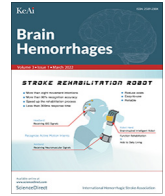




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Correspondence

The etiology of SARS-CoV-2 associated intra-cranial hemorrhage is broad

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Letter to the Editor

With eagerly read the review article by Daly et al. about SARS-CoV-2 associated intra-cranial haemorrhage (ICH) (Daly et al., 2021). It was found that SARS-CoV-2 infections not only require treatment of acute respiratory distress syndrome (ARDS), vasculopathy, and coagulopathy, but also of neurological comorbidity, and that evidence-based treatments which reduce COVID-19 mortality may increase the risk of developing ICH (Daly et al., 2021). The study is appealing but raises concerns which require discussion.

A pathophysiological mechanism explaining ICH in SARS-CoV-2 infected patients not discussed in the review is immune thrombocytopenia (ITP). Though ITP and consecutive bleeding has been particularly reported in association with SARS-CoV-2 vaccinations (Finsterer & Redzic, 2021), it has been also reported in patients with SARS-CoV-2 infections (Lévesque et al., 2020). Since platelet receptors bind various auto-antibodies, immune complexes, damage-associated molecular patterns (DAMPs), and complement factors, not only thrombus formation but also a propensity to bleeding may ensue from dysfunctional platelets (Sun et al., 2021). As circulating platelets also serve as a reservoir of immunomodulatory molecules, they play a role not only in the pathogenesis of autoimmune diseases, but can also predispose

for thrombocytopenia and are thus linked to bleeding events (Sun et al., 2021).

Another pathophysiological mechanism not considered are drugs that increase the propensity of bleeding as a side effect. In a recent report about a patient who was treated with bortezomib for COVID-19 intracerebral bleeding occurred (Finsterer & Scorza, 2021).

A third pathophysiological mechanism to explain cerebral bleeding in SARS-CoV-2 infected patients is arterial hypertension. Since SARS-CoV-2 infections can be complicated by autonomic dysfunction and autonomic dysfunction may be associated with arterial hypertension, it is conceivable that newly developing arterial hypertension during a SARS-CoV-2 infection may be complicated by ICH if not treated adequately in due time.

The review also lacks any discussion about endothelialitis as a cause of vessel rupture and thus micro- or macro-bleeding. In an autopsy study of patients dying through COVID-19, 56 patients had perivascular petechial haemorrhages (Bugra et al., 2021). In a recent study by means of high-resolution vessel wall MRI imaging (high-resolution vascular black blood sequences) it has been found that the majority of patients with COVID-19 associated encephalopathy had a circular enhancement and thickening of the basilar and vertebral arteries (Uginet et al., 2021). However, no correlation with ischemia or bleedings, reported in 21% and 59% of patients respectively, was found (Uginet et al., 2021).

A type of cerebral bleeding not discussed in the review is micro-bleeding. Microbleeds have been reported in association with

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SARS-CoV-2 associated leuco-encephalopathy (Witvoet et al., 2021). Cerebral microbleeds have been also reported in association with critical ill disease (Edlow et al., 2021) and with extra-corporeal membrane oxygenation (ECMO) therapy (Topiwala et al., 2021).

Overall, the elegant study has some limitations which challenge the results and their interpretation. These limitations should be addressed to further strengthen the conclusions. The etiological spectrum of ICH in COVID-19 patients is much broader than usually anticipated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Ethical statement and patient's consent

Informed consent was waived because of the retrospective nature of this study, which was approved by the Institutional Review Board of the Universidade Federal de São Paulo.

Consent for publication

All the authors have consented for publication of this manuscript.

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