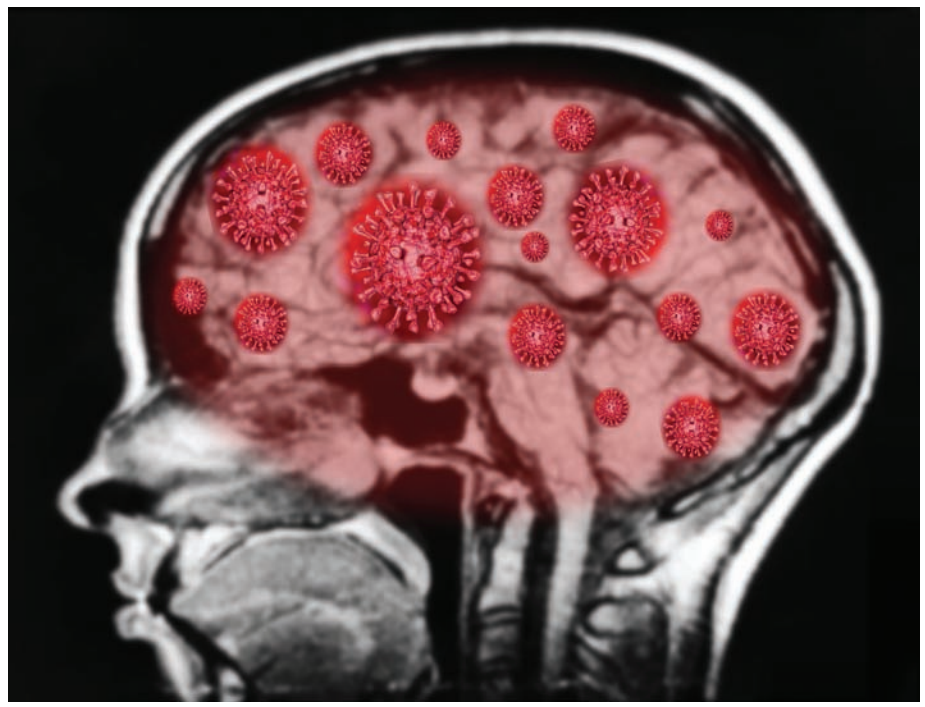
Your Patient's Brain

COVID-19 and the Brain

Timothy Gaulton, MD, MSc **Daniel J. Cole, MD, FASA**

"He seems a little off."

He was one of the first patients admitted to my (TG) hospital's ICU with hypoxemic respiratory failure from COVID-19. Yet in contrast to the majority of other patients with this disease who presented near the beginning of the pandemic, he did not require intubation. His oxygenation stabilized after a few days of non-invasive respiratory support and steroid administration. During rounds one day, he asked about setting up a video chat with his daughter. She lived only a few miles away from the hospital, but in this pandemic it could have been a thousand miles away. After they talked, I spoke with her to answer questions she had and to let her know that he might be able to leave the ICU soon. She was very happy to see him and grateful for his improvement. Before we ended the video chat, she told me about her father, that he was a man with incredible sharpness and wit. And now he seemed like a different person, that there was a "dullness" in his thinking which was not present a few weeks ago. We both hoped this would improve with time.



As an anesthesiologist trained in critical care medicine (TG), I am used to seeing the wide range of neurologic effects of acute infection, from hyperactive delirium and severe encephalopathy to the more subtle changes in cognition that the daughter of my patient had noticed. I have been taught, and teach trainees, that if there is a problem with cognition, always look for infection. This is consistent with new definitions of sepsis that now incorporate changes in mental status as an early warning sign. However, in regard to COVID, it remains unclear whether adverse neurologic effects on the brain are specific to SARS-CoV-2 or simply a more general phenomenon related to inflammation, cytokine storm, or the immune response that is a central driver of critical illness.

Prior coronaviruses have demonstrated the potential for direct neurological invasion (*JAMA Neurol* 2020;77:1018-27). SARS-CoV-2 is known to replicate in neurons and may enter the central nervous system via the angiotensin converting enzyme 2 receptor. However, a case series of brain autopsies performed in patients with confirmed COVID-19 did not show any specific changes in the brain that could be directly attributable to the virus (*N Engl J Med* 2020;383:989-92). On immunohistochemical analysis, staining of SARS-CoV-2 was not detected in the neurons, glia, endothelium, or immune cells of the brain specimens of infected patients. Moreover, electroencephalography, cerebral spinal fluid analysis, and cerebral imaging have yielded non-specific findings (*JAMA Neurol* 2020;77:1018-27). Although a direct causal link between SARS-CoV-2 and neurologic complications is biologically plausible, the supporting evidence is embryonic in nature – but the bottom line is that neurologic complications are well documented to occur in patients with COVID-19.

At least half of COVID-19 patients present with a neurologic symptom, and certainly more develop symptoms during their hospitalization. They may be as mild as a headache or myalgias or more severe such as disorientation, paresis, convulsions, and stroke. While these symptoms are non-specific and may or may not be directly related to the virus, their high prevalence alone requires constant vigilance and investigation from perioperative physicians to ensure our own safety and the safety of our patients. We must also consider all root causes regarding the differential diagnosis of neurologic symptoms in a patient with COVID-19.

Ironically, the first patients I (TG) treated with COVID-19 were in a dedicated unit that was converted from a combined neurology and neurosurgery ICU. As the pandemic worsened, our hospital stopped elective surgery and surgical volume decreased, making room for the increasing number of critically ill patients with COVID-19. But unexpectedly, we also saw a decreased volume of admissions for non-surgical neurologic diseases, especially for stroke. This was surprising to us given the known associations between COVID-19 infection and elevated d-dimer and C-reactive protein levels that appeared to create a state of hypercoagulability and predispose patients to stroke. Our anecdotal experience was later confirmed from a large observation description from China where, compared to the prior year, the authors reported a 40% decrease in hospital admissions from stroke and a 25% decrease in cases that required thrombectomy or thrombolysis (*Stroke* 2020;51:1996-2001).

The reasons for these decreases are speculative yet raise significant concern regarding salient downstream consequences of COVID-19 on population health, even to people who have not been infected from the virus. Perhaps they delay seeking medical attention out of fear of contracting the virus within a health system, or lack the usual social support that may recognize a change in their health. Whatever the reasons may be, they are certainly impactful – over 30% of the excess deaths in the United States in the first months of the pandemic were not attributable to COVID-19 (*JAMA* 2020;324:510-13). And as is the case for acute conditions, the management of chronic conditions such as dementia likely has suffered as well. For us as anesthesiologists, this will make promoting perioperative brain health even more challenging than it already is, as patients may present later in their disease, in worse states of health, and without appropriate optimization and counseling before surgery.

As I (TG) think about my patient, I worry that his prior sharpness will continue to escape him. Some patients experience "long COVID," or symptoms that persist for months following infection. Neurologic symptoms for long COVID include fatigue, mood swings, cognitive difficulties, and "brain fog." Long COVID may impact population health, with a potential to impact anesthetic risk when these patients present for surgery (*JAMA* 2010;304:1787-94). Patients can also develop a number of other distressing chronic conditions such as post-traumatic stress disorder, chronic anxiety, and chronic pain. There is little doubt that cognitive impairment has occurred and will continue to occur in a cohort of the many millions of patients who have survived COVID-19.

Although thousands of papers have been published on COVID-19, we are indeed in the midst of a pandemic for which we lack a scientific-based comprehensive solution and which may well have consequences beyond the timespan of the pandemic. It is a sober reminder of the need for ongoing clinical and research efforts to promote better brain health from this disease. ■

Timothy Gaulton, MD, MSc
Assistant Professor of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

Daniel J. Cole, MD, FASA
Vice President, Anesthesia Patient Safety Foundation, and Professor of Clinical Anesthesiology, Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine, University of California, Los Angeles.