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Neurological Impact of Coronavirus Disease of 2019: Practical Considerations for the Neuroscience Community

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Key words
- COVID-19
- Encephalitis
- Guideline
- Neuroscience
- SARS-COV-2

Abbreviations and Acronyms
ACE: Angiotensin-converting enzyme
ACE2R: Angiotensin-converting enzyme 2 receptor
AIS: Acute ischemic stroke
AMS: Altered mental status
ARDS: Acute respiratory distress syndrome
AVM: Arteriovenous malformation
CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus disease of 2019
CSF: Cerebrospinal fluid
CT: Computed tomography
HSV: Herpes simplex virus
ICU: Intensive care unit
IVIG: Intravenous immunoglobulin
MRI: Magnetic resonance imaging
NHS: National Health Service
PPE: Personal protective equipment
RT-PCR: Reverse transcriptase polymerase chain reaction
SARS-CoV-1: Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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BACKGROUND: **The coronavirus disease of 2019 (COVID-19), which is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has recently been designated a pandemic by the World Health Organization, affecting 2.7 million individuals globally as of April 25, 2020, with more than 187,000 deaths. An increasing body of evidence has supported central nervous system involvement.**

METHODS: **We conducted a review of the reported data for studies concerning COVID-19 pathophysiology, neurological manifestations, and neuroscience provider recommendations and guidelines.**

RESULTS: **Central nervous system manifestations range from vague nonfocal complaints to severe neurological impairment associated with encephalitis. It is unclear whether the neurological dysfunction results from direct viral injury or systemic disease. The virus could affect brainstem pathways that lead to indirect respiratory dysfunction, in addition to direct pulmonary injury. Necessary adaptations in patient management, triage, and diagnosis are evolving in light of the ongoing scientific and clinical findings.**

CONCLUSIONS: **The present review has consolidated the current body of data regarding the neurological impact of coronaviruses, discussed the reported neurological manifestations of COVID-19, and highlighted the recommendations for patient management. Specific recommendations pertaining to clinical practice for neurologists and neurosurgeons have also been provided.**

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) has recently been designated as a pandemic by the World Health Organization.[1] COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV),[1] a member of the pathogenic *Coronaviridae* family. The *Coronaviridae* family includes enveloped positive sense single stranded ribonucleic acid viruses typically responsible for a spectrum of respiratory and gastrointestinal diseases.[1] Confirmed COVID-19 had afflicted 2.7 million patients globally as of April 25, 2020, with an associated mortality of 187,700 (7.0%).[2] SARS-CoV-2 is most closely related to severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), with a genetic homology of 76.9%.[3]

Although coronaviruses predominantly cause enteric and respiratory illness, members of *Coronaviridae* have a demonstrated ability to produce neuromuscular and neurological symptoms.[4-9] Experimental and clinical studies have suggested brainstem involvement and the potential for transneuronal virus transmission, in addition to misdirected host immune responses.[10-13] The exact mechanisms, however, for clinical neurological disease secondary to coronavirus infection remain unclear. Recent reports have indicated that SARS-CoV-2 is similarly capable of causing severe neurological disease,[14-16] including meningoencephalitis, various viral-associated necrotizing encephalitides similar to influenza-associated encephalopathy, and secondary cytokine-induced acute necrotizing syndromes seen with hemagglutinin 1 neuraminidase 1 influenza virus.[14-16] These findings highlight the dramatic effect on daily healthcare delivery during this pandemic,[17-20] making

COVID-19 an additional challenge in clinical neuroscience. The present review has consolidated the current body of knowledge on coronaviruses, with a focus on the nervous system, discussed the reported neurological manifestations of COVID-19, and highlighted the recommendations for patient treatment. Specific recommendations pertaining to clinical practice for neurologists and neurosurgeons have also been provided.

METHODS

We performed a review of the reported data using PubMed and Google Scholar to identify relevant English-language studies reported through April 25, 2020. The general terms included "coronavirus," "severe acute respiratory syndrome coronavirus," "SARS-CoV-2," "SARS-CoV," "MERS" [Middle East respiratory syndrome], and "COVID-19." These terms were used in combination with the terms "neurology," "neurological," and "neurosurgery" to identify case reports, retrospective studies, and studies on nervous system pathophysiology. Additional searches with the terms "management," "guidelines," "spine," "stroke," "trauma," "brain tumors," "transnasal," and "pediatrics" were used to identify studies with guidelines or recommendations for providers. We screened the studies for relevant reports using the title and abstract. Additional relevant studies were identified from a review of the citations referenced. The included number of studies stratified by subject was as follows: 27 that described pathophysiology, 18 that discussed guidelines for providers, 18 that presented or analyzed retrospective studies, 5 that included 6 case reports of neurological manifestations of COVID-19, and 4 that provided general information concerning disease history or epidemiology.

PATIENT DEMOGRAPHICS

Early prospective evidence from the presumptive origin of SARS-CoV-2 infection in Wuhan, the capital of the Hubei Province in the People's Republic of China, reported that the first 41 hospitalized patients with confirmed COVID-19 had had preexisting diabetes mellitus type 2 (20%), hypertension (15%), and cardiovascular disease (15%).[21] Expansion of this cohort to include an additional 162 confirmed cases in a subsequent, retrospective, multicenter study demonstrated the unique finding that older age was significantly associated with greater odds of mortality for every additional year of patient age.[22] This finding has been supported by the trends reported in other populations suggesting that COVID-19 disproportionately affects the elderly and is not consistent with the bimodal patterns of age distribution typical of moderate to severe viral disease.[23,24]

A systematic review and meta-analysis by Wang et al. evaluated 1558 patients with positive COVID-19 across 6 studies[21,25-29] and further identified chronic obstructive pulmonary disease (COPD) and cerebrovascular disease as significantly associated comorbidities.[30] Further studies identified obesity and kidney disease as potential risk factors for SARS-CoV-2 infection and predictors of COVID-19 severity.[31-34] Because many of these comorbidities will be present in patients undergoing treatment of neurological conditions, especially obese patients with ischemic occlusive and hemorrhagic cerebrovascular disease, neurological and neurosurgical patients will have increased risk.[22-31]

It is intuitive that severe pulmonary dysfunction via acute respiratory distress syndrome (ARDS) would exacerbate preexisting systemic disease via increased intrapulmonary shunting, decreased alveolar recruitment, increased pulmonary resistance, and hypoxemia.[22-31] Furthermore, a preexisting history of ischemic or hemorrhagic stroke has been demonstrated to be a significant risk factor for the development of ARDS in the neurointensive setting,[22-31] and, therefore, it becomes critical to differentiate direct viral injury from systemic pathophysiology.

TRANSMISSION, PATHOPHYSIOLOGY, AND PRESENTATION OF NEUROLOGICAL DISEASE

Most of the available knowledge on SARS-CoV-2 pathophysiology has been derived from data regarding SARS-CoV-1.[32] Both viruses have been shown to enter lower respiratory epithelium via a spike protein (encoded by the viral S gene) attachment to the angiotensin-converting enzyme (ACE) 2 receptor (ACE2R).[32-34] Although the similarity is less than 75% between the S gene in the 2 viruses and the receptor-binding domain is well conserved, SARS-CoV-2 S still provides a significant increase in receptor affinity.[3,32-34] Early reports recommended avoidance of ACE inhibitors and angiotensin receptor blockers because of a presumed increase in the available binding sites resulting from decreased functional competitive inhibition.[35] However, these agents have not been shown to increase ACE2R density, and preliminary studies have shown that ACE inhibitors and angiotensin receptor blockers might actually confer benefit.[35-39]

Although ACE2R is found primarily in lung alveolar epithelium,[40] it is also present on the surface of central nervous system (CNS) neurons, which suggests potential neurotropism.[41] SARS-CoV-2 can enter the CNS either directly from contiguous spread from nasopharyngeal mucosa through the cribriform plate or hematogenously secondary to viremia,[42] because both upper airway epithelium and vascular endothelium express ACE2R.[40] An axodendritic transsynaptic route has been reported as a potential mechanism for CNS dissemination.[10,43] Rodent models infected with intranasal SARS-CoV-1 have demonstrated particular tropism for the cerebrum, thalamus, and rhombencephalon derivatives typical of viral encephalitis.[44]

Although *Coronaviridae* CNS entry has been well documented, the role in neurological disease remains under investigation.[45,46] Reports have implicated potential central involvement of respiratory failure compounding primary pulmonary injury via direct infection of the pontine and medullary respiratory centers by COVID-19.[10] With a median symptom onset of 8 days for the development of ARDS, SARS-CoV-2 CNS involvement is possible by the time of intensive care unit (ICU) admission, strengthening the consideration of a mixed central and peripheral etiology of pulmonary compromise.[25]

Additionally, SARS-CoV-2 can incite noninflammatory encephalopathy, which has been previously implicated in SARS-CoV-1 infection.[47] Neurological manifestations of SARS-CoV-1 include seizure, generalized polyneuropathy,

Table 1. Published Case Reports of Severe Neurological Manifestations of Coronavirus Disease of 2019

Pt. No.	Investigator	Age; Sex	Symptoms	Diagnostic Testing	Other Testing	Treatment	Outcome
1	Poyiadji et al.[15]	Late 50s; F	Neur: AMS; non-Neur: fever, cough	Swab: influenza (−), COVID-19 (+); CSF: HSV-1/2 (−), VZV (−), WNV (−), COVID-19 (NA)	MRI: hemorrhagic rim enhancing lesions within bilateral thalami, medial temporal lobes, subinsular regions	IVIG	NR
2	Filatov et al.[14]	74; M	Neur: HA, AMS; non-Neur: fever, cough	CXR: right pleural effusion with bilateral GGO; swab: influenza (−), COVID-19 (+); CSF: HSV-1/2 (−), VZV (−), CMV (−), RSV (−) COVID-19 (NA)	CT head: no acute abnormalities, encephalomalacia in left PCA territory consistent with history of embolic stroke; EEG: bilateral slowing and focal slowing in left temporal region with sharply countered waves	AEDs, vancomycin, meropenem, acyclovir, HCQ, lopinavir, ritonavir	Remained in ICU with poor prognosis
3	Moriguchi et al.[16]	24; M	Neur: HA, AMS, seizure, neck stiffness; non-Neur: fever, fatigue, sore throat	CXR (−); CT chest: GGO; swab: influenza (−), COVID-19 (−); CSF: 320 mm H_2O, HSV-1/2 (NA), VZV (NA), COVID-19 (+); serum: HSV-1 (−), VZV (−)	CT head: no evidence of brain edema; MRI, DWI: HI along wall of inferior horn of right lateral ventricle; FLAIR: HI in right mesial temporal lobe and hippocampus with slight hippocampal atrophy; no dural enhancement with contrast	Laninamivir, ceftriaxone, vancomycin, acyclovir, levetiracetam, favipiravir	Remained in ICU
4	Yin et al.[52]	64; M	Neur: AMS, neck stiffness, ankle clonus; non-Neur: fever, cough, muscle soreness	Chest CT: GGO; swab: COVID-19 (+); CSF: 200 cm H_2O, COVID-19 (−)	Physical examination: Brudzinski (+), left Babinski (+), right Chaddock (+); head CT (−)	Arbidol, ribavirin	Full recovery except for left lower extremity Babinski; discharged to quarantine facility
5	Gutiérrez-Ortiz et al.[53]	50; M	Neur: diplopia, perioral paresthesia, gait instability, anosmia, ageusia, HA; non-Neur: fever, cough, low back pain	Chest CT (−); CXR (−); swab: COVID-19 (+); serum: GD1b-IgG (+); CSF: 110 cm H_2O, COVID-19 (−)	Physical examination: broad-based ataxic gait; absent DTR in UE/LE; relevant afferent pupillary defect; right internuclear ophthalmoparesis; right fascicular oculomotor palsy	IVIG	Resolution of all neurological features, except for residual anosmia and ageusia
6	Gutiérrez-Ortiz et al.[53]	39; M	Neur: diplopia, ageusia; non-Neur: fever, diarrhea	Chest CT (−); CXR (−); swab: COVID-19 (+); CSF: 100 cm H_2O, COVID-19 (−)	Physical examination: esotropia; bilateral abducens palsy; absent DTR in UE/LE	Supportive	Full neurological recovery in 2 weeks

Pt. No., patient number; F, female; Neur, neurological; AMS, altered mental status; HA, headache; COVID-19, coronavirus disease of 2019; CSF, cerebrospinal fluid; HSV, herpes simplex virus; VZV, varicella zoster virus; WNV, West Nile virus; NA, not available; MRI, magnetic resonance imaging; IVIG, intravenous immunoglobulin; NR, not reported; M, male; CXR, chest radiograph; GGO, ground glass opacities; CMV, cytomegalovirus; RSV, respiratory syncytial virus; CT, computed tomography; PCA, posterior cerebral artery; EEG, electroencephalography; AEDs, antiepileptic drugs; HCQ, hydroxychloroquine; ICU, intensive care unit; DWI, diffusion weighted imaging; HI, hyperintensities; FLAIR, fluid-attenuated inversion recovery; DTR, deep tendon reflexes; UE/LE, upper extremity/lower extremity.

mixed axonal neuropathy, and primary myopathy.[7,48,49] Tsai et al.[49] noted that although the neuromuscular disorders were considered secondary to critical illness, evidence remained for direct viral injury of motor units. Similarly, in Middle East respiratory syndrome, viral-associated encephalopathy has been reported with confusion, coma, ataxia, and focal motor deficits.[9]

An early retrospective series from clusters in Wuhan reported associated clinical CNS involvement in 36.4% of COVID-19 cases throughout the disease course, which increased to 45.5% in those with severe disease.[50] Mild CNS involvement entailed dizziness (16.8%), headache (13.1%), ataxia (0.5%), hypogeusia (5.6%), and hyposmia (5.1%) and peripheral symptoms such as neuralgia (2.3%).[50] Severe neuromuscular and CNS manifestations included skeletal muscle injury (10.7%), acute cerebrovascular disease (2.8%), and epilepsy (0.5%).[50] An additional observational series by Helms et al.[51] showed that 84% of their patients had neurological signs, including confusion (65%), agitation (69%), corticospinal tract signs (67%), and dysexecutive syndrome (36%).[51] Of 13 patients who had undergone brain magnetic resonance imaging (MRI), 8 (62%) showed leptomeningeal enhancement.[51]

It is difficult to differentiate symptoms due to primary viral injury from those resulting from secondary systemic involvement characteristics in an ICU setting.[50,51] Just as for all critically ill patients, it is vital that intensivists and primary care physicians monitor for neurological manifestations of COVID-19, because these could indicate, and potentially precede, progression to severe disease.[44-50]

CASE REPORTS OF SEVERE NEUROLOGIC MANIFESTATIONS OF COVID-19

To the best of our knowledge, 6 individual cases of neurological manifestations have been reported (**Table 1**). The symptoms ranged from generalized encephalopathy to those consistent with viral encephalitis/meningitis and peripheral neuropathy.[14-16,52,53] Encephalitides were heterogeneous, with those of 1 patient resembling the necrotizing form typical of orthomyxoviruses and those of another having focal mesial involvement characteristic of the herpesviruses.

Case 1 involved a female airline worker in her late 50s with real-time reverse transcriptase polymerase chain reaction (RT-PCR)–confirmed COVID-19 who had presented with a 3-day history of cough, fever, and altered mental status (AMS).[15] Noncontrast-enhanced computed tomography (CT) demonstrated symmetric hypoattenuation within bilateral medial thalami.[15,44] The vascular imaging findings were normal, but MRI demonstrated hemorrhagic rim-enhancing lesions within bilateral thalami, medial temporal lobes, and subinsular region, reminiscent of acute necrotizing encephalopathy associated with influenza-associated encephalopathy.[14-16] Cerebrospinal fluid (CSF) analysis was sterile at 3 days and negative for herpes simplex virus (HSV)-1 and -2, varicella zoster virus, West Nile virus, and fungal antigens.[15] The CSF chemistry findings were nondiagnostic.[15] A presumptive diagnosis of viral-associated acute hemorrhagic necrotizing encephalopathy was given, and the patient was treated with intravenous immunoglobulin (IVIG).[15] The patient's outcome was not reported[15] but was presumably poor, considering the high mortality associated with this condition.

The second case involved a 74-year-old man with a history of atrial fibrillation, acute ischemic stroke (AIS), Parkinson's disease, and COPD who had presented with fever and cough.[14] The results of the chemistry panels and chest radiographs were normal. However, after being discharged and treated for COPD exacerbation,[14] the patient was readmitted within 24 hours with worsening respiratory symptoms, headache, and delirium.[14] A repeat chest radiograph confirmed a small right pleural effusion and bilateral ground glass opacities. The SARS-CoV-2 PCR test was positive.[14] The patient deteriorated neurologically into a nonverbal, unresponsive state and localized to stimulation.[14] Head CT was unrevealing. However, electroencephalography showed bilateral diffuse slowing typical of encephalopathy and focal slowing in the left temporal region, with sharply contoured waves suspicious for epileptiform activity.[14] Antiepileptic drugs were given for nonconvulsive seizures.[14] Brain MRI was not conducted.

The patient developed ARDS requiring intubation and anti-inflammatory drugs, viral protease inhibitors (i.e., hydroxychloroquine, lopinavir, and ritonavir), and broad-spectrum antibiotics were started.[14] CSF analysis was normal, except for slightly elevated protein levels (68 mg/dL).[14] The PCR results for HSV-1 and -2, cytomegalovirus, and respiratory syncytial virus were negative.[14] The source of encephalopathy was indeterminate because of an incomplete workup.

Case 3 involved a 24-year-old man with confirmed COVID-19 who had presented with a 9-day history of worsening headache, fatigue, fever, and sore throat.[16] The patient developed a generalized tonic clonic seizure during transport to the hospital.[16] A Glasgow coma score of 6 necessitated intubation, and he progressed to status epilepticus.[16] The head CT findings were negative, but the chest CT scan demonstrated small ground glass hyperdensities in the right superior and bilateral inferior lobes.[16] The CSF test results were normal, and the opening pressure was 32 cm H_2O. Antibodies against HSV-1 and varicella zoster virus were negative.[16] However, COVID-19 infection was confirmed by CSF SARS-CoV-2 real-time RT-PCR despite negative nasopharyngeal swab results.[16] The patient was treated with intravenous ceftriaxone, vancomycin, acyclovir, corticosteroids, and levetiracetam.[16] The viral protease inhibitor favipiravir was started on the second day of admission.[16] Brain MRI showed diffusion restriction along the wall of the right temporal horn, and fluid-attenuated inversion recovery sequences revealed hyperintensity of the right mesial structures common in herpes encephalitis.[16] The patient remained in the ICU with a poor prognosis.

Case 4 involved a 64-year-old man who had initially had 2 days of fever, cough, insomnia, and muscle soreness.[52] His fever and cough had resolved with symptomatic treatment; however, 10 days later he was found lethargic and unresponsive. Head CT showed no abnormalities. A throat swab RT-PCR assay performed the next day was positive for SARS-CoV-2. Neurologic examination showed neck stiffness, AMS,

Table 2. Summary of Provider Guidelines Related to Neurology and Neurosurgery Patients, Adapted From Current Data as of April 25, 2020

Management guidelines pertaining to neuroscience community
General practice
Have all personnel trained on proper PPE wear, nasopharyngeal sampling techniques, and examining patients with COVID-19[19]
Use telemedicine for consultations when appropriate[19]
Wear proper PPE when performing LPs and placing EVDs
Clinic
Use telemedicine when appropriate[59]
Surgery
Elective: halt all elective cases[59]
Urgent: consult multidisciplinary review committee[59]
Emergent: continue as indicated, with heightened attention to PPE[59]
Operating room safety: act as if every patient is infected with SARS-CoV-2 and wear PPE (N95 mask and droplet attire) accordingly[60]
Management for specific fields
Stroke
Wear proper PPE when in contact with the patient[20,61]
Require COVID-19 screening before stroke scale assessment[19]
Consider mobile CT units and designated areas for COVID-positive or COVID-suspected patients, where available[62]
Consider prophylactic intubation before angiography or MT for patients at high risk of respiratory failure[61]
Neuro-oncology
Low grade: consider delaying treatment if possible[63]
Malignant: consider treatment on a case by case basis, weigh risks of tumor progression versus risk of COVID-19 complications[63]
Chemotherapy: minimize contact with patient, consider conservative doses, halt chemotherapy if patient develops viral symptoms[63]
Radiotherapy: continue for younger patients with mild symptoms, consider shorter courses for older patients with comorbidities[63]
Transnasal surgery
Implement preoperative COVID-19 testing[64]
Postpone nonemergent cases for patients who test positive until their infection has cleared and a repeat test result is negative[64]
PAPR for emergent cases with patients who test positive[64]
Spine surgery
Determine whether pathology requires emergent intervention and consider conservative management when appropriate, especially for patients with COVID-19[65-67]
Use minimally invasive procedures, prone positioning, special care with suction devices, and gentle procedures when possible[65]
Pediatrics
Limit patient interactions for staff and visitors[68]

PPE, personal protective equipment; COVID-19, coronavirus disease of 2019; LP, lumbar puncture; EVD, external ventricular drain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CT, computed tomography; MT, mechanical thrombectomy; PAPR, powered air-purifying respirator.

bilateral ankle clonus, and positive Brudzinski, left Babinski, and right Chaddock signs. The patient was treated with oxygen, umifenovir (Arbidol, JSC Pharmstandard, Dolgoprudny, Russia), ribavirin, traditional Chinese medicine, and supportive care. Five days later, the CSF findings were normal and the opening pressure was 20 cm H_2O. CSF was negative for SARS-CoV-2. Nine days later, his neurological examination findings had normalized, and he was discharged on day 11 after 2 consecutive throat swabs with negative findings.

Case 5 was of a 50-year-old man who had presented with a 2-day history of diplopia, perioral paresthesia, anosmia, ageusia, and gait instability, in addition to a 5-day history of fever, cough, headache, and low back pain.[53] His examination findings were consistent with right internuclear ophthalmoparesis and right fascicular oculomotor palsy. His serum was positive for the GD1b-IgG antibody, and an oropharyngeal swab was positive for SARS-CoV-2 using real-time RT-PCR. However, the CSF results were negative.

He was treated with IVIG 0.4 g/kg for 5 days and had resolution of his neurological symptoms (except for anosmia and ageusia) within 2 weeks. Case 6, reported by the same investigators, was of a 39-year-old man who had presented with a 3-day history of diplopia, diarrhea, and a low-grade fever.[53] Although his mentation was normal, he had bilateral abduction deficits and fixation nystagmus. His deep tendon reflexes were absent. The oropharyngeal swab was positive for SARS-CoV-2 using real-time RT-PCR; however, the CSF results were negative. The patient was treated symptomatically and had completely recovered by the 2-week follow-up examination.

These cases illustrate the different manifestations and rapid progression of CNS involvement. In the first 4 cases, each patient had presented with cough and fever and had rapidly developed AMS.[14-16,52] In patients 5 and 6, their mental status had remained normal but both patients had presented with cranial and peripheral nerve deficits.[53] In all cases, the CSF analysis was unrevealing, except for that for patient 3, which had confirmed the presence of SARS-CoV-2 despite negative nasopharyngeal swab results.[16] This raises significant concern for provider safety for those performing intrathecal procedures, because it is unclear whether the virus can be transmitted from CSF to the mucus membranes, which has been demonstrated for in human immunodeficiency virus 1 and 2.[54] This also underscores that a negative nasopharyngeal swab finding cannot definitively rule out active COVID-19 infection and might indicate the need for CSF PCR testing in neurologically affected patients.

GUIDELINES FOR MANAGEMENT OF NEUROLOGICAL SYMPTOMS

General Guidelines for Approaching Patients

Although severe COVID-19–associated CNS disease is rare,[14-22] mild neurological symptoms are common.[14,50] These symptoms include loss of smell and taste, headache, nausea, vomiting, paresthesia, and mild seizures.[16,55,56] A study by Beltrán-Corbellini et al.[56] showed that new-onset anosmia and ageusia were significantly more frequent among patients with COVID-19 than among those with influenza and can suggest infection. Although mild involvement is difficult to attribute to primary viral injury,[55] it is critical to also recognize CNS signs such as AMS and seizures as potential presenting symptoms of SARS-CoV-2 infection.[16] Management strategies have highlighted the need for urgent screening and detection of SARS-CoV-2 in these patients; however, it should be noted that a negative nasal swab real-time RT-PCR finding does not necessarily rule out the presence of COVID-19.[16] Studies have reported cases of patients with vague complaints of fever and headache who were admitted to the neurology service after testing negative for COVID-19 but who later tested positive using real-time RT-PCR as their symptoms progressed.[50] Early CSF analysis should be considered when early CNS involvement is detected to allow for implementation of anti-inflammatory interventions and escalation of care.[19,55] Waldman et al.[19] established guidelines for patients with neurological symptoms that minimize healthcare exposure by limiting the number of providers in patient rooms, bundling laboratory orders, adjusting medication administration, and altering the frequency of neurological examination to a minimum necessary to provide effective care.

Specific Diagnosis Strategies

As the current pandemic evolves, diagnostic and treatment strategies will be updated.[55] The case of patient 3 underscores the need for increased vigilance of patients with neurological manifestations with initial negative test results using the nasopharyngeal swab and suggests the utility of CSF PCR for diagnosis.[16] Cranial imaging should be used judiciously to minimize the risk of transmission to healthcare workers. Patients with CNS involvement have had significantly lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels than patients without CNS involvement, which could aid in evaluating and stratifying disease severity.[50]

Treatment Strategies

Treatment with IVIG and corticosteroids has varied.[15] IVIG might mitigate severe cytokine storming and alleviate secondary vasogenic edema.[15,55] Seizures should be managed with antiepileptic drugs[14] and, given anecdotal evidence, anti-inflammatory and/or antiparasitic drugs, hydroxychloroquine, and viral protease inhibitors such lopinavir and ritonavir could be considered.[14,57]

The increased prevalence of acute cerebrovascular disease in patients with severe infection is thought to be related to elevated D-dimer levels, which have been previously shown to correlate with unfavorable outcomes in stroke patients.[50,58] Patients with COVID-19 appear to be hypercoagulable with a propensity for thromboemboli, and venous thromboembolism prophylaxis should be started when indicated. Furthermore, cerebrovascular disease is a known predisposing factor for the development of ARDS,[50,58] and, although no specific guidelines exist regarding preexisting stroke or elevated D-dimer levels, these patients require increased vigilance.

GUIDELINES FOR NEUROLOGY AND NEUROSURGERY DEPARTMENTS

A summary of reported guidelines and recommendations is provided **Table 2**.

Ensuring the Safety of Providers Throughout the Hospital

Waldman et al.[19] advocated for training of all neurology team members on nasopharyngeal sampling techniques, personal protective equipment (PPE) conservation and usage, and protocols for examining patients with suspected infection, with special care during lumbar punctures and ventriculostomies.[16]

Providers at Columbia University Irving Medical Center and New York Presbyterian Hospital have emphasized a transition to "curbside" consultations for nonurgent patients and telemedicine, especially for strokes,[19] which has had widespread success in the management of acute cerebrovascular disease in accredited comprehensive stroke centers.[54] Other changes include cessation of all clinical trials that require patent contact in facilities lacking PPE.[19]

To protect operating staff, Forrester et al.[60] advocated for treating all patients as presumptively positive for COVID-19 unless definitely shown otherwise. For urgent surgery that could be delayed 24 hours, SARS-CoV-2 real-time RT-PCR was conducted before the procedure.[60] For confirmed positive or presumptively positive patients in the absence of testing, N95 respirator masks and droplet attire were required for every person in the operating room, including the cleaning staff.[60] Providers not directly involved in intubation were advised to leave the room owing to the high risk of virus transmission.[60] Zou et al.[65] described additional safety measures such as using minimally invasive approaches, prone positioning, and caution when suctioning. Burke et al.[69] reported a checklist that can be distributed to anesthesia, nursing, and operating room staff to provide objective data about which neurosurgical cases will be scheduled and the resources required.

The adequacy of protection provided by N95 respirators for both aerosolizing and nonaerosolizing procedures is uncertain and controversial, with some advocating their use is excessive for nonaerosolizing interventions and not cost-effective, and others arguing the opposite.[70,71] Until the transmission risk is better understood, the safest option is to use respirators for all procedures involving positive and presumptively positive patients.

Guidelines for Clinic and Elective Cases

To decrease exposure while maintaining consultative services, many neurosurgical and neurology departments have shifted to a telemedicine approach for both clinic and postoperative care.[19,55,59,69,72] Secure videoconferencing and proper documentation of telehealth visits are reimbursable, and although they can decrease the number of clinic visits overall, persistent numbers of patient interactions have been reported.[59] Ochsner Health Neurosciences in New Orleans (Louisiana, USA) has converted to an almost exclusive telemedicine platform using audio and video virtual clinic visits, except in the event of neurological deficits or situations requiring wound management. Patients can be screened virtually and, if found to have a neurological deficit, a traditional clinic visit can be scheduled. For specific conditions such as migraine management, providers have called for insurance companies to relax regulations and broaden access to anti–calcitonin gene-related peptide drugs to decrease the number of botulinum injections in the clinic.[72] However, Waldman et al.[19] proposed continuing botulinum injections in an effort to decrease emergency department usage and exposure.

Guidelines for Urgent and Emergent Cases

Burke et al.[69] described a neurosurgical treatment algorithm that provides scheduling recommendations for elective and urgent cases according to the disease burden in the community. Moreover, they recommended limiting the number of cases, instead of the types of cases, to allow surgeons to triage their own schedule.[69] Eichberg et al.[59] described developing a multidisciplinary review committee for all urgent cases, including malignant brain tumors and progressive cervical spondylotic myelopathy. Emergent cases such as cauda equina syndrome, AIS, and ruptured intracranial aneurysms or arteriovenous malformations (AVMs) that require emergent or urgent surgery should be continued without need for the review committee.[59] Patients should be screened for COVID-19 in the preoperative window and, if possible, a 2-week delay implemented for those with a positive result.[59] Postoperative management of uncomplicated craniotomies and endoscopic skull-based procedures could even defer ICU placement, with a greater emphasis placed on step-down units in an effort to conserve ICU availability.[59]

Lombardy, Italy, implemented a comprehensive, largescale neurosurgical approach.[73] The regional neurosurgical infrastructure was restructured, with 4 of 21 hospitals deemed “hubs” for accepting all urgent and emergent neurosurgical cases.[73] These included cerebral hemorrhages (subarachnoid and intraparenchymal), acute hydrocephalus, and spinal cord compression.[73]

Guidelines for Stroke Care Providers

Because emergent mechanical thrombectomy is the reference standard for the treatment of large vessel occlusion, there is little room to alter the assessment process.[74] Khosravani et al.[20] advocated for continued telemedicine and, when direct clinical evaluation is necessary, maximum PPE usage from the initial paramedic evaluation and hospital code determination to the intraoperative intervention. Additionally, the Society of NeuroInterventional Surgery has recommended that providers continue the normal inclusion and exclusion therapy for mechanical thrombectomy.[61] Prophylactic intubation should be considered for patients with severe deficits owing to the high contamination risk of intraprocedural intubation.[61]

All patients presenting with stroke symptoms should undergo infection screening.[20] The stroke protocol at Columbia University Irving Medical Center and New York Presbyterian Hospital was updated to include COVID-19 screening, including temperature and oxygen saturation levels, before performing the National Institutes of Health stroke scale.[19] Baracchini et al.[62] maintained a safe stroke unit in Veneto, Italy by using a mobile CT scanner for patients positive or suspected to be positive for COVID-19. Fraser et al.[61] recommended that if multiple angiography suites are available, one should be designated a “COVID-19 room” and stocked with enhanced PPE. In addition, if possible, all patients with AIS who have undergone thrombectomy should undergo COVID-19 testing to help preserve resources during their postoperative care.[61]

Guidelines for AVMs and Aneurysms

Patients with ruptured aneurysms should be treated according to the emergent nature of the disease[59] and should be admitted to the neurocritical care unit or a COVID-19–equipped respiratory critical care unit with appropriate neurocritical care services to maintain subarachnoid hemorrhage management protocols. Although no specific guidelines pertaining to aneurysms and AVMs are available, conservative treatment should be used until elective cases can be resumed, if possible. Both symptomatic and nonsymptomatic giant unruptured aneurysms should be considered on an individual basis. The risks and benefits of treatment timelines should be discussed with interdisciplinary care

teams and family members. Patients with ruptured AVMs should be admitted to an appropriate critical care unit with recommended management protocols in place to stabilize the intracranial hemorrhage, monitor for hydrocephalus and intracranial hypertension, and screen for high-risk associated aneurysms that might require urgent intervention. Most patients with ruptured AVMs might be able to be discharged once the primary bleeding site has been stabilized and plans for delayed, elective treatment have been completed. When cases are emergent or cannot be delayed, patients should undergo rapid COVID-19 testing, if available, and should be treated as presumed positive with maximum PPE used.

Guidelines for Brain Tumor Management

Treatment of slowly progressive tumors without significant associated vasogenic edema such as low-grade gliomas and extra-axial masses can be delayed, and these patients should be monitored with surveillance imaging.[63] For high-grade gliomas, Mohile et al.[63] reported specific guidelines and advocated for continuing the standard of care for younger patients but possibly refusing surgical intervention for older patients with frailty or comorbidities. The European Organization for the Research and Treatment of Cancer glioblastoma calculator (available at: https://www.eortc.be/tools/gbmcalculator/) can be used to help make objective decisions based on the patient's health status. Regardless of age, the benefit of standard therapy for high-grade gliomas likely outweighs the risk of complications or death from COVID-19.[63] Conservative measures and denial of life-extending therapy should be carefully considered and addressed with the patient and family.

Clinic visits for neuro-oncology patients should be reserved for those absolutely requiring an in-person examination or radiotherapy.[63] Telemedicine should be used, and patients requiring chemotherapy should practice strict social distancing. Conservative doses of chemotherapy should be considered to avoid immunosuppression in susceptible patients.[63] If a patient develops COVID-19 symptoms during treatment, the chemotherapy should be stopped immediately, and the patient should be tested regardless of previous test results.[63] If positive, chemotherapy should be withheld until the patient has recovered.[63] For patients requiring radiotherapy and frequent visits, Mohile et al.[63] suggested continuing therapy for younger patients with COVID-19 with mild symptoms. For older patients with comorbidities, possible exposure during radiotherapy might outweigh the risks of COVID-19; therefore, shorter courses or withholding radiotherapy should be considered.

Guidelines for Transnasal Surgery

Anecdotal evidence from a cohort of international otolaryngologists and neurosurgeons reported a high incidence of surgeons and surgical staff contracting COVID-19 after being involved in transnasal surgeries, several of whom developed severe sequelae of COVID-19, including death.[64] They warned of the increased risks associated with transnasal surgeries owing to the high viral shedding from the nasal and oropharyngeal cavity. It was recommended that all operating room staff wear the same PPE.[64]

Surgery was limited to urgent and emergent cases, such as pituitary apoplexy, and preoperative testing was implemented. Normal PPE was acceptable when treating asymptomatic patients with negative test results. In contrast, use of a full powered air-purifying respirator was recommended for emergent cases when patients had tested positive. For those who test positive and for whom the surgery is not emergent, surgery should be postponed until their infection has cleared and a repeat test result is negative.[64]

Guidelines for Spine Surgery and Neurotrauma

The UK's National Health Service (NHS) released guidelines regarding the management of spine surgery, illustrating the need to expedite emergency cases of spinal infections and metastatic spinal cord compression to decrease exposure risk and patients' length of stay.[66] The NHS recommended greater scrutiny of patients with urgent elective cases who could have imminent neurological decompensation and continue day procedures such as discectomy and injection for severe radicular pain.[66] Conservative treatment should be given priority unless operative management is unavoidabe.[66] These strategies are similar to those proposed by US hospitals, with an aim of decreasing the exposure burden and streamlining discharge for in-patient neurosurgical patients.[65,67]

In relation to neurotrauma, the NHS has recommended that specialized major trauma centers should prioritize patients with easily reversible conditions such as extradural and subdural hematoma with mass effect instead of accepting patients with diffuse injuries that will require advanced monitoring and critical care resources for which the benefit is relatively limited.[66] Some strategies have suggested a more conservative approach to managing cranial and spine injuries with the use of telemedicine with local nonspecialists.[19] In accordance with measures to preserve resources and combat critical care staffing issues, traumatic brain injury management should focus on treatment futility at an earlier stage compared with nonpandemic conditions.

Guidelines for Pediatrics

Regarding pediatric neurosurgery cases, Wellons et al.[68] recommended limiting patient interactions for staff and visitors at children's hospitals and proposed greater reliance on telephone triaging for patients with chronic neurosurgical issues. Because these patients could require regular clinic visits, it is important to screen for urgency. Regarding equipment, pediatric neurosurgeons should be prepared to loan out pediatric ventilators and to convert ICU units for use by adult patients.[68]

Considerations for Managing a Decreased Patient Load

The cessation of elective cases has substantially decreased the neurosurgical patient volume.[59] With smaller caseloads, fewer physicians are needed.[59] Similar to the strategy recommended by Burke et al.,[69] our institution halved the

number of neurosurgery residents on inpatient service in an effort to limit exposure and prevent the spread of COVID-19 among the residents. The residents were divided into 2 teams, which alternate inpatient duties every 2 weeks, resulting in fewer residents in the hospital for nonemergent consultations. The rationale is decreased exposure to potential COVID-19 carriers and decreased turnover of PPE materials with an alternating 2-week "off period" that also serves as a functional self-quarantine period. Residents and attendings from the neuroscience specialties have been redeployed to cover the respiratory ICU for critical patients with COVID-19. With a decrease in the clinical workload, greater emphasis has been focused on academics and research.

CONCLUSIONS

Although most patients with COVID-19 will either not have or have only mild neurological manifestations, it is clear that SARS-CoV-2 affects the CNS. As the pandemic increases, so too will the collective understanding of how to manage this novel virus. Because some of the neurological sequelae of this disease can be devastating, the neuroscience community must be aware of the neurological effects of COVID-19 and how to approach them.

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