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NEUROCRITICAL CARE SOCIETY

INVITED COMMENTARY

Invited Commentary on Intracerebral Hemorrhage in COVID-19 Patients with Pulmonary Failure: A Propensity Score-Matched Registry Study

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Early in the coronavirus disease 2019 (COVID-19) pandemic, reported cases of ischemic stroke and intracranial hemorrhage (ICH) complicating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused considerable alarm. As more systematic data emerged, it became apparent that these events were, fortunately, relatively uncommon. For example, at our center in Philadelphia we identified ischemic stroke in 2.4% and ICH in 0.9% of 844 hospitalized patients with COVID-19 admitted from March to May 2020 [1]. The mechanistic linkage between SARS-CoV-2 infection and these events is of great interest. Is there something specific about SARS-CoV-2 infection that increases the risk of these events? Or are we just seeing complications related to the diffuse inflammatory response which might be produced by any infectious disease lacking effective treatment or preexisting immunity? Relatedly, because a majority of patients with stroke in the setting of COVID-19 are critically ill, how much of the association is simply due to severe systemic illness or the complications of the treatments for this illness, such as anticoagulation and extracorporeal membrane oxygenation (ECMO)?

Of the many lessons to be learned from the pandemic, one is that the sheer volume of anecdotal observations from the onslaught of critically ill patients in the initial epicenters limited our ability to make sound comparisons to rates of these events in other, much rarer, infectious diseases or illnesses. In this issue of *Neurocritical Care*, Lang et al. [2] provide just such comparative data. They analyzed the rate of intracerebral hemorrhage in patients with acute respiratory distress syndrome treated at their center from 2018 to 2020, which encompasses the pre-pandemic and early COVID-19 pandemic time periods. Of the 163 patients identified, they observed ICH in 9 of 47 (19%) of those with COVID-19, compared with 13 of 116 (11%) of those without COVID-19, a nonsignificant difference. The patients with COVID-19 were significantly older (mean age 66 vs. 58 years), an important contributor to ICH risk. They were also more likely to be treated with antiplatelet agents or aggressive anticoagulation regimens. When analyzed by using propensity score matching, the difference in ICH rates between the two groups was further attenuated (19% vs. 13%). In short, it appears that if there is any increased risk of hemorrhage specific to SARS-CoV-2 infection, it is likely to be small, with the generic state of critical illness and associated treatments far more important contributors to risk.

Of those with ICH (both with and without COVID-19) in the report, roughly half were treated with ECMO. The mechanistic implications of this are not as obvious as one might hope. ICH in this setting might be due to coagulopathy—deliberately from anticoagulation or unintentionally from the mechanical effects of the ECMO circuit. But given the thrombotic risk associated with ECMO, it is also possible that some of the intracerebral hemorrhage seen complicating ECMO is actually unrecognized ischemic stroke with subsequent massive hemorrhagic conversion. The limited ability to perform frequent

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surveillance brain imaging and continuous neurologic monitoring in these patients means it is often impossible to be certain which is the primary event, thrombosis or hemorrhage. Nevertheless, these data do suggest that in many cases ICH is, to an extent, a complication of necessary life-saving treatment, as opposed to directly due to the underlying disease. A second observation is that four of the nine patients with COVID-19 with ICH had multicompartment hemorrhage, compared with 0 of the 13 patients without COVID-19. This would seem to raise the possibility of either a specific underlying coagulopathy or vascular vulnerability (with endothelial inflammation often put forth as a putative mechanism) in COVID-19, as opposed to other causes of acute respiratory distress syndrome. However, given the small number of patients and variability in antithrombotic treatment, this finding should be interpreted with caution. Examination in larger cohorts, likely requiring multicenter collaborative efforts, would be helpful to confirm this observation.

The data generated by Lang et al. [2] represent a fine initial effort at putting the interaction between COVID-19 and cerebrovascular disease in perspective by using an appropriate comparator group. To date, relatively few studies of COVID-19 have undertaken such analyses. Future investigations should strive to include historical or contemporaneous control cohorts; this will allow us to better understand the basic mechanisms linking infection and critical illness to cerebrovascular disease. Such understanding may have lasting importance even after COVID-19 has moved off center stage.

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