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Coronavirus disease 2019 (COVID-19) in neurology and neurosurgery: A scoping review of the early literature

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a devastating respiratory illness that has dramatically changed the medical landscape around the world. In parallel with a rise in the number of cases globally, the COVID-19 literature has rapidly expanded with experts around the world disseminating knowledge and collaborating on best practices. To date, the literature has predominantly consisted of case reports, case series, and systemic protocols for dealing with this deadly disease from a plethora of specialties with larger observational and randomized studies only now starting to emerge. This scoping review of MEDLINE, EMBASE, SCOPUS, and the Cochrane Library aims to evaluate and summarize the current status of the COVID-19 literature at it applies to neurology and neurosurgery. Neurological symptomatology, neurological risk factors for poor prognosis, pathophysiology for neuroinvasion, and actions taken by neurological or neurosurgical services to manage the current COVID-19 crisis are reviewed.

1. Introduction

Several cases of pneumonia occurring in Wuhan, China including several patients with exposure to a large seafood market selling live animals was announced by Chinese authorities in late December 2019 [1]. The pathogen was isolated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in Coronavirus Disease 2019 (COVID-19). The disease has since spread rapidly to most countries around the world. The World Health Organization declared COVID-19 a global pandemic as of March 11, 2020.

Early reports have demonstrated respiratory predominant symptomatology including fever, cough, dyspnea, and fatigue [2]. However, as the prevalence of COVID-19 continues to increase globally, other disease manifestations such as those affecting the central nervous system (CNS) are reported [3]. Furthermore, the emergence of cases involving less commonly afflicted organ systems has necessitated rapid and dramatic changes in practice patterns and has significant implications for all specialties of medicine. This scoping review evaluates the current status of the COVID-19 literature as it relates to neurology and neurosurgery.

2. Methods

The 26-item 2018 PRISMA extension for Scoping Reviews (PRISMA-ScR) checklist was used as an outline for this study [4]. An a priori protocol was not pre-registered. A search of MEDLINE, EMBASE, Scopus, and the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Cochrane Special Collections) from inception to April 7, 2020 was performed in order to identify articles evaluating both COVID-19 and neurology or neurosurgery. Variations of “COVID” AND “neuro OR brain OR spine OR peripheral nerve” related title/abstract/keywords and medical subject heading terms were performed with individual database search strategies outlined in Table 1. No language restrictions were applied. Database searches were combined and duplicates were removed.

Title and abstracts were then reviewed for relevance and articles evaluating COVID-19 with relevance to neurology and/or neurosurgery were reviewed in full text by two authors with 6 and 9 years of experience in the neurosciences. Studies not relating to COVID-19 or the clinical neurosciences were excluded from review. Relevant references were reviewed. Forward searching of key articles was also performed in Google Scholar. A gray literature search of conference abstracts was not

Abbriviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; SARS-CoV, severe acute respiratory syndrome coronavirus; ACE2, angiotensin-converting enzyme 2

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Table 1
Search strategy by database. The systematic search was performed on April 7, 2020.

MEDLINE: (COVID.mp. OR COVID-19.mp. OR coronavirus disease 2019.mp. OR 2019-nCoV.mp. OR severe acute respiratory syndrome coronavirus 2.mp.) AND ([neurosurgery.mp. OR exp Nuerosurgery/] OR [neurology.mp. OR exp Neurology/] OR [neuroscience.mp. OR exp Neurosciences/] OR [exp Brain/ OR brain.mp.] OR [exp Spine/ OR spine.mp.] OR [peripheral nerve.mp. OR exp Peripheral Nerves/] OR [cerebrospinal fluid.mp. OR exp Cerebrospinal Fluid/])
EMBASE: (COVID OR COVID 19 OR coronavirus disease 2019.mp. OR 2019-nCoV.mp. OR SARS-CoV-2.mp. OR severe acute respiratory syndrome coronavirus 2.mp.) AND ([neurosurgery.mp. OR exp Nuerosurgery/] OR [neurology.mp. OR exp Neurology/] OR [neuroscience.mp. OR exp Neuroscience/] OR [exp Brain/ OR brain.mp.] OR [exp Spine/ OR spine.mp.] OR [peripheral nerve.mp. OR exp Peripheral Nerves/] OR [cerebrospinal fluid.mp. OR exp Cerebrospinal Fluid/])
Scopus: (TITLE-ABS-KEY(COVID OR COVID 19 OR [coronavirus AND disease 2019] OR 2019-nCoV OR SARS-CoV-2 OR [severe AND acute AND respiratory AND syndrome AND coronavirus 2]) AND TITLE-ABS-KEY(neurosurgery OR neurology OR neuroscience OR brain OR spine OR [peripheral AND nerve] OR [cerebrospinal AND fluid]))
Cochrane Library: COVID AND (neuro* OR brain OR spine OR peripheral nerve OR cerebrospinal fluid)

performed given the short interval since inception of COVID-19.

Relevant content related to neurological symptomatology, neurological risk factors for poor prognosis, pathophysiology for neurological involvement, and action taken by neurological or neurosurgical services to manage the current COVID-19 crisis was collected. Critical appraisal of individual sources of evidence was not applied given variability of relevant content by study. Data from each article was extracted into Microsoft Excel v15.14 (Microsoft, Redmond, Washington, USA).

3. Results

A total of 29 articles were identified from the databases after duplicate removal. Nineteen articles were excluded for lack of relevance to COVID-19 or the clinical neurosciences. A total of 10 articles including 4 articles discussing clinical symptomatology and/or the neuroinvasive potential of SARS-CoV-2 [5–8] and 6 articles discussing recommendations for modified neurosurgical [9–11], stroke [12], and spine [13,14] practices during the COVID-19 crisis. Three additional articles discussing neurological symptoms and invasive neurological potential of SARS-CoV-2 were identified through search article references and forward searching [15–17].

3.1. Neurological symptoms and prognostic risk factors in COVID-19

Neurological symptomatology has been increasingly reported in recent publications. More frequent neurological symptoms can include headache (11–13 %), dizziness (8–17 %), and altered level of consciousness (8–9 %) [5,15]. Several peripheral nervous system findings are also now reported in up to 5% of cases including include hypogeusia, hyposomia or anosmia, and neuralgia [15]. Less commonly, acute cerebrovascular disease (3%), epilepsy (1%), and ataxia (1%) have also been reported [15]. Although uncommon, background cerebrovascular disease may be a risk factor for poor outcome in COVID-19 patients [5].

3.2. Invasive neurological potential of COVID-19

SARS-CoV-2 is a single stranded RNA enveloped virus with an amino acid sequence similar to severe acute respiratory syndrome coronavirus (SARS-CoV) [8]. The virus is believed to use the angiotensin-converting enzyme 2 (ACE2) receptor for cellular adherence [1]. Typically causing respiratory or gastrointestinal disease, these ACE2 receptor epithelial and endothelial cells have been identified throughout the chest and abdomen [18,19]. Although the expression of ACE2 is low in the brain, autopsy studies have previously demonstrated SARS-CoV particle presence brain tissue [20]. Moreover, neurological deposition has been demonstrated in most other beta-coronaviruses including SARS-CoV, MERS-CoV, HCoV-229E, HCoV-229E, mouse hepatitis virus, and porcine hemagglutinating encephalomyelitis coronavirus (HEV) [6]. Some authors have postulated a mechanism other than ACE2 epithelial or endothelial cell adherence as a route for CNS infiltration such as trans-synaptic viral transfer after initial peripheral nerve invasion [6]. This would then explain findings of some studies demonstrating the virus' predominant presence in neurons [20–22]. However, the higher relative prevalence of SARS-CoV in the cerebrum (where glial cells are more common) compared to the cerebellum in autopsy studies has led others to postulate a glial presence of ACE2 [17,20].

Human cases of SARS-CoV related polyneuropathy and encephalitis have been previously reported and a similar risk has been assumed for SARS-CoV-2 [8,23]. To date, at least three case reports of SARS-CoV-2 encephalitis have been reported [24–26]. The first case was reported in a Beijing hospital upon a SARS-CoV-2 RNA positive test of a patient's cerebrospinal fluid (CSF) [8,16,24]. The second case was a 24-year-old Japanese man with sinusitis complicated by medial temporal lobe encephalitis and lateral ventriculitis [25]. The CSF also tested positive for SARS-SoV-2 RNA in the latter patient. A third case involving hemorrhagic necrotizing encephalopathy of the medial temporal lobes and thalami in a female airline worker in her fifties was recently reported in the United States [26].

The mechanism of action for SARS-CoV-2 neurological invasion is not yet specified. Several theories have been postulated including: direct invasion, blood circulation pathway, neuronal pathway, hypoxia injury, immune injury/cytokine storm syndromes, ACE2 receptor expression, among others [8,26]. As previously described, perhaps the leading current theory is direct seeding and trans-synaptic infiltration via the olfactory nerve or perineuronal cells. This route of invasion has been documented in animal studies for other coronaviruses [27–30]. For example, experimental studies in transgenic mice injected intranasally with SARS-CoV have demonstrated brain entry via the olfactory nerves with subsequent rapid spread to medial brain structures including the medial temporal lobe, basal ganglia, thalami, and midbrain [30]. These findings would be consistent with the limited case report data available to date.

Animal studies of other beta-coronaviruses have also suggested a link with some long-term neurodegenerative diseases [31]. Long-term persistent psychological distress has been shown in SARS survivors [32]. The potential long-term neurodegenerative and psychological effects of COVID-19 have yet to be determined.

3.3. Impact of COVID-19 on practice management

COVID-19 has dramatically altered practice patterns around the world. Early studies have been published with experiences and recommendations, predominantly from locations substantially affected by the COVID-19 crisis including China [9,12,13] and Northern Italy [10,11]. Thus far, early experience and recommendations in neurosurgical [9–11,33], stroke [12], and spine [13,14] practices have been reported (Table 2). Included among these are algorithms pertaining to the deployment of healthcare personnel, and the prioritization, scheduling and cancelling of surgical cases. Algorithms and protocols such as these have been created through interdisciplinary expert panel consensus with the goal of addressing critical neurological and neurosurgical issues and allowing for the safe and continued care of neurological patients in the context of the COVID-19 pandemic. Ongoing study of the effectiveness of these treatment algorithms will be necessary to ensure the implementation of optimum patient management strategies during this pandemic.

Preliminary consensus guidelines surrounding specific COVID-19 related management are also beginning to be published in

Table 2
Early experience and recommendations for neurosurgical, stroke, and spine practices during the COVID-19 crisis.

Author	Service	Practice Location	Experience and/or Recommendations
Tan	Neurosurgery	Wuhan, China	Screened and used proper protection for all patients All admitted patients were screened with throat swab and chest CT Segmented the neurosurgery unit into infected and clean areas Daily sterilization of each room was performed Anesthetist pre-operative consultation for all cases was obtained Operations performed in negative pressure suction room for COVID-19 cases Optimized surgical team to shorten duration of operation Decreased speed of bone drilling to reduce spread of bone dust
Veiceschi	Neurosurgery	Bergamo, Italy	Discontinued elective surgeries where possible Created a "Neuro-COVID" unit of the hospital Specifically assigned neurosurgical staff to COVID patients/units (25 % → 50 % → 75 % neurosurgeons) Regionalized neurosurgical services by hospital into 4 hubs (3 general cranial or spinal emergencies and 1 for oncologic pathologies) Combined private and public hospitals to achieve regional efforts
Zoia	Neurosurgery	Lombardy, Italy	Suspended all non-urgent outpatient activities Four surgical "hub" hospitals were created with 3 guaranteeing 24/7 acceptance; 4th hub for urgent oncological cases Oncological patients categorized into 3 levels of priority: [1] immediate (ex: worsening level of consciousness) [2]; 7 − 10 day (ex: mass effect or progressive defect without alteration of consciousness) [3]; within 1 month (ex: mass with neurological deficit) Improved collaboration between hospitals for resources including personnel
Zhao	Stroke	Shanghai, China	In addition to challenges in hospital management, some patient may be reluctant to present to hospital risking late presentation Cases of wrong hospital presentation and suboptimal management were experienced in as the system rapidly evolved to adjust to the COVID-19 crisis Cases in Shanghai decreased by 50 % in the first month of crisis Establish stroke networks and care systems able to deliver emergent stroke care in time of crisis Establish centralized stroke treatment centers where sufficient stroke care resources can be secured Notify emergency medical system that stroke centers are protected and will remain open during crisis Improve education of health professionals and public, especially those at risk of stroke, to recognize the recognize stroke and call for help immediately Recommend improved online resources for patients and physicians during time of crisis
Zou	Spine	Suzhou, China	Appropriate screening for all cases Favor conservative management where appropriate Divide waiting rooms between symptomatic and non-symptomatic Surgery for patients with severe nerve compression, spinal cord injury, progressive aggravation of nerve dysfunction, or spinal fracture with displacement or compression Patients with COVID-19 requiring operation: • Use minimally invasive surgery where possible • Reduce scope and time of operation where possible • Prone position is preferred • Reduce risk of aerosolizing where possible (ex: use suction with caution) • Reduce splatter in operative field • Screening of operating room staff is also necessary
Donnally	Spine	Philadelphia, United States	Divide spine list into three levels of urgency: Level 1 (proceed with surgical intervention): cervical or thoracic myelopathy, acute spine trauma, oncology, epidural abscess, cauda equine or sever nerve root compression Level 2 (proceed with surgical intervention at ambulatory surgical center versus consider at hospital if low COVID-19 census): Acute or subacute lumbar disc herniations, cervical radiculopathy, acute hardware failure, lumbar adjacent segment disease Level 3 (defer surgery if able): Compression fracture, odontoid fracture, adult degenerative scoliosis, lumbar degenerative stenosis, proximal junction kyphosis, axial back pain
Burke	Neurosurgery	San Francisco, United States	Created a three tier surge level based on factors including: number of community cases, number of COVID-19 positive inpatients, and percentage of staffing shortages Created a checklist to determine the case urgency and to determine the availability of operating rooms and post-operative beds dependent on needs Green surge level (1 − 9 community cases, or < 6 COVID-19 positive patients, and no staffing shortages): operate on all emergent, urgent, and elective cases Yellow surge level (10 − 99 community cases, or 7 − 16 COVID-19 positive inpatients, or < 20% staffing shortages): Proceed with emergent and urgent cases. Limit operating room schedule for elective cases over a 3 week period including a 25% reduction in procedural cases and re-assess Red surge level (> 100 community cases, or > 17 COVID-19 positive inpatients, or > 21 % staffing shortages): Proceed with emergent and urgent cases. Limit operating room schedule for elective cases over a 3 week period including a 50 % reduction in procedural cases and re-assess Black surge level (significant assistance needed from outside institutions): Emergent cases only Created a three tiered coverage plan including two teams and an alternate team for each of four local hospitals Promoted reduction in people as possible including: increased teleconferencing as able, restricting hospital access to workers over the age of 65, not allowing patient visitors

subspecialties within neurology and neurosurgery based on pre-COVID-19 literature and expert consensus. For example, early guidelines are recommending strict precautions in patients with unknown or suspected COVID-19 requiring emergent endovascular thormbectomy [34]. At present, best practice regarding general anesthesia and monitored anesthesia care remains unclear and controversial, but more conservative measures with decreased risk of aerosolizing virus are favored when possible [34].

4. Discussion

Limited literature is available to date on the COVID-19 as it relates to the clinical neurosciences. This scoping review identifies several significant findings pertaining to the practice of neurology and neurosurgery, including:

1 Pre-existing cerebrovascular disease may be a risk factor for poor outcome in patients infected with COVID-19.
2 COVID-19 infection may manifest as neurological symptomatology, including: headache, dizziness, hypogeusia and/or anosmia, altered level of consciousness, acute cerebrovascular events, seizure(s), and ataxia.
3 Although the mechanism of invasion is not fully understood, COVID-19 appears to demonstrate neuroinvasive potential. Viral encephalitis +/- hemorrhagic necrosis involving mesial brain structures such as the mesial temporal lobes and thalami have been reported to date.
4 Long-term neurodegenerative effects of COVID-19 have yet to be elucidated, but are theorized based on past experience with other beta-coronaviruses.
5 Neurology and neurosurgical practice patterns are being changed dramatically and constantly updated with publications demonstrating early experiences and recommendations based on facilities and regions most affected.

As an early scoping review of available literature to date, this study has certain limitations. First, symptoms classified as neurological including headache, dizziness, and altered level of consciousness are nonspecific with multiple potential causes. These symptoms may relate to an alternative system of origin, may be therapy related, and/or may be of psychosocial origin. The extent to which these symptoms may impact the practice of neurology and neurosurgery is uncertain. Second, the predominant limitation of this scoping review pertains to limited available early literature. As the number of COVID-19 cases continues to rise dramatically across the world, we anticipate that the literature will also continue to evolve. As the prevalence of COVID-19 increases, more cases reporting rare neurological presentations of COVID-19 are likely to be published. A better understanding of the mechanism and therapeutic options for invasive neurological cases may also evolve. Consensus statements and society guidelines will likely require continual refinement based on emerging COVID-19 specific data. Finally, optimal practice patterns will likely vary widely with nuanced configurations based on regional prevalence and available health care resources. In order to ensure optimum neurological patient management, ongoing study of treatment algorithms will be essential for updating and adapting these approaches as the COVID-19 pandemic evolves.

IRB STATEMENT

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