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Intracerebral Hemorrhage in COVID-19 Infection
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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic with over 174 million documented cases of COVID-19 infection. Typically, COVID-19 presents with respiratory disease; however, there have been numerous reports of neurologic manifestations including encephalopathy, seizure, and cerebrovascular disease. Spontaneous intracerebral hemorrhage (ICH) has been reported as one of the most devastating manifestations of COVID-19. ICH is considered the most catastrophic stroke subtype with a >40% mortality rate and significant morbidity in survivors. Roughly 40% of ICH deaths occur within the first month of the stroke, and it is approximated that only 20% of patients will make a full recovery. Significant morbidity is associated with ICH, as hemorrhage-related injury may cause motor, memory, and language deficits.

Currently, the pathophysiology of ICH in COVID-19 is unknown, although there have been multiple proposed mechanisms. Potential mechanisms that may be involved include direct and indirect endothelial damage, ultimately promoting vessel rupture. Directly, SARS-CoV-2 can invade endothelial cells through the ACE-2 receptor, resulting in cellular injury. Indirectly, endothelial toxicity can result systemically from a massive cytokine release, prothrombotic factors, and activation of the coagulation cascade, ultimately resulting in failure of the blood-brain barrier. Another potential theory is that a hypoxic state, as a result of respiratory disease, may predispose to endothelial dysfunction and potentially microscopic damage of cerebral veins. In addition, there has been speculation about a disseminated intravascular coagulation–type reaction that would lead to a higher propensity for bleeding in the brain parenchyma. An alternative explanation involves the neuroinvasive potential of the coronavirus family. Specifically, the SARS-CoV-2 virus can bind on neuronal and glial ACE-2 receptors, hence a pathway for direct intracranial invasion. An extrinsic process could also contribute to ICH in COVID-19. Because COVID-19 patients are at an increased risk of thrombotic events, anticoagulation is often used and may play a causative role in the manifestation of ICH.

Given the severe sequelae of ICH and prevalence of COVID-19, several studies have assessed the clinical characteristics, treatments, and outcomes of ICH patients with COVID-19. Benger et al reported a series of cases characterizing ICH in patients with COVID-19. These patients were relatively young (mean age of 52.2) and had evidence of prolonged inflammation (elevated D-dimer) and ICH located in lobar territories. Lawton et al identified ICH patients from a single hospital who were COVID-19 positive and demonstrated that compared with a control group of COVID-19–negative ICH patients, the patients were younger, had worse outcomes, and longer lengths of stay in the hospital. Melmed et al analyzed COVID-19 patients from the New York University Langone Health System and determined that older age, respiratory failure, ethnic minorities, and therapeutic anticoagulation were associated with ICH. Using a national claims database, Ravindra et al demonstrated that patients with ICH and COVID-19 infection had higher rates of in-hospital death and longer lengths of stay (in both the ICU and hospital) and were more likely to be a racial or ethnicity minority.

Studies have also examined the presence of ICH in COVID-19 hospitalized patients and their anticoagulation status. Kvernland et al reported an overall low rate of hemorrhage among COVID-19 patients with the majority of cases occurring in those who received therapeutic anticoagulation. Dogra et al similarly reported that the majority of COVID-19 patients who developed ICH received anticoagulation therapy (either prophylactically or therapeutically) before ICH diagnosis. Moreover, Melmed et al demonstrated that anticoagulation was associated with a 5× increased risk of ICH. However, these studies were retrospective and observational and had a relatively small sample size.

A recent report from the American Heart Association COVID-19 Cardiovascular Disease registry examined the prevalence of ICH among hospitalized patients with COVID-19. Similar to Kvernland et al, this analysis suggests that ICH is rare among patients hospitalized for COVID-19. In addition, COVID-19–positive patients with ICH had more vascular risk factors and higher mortality compared with those without ICH. Similar to previous studies, this study reported a higher use of anticoagulation in ICH patients who are COVID-19 positive. Although these analyses show that ICH may be a rare finding in COVID-19 patients, it is nevertheless important for clinicians to consider given the severe sequelae. Recognizing the difficulty in conducting a proper neurologic examination in heavily sedated patients, at minimum, pupillary reflex should be monitored in patients with COVID-19 requiring ICU-level care, especially for patients on anticoagulants.

We should note several limitations. First, the American Heart Association COVID-19 registry only included patients who were hospitalized with COVID-19, thus excluding those who were COVID-19 positive and did not seek hospital care. Also, the study lacked timing data, which prevented conclusions regarding the sequence of ICH, COVID-19 diagnosis, and anticoagulation therapy. Furthermore, this study lacked relevant neuroimaging data on the location and severity of ICH. Lastly, even though this was a multicenter study, the reporting hospitals may not adequately represent U.S. hospitals at large.

Myriad questions still need to be addressed in order to enhance our understanding of ICH and COVID-19. Determining the optimal role of anticoagulation in the treatment of COVID-19 will be essential as many hospitals use it for prophylaxis. Identifying risk factors and outcomes associated with ICH in patients with COVID-19, as well as describing the incidence of ICH during the COVID period compared with the pre-COVID period, will inform...
treatment approaches and development of clinical protocols. Characterizing ICH in patients with and without COVID-19 from a large, nationally representative registry will be important in confirming the aforementioned findings and proposed associations. Furthermore, obtaining details regarding the timing of ICH relative to hospital admission, COVID-19 diagnosis, and anticoagulation will aid in establishing a potential causal effect of COVID-19 and ICH.

REFERENCES

1. Ravindra VM, Grandhi R, Delic A, et al. Impact of COVID-19 on the hospitalization, treatment, and outcomes of intracerebral and subarachnoid hemorrhage in the United States. PLoS One. 2021;16:16.

2. Rymer MM. Hemorrhagic stroke: intracerebral hemorrhage. Mo Med. 2011;108:30-34.

3. Karimy JK, Reeves BC, Kahle KT. Targeting TLR4-dependent inflammation in post-hemorrhagic brain injury. Expert Opin Theraupt Targets. 2020;24:525-533.

4. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: clinical characteristics from a case series. Brain Behav Immun. 2020;88:940-944.

5. Melmed KR, Cao M, Dogra S, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. J Thromb Thrombolysis. 2021;52:953-960.

6. Kvernland A, Arooshi K, Shadi Y, et al. Anti-coagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a New York healthcare system [e-pub ahead of print]. Neurorit Care. 2020. https://doi.org/10.1007/s40104-020-01077-0. Accessed August 24, 2020.

7. Lawton MT, Alimohammadi E, Baghei SR, et al. Coronavirus disease 2019 (COVID-19) can predispose young to intracerebral hemorrhage: a retrospective observational study [e-pub ahead of print]. BMC Neurol. 2020. https://doi.org/10.1186/s12883-021-01010-9. Accessed February 19, 2021.

8. Siddhant D, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis. 2020;29:104984.

9. Leasure AC, Khan YM, Iyer R, et al. Intracerebral hemorrhage in patients with COVID-19: an analysis from the COVID-19 Cardiovascular disease registry. Stroke. 2021;52:e321-e323.

10. Carroll E, Lewis A. Catastrophic intracranial hemorrhage in two critically ill patients with COVID-19. Neurorit Care. 2020;1-5.