT with symmetric hypoattenuation within bilateral medial thalami with normal CT angiogram and venogram; brain MRI with hemorrhagic rim-enhancing lesions within bilateral thalami, medial temporal lobes, and subinsular regions	CSF: traumatic puncture, unable to test for SARS-CoV-2 via RT-PCR	Poyiadji et al., 2020[47]
Retrospective case study	Leiden and Rotterdam, the Netherlands	Analysis of 184 COVID-19+ admitted to the ICUs of 3 hospitals for 1 mo; 3/184 (1.6%) had strokes, patient characteristics not described	COVID-19 pneumonia requiring ICU admission followed by development of coagulopathy and stroke	Ischemia stroke diagnosed with CT	None described	Klok et al., 2020[53]

Continued

Table 2 Summary of Current Reports on Acute Neurologic Sequelae of COVID-19 *(continued)*

Study type	Location	Patient characteristics	Neurologic symptoms	Imaging	Laboratory findings	Reference
Case series	New York, NY	5 adult patients aged 33–49 y, 1 female, 4 males with mild COVID-19	2 patients were asymptomatic with COVID-19, 3 had fever, cough, or fatigue; all developed symptoms of severe stroke with reduced consciousness, gaze palsy, dysarthria, and/or hemiplegia	CT, CTA, CTP, and/or MRI showed large vessel occlusions in all patients	Blood: ↑ fibrinogen (60%), ↑ D-dimer (60%)	Oxley et al., 2020[55]
Case report	Barcelona, Catalonia, Spain	50-y-old man with severe COVID-19	While in ICU with bilateral pneumonia developed acute-onset right facial paralysis and left limb weakness	Head CT perfusion map showed hypoperfusion in the left paramedian thalamic artery; head MRI showed left medial thalamic infarct	None described	Rudilosso et al., 2020[56]
Case series	Wuhan, Hubei, China	69-y-old male, 70-y-old male, and 65-y-old female patients with severe COVID-19	Presented with fever, cough, dyspnea, and headache and later developed evidence cerebral infarcts; 1 patient also had distal limb ischemia	Head CT showed diffuse acute cerebral infarctions in cerebral hemispheres in all patients, 2 patients also had cerebellar infarctions	Blood: ↓ lymphocytes, ↓ platelets, ↑ D-dimer, ↑ fibrinogen; all had positive anticardiolipin IgA and anti–β2-glycoprotein I; IgA and IgG	Zhang et al., 2020[58]
Case report	Boca Raton, FL	74-y-old male patient with severe COVID-19	Fever, cough, headache, and altered mental status	Head CT showed evidence of distant posterior cerebral artery stroke; EEG described as consistent with encephalopathy, left temporal lobe dysfunction, and possible epileptogenicity	CSF: no evidence of infection	Filatov et al., 2020[59]
	Rome, Italy	78-y-old female patient with mild COVID-19	Focal status epilepticus followed by fever 12 h later	Head MRI showed no evidence of new cerebral lesions; ictal EEG showed seizure activity localized over left-fronto-centro-temporal regions	Blood: ↓ lymphocytes, ↓ platelets, ↑ CRP	Vollono et al., 2020[61]
Case report	Jingzhou, China	66-y-old female patient with moderate COVID-19	Progressive arm and leg weakness with decreased distal sensation—treated with IVIg	Nerve conduction studies supporting demyelinating neuropathy	SARS-CoV-2 in oropharyngeal swab by RT-PCR, lymphocytopenia, thrombocytopenia, normal CSF	Zhao et al., 2020[49]

Continued

Table 2 Summary of Current Reports on Acute Neurologic Sequelae of COVID-19 *(continued)*

Study type	Location	Patient characteristics	Neurologic symptoms	Imaging	Laboratory findings	Reference
Case series	Pavia, Italy	5 patients, aged 23–77 y; female: 1 (20%), male: 5 (80%); all had mild COVID-19	Flaccid tetraparesis (60%), flaccid paraplegia (20%), flaccid tetraplegia (20%), facial diplegia (20%), facial weakness (40%), paresthesias (100%), respiratory failure (60%)—treated with IVIg	MRI brain performed in 4 patients with one showing facial nerve enhancement in patient with facial diplegia; MRI spine performed in all patients with caudal nerve root enhancement found in 1 patient	CSF in 4 patients tested: ↑ protein, SARS-CoV-2 negative by RT-PCR; negative antiganglioside antibodies in 4 patients tested	Toscano et al., 2020[48]
Case report	Saint-Etienne, France	64-y-old male patient with fever and cough for 2 d, admitted to hospital after rotator cuff injury, found to be SARS-CoV-2 positive on nasal swab	Bilateral upper and lower extremity flaccid severe paresthesia developed beginning 11 d after initial symptom onset, swallowing disturbance—treated with IVIg	None reported	SARS-CoV-2 in oropharyngeal swab by RT-PCR, demyelinating pattern on EMG	Camdessanche et al., 2020[63]
Case report		54-y-old Caucasian female patient with no preceding fever or respiratory symptoms but with temporary loss of taste and smell	Progressive proximally pronounced paraparesis, areflexia, and sensory loss with tingling of all extremities consistent with an acute demyelinating inflammatory polyneuropathy beginning 10 d before admission—treated with IVIg	None reported	SARS-CoV-2 in oropharyngeal swab by RT-PCR. CSF with albuminocytologic dissociation, demyelinating pattern on EMG	Scheidl et al., 2020[62]

Abbreviations: AIS = acute ischemic stroke; BUN = blood urea nitrogen; CH = cerebral hemorrhage; COVID-19 = coronavirus disease 2019; Cr = creatinine; CRP = C-reactive protein; CVST = central venous sinus thrombosis; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; Ig = immunoglobulin; PNS = peripheral nervous system; RT-PCR = reverse transcription PCR; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; T2WI = T2-weighted imaging; WBC = white blood cell.

Large vessel strokes have also been reported in relatively healthy individuals aged 30–50 years with only minor COVID-19 symptoms.[55] As discussed in the next sections, infection of endothelial vasculature by SARS-CoV-2 could lead to endothelial dysfunction, and this dysfunction combined with hypercoagulability could predispose to either thrombotic or hemorrhagic stroke. Another possible mechanism explaining stroke-associated COVID-19 could be the development of prothrombotic immunoglobulins, such as antiphospholipid antibodies and lupus anticoagulant that have now been reported in some patients with COVID-19, both with and without signs of stroke (table 2).[54,57,58] Procoagulant antibodies, however, may be transiently expressed in many disease states, and more work is needed to understand their prevalence and significance in COVID-19–associated stroke.

Encephalitis and Encephalopathy

There have been 2 cases of viral encephalitis or meningitis/encephalitis with SARS-CoV-2 RNA found in the CSF (table 2).[46,50] Detection of SARS-CoV-2 in the CSF, the gold standard for causal diagnosis of CNS infection, suggests a neuroinvasive potential for this virus. Encephalopathy may be an indirect (i.e., non-CNS invasion) presenting feature of severe COVID-19, particularly in the elderly, and COVID-19 should be included in the differential for those presenting with signs of illness and altered mental status (AMS).[59] Acute necrotizing encephalopathy, which is likely an inflammatory disorder related to a viral-induced cytokine storm, was described in an airline worker in her late fifties with SARS-CoV-2 infection who experienced AMS that rapidly progressed to coma (table 2).[47] This case highlights the potential for more than 1 viral-induced indirect (i.e., noninvasive) mechanism to cause encephalopathy.

Seizure

A retrospective study of 304 patients with no history of epilepsy or seizure showed no increase in risk for developing new-onset seizures following COVID-19 infection.[60] However, viral illnesses can lower seizure thresholds in those with epilepsy due to alterations in medication metabolism during illness, as illustrated by a case report of a patient with COVID-19 and a history of well-controlled seizures due to remote history of herpes encephalitis who presented with focal status epilepticus despite an absence of respiratory symptoms (table 2).[61] This case highlights the need to monitor for changes in those with epilepsy and SARS-CoV-2 exposure.

Guillain-Barré Syndrome

Several single case reports detail the emergence of Guillain-Barré syndrome (GBS) as a postinfectious complication SARS-COV-2 (table 2).[48,49,62,63] In addition, 5 patients in Northern Italy were reported to develop flaccid limb weakness and tingling consistent with GBS following SARS-CoV-2 infection.[48] Outcomes for the Italian patients were poor, with 2 patients requiring continued ventilation and 4 with significant weakness at 4-week follow-up despite treatment with IV immunoglobulin.[48,49] With time, the full extent and prognosis of GBS associated with COVID-19 will be better understood.

Impact on Preexisting Inflammatory Disorders of the Nervous System

The CDC reports that immunocompromised individuals are at a higher risk of severe illness from SARS-CoV-2 infection, but a specific evidence of such and outcomes are lacking.[37] Before advising patients to alter ongoing therapies that target the immune system, the risk of neurologic disease progression must be weighed against the current unknowns related to COVID-19. There exists a balance between suppressing the inflammatory response and creating an environment that promotes viral proliferation. Broadly acting agents, glucocorticoids, which suppress both innate and adaptive arms of the immune system, have been used during the severe respiratory phase of COVID-19, although recommendations against glucocorticoids in COVID-19 exist.[64] Other agents, such as alemtuzumab (targets CD52 present on T and B lymphocytes) and cladribine (depletes B and T lymphocytes), can cause profound lymphopenia and may exacerbate the lymphopenia and immune dysregulation already seen in severe COVID-19. More narrow targeting of proinflammatory cytokines may actually be beneficial in COVID-19, including drugs such as baricitinib (inhibits Janus kinase inflammatory pathway), tocilizumab (anti–IL-6 receptor), and siltuximab (anti–IL-6). Use of these drugs in COVID-19 has some shown some promise in small trials, but data from randomized controlled trials are pending.[65,66] Many of the immunomodulatory or immunosuppressive agents commonly used for inflammatory neurologic disorders, such as rituximab, ocrelizumab, fingolimod, natalizumab, and azathioprine, have unknown impact on the risk of infection with SARS-CoV-2 and on the severity of complications from COVID-19. The decision to continue on these agents with careful monitoring for COVID-19 symptoms to prevent exacerbation of devastating neurologic disorders should be made on a case-by-case basis until further data are available.[67]

Neurologic Sequelae of Other HCoVs

It is noteworthy that neuroinvasion has been demonstrated in almost all the other β-CoVs.[3,68–80] Table 3 details all studies described in this section. A series of postmortem studies on individuals who died as a result of SARS-CoV-1 in 2003, some with neurologic symptoms before death, revealed that SARS-CoV-1 can become widely disseminated during infection and can be found within the CNS.[70,72,74,79,80] SARS-CoV-1 virus was identified by several different methods, including by RT-PCR in CSF and brain tissue and by immunohistochemistry in cortical and hypothalamic neurons.[71,72,74,79] Rare cases studies have also implicated HCoV-OC43 and -229E as causes of encephalomyelitis, encephalitis, and acute flaccid paralysis in children.[75,77,78] Histopathology is not available for any cases of MERS-CoV. Neurologic symptoms of

Table 3 Summary of Studies on the Neurologic Sequelae of Human Coronaviruses Before SARS-CoV-2

HCoV	Study type	Patient characteristics	Neurologic symptoms	CNS imaging	Specimen examined	Cells/tissue CoV	Reference
SARS-CoV-1	Case series	Postmortem samples from 4 patients with confirmed SARS, 3 males aged 25–57 y, 1 female aged 62 y	1 patient had headache; no other neurologic symptoms described	None described	Cerebrum, cerebellum, pituitary, lung, lymph node, spleen, heart, liver, kidney, adrenal gland, parathyroid gland, bone marrow, skin, esophagus, gastric fundus, small intestine, pancreas, thyroid, aorta, testis, ovary, uterus, and striated muscle by IHC and ISH	SARS in neurons of the cerebrum by IHC and ISH; pituitary, lung, stomach, small intestine, kidney, adrenal, skin, parathyroid, and liver by IHC and ISH	Ding et al., 2003[71]; Ding et al., 2004[70]
SARS-CoV-1	Case series	Postmortem samples from 8 patients with confirmed SARS, no further clinical descriptions provided	None described	None described	Brain by light microscopy, EM, RT-PCR; lungs, trachea, esophagus, small intestines, large intestines, kidneys stomach, liver, spleen, pancreas, testes, heart, adrenals, thyroid, and skeletal muscle by ISH and EM	Virus in neurons of hypothalamus and cortex light microscopy, EM, and detectable in brain tissue by RT-PCR; lungs, trachea, esophagus, small intestines, large intestines, and kidneys by ISH and EM	Gu et al., 2005[72]
SARS-CoV-1	Case report	59-y-old woman, hx of IgA nephropathy with fevers, chills, cough, and diarrhea	Vomiting, confusion, seizures, and status epilepticus	CT showed no abnormalities	Tracheal aspirate, serum, CSF by RT-PCR	Tracheal aspirate, serum, CSF by RT-PCR	Hung et al., 2003[79]
SARS-CoV-1	Case report	32-y-old woman 26-wk pregnant with fevers, chills, myalgias, and cough	Seizures	MRI showed no abnormalities	CSF by RT-PCR	CSF by RT-PCR	Lau et al., 2004[74]
SARS-CoV-1	Case report	39-y-old man with fever and progressive pneumonia	Dysphoria, vomiting, delirium, and coma	CT showed broad ischemia, necrosis, and edema	Brain tissue with IHC, RT-PCR, viral culture, EM	Virus in glia and neurons by IHC, detectable from brain tissue by RT-PCR, viral culture, EM	Xu et al., 2005[80]
HCoV-OC43	Case report	11-mo-old male with severe combined immunodeficiency, no prodrome noted	Irritability, sleepiness, feeding problems, and abnormal posturing	MRI showed volume loss and abnormal gray matter signal by T2WI	Brain biopsy by RT-PCR and IHC	Brain tissue by RT-PCR, HCoV antigen in neurons and neuropil by IHC	Morfopoulou et al., 2006[75]
HCoV-OC43 and 229E	Case report	3-y-old female with URI prodrome	Acute flaccid paralysis following viral URI	None	Nasal swabs, CSF by RT-PCR	Nasal swabs by RT-PCR	Turgay et al., 2015[77]
HCoV-OC43	Case report	15-y-old male with URI prodrome	Acute disseminated encephalomyelitis	MRI showed diffuse white matter lesions brain and spinal cord on T2WI	Nasal swabs, CSF by RT-PCR	Nasal swabs, CSF by RT-PCR	Yeh et al., 2004[78]

Continued

Table 3 Summary of Studies on the Neurologic Sequelae of Human Coronaviruses Before SARS-CoV-2 *(continued)*

HCoV	Study type	Patient characteristics	Neurologic symptoms	CNS imaging	Specimen examined	Cells/tissue CoV	Reference
MERS-CoV	Case series	70 patients with laboratory-confirmed MERS, 65.7% male, 34.3% female, median age 62 y (range 1–90 y)	Headache (12.9%) and confusion (29.7%)	None	Respiratory swabs by RT-PCR	Respiratory swabs by RT-PCR	Saad et al., 2014[76]
MERS-CoV	Case series	3 adult patients aged 45–72 y all with symptoms of respiratory disease or fever	1 patient had ataxia, vomiting, and confusion; 1 patient had stroke with hemiparesis followed by coma; 1 patient had coma and encephalitis	MRI with widespread white matter and subcortical lesions on T2WI in all 3 patients	Tracheal aspirate in 3 patients, CSF in 2 patients by RT-PCR	Tracheal aspirate in 3 patients by RT-PCR	Arabi et al., 2015[69]
MERS-CoV	Case series	2 patients: 34-y-old woman with fever and 28-y-old man with fever, myalgias, cough, and dizziness	A 34-y-old woman developed headache, nausea, vomiting, and coma 2 wk following MERS; a 28-y-old man developed lower limb paraplegia with numbness in stocking distribution	34-y-old woman, CT showed frontal lobe hemorrhage and edema; a 28-y-old man had abnormal nerve conduction studies and normal MRI	Both had respiratory swabs by RT-PCR; a 28-y-old man had CSF studies	Respiratory swabs by RT-PCR	Algahtani et al., 2016[68]
MERS-CoV	Case series	2 male, 2 female adult patients aged 38–55 y with symptoms of respiratory disease	1 patient had hypersomnolence and weakness in all 4 limbs; 1 patient had tingling in hands and legs, with leg weakness; 1 patient had tingling in both hands and feet; 1 patient had tingling in both hands	None described	Nasal swabs in 3 patients, 1 patient with confirmed exposure	Nasal swabs	Kim et al., 2017[73]

Abbreviations: CoV = coronavirus; EM = electron microscopy; HCoV = human coronavirus; IHC = immunohistochemistry; ISH = in situ hybridization; MERS = Middle East respiratory syndrome; RT-PCR = reverse transcription PCR; SARS = severe acute respiratory syndrome; T2WI = T2-weighted imaging; URI = upper respiratory infection.

headache and confusion were reported in 10%–25% of patients with MERS-CoV during acute infection.[76] There are 2 reports of MERS-CoV–associated hemorrhagic stroke.[68,69] MERS-CoV has been more commonly associated with postinfectious complications such as GBS.[68,69,73,76] One case series documented diffuse subcortical gray and white matter damage in 3 patients following severe MERS-CoV infection, possibly due to hypoxic-ischemic injury, although 1 patient may have had acute disseminated encephalomyelitis, a demyelinating disease that attacks white matter in the brain and spinal cord.[69] There have also been 5 cases of patients who developed GBS-like flaccid paralysis and paresthesia following MERS-CoV infection.[68,73]

Possible Mechanisms of HCoV Neuroinvasion

Given our knowledge of other HCoVs, we describe 2 potential methods by which SARS-CoV-2 could invade the nervous system: hematogenous and transsynaptic spread (figure 2, B–D).

Potential for Hematogenous Spread to the CNS

For many viruses, initial infection of the lungs has been demonstrated to lead to access to the circulatory system with the presence of virus in the blood (e.g., viremia). ACE-2 is expressed on vascular endothelium of arteries and veins in humans and could serve as a gateway to multiorgan HCoV disease.[81] In addition, infected monocytes and lymphocytes could carry HCoV to multiple sites throughout the body; a prior study demonstrated SARS-CoV-1 infection of monocytes and lymphocytes in 6 out of 22 blood samples from infected patients.[72] Monocytes and lymphocytes could, therefore, act as Trojan Horses for viral CNS access, as has been shown in coxsackie B3 virus and cytomegalovirus infections.[82] Taken together, it is possible that viremia and hematogenous trafficking via infected white blood cells may allow for SARS-CoV-2 access to the CNS via CNS capillaries, which are particularly extensive and highly permeable within circumventricular organs (CVOs) that localize to periventricular regions of the brain and lack a blood-brain barrier (BBB) (figure 2, B and C).[81,83] ACE-2 expression in several CVOs are responsible for detecting compositional changes in the peripheral circulation and transmitting this information to autonomic control centers in the hypothalamus and brainstem.[84] A study investigating ACE-2 expression in wild type mice found that ACE-2 is expressed in the subfornical organs, the vascular organ of the lamina terminalis, the median eminence, and the area postrema[85] (figure 2C). The latter has projections to other ACE-2–expressing regions of the brainstem, notably the dorsal motor nucleus of the vagus nerve (CN X) and the nucleus of the solitary tract, which is involved in taste processing. Furthermore, ACE-2 is highly expressed in the choroid plexus of humans. Inflammation produced by pathologic conditions, such as hypoxic-ischemic injury that occurs with severe COVID-19, can lead to the release of proinflammatory cytokines by microglia and brain endothelial cells, which, along with oxidative stress and increased nitric oxide production, degrading the BBB[86] and increasing susceptibility for viral entry via hematogenous spread. In this pathologic state, virus and leukocytes could enter the CSF via the choroid plexus and lead to infiltration of brain tissue[86] (figure 2C).

Consideration of Transsynaptic Spread to the CNS

Another potential route to the CNS is transsynaptic spread through tissues innervated by nerves for taste and smell (figure 2D), particularly in light of the numerous case reports and emerging studies describing disturbances in taste and/or smell without rhinorrhea in patients with confirmed COVID-19 (see table 2 for details).[39–41,44,45] When considering transsynaptic spread via gustatory system components, it is important to note that ACE-2 is crucial to sodium homeostasis, which influences salt appetite and perception of salty taste. ACE-2 is highly expressed in the lingual taste buds and in the tongue epithelium of mice, along with other renin-angiotensin aldosterone system components that are innervated by gustatory afferents,[87] although the expression of ACE-2 in human gustatory afferents has not been characterized. Recent work describes significant expression of ACE-2 in human oral tissues in the epithelial cells, including the tongue and palate, where taste buds—which are comprised of specialized epithelial cells innervated by gustatory afferents—reside. ACE-2 receptors are also widely expressed in the human CNS and particularly widely throughout the brainstem. Renin-angiotensin system components (ACE and AngIIR) have also been detected specifically throughout the human nucleus of the solitary tract—where gustatory afferents terminate—as well as in the dorsal motor nucleus of the vagus nerve and both the rostral and caudal ventrolateral reticular nucleus of the human brainstem.[88] In addition to receiving gustatory information, the nucleus of the solitary tract receives general visceral afferents from the cardiovascular, pulmonary, and gastrointestinal systems. If SARS-CoV-2 were capable of invasion via chemosensory and/or chemoreceptive neurons, this could account for the variety of symptoms observed in patients with COVID-19, including taste disturbances, hypoxia, cardiac complications, and even gastrointestinal complaints.

A significant effort is being made to understand the role of the olfactory system in COVID-19 symptomatology. Although ACE-2 is known to be expressed in the olfactory system and in the olfactory bulbs of mice,[87] the anosmia of COVID-19 is more likely mediated through non-neuronal cell types of the olfactory epithelium. Human olfactory sensory neurons have little expression or coexpression of ACE-2, whereas non-neuronal cell types of the olfactory epithelium had high levels of expression and coexpression of these SARS-CoV-2 entry genes.[89–91] These findings suggest that disruption or loss of smell is more likely a result of damage to or dysfunction of non-neuronal cell types rather than infection of neuronal cells (figure 2D).

Table 4 A Sampling of COVID-19 Reporting Databases for Neurologic Conditions and Registries Outside of Neurology

Database	Location	Purpose	Partners/institutions
COVID-19 reporting databases for neurologic conditions			
COVID-19 infections in MS & Related Conditions	North America	Define the impact of COVID-19 on patients with MS and how factors such as age, comorbidities, and MS treatments affect COVID outcomes	National MS Society, Consortium of MS Centers
COVID-19 Cardiovascular Disease Registry (includes stroke)	United States	Aggregate data and aid research on the disease, treatment protocols, and risk factors tied to adverse cardiovascular outcomes	American Heart Society
Acute Encephalopathy in Critically Ill Patients with COVID-19	France	Reporting the prevalence of acute encephalopathy at initial management in critical/intensive care or neurocritical care, to report its morbidity and mortality and to identify prognostic factors	
COVID-19 registries outside of neurology			
ASH RC COVID-19 Registry for Hematologic Malignancy	United States	Collect and disseminate surveillance data on the natural history of patients with COVID-19 and hematologic malignancies	ASH Research Collaborative
COVID-19 Dermatology Registry	International	Understand dermatologic manifestations of the COVID-19 virus	American Academy of Dermatology
COVID-19 in Pregnancy and Newborns	United States	Understand course of COVID-19 in pregnant women	University of California San Francisco
ASCO Survey on COVID-19 in Oncology Registry	United States	Collect both baseline and follow-up data on how the virus affects cancer care and cancer patient outcomes during the COVID-19 pandemic and into 2021	
The COVID-19 Global Rheumatology Alliance Registry	International	Create a secure, deidentified, international case reporting registry for cases of COVID-19 in rheumatology patients and then curate and disseminate the outputs from that registry	The COVID–19 Global Rheumatology Alliance Steering Committee
COVID-19 Pediatric Observatory	France	Describe the clinical phenotypes of hospitalized pediatric patients with COVID-19 in France, according to age groups	Centre Hospitalier Intercommunal Creteil
COVID-19 in patients with HIV	United States	Characterize the clinical presentation and disease course of COVID-19 in patients with HIV	University of Missouri–Columbia

Abbreviations: ASCO = American Society of Clinical Oncology; ASH RC = American Society of Hematology Research Collaborative; COVID-19 = coronavirus disease 2019.

Additional gaps remain in our understanding of CNS invasion. First, although it is certainly plausible that ACE-2—the known SARS-CoV-2 receptor—plays a role in CNS infection, other receptors that remain to be discovered might better explain COVID-19 CNS manifestations. Second, other host factors may be necessary to explain pathogenesis in specific tissues. This is most evident in tissues that have high expression of ACE-2 receptors, yet appear to not be significantly affected by infection. For example, ACE-2 is strongly expressed in the digestive system according to the Human Protein Altas,[92] and yet, gastrointestinal symptoms are reported in a minority of patients with COVID-19.[25]

Long-term Neurologic Sequelae of CoV Infection

An important consideration for HCoVs is the evidence for potential long-term persistence in CNS tissue. Infection of immortalized neuronal and oligodendrocyte cells lines with HCoV-OC43 and -229E, respectively, revealed viral antigen and infectious particles in a small proportion of the cell populations through dozens of cell passages.[93,94] T lymphocytes from patients with multiple sclerosis contain antigens that cross-react with antigens of HCoV-229E, previously suggesting a link between HCoV infection and CNS immune-related disease,[95] and mice infected intracerebrally with HCoV-OC43 developed long-term behavioral deficits with chronic loss of hippocampal neurons and viral RNA detected by RT-PCR for up to 1 year postinfection.[96]

There has been significant interest in the link between chronic neurologic disease and infectious events, and some viral infections are known to cause persistent neurologic disease. For example, measles persistence in the CNS can cause subacute sclerosing panencephalitis to begin 1 month to 27 years after initial infection.[97] There is also growing evidence that viral infections could be among the many environmental factors predisposing individuals to development of neurodegenerative diseases. West Nile virus infection in the CNS results in upregulation of α-synuclein, which appears to have an innate immune function, suggesting a mechanistic link between viral infection and the development of Parkinson disease.[98] Varicella zoster virus (VZV), which infects >90% of the world population, can reactivate in sensory ganglia to cause shingles and other sequelae cerebrovascular infection and stroke.[99] VZV can increase the production of amylin and amyloid β and has a theoretical potential to be associated with the risk of Alzheimer disease.[99]

Monitoring the long-term association of viruses with neurologic disease has a historic precedent. Between 1916 and 1927, the world was swept with a phenomenon known as encephalitis lethargica (EL).[100,101] This syndrome resulted in symptoms of extreme fatigue, abnormal eye movements, and parkinsonian-like motor symptoms. Estimates suggest that EL afflicted over 1 million people to cause up to 500,000 deaths.[100,101] The most likely culprit for this widespread phenomenon has been thought to be a viral infection, such as the 1918 H1N1 influenza, but historical, epidemiologic, and histologic examinations have been inconclusive.[100] Neurologists should be prepared to monitor for changes and future neurologic sequelae related to the COVID-19 pandemic.

Clinical Recommendations and Resources

To effectively understand the neurologic consequences of COVID-19 and the potential for neurologic disorders and their therapies to be risk factors for COVID-19 complications, standardized and large-scale collaborative data collection is necessary. Multiple medical specialty groups, such as the American Society of Clinical Oncology and the Global Rheumatology Alliance, have developed registries for their respective patient populations. Recently, the Consortium of Multiple Sclerosis Centers and the National Multiple Sclerosis Society created COViMS to capture data on clinical outcome–related COVID-19 in patients with prior diagnosis of MS and related disorders and to learn about relative risks associated with disease-modifying treatments in the setting of COVID-19. As the list of registries continue to grow (table 4), we must keep in mind that the true prevalence of disease will remain uncertain without large-scale testing in asymptomatic people and serology for antibodies to SARS-CoV-2. Reports of increased incidence of death at home in major cities point to the lack of accurate data, and future registry data will be a biased sample without more widespread testing.

Conclusions

HCoVs have the capacity to be neuropathogenic. There is increasing evidence that SARS-CoV-2 can cause both direct and indirect neurologic disease, but much remains to be learned. For now, caution must be taken in regard to attributing neurologic disease to direct neuronal infection by SARs-CoV-2 until protocols can be developed that allow for postmortem tissue investigations, and, in the absence of that, it is prudent to view neurologic outcomes, signs, and symptoms associated with COVID-19 through the lens of prior discoveries related to other HCoVs. The impact of COVID-19 on preexisting neurologic disorders and the impact of immunosuppressive and immunomodulatory therapies on the course of COVID-19 are currently unknown. Patient registries and improved testing for acute infection and exposure to SARS-CoV-2 will improve clinical decision-making in the management of neurologic disorders during the COVID-19 pandemic.

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TAKE-HOME POINTS

- Human coronaviruses have been shown to be neuropathogenic.
- Potential mechanisms of neuropathogenesis of SARS-CoV-2 include hematogenous and transsynaptic spread based on viral receptor expression.
- Neurologic sequelae of COVID-19 involve indirect, direct, and postinfectious disease mechanisms with consequences that include stroke, encephalitis/encephalopathy, and Guillain-Barré syndrome.
- Patient registries will be useful to identify and track neurologic sequelae of SARS-CoV-2 infection and will improve our understanding of the impact of COVID-19 on the nervous system.

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