Potential neuroinvasive pathways of SARS-CoV-2: Deciphering the spectrum of neurological deficit seen in coronavirus disease-2019 (COVID-19)

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Abstract
Coronavirus disease-2019 (COVID-19) was declared a global pandemic on 11 March 2020. Scientists and clinicians must acknowledge that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential to attack the human body in multiple ways simultaneously and exploit any weaknesses of its host. A multipronged attack could potentially explain the severity and extensive variety of signs and symptoms observed in patients with COVID-19. Understanding the diverse tactics of this virus to infect the human body is both critical and incredibly complex. Although patients diagnosed with COVID-19 have primarily presented with pulmonary involvement, viral invasion, and injury to diverse end organs is also prevalent and well documented in these patients, but has been largely unheeded. Human organs known for angiotensin-converting enzyme 2 (ACE2) expression including the gastrointestinal tract, kidneys, heart, adrenals, brain, and testicles are examples of extra pulmonary tissues with confirmed invasion by SARS-CoV-2. Initial multiple organ involvement may present with vague signs and symptoms to alert health care professionals early in the course of COVID-19. Another example of an ongoing, yet neglected element of the syndromic features of COVID-19, are the reported findings of loss of smell, altered taste, ataxia, headache, dizziness, and loss of consciousness, which suggest a potential for neural involvement. In this review, we further deliberate on the neuroinvasive potential of SARS-CoV-2, the neurologic symptomology observed in COVID-19, the host-virus interaction, possible routes of SARS-CoV-2 to invade the central nervous system, other neurologic considerations for patients with COVID-19, and a collective call to action.

KEYWORDS
brain, central nervous system, cerebrospinal fluid, coronavirus, COVID-19, neuroinvasive, neuron, neurotropic, olfactory, SARS-CoV-2, transcribrial

1 | INTRODUCTION

The first reports of a cluster of viral pneumonia in Wuhan, China emerged in late December 2019.1-3 The complete genome of SARS-CoV-2 from Wuhan, China was submitted on in the National Center for Biotechnology database on 17 January 2020.4 On 11 February 2020, the virus was given the taxonomic designation “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) and the World Health Organization (WHO) officially renamed the associated disease as coronavirus disease-2019 (COVID-19).1-3 On 11 March 2020,
WHO declared COVID-19 a global pandemic.\textsuperscript{1} As of 25 May 2020, per the Johns Hopkins COVID-19 Dashboard, there are currently 5,408,301 cases globally, with 345,104 associated deaths worldwide.\textsuperscript{5} In the United States (US) alone, there are 1,643,499 cases (30.3% of global cases) with 97,722 associated deaths (28.3% of global deaths).\textsuperscript{5} Despite entering the seventh month from the initial identification and spread of the zoonotic pathogen SARS-CoV-2, very little is known about viral transmission, organotropism, and pathogenesis, including the mechanisms behind the disturbing prevalence of cardiorespiratory failure in patients with COVID-19. The differential mortality observed in diverse populations concerning geography, culture, policy, age, sex, comorbidities, genetics, epigenetics, and systemic health inequity are captivating and require further study. Similarly, the overlaid and highly varied responses of the human immune system to SARS-CoV-2 are intriguing.

Since originating in China, the overarching spectrum of syndromic manifestations seen in patients with COVID-19 continues to perplex physicians and scientists worldwide.\textsuperscript{6,7} After a comprehensive examination of the potential routes of infection available to SARS-CoV-2 in humans, we postulate that widespread organ invasion as the major life-threatening aspect of viral pathogenesis, which also corresponds with the varied symptomatology seen in patients with COVID-19 (Figure 1). Involvement of the cardiorespiratory system and central nervous system (CNS) is particularly ominous, as they have been reported as the leading causes of morbidity and mortality in patients with COVID-19.\textsuperscript{6,7} Moreover, the sophisticated susceptibility of neuronal cells to injury, the location of cardiopulmonary regulatory centers in the brainstem, and the homeostatic regulatory functions performed by a healthy CNS in microbial infections are a few examples of the many functions the CNS is known to execute in health and diseases. This review explores current evidence of neurotropism and neurological injury caused by SARS-CoV-2 and further hypothesizes the multiple pathways to access and damage the CNS in COVID-19.

\textbf{FIGURE 1}  Proposed pathogenesis of SARS-CoV-2 to invade the human CNS. Source: Possible access to the human CNS by viral invasion includes the hematogenous route, neuronal retrograde dissemination route, and transcribrial route detailed in this manuscript. The virus can access the CNS through the blood vessels, peripheral neurons, or cerebrospinal fluid (CSF), and then directly damage the brain and nerves, as evidenced by recent autopsy studies.\textsuperscript{8-13} Access to the vasculature has been established by the extensive endothelial damage seen in postmortem examinations and pathological study of patients with COVID-19.\textsuperscript{8-17} SARS-CoV-2 has been found in the mucosa of the nose, mouth, and eyes, lungs, liver, kidney, heart, brain, gastrointestinal tract, sperm, and placenta suggesting an affinity for organs with a higher angiotensin-converting enzyme 2 (ACE2) receptor count/expression.\textsuperscript{8-13,18-19,43} Interestingly, the CNS, eyes, testes, and placenta are all immune-privileged organs. The local endotheliitis, tissue, and organ damage, can lead to widespread inflammation potentially resulting in a cytokine storm picture that has also been frequently observed in patients with COVID-19.\textsuperscript{44-47} Furthermore, as the ACE2 receptor is the host binding site for SARS-CoV-2, there is potential for decreased available ACE2 in the serum and increased circulating angiotensin II (AngII), creating a hypercoagulative state, and predisposing patients with COVID-19 to pulmonary embolism (PE), deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), and stroke.\textsuperscript{48-51} COVID-19, coronavirus disease-2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
2 | NEUROTROPIC VIRAL PATHOGENS: OTHER CoVs AND SARS-COV-1

SARS-CoV-2 causes a wide variety of symptoms across organ systems in patients with COVID-19. A significant amount of evidence exists showing that other viruses and coronaviruses specifically can invade the CNS and induce neurological symptoms. In addition, one study of 18 autopsies positive for SARS-CoV-1 found that viral genome sequences were detected in the brains of all SARS autopsies with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays. The route of initial SARS-CoV-1 infection to the brain remains unclear, but the viral presence was definitively established in the CNS. Animal studies using transgenic mice have shown that SARS-CoV-1 administered via transnasal route could enter the brain, potentially along the olfactory nerves and spread to specific brain areas including the thalamus and brainstem.

3 | NEUROLOGIC SYMPTOMATOLOGY IN COVID-19

3.1 | Hyposmia, hypogeusia, headache, and dizziness

An ongoing, yet neglected element of the syndromic features of COVID-19, is the reported findings of loss of smell and altered taste (Figure 2A,B), ataxia, headache, dizziness, and loss of consciousness. Initial reports from China detailed various clinical features of patients with COVID-19, including symptoms concerning for possible neurological deficit confirmed by physical examination (Figure 2C-E). Of over 200 initial patients evaluated in China, researchers found that severe neurological symptoms were more likely to occur in patients with severe disease. However, nonsevere patients also had episodes of
acute cerebrovascular disease, impaired consciousness, respiratory failure (Figure 2F), and skeletal muscle injury. Rates of dizziness (17 [19.3%], 19 [15.1%]) and headache (15 [17%], 13 [10.3%]) were similar in both severe and nonsevere groups. Interestingly, both hypogeusia (9 [7.1%], 3 [3.4%]) and hyposmia (8 [6.3%], 3 [3.4%]) were significantly higher for the nonsevere group vs severe group, respectively, suggesting an early stage of viral transmission causes direct injury to the epithelium of the nasal/oral mucosa or nasal/oral peripheral nerves. The US Centers for Disease Control and Prevention, WHO, American Society of Otolaryngology and Head-Neck Surgery, as well as the Ear, Nose, and Throat surgeons in the United Kingdom (UK) at the Royal College of Surgeons, have newly recognized loss of smell and altered taste as significant symptoms in patients with COVID-19.

3.2 | Altered mental status and cardiorespiratory failure

The neuroinvasive potential of SARS-CoV-2 and possible role in the acute cardiorespiratory failure of patients with COVID-19 was first proposed by Li et al. in February 2020. In early March 2020, neurotropic mechanisms of SARS-CoV-2 targeting the human CNS were further described. Since that time, several more studies have questioned the impact of SARS-CoV-2 on the human neurological system. Further consideration is warranted that the acute cardiorespiratory failure observed in patients with COVID-19 could directly result from the neurovirulent effect of SARS-CoV-2 to induce the cessation of cardiac function and spontaneous breathing at the level of the brainstem (Figure 3B), which has necessitated the current demand and use of mechanical ventilators (Figure 2F) in the management of these patients.

**FIGURE 3** Route of CNS Spread of SARS-CoV-2 via Transcribrial Route. Olfactory mucosa and olfactory bulb (OB) are affected by SARS-CoV-2 entry via the nose (A and B). The nasal and the oral loads cause the virus to then enter the lungs via trachea and bronchi (B, downward arrow) resulting in pneumonia. The nasal load can become a source to affect the olfactory bulb and cleft (B, green circle) by initial infection and inflammation around the cells present in the olfactory mucosa (A, bottom segment) resulting in anosmia. The viral load resulting from rupture of the cells extending from the nasal mucosa to the olfactory bulb (A and B) via cribriform plate (A) can then be transported by the CSF (A, blue waves) to the adjacent and distant areas of the CNS. As CSF is present in the subarachnoid space of the meninges directly supporting the olfactory nerves, the virus can reach the CNS without breaching the BBB. [CNS, central nervous system; CSF, cerebrospinal fluid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2]
3.3 | Guillain-Barré syndrome

The New England Journal of Medicine, recently published a case series from Italy on five patients with COVID-19 who presented with Guillain-Barré syndrome (GBS). Of the five reported cases, four developed flaccid tetraparesis or tetraplegia, and three required mechanical ventilation.\(^\text{105}\) Notably, the cerebrospinal fluid (CSF) of all five patients tested negative for SARS-CoV-2 by RT-PCR assay. A recent publication from Spain also noted two patients with COVID-19 presenting with Miller Fisher syndrome, a variant of GBS, and polynueuritis cranialis.\(^\text{106}\) The CSF of both patients tested negative for SARS-CoV-2 by RT-PCR assay.\(^\text{106}\) Whether the prevalence of GBS is due to direct viral attack of the myelin sheath resulting in demyelination, or a secondary effect of blood-brain barrier (BBB) permeability due to widespread inflammatory response and cytokine storm in the CNS remains to be determined.\(^\text{44}\)

In addition, long and short term postviral sequelae will be important to monitor. Other neuroinvasive viruses including influenza, poliovirus, and human herpesviruses have invaded and damaged the CNS in a multitude of ways over time.\(^\text{61,107-109}\) Capacity for viral persistence, latency, or reactivation of SARS-CoV-2 are important areas of further study.

3.4 | Multisystem inflammatory syndrome in children

Of recent concern are the increasing cases in Italy, the United States (US), and the United Kingdom (UK) of a Kawasaki-type viral inflammatory illness in children newly termed multisystem inflammatory syndrome in children. A 14-year-old boy in the UK and three children in New York passed away from complications of this disease.\(^\text{110,111}\) Out of the series of eight published in the UK, the 14-year-old boy presented with a headache and suffered from a right middle cerebral artery and anterior cerebral artery infarction.\(^\text{110}\) The only other child to report an initial headache in the series had a severe biventricular impairment.\(^\text{110}\) Despite having close SARS-CoV-2 positive contacts, most children tested negative for the virus via nasal swab. However, five presented with conjunctivitis. Viral conjunctival swab results were not reported. Shockingly, all of the children “progressed to warm, vasogenic shock, refractory to volume resuscitation, and eventually requiring noradrenaline and milrinone for hemodynamic support,” despite a lack of significant respiratory involvement by SARS-CoV-2.\(^\text{110}\) In fact, seven children required mechanical ventilation for cardiovascular stabilization.\(^\text{110}\) These growing cases beg the question of both an occult route of infection as well as possible disruption of cardiorespiratory stability as a pathogenic mechanism of SARS-CoV-2 (Figure 1). Interestingly, the eye is also an immune-privileged site, conjunctivitis has been a documented phenomenon in COVID-19, and RT-PCR of conjunctiva and tears have tested positive for SARS-CoV-2 in several published studies.\(^\text{39,41,112-113,119}\)

4 | CASE REPORTS: POSITIVE CSF DATA AND ENCEPHALOPATHY

In addition to the cases cited above, there have been several other published case reports of encephalopathy in the literature.\(^\text{74,120-123}\) Of the five additional recently published cases of encephalopathy, three patients also had mild/moderate lung findings on chest radiograph and computed tomography (CT) of the chest. Two patients required intubation (Table S1).\(^\text{74,120-123}\) Furthermore, both China and Japan have documented cases of SARS-CoV-2 detected in the CSF.\(^\text{74,120}\)

4.1 | China

In China, a patient was diagnosed with viral encephalitis and SARS-CoV-2 was detected in CSF by gene sequencing. However, the official case report and further details have not yet been published.\(^\text{74}\)

4.2 | Japan

Japan reported a 24-year-old male with transient generalized seizures and negative nasopharyngeal (NP) swab, ultimately diagnosed with aseptic meningitis/encephalitis, and SARS-CoV-2 was detected in CSF by RT-PCR assay on day 1. The NP and CSF samples were retested with the same results.\(^\text{120}\) Imaging also revealed panparanasal sinusitis.\(^\text{120}\) Sampling technique, specimen transport process, lab processing, limited gene presence, or true testing error could all contribute to a false negative result on the NP swab. However, a negative NP swab also suggests the possibility of a viral invasion of the ocular or oral epithelium and peripheral nerve terminals via a synapse connected route, as there have been multiple reported cases of patients with COVID-19 and a negative NP swab test result.\(^\text{110,124}\)

4.3 | United States

In Michigan, a 58-year-old female with altered mental status (AMS), positive NP swab by RT-PCR assay, and suspected SARS-CoV-2 associated acute necrotizing encephalopathy was diagnosed by head CT and magnetic resonance imaging (MRI) of the brain. Unfortunately, the CSF sample was unable to be tested for SARS-CoV-2.\(^\text{121}\) The cause of these symptoms is still unclear, as to whether they were a result of intracranial cytokine storm compromising the BBB or direct viral neuroinvasion. In Florida, a 74-year-old male was diagnosed with encephalopathy and had a positive NP swab by RT-PCR assay, but again, CSF was unable to be tested for SARS-CoV-2.\(^\text{122}\) California also reported a 41-year-old female with meningoencephalitis and positive NP swab who presented with new-onset seizures in early April.\(^\text{123}\) After 9 days of hospitalization, the physicians were still unable to test her CSF for SARS-CoV-2. In addition, a 5-year-old girl
from Michigan with positive NP swab and meningoencephalitis requiring intubation and ventilation succumbed to her injuries on April 19th.\textsuperscript{125} A case report has not yet been published. As this is the second documented case of encephalitis with COVID-19 in Michigan, exploration of a more virulent strain of SARS-CoV-2 to the CNS may be justified, as China has released preliminary evidence that SARS-CoV-2 has acquired mutations capable of substantially changing its pathogenicity.\textsuperscript{126}

### 4.4 | Italy

A case from Italy was recently published involving a 60-year-old male with new-onset akinetic mutism and encephalopathy, positive NP swab, and negative CSF by RT-PCR assay tested twice.\textsuperscript{127} Specifics regarding the above cases have been detailed in Table S1; again exposing the diverse ways that COVID-19 challenges clinical diagnosis and management.

## 5 | VIRAL ATTACHMENT TO ACE2 EXPRESSED IN HOST CELLS

The variety of symptoms observed in patients with COVID-19 could be explained by the distribution of ACE2 receptors and multiplicity of their expression as described in the legend of Figure 1.\textsuperscript{18-24} Regarding viral transmission, recent data have shown high expression of ACE2 in the nose and mouth.\textsuperscript{25-29} ACE2 receptors have also been documented in the aqueous humor and retina but there is an overall scarcity of recent data on the eye concerning SARS-CoV-2.\textsuperscript{30-41,112,113,119}

### 6 | POTENTIAL NEUROINVASIVE ROUTES OPTED BY SARS-CoV-2

From our current understanding, SARS-CoV-2 is primarily transmitted via respiratory droplets to the mucous membranes through the inhalation route.\textsuperscript{2,3} Following local invasion, the virus could reach the CNS by several routes (Figures 1 and 3B).

#### 6.1 | Olfactory/transcribrial route to the CNS

Viruses causing upper respiratory tract infections can exploit the olfactory epithelium (OE) as a site for proliferation due to its location both being adjacent to the respiratory epithelium and having direct exposure to the host’s environment.\textsuperscript{128} SARS-CoV-2 possibly attaches to the OE via ACE2 receptors.\textsuperscript{2,3} The virus could then further invade the cells in the OE including the olfactory ensheathing cells that surround the olfactory neurons (ON). Preliminary evidence shows that non-neuronal cells in the OE (Figure 3A) express SARS-CoV-2 entry genes and are potentially direct targets for the virus.\textsuperscript{25} In Italy, ultrastructural analysis of a postmortem patient with COVID-19 examined the olfactory nerve, the gyrus rectus, and the brainstem at the level of the medulla oblongata (Figure 3B).\textsuperscript{129} Researchers found severe and widespread tissue damage and SARS-CoV-2 virion particles involving the neurons, glia, nerve axons, and myelin sheath.\textsuperscript{129} These findings support the potential for viral invasion of the olfactory mucosa (Figure 3A). In addition, a postmortem MRI study of patients with COVID-19 from Belgium revealed asymmetric olfactory bulbs (Figure 3A) with or without olfactory cleft obliteration in 4 out of 19 decedents.\textsuperscript{130}

Given the known cytopathic effects, replication of the virus likely potentiates cell rupture, resulting in the release of more virion into the surrounding tissues. It is well established that the OE via ON directly access the olfactory bulb (OB) through a horizontal segment of the ethmoid bone called the cribriform plate (Figure 3A).\textsuperscript{101,104} As the ON travel through the olfactory foramina in the cribriform plate, they also pass directly through the three layers of the cranial meninges (dura mater, arachnoid mater, and pia mater) before reaching the OB (Figure 3A).\textsuperscript{101,104} Consequently, the rupturing of infected cells through the subarachnoid space could directly release virion into the CSF (Figure 3A, blue zone). As evidence of the presence of CSF in the meninges that support the OB above is, the phenomenon of CSF rhinorrhea resulting from a fracture of the cribriform plate in trauma involving the base of the skull.\textsuperscript{131,132} The CSF circulation can then transport the virus throughout the CNS with or without overt damage to the BBB or the OB (Figure 3A). The intrathecal renin-angiotensin system and brain both express ACE2 and could also be potential targets for SARS-CoV-2.\textsuperscript{133,134}

SARS-CoV-2 selecting to manipulate this direct pathway would not be unexpected, as a plethora of viruses and pathogens have been reported to invade the CNS utilizing this exact route.\textsuperscript{88-100} The transcribrial route (Figure 3A, between the olfactory mucosa and olfactory bulb) has also been proposed as a potential route for drugs to bypass the BBB and also for stem cell delivery in neurodegenerative diseases.\textsuperscript{96,97} Localized epithelial inflammation, destruction, and damage to the OB (Figure 3A, TOP layer) has already been observed with other viral pathogens and correlated with decreased olfaction.\textsuperscript{98-100} This mechanism could potentially explain the diminished senses of smell and associated altered taste (Figure 2A,B) in patients with COVID-19.\textsuperscript{128}

#### 6.2 | Other potential routes to the CNS

Primary transmission via respiratory droplets supports further investigation of the mucous membranes of the eyes and mouth as other possible candidates for viral peripheral nerve invasion (Figure 1), as both the oral and ocular epithelium express ACE2.\textsuperscript{28-41} Direct invasion of the peripheral nerves in the nasal cavity leading to the trigeminal nerve has been proposed as a potential cause for headache symptoms in patients with COVID-19.\textsuperscript{30} There is also the potential for the virus to enter the peripheral vasculature via epithelial erosion and directly invade the circulation. Once in the blood, the virus may be able to
cross the BBB by causing damage to vessel integrity (Figure 1) and thus increasing permeability.\textsuperscript{48-51} Recently, the ultrastructural analysis of a postmortem patient with COVID-19 detected SARS-CoV-2 in the frontal lobe of the human brain (Figure 3B), specifically in the neurons and propagating in the capillary endothelium, (Figure 3) bolstering the possibility of a hematogenous route.\textsuperscript{78}

7 | ADDITIONAL NEUROLOGIC CONSIDERATIONS WITH COVID-19

7.1 | Cytokine storm and blood-brain barrier

From a neurological perspective, there are several other essential components to be considered. The significant burden of infection and associated organ and tissue damage could result in a cytokine storm (Figure 1), which has already been reported and could lead to clotting complications and potentially compromise the BBB.\textsuperscript{44-47}

7.2 | Increased risk for clot/stroke

In addition to neurotropism, the presence of a virus utilizing existing ACE2 receptors in endothelia of the blood vessels of multiple organs and serum, would reduce available circulating ACE2, and increase serum levels of angiotensin II. This phenomenon could predispose patients to microthrombi, acute clot, and stroke, which could explain the reported incidence of hypercoagulability in patients with COVID-19 (Figure 1).\textsuperscript{48-51}

8 | CALL FOR ACTION

8.1 | Autopsy evaluation of the CNS

Autopsy examinations and histopathology of patients infected with COVID-19 are expected to provide essential information and clarity in the coming weeks. Of the reported autopsies in China, the US, and worldwide, there is very limited data on the CNS, brainstem, or peripheral nerves of the eye, nose, and mouth.\textsuperscript{8-13} New postmortem examinations of patients with COVID-19 in Germany revealed that of 21 brains tested, > 8 were positive for SARS-CoV-2 by RT-PCR.\textsuperscript{13} The same authors initially reported on nonspecific brain findings including two patients with cerebral sclerosis and another with suspected septic encephalomalacia, although brain dissections are still pending.\textsuperscript{12}

8.2 | Increased data acquisition from COVID-19 autopsies

Notably, China has had markedly more time than the rest of the world to perform clinical investigations and autopsy examinations. Despite this advantage, there was an initial paucity of published autopsy and pathology reports on the CNS. Physicians and scientists from China have been vocal about their recommendations and need for more data.\textsuperscript{135-137} Dr Bin Cong, physician, and dean of the Hebei Medical University School of Forensic Medicine published a paper in February 2020 requesting to strengthen the use of autopsy to better comprehend SARS-CoV-2.\textsuperscript{136} Dr Hujun Wang, physician and chief expert in forensic medicine at Southern Medical University, also recognized the need of pathologic data on patients with COVID-19 to better understand human SARS-CoV-2 infection.\textsuperscript{137} The majority of initial published and available reports from China involving autopsy, predominately focused on procedure safety with scarce actual autopsy and pathology reports.\textsuperscript{11,14-17,137,138-140} Remarkably, only one full autopsy report was identified and able to be accessed in the full text during the early days of the COVID-19 outbreak in China.\textsuperscript{11} Even after the spread of COVID-19 in the US and Europe, with hundreds of deaths daily, autopsy examinations were not routinely performed and crucial data on organ involvement, and the CNS in particular, remained uninvestigated.

8.3 | Clinical attention to neurologic symptoms

Future neurologic case reports in patients with COVID-19 should include thorough consideration and evaluation of patients with AMS. Physical exams noting the extent of AMS, loss of frontal release reflexes, decerebrate or decorticate posturing, Glasgow Coma Scale, opisthotonos, Adie’s pupil, and trigeminal neuralgia will also be helpful to document an overt neurological deficit (Figure 2D,E). Patient symptoms of anosmia, dysgeusia, headache, eye pain, conjunctivitis, and sore throat are also important to report to better understand possible transmission pathways (Figure 2A,B). Radiological notation of the orbits, sinus, and dura may help further explain the route of infection. CSF testing for SARS-CoV-2 by RT-PCR assay should be done whenever possible and a negative test should be repeated to avoid a testing error. Notation of anticoagulation or cardiac studies would also be beneficial. In addition to imaging studies, there may also be a role for electroencephalogram in these patients, but widespread utility and guidelines have not yet been established.

8.4 | CSF testing

Many countries currently lack any approved testing for SARS-CoV-2 in the CSF. Frontline health care professionals need appropriate RT-PCR assay for CSF, as well as national and global guidance on who to test, when to test, and when to repeat testing.

9 | CONCLUSION

As observed with the taxonomically related SARS-CoV-1, SARS-CoV-2 has the potential to invade the CNS, as this pathogen has been isolated
from the brain and CSF of patients with COVID-19.\textsuperscript{13,74,120,129} Regardless of the multiple routes (Figure 1), the virus could take to reach the CNS, data is continuously emerging on the true extent of neurologic involvement of SARS-CoV-2. Acute respiratory failure resulting from neuronal damage to the medullary centers (Figure 2B) that control the spontaneous breathing process and cardiac function is conceivable and harrowing. In addition, a more avid receptor-binding domain is postulated to allow SARS-CoV-2 to attach more securely to the human ACE2 receptor and enable it to better infect cells and spread than SARS-CoV-1.\textsuperscript{1,41} The above literature and clinical observations merit urgent investigation by healthcare professionals and the scientific community into the extent of neuroinvasive potential with SARS-CoV-2, which if overlooked, could result in significantly higher morbidity and mortality for patients with COVID-19.

To fight this virus, we need transparency. We need access to all of the available autopsy and pathology data worldwide. The CNS, brainstem, and peripheral nerves of the eyes, nose, and mouth should be further examined in any existing autopsy specimens. Frontline clinicians also need appropriate testing of CSF with national and global testing guidelines.

Regardless of current specialty in surgery or medicine, the reality is that SARS-CoV-2 and COVID-19 will affect us all. The sub-specialization of medicine has siloed health care professionals, preventing us from seeing the true scope and complexity of this pathogen. The scientific and medical communities must collectively unite and form a multidisciplinary approach to understanding the effects this virus has on all of the various organ systems in the human body and we must act now.

CONFLICT OF INTERESTS
The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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