

## Stroke Management in the Time of COVID

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### Introduction

In December 2019, a cluster of acute respiratory illness, known as novel coronavirus–infected pneumonia, occurred in Wuhan, Hubei Province, China. [1] This outbreak was confirmed to be caused by a novel coronavirus (CoV). Now known as the 2019 novel coronavirus (2019-nCoV), the virus was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of the disease. [2]

Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds causing respiratory, enteric, hepatic, and neurologic diseases. [2] Six coronavirus species are known to cause human disease. [3] While the full-genome sequencing and phylogenetic analysis indicated that COVID-19 is distinct from the beta coronaviruses associated with the human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), this novel CoV was reported to cause symptoms resembling SARS-CoV in 2003. [2,4] Both shared the same receptor, angiotensin-converting enzyme 2 (ACE2); therefore, this virus was named SARS-CoV-2. In February 2020 the World Health Organization named the disease coronavirus disease 2019 (COVID-19). [5] COVID-19 infection in humans often leads to severe clinical symptoms with a high mortality. Several studies described typical clinical manifestations including fever, cough, diarrhea and fatigue. [6] This disease also has characteristic laboratory findings and lung computed tomography (CT) abnormalities.

### Neurological manifestations of COVID-19

One of the first reports to identify neurological manifestations of COVID was from China that showed of a total 214 patients, 78 (36.4%) had various neurologic manifestations involving central nervous system, peripheral nervous system, and skeletal muscles. [5] The most common neurological manifestations were dizziness (16.8%), headache (13.1%), and encephalopathy (2.8%). The most common peripheral signs and symptoms were anosmia (5.1%), dysgeusia (5.6%), and muscle injury (10.1%, detected by elevated creatine kinase). Stroke complicated COVID-19 infection in 5.9% of patients at a median of 10 days after symptom onset; patients with stroke were older, had more cardiovascular comorbidities, and more severe pneumonia. [7] Patients with severe infection were more likely to develop neurologic manifestations, especially acute cerebrovascular disease, reduced level of consciousness, and skeletal muscle injury. [5] Most neurologic manifestations occurred early in the illness (the median time to hospital admission was 1-2 days). [5] Moreover, some patients without typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19 came to the hospital with only neurologic manifestation as their presenting symptoms.

### Stroke

During this unprecedented time of the pandemic, there has been an insurmountable stress on the US healthcare system. The AHA/ASA stroke council has acknowledged the overwhelming concern regarding optimal stroke care during the COVID-19 pandemic among vascular neurologists and other clinicians who care for patients with stroke. Several newly published reports corroborate these concerns. A case series involving 6 patients suggested that stroke developed mostly in patients with severe pneumonia and

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multi organ failure; the liver enzymes and LDH were markedly increased in all cases, and the outcome was poor. [8] Another case reported from New York showed that a total of five patients (less than 50 years of age) presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for COVID-19 [9] with a similar case series reported in France [10].

Our colleagues at the University of Louisville (UofL) Stroke Center have also sited potential links between the COVID respiratory illness and blood clots, which is said have caused young adults without preexisting conditions to suffer strokes. [11]. Our team has cared for young adults with strokes who have no typical risk factors for stroke, i.e., they do not smoke, do not have atherosclerosis, do not have high blood pressure, do not have diabetes, do not have high cholesterol and do not have heart disease. The link between COVID-19 and stroke needs to be investigated thoroughly so we may learn how to prevent stroke in this population. Consider that the link is coagulopathies.

### *Coagulopathies*

Coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19. [12] A series of PCR confirmed COVID-19 cases presented initially as stroke early in the stages of illness. [13] The pathophysiology of thrombotic cerebrovascular events has been attributed to bacterial or viral infections with a recent study demonstrating 31% of critically ill ICU patients developing thrombotic complications. [14] Another study of COVID-19 patients concluded that time-based clot waveform analyses demonstrate hypercoagulability that precedes or coincides with severe illness. [15] The most plausible mechanism of early stroke has been attributed to hypercoagulability leading to macro and micro thrombi formation in the vessels. [13]

Timely assessment and hyperacute treatment is the key to minimize mortality and morbidity in patients with acute stroke. [13] Stroke teams should include COVID-19 as a possible contributing etiology in every patient. Further studies are urgently needed for a comprehensive understanding of the neuropathological manifestations of COVID-19 and its effects on the brain and the nervous system.

### **Neurological treatment implications and future directions**

Novel and reemerging pathogens are global challenges for public health. While several *in vitro*, *in vivo* and genomic studies have confirmed the pathogenicity of COVID-19 [2, 16], the world still lacks an effective therapy or vaccine to deal this pandemic. Concerted efforts are being made on a global scale to develop a successful vaccine.

The COVID-19 pandemic necessitates that extra measures be taken to provide care for stroke patients along with measures aimed at minimizing the spread of the infection. One challenge encountered while treating acute stroke patients during this pandemic is the absence of family members when patients are unable to communicate effectively. Clinicians usually rely on family members to provide critical history that guides treatment decisions, but most hospitals have instituted a no-visitor policy during the pandemic. [13]

COVID-19 associated stroke mechanisms have not been confirmed but could include hypercoagulability from critical illness and cardioembolism from virus-related cardiac injury. [17, 18] The obligate receptor for the virus spike protein, the human ACE2, is expressed in epithelial cells throughout the body, including cells in the central nervous system, raising the tantalizing possibility of a direct role in viral infection. [19] SARS-CoV-1 and MERS-CoV have been identified in the brains of patients (case reports) and heavily in the brains of mice that express human ACE2. [17] However, there are no peer-reviewed published reports yet of clinical signs of SARS CoV-2 encephalitis or meningitis.

A protected code stroke (PCS) concept [20] has been proposed during this pandemic which provides a framework for key elements like screening guidelines, PPE, and crisis resource management. Based on previous studies, one of the key recommendations for PCS indicate that paramedics should develop an infectious screening policy on all patients with stroke-like presentations, before moving them to the hospital. Another key recommendation is that outside transfers should be minimized, and even the ones that need transfer should have an infectious screening before the transfer. A dedicated neurology hot-spot along with a mobile CT unit for COVID-19 patients with stroke-like symptoms may also be beneficial. The clinically stable patients after thrombolysis can be monitored on non-intensive care units. [13] The UofL Stroke Center has seen a significant reduction in both thrombolysis and thrombectomy due in part to late arrival to the hospital, the same observation reported by Zhao, et al in *Stroke*. [21] This may have serious implications as the patients who were not admitted to the hospital potentially lost the opportunity for symptom reversal or effective acute treatments. Many patients refuse to go to the hospital for fear of being infected by COVID-19, losing the opportunity for secondary prevention treatments such as carotid revascularization, anticoagulation for atrial fibrillation and antiplatelet therapies.

Lack of stroke awareness compounded with fear of the virus has made patients with stroke much less likely to seek

help. The emphasis on social distancing has in a way acted as a double-edged sword making patients with acute stroke avoid in-person medical care, thereby contributing to poor outcomes. Two patients in a reported case series delayed calling an ambulance because they were concerned about going to a hospital during the pandemic. [12] Increased social isolation is also likely to have decreased the chance of family and friends in recognizing that an individual might be having a stroke. Another critical aspect that should strongly be taken into consideration involves possible post COVID-19 sequelae, which may require close follow-up, as recommended in previous pandemics, such as encephalitis lethargica and postpolio syndrome. [22]

In the current global healthcare emergency, the AHA/ASA seek to provide guidance for the care of stroke patients in the midst of the crisis. While national recommendations go through a rigorous process of development, refinement, peer review, and thoughtful promulgation, a newly released emergency guideline has recently been published due to the substantial need for a broad policy statement that incorporates both the commonality of the pandemic across the US and the individual variability necessary at local sites. [17]

Proper education including stroke awareness and COVID-19 knowledge is absolutely essential during this pandemic. In this context the importance and timely utilization of telemedicine/telestroke can not be emphasized enough, with its robust and rapid scalability. Telestroke can help maintain a seamless transition of inpatient and outpatient care during the pandemic. [23] COVID-19 reflects an unprecedented situation with a significant impact on the practice of neurology on a national and international level. The awareness gained during these difficult times must propel us to carefully and proactively plan for the future so that the crucial role of neurology in managing neurological emergencies and chronic diseases is safeguarded and optimized. [22]

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