Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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.[1] 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.[2] 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.[2,3] Significant morbidity is associated with ICH, as hemorrhage-related injury may cause motor, memory, and language deficits.[3]

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.[4] 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.[4] 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.[5] 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.[5] 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.[6] 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.[4] Lawton et al[7] 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[5] 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[1] 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.[5,6,8] Kvernland et al[6] 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[8] 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[5] 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.[9] Similar to Kvernland et al,[6] 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.[5,6,8] 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.[10]

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 multicentered 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.

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