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.

Letter to the Editor Regarding "Subarachnoid Hemorrhage and COVID-19: An Analysis of 282,718 Patients"

Letter:

I read with great interest the article by Qureshi et al.[1] Many manuscripts have appeared in the literature about the subarachnoid hemorrhage (SAH)-producing effect of COVID-19 infection.[2-5] In the mentioned study, the authors studied the risk of SAH in 85,645 patients with COVID-19 infection. The authors found a lower risk of SAH in patients with COVID-19 (odds ratio 0.5, 95% confidence interval 0.4e0.7, $P < 0.0001$) after adjusting for sex, age strata, race/ethnicity, hypertension, and nicotine dependence/tobacco use.[1] They also noted that pneumonia (58.1% vs. 21.3%, $P < 0.0001$), acute kidney injury (43% vs. 27.7%, P [0.0005), septic shock (44.2% vs. 20.7%, $P < 0.0001$), and respiratory failure (64.0% vs. 39.1%, $P < 0.0001$) were significantly higher among patients with SAH and COVID-19 compared with patients without COVID-19. My main concern is that all the COVID-19 patients had been analyzed in only 1 uniform group; that is, the authors did not divide the mild and severe COVID-19 patients. In mild or asymptomatic patients, a low incidence of SAH may be seen. In those cases, SAH incidence may be lower than that of severely affected patients. We published a SAH and COVID-19 case series with only 4 patients and noted that all of the cases had severe COVID-19 infections.[2] We think that the severity of findings on chest computed tomography was a strong predictor of fatal SAH in patients with COVID-19 infection. Respiratory disturbances of patients with severe COVID-19 infection may be a predisposing risk factor. Microvascular dysfunction and the role of vascular endothelial dysfunction may also occur in COVID-19 infection.

The sympathetic nervous system may also have a role in SAH.[6] The cerebral vasculature, in particular the pial vessels, is densely supplied with sympathetic nerve fibers mainly originating in the superior cervical ganglion, accompanying the carotid artery, and projecting into the ipsilateral hemisphere.[7] Lung injury and enhanced activation of the sympathetic nerve system, as well as coagulation combined with dysfunction of the anticoagulant mechanisms, may constitute the SAH in patients with COVID-19 infection. Cranial vascular endothelial dysfunction or inflammation in COVID-19 patients may promote severe vessel weakening and SAH. The blood-brain barrier (BBB) has a value concerning brain function.[8] There is a complex interconnection between the lungs and brain.[9,10] Severe lung involvement in COVID-19 infection may lead to respiratory disturbances and increased intracranial pressure. There is also the blood-brain barrier in the brain,[11] changing the permeability this barrier may occur after COVID-19 infection. SAH may also lead to the blood-brain barrier (BBB) breakdown.[12] After extravasated arterial blood enters the subarachnoid space in a SAH and blood mixes with cerebrospinal fluid,[12] BBB breakdown occurs. I think that COVID-19 disease has an important effect on the cerebral vasculature by direct and indirect mechanisms that lead to endothelial damage and dysfunction. As mentioned earlier, in the study of Qureshi et al,[1] more cases of pneumonia were observed in SAH patients with COVID-19 infection than non–COVID-19 infection (58.1% vs. 21.3%). The problem is that all patients with pneumonia were in the same category, but the results of severe and mild pneumonia may not be the same.

Another concern is about fever and anticoagulant therapy. In our paper, 3 of 4 cases had been admitted to the hospital with a high fever[2] and 2 of 4 cases received anticoagulant therapy.[2] The patient's fever and anticoagulant therapy were not analyzed in the study by Qureshi et al.[1]

A comprehensive understanding of pathophysiology is an important issue in neurosurgery.[13,14] However, Qureshi et al[1] reported that the risk of SAH was not increased in patients with COVID-19. Although the authors of the paper are well-known neurosurgeons and experts in neurosurgery, I disagree with them. Our clinical practice is guided by scientific principles rather than expert opinion and authority.[15,16] Another concern is that the study by Qureshi et al[1] is a multicenter study, which, by nature, has disadvantages.[17] Pooling data from many centers resolves the problem of insufficient patient numbers, but it makes it harder to ensure stable conditions.[17]

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