Letter: Hemorrhagic Conditions Affecting the Central Nervous System in COVID-19 Patients

To the Editor:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) is a new pathogenic agent first described in Wuhan, China. As of May 11, Spain was the second in terms of number of confirmed cases (268 143) and the fourth in number of fatalities (26 744). During the last 2 mo, more than 1000 patients were admitted to our hospital and nearly 150 died.

Herein we report 4 cases of COVID-19 with neurological symptoms and central nervous system (CNS) hemorrhages with atypical and distinct patterns. (1) A 68-yr-old female with a personal history of dyslipidemia was admitted after suffering a sudden faint and a brief loss of consciousness. She explained a 3-d history of moderate weakness. Polymerase chain reaction (PCR) and thoracic computed tomography (CT) were positive for COVID-19. Neurological exploration was normal and the head CT scan showed a small pontine hemorrhage (Figure A). A 24-h control scan yielded no progression of the hemorrhage. Pneumonia was successfully treated and no further neurological symptoms were observed during her 10-d hospitalization. (2) A 59-yr-old male with a personal record of hypertension was transferred from a secondary institution to our intensive care unit (ICU) to start extracorporeal membrane oxygenation (ECMO) therapy after unsatisfactory response to antivirals, antibiotics, and respiratory support. On day 1 he presented with generalized seizures. The cranial CT demonstrated multiple hemorrhagic foci bilaterally displayed (Figure B-D). The patient's life-threatening situation made ECMO mandatory and therefore was not interrupted. A 24-h control scan ruled out any progression of the hemorrhages. Unfortunately, the patient died 17 d later due to respiratory complications. (3) Similarly, a 60-yr-old male who consulted for dyspnea was diagnosed with COVID-19. A head CT was performed after an episode of seizures, revealing a bilateral frontal subarachnoid hemorrhage (SAH) (Figure E). After failed respiratory support, the patient received ECMO therapy. Most likely due to anticoagulation, 5 d later he suffered a fatal progression of the aforementioned hemorrhage (Figure F). Indeed, the brainstem and basal cisterns displayed radiological features compatible with brain swelling (Figure G), which would better explain the sudden bilateral mydriasis that motivated the CT scan. (4) Finally, to illustrate the heterogeneity of neurological symptoms and distinct hemorrhagic patterns we came across with, an 81-yr-old female with diabetes and hypertension who consulted for an episode of facial numbness, right ptosis, right labial commissural deviation, and mild left upper limb paresis. As part of the admission protocol, she underwent a PCR and a thoracic CT scan, which resulted positive for COVID-19. The head scan showed a small hemorrhage in her right pons (Figure H). The neurological symptoms progressively resolved in 48 h without any specific treatment. The patient could then be discharged since her respiratory status did not require hospitalization.

It might be argued that the COVID-19 epidemiological situation in our region may explain its association with, otherwise, idiopathic neurological findings. However, the increased incidence of these clinical features and the growing evidence of COVID-19 implication in neurological syndromes urged us to disclose our experience.[1,2] Various physiopathological mechanisms have been suggested for neurological manifestations in COVID-19. Neurotropism in other coronaviruses has been clinically and pathologically demonstrated. Similarly, COVID-19 has displayed a wide variety of neurological symptoms from mild disturbances (anosmia, ageusia, transient diplopia) to severe syndromes (necrotizing encephalopathy).[1] It has been proposed that the olfactory neuroepithelium may act as a neural entry path into the CNS. Moreover, the systemic invasion of the virus through angiotensin-converting enzyme 2 (ACE2) channels present in neurons and in the endothelium of body and cerebral vessels seems a more plausible spread mechanism of the virus onto the CNS.[3] Some warnings have been issued regarding an increased incidence of ischemic and hemorrhagic strokes in COVID-19 patients.[1,3] However, no specific hemorrhagic patterns have been reported so far. Involved mechanisms injuring the CNS and making patients prone to bleeding can be hypothesized: vessel increased permeability or vasculitis in the context of the cytokine storm developed in response to virus antigens; thrombotic phenomena; increased central venous pressure in ventilated patients; secondary hemophagocytic lymphohistiocytosis; specific treatments requiring anticoagulation, etc.[4,5] These mechanisms might present isolated, therefore explaining the mildest forms of bleedings or complicating baseline conditions, or may accrue to devastate the integrity of the vessel wall, leading to massive bleedings. Thus, some neurological manifestations of COVID-19 could be explained by systemic inflammatory cascades, and, conversely, some systemic manifestations could be due to CNS involvement. Acute respiratory distress, or neurogenic pulmonary edema, following traumatic or spontaneous SAH might occur in up to 20% of patients.[6] With the current lack of evidence, whether this condition is involved in some rapidly developed pulmonary insufficiency in COVID-19 patients may be only theorized. Further pathological studies such as necropsies or, more conveniently, given the particular current sanitary emergency, minimally invasive brain autopsies would be desirable to elucidate the actual implications, mechanisms, and systemic consequences of CNS involvement in COVID-19 patients.

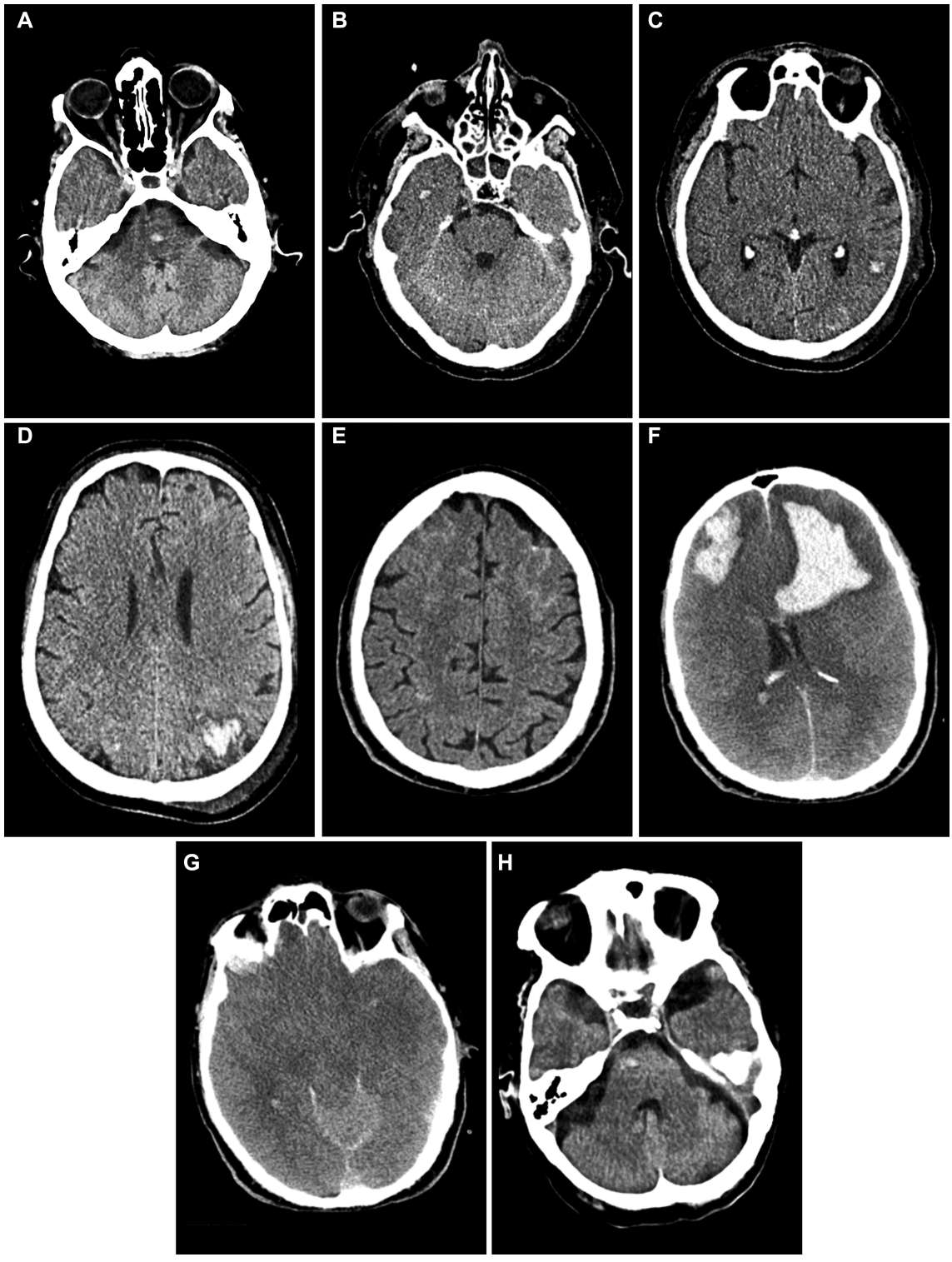

FIGURE. *Head CT scans of reported patients.* **A**, *Central pontine acute hemorrhage in patient 1.* **B-D**, *Acute bilateral hemorrhagic foci in patient 2 affecting both temporal lobes and the left parietal lobe.* **E**, *Initial head scan of patient 3 demonstrating a bilateral frontal subarachnoid hemorrhage.* **F-G**, *Progression of the initial bleeding developing into bilateral frontal acute intraparenchymal hemorrhages that compress the frontal horns of lateral ventricles. In a more caudal slice of the same scan, a severe brain swelling and effacement of basal cisterns is demonstrated.* **H**, *Right pontine acute hemorrhage in patient 4.*

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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REFERENCES

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. published online: April 10, 2020 (doi:10.1001/jamaneurol.2020.1127).
2. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998.
3. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. published online: April 15, 2020 (doi:10.1056/NEJMc2008597).
4. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet North Am Ed*. 2020;395(10229):1033-1034.
5. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet North Am Ed.* 2020;395(10234):1417-1418.
6. Elmer J, Hou P, Wilcox SR, et al. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage. *Crit Care Med*. 2013;41(8):1992-2001.

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