Radiology

ORIGINAL RESEARCH • CASE SERIES

COVID-19–associated Diffuse Leukoencephalopathy and Microhemorrhages

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Coronavirus disease 2019 (COVID-19) has been reported in association with a variety of brain imaging findings such as ischemic infarct, hemorrhage, and acute hemorrhagic necrotizing encephalopathy. Herein, the authors report brain imaging features in 11 critically ill patients with COVID-19 with persistently diminished mental status who underwent MRI between April 5 and April 25, 2020. These imaging features include *(a)* confluent T2 hyperintensity and mild restricted diffusion in bilateral supratentorial deep and subcortical white matter (in 10 of 11 patients) and *(b)* multiple punctate microhemorrhages in juxtacortical and callosal white matter (in seven of 11 patients). The authors also discuss potential pathogeneses.

Online supplemental material is available for this article.

Coronavirus disease 2019 (COVID-19) started with an outbreak in Wuhan, China, in December 2019, and quickly became a worldwide public health crisis. A variety of neurologic manifestations have been reported (1), and a few reports of brain imaging findings, encompassing ischemic infarct, hemorrhage, and acute hemorrhagic necrotizing encephalopathy, are available (2,3). Herein we report diffuse leukoencephalopathy and juxtacortical or callosal microhemorrhages as two brain imaging features in patients with COVID-19 and discuss the possible pathogeneses.

Materials and Methods

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and approved by the institutional review board. The requirement for informed consent was waived. Critically ill patients with confirmed diagnoses of COVID-19 by means of reverse-transcriptase polymerase chain reaction assay (Cobas 6800; Roche Diagnostics, Rotkreuz, Switzerland) of a nasopharyngeal swab specimen, who underwent brain MRI between April 5 and April 25, 2020, at New York University Langone Medical Center campuses (Manhattan and Brooklyn) were included. MRI examinations were performed according to a routine brain protocol (detailed protocol is available in Appendix E1 [online]). Two academic neuroradiologists (A.R. and A.D., with 6 and 9 years of experience, respectively) reviewed brain MRI scans independently, with no disagreements. Patients with abnormal white matter T2 hyperintensities (more than expected for age-related microangiopathy on the basis of visual qualitative assessment) and/or microhemorrhages (≤4 mm in size) were included in the series. Microhemorrhages confined to any areas of acute and/or subacute infarcts were excluded. Diffusion characteristics of white matter were investigated and qualitatively graded as mild or severe on the basis of apparent diffusion coefficient maps. Electronic health records were reviewed for all included patients.

Results

Twenty-seven critically ill patients with COVID-19 underwent brain MRI between April 5 and April 25, 2020. Of those 27 patients, 11 (mean age, 53 years; age range, 38–64 years; nine men, two women) were included in our series. Four patients had only diffuse leukoencephalopathy, one patient had only microhemorrhages, and six patients had a combination of both. Among the 16 excluded patients, MRI findings were as follows: acute or subacute infarcts in 11 patients (including three with microhemorrhagic transformation), parenchymal hemorrhages larger than 4 mm in four patients (all >1 cm), and thalamic expansile T2 hyperintensity in one patient (presumed acute hemorrhagic necrotizing encephalopathy).

All 11 patients in our series were on mechanical ventilation at the time of imaging (mean duration, 26.5 days), and the lowest blood oxygen saturation levels were 60%–85% (mean ± standard deviation, 73% ± 8). The indication for brain imaging in all patients was persistently diminished mental status. The neurologic examinations showed preserved brainstem reflexes and diminished-to-absent grimace or response to noxious stimuli in extremities. No patient required extracorporeal membrane oxygenation. None of the patients had overt disseminated intravascular coagulation based on the International Society on Thrombosis and Hemostasis diagnostic scoring system (4). Additional individual clinical and laboratory data can be found in Appendix E1 (online). Cerebrospinal fluid workup was available in only one patient (with both leukoencephalopathy and microhemorrhages) and was negative for infectious or inflammatory meningitis

Abbreviations

COVID-19 = coronavirus disease 2019, DPHL = delayed posthypoxic leukoencephalopathy

Summary

Diffuse leukoencephalopathy and juxtacortical and/or callosal microhemorrhages were brain imaging features in critically ill patients with coronavirus disease 2019.

or encephalitis and negative for coronavirus polymerase chain reaction assay. Three patients were diagnosed with bacteremia and treated with antibiotics before MRI (Appendix E1 [online]).

During the 3–5 weeks after brain MRI, six of the 11 patients died (three had leukoencephalopathy, one had microhemorrhages, and two had both). The other five patients continue to receive critical care.

Diffuse Leukoencephalopathy

The 10 patients with leukoencephalopathy had T2 hyperintensities that were symmetric and confluent, demonstrated mild restricted diffusion, and involved bilateral deep and subcortical white matter (Fig 1). The restricted diffusion in all cases was equally or more conspicuous compared with T2 hyperintensity (Fig 2).

Abnormalities extended from the precentral gyrus down to the centrum semiovale and corona radiata. At the level of the temporal and occipital horns, the posterior cerebral white matter in all patients was involved more than the anterior (Fig 2, *G–I*). The deep gray nuclei were spared. The juxtacortical white matter was also relatively spared (Fig 1, *A*), with the exception of the precentral gyrus in all 10 patients (Fig 2, *A–C*) and occipital lobes (Fig 2, *G–I*) in seven patients. One patient received intravenous contrast material for MRI, and there was no abnormal intracranial enhancement.

The infratentorial parenchyma tended to be less affected; only four patients had mild involvement of middle cerebellar peduncles and medial cerebellar hemispheres (Fig 3).

Juxtacortical and Callosal Microhemorrhages

Microhemorrhages were seen in seven of the 11 patients and varied in number from a few (five or six) to innumerable. Microhemorrhages were predominantly punctate, and in all cases smaller than 3 mm. There was no concomitant larger intracranial hemorrhage. Punctate microhemorrhages predominantly

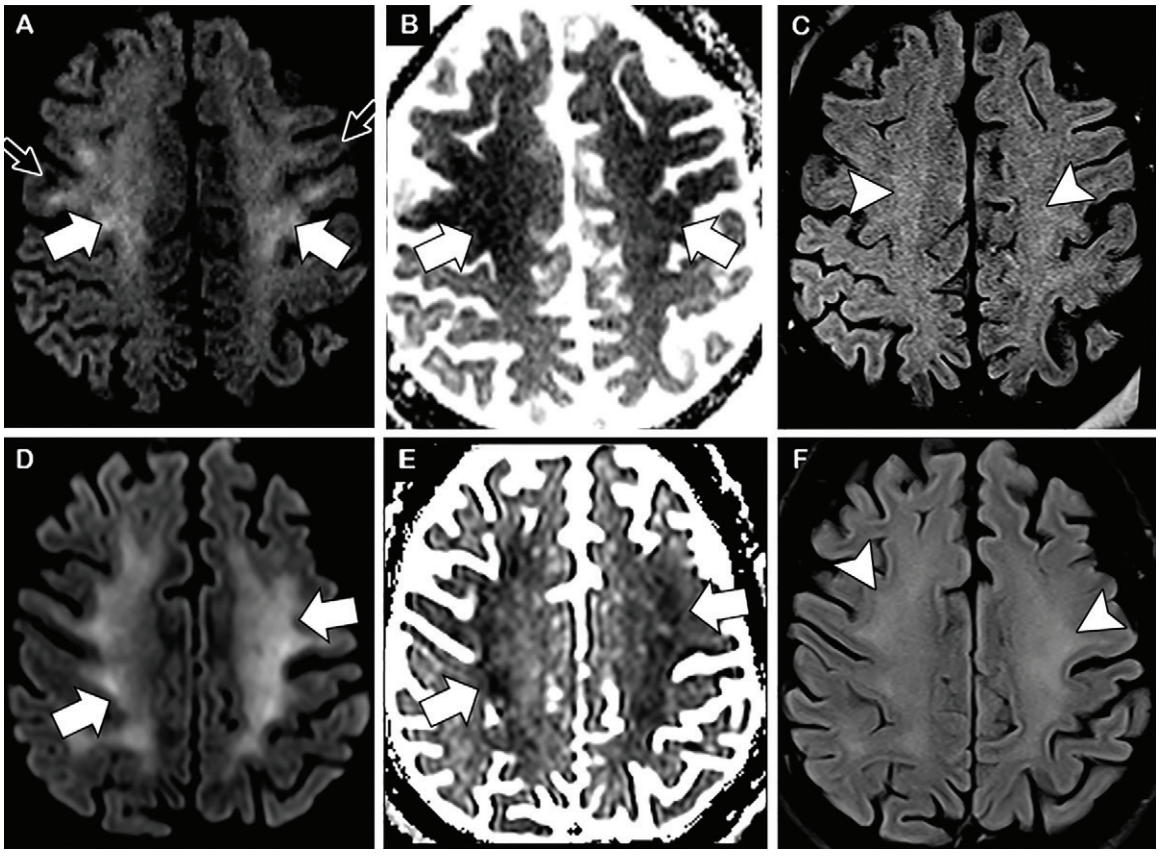

Figure 1: Axial brain MRI scans in two critically ill patients with coronavirus disease 2019 with persistently diminished mental status. *A–C*, Images in a 56-year-old man. *D–F*, Images in a 64-year-old man. *A*, *D*, Diffusion-weighted images, *B*, *E*, apparent diffusion coefficient maps, and, *C*, *F*, fluid-attenuated inversion recovery images at the level of centrum semiovale demonstrate symmetric diffuse T2 hyperintensity (arrowheads) and mild restricted diffusion (thick arrows) involving the deep and subcortical white matter with relative sparing of juxtacortical white matter (thin arrows) in both patients. The restricted diffusion is more conspicuous than the T2 hyperintensity.

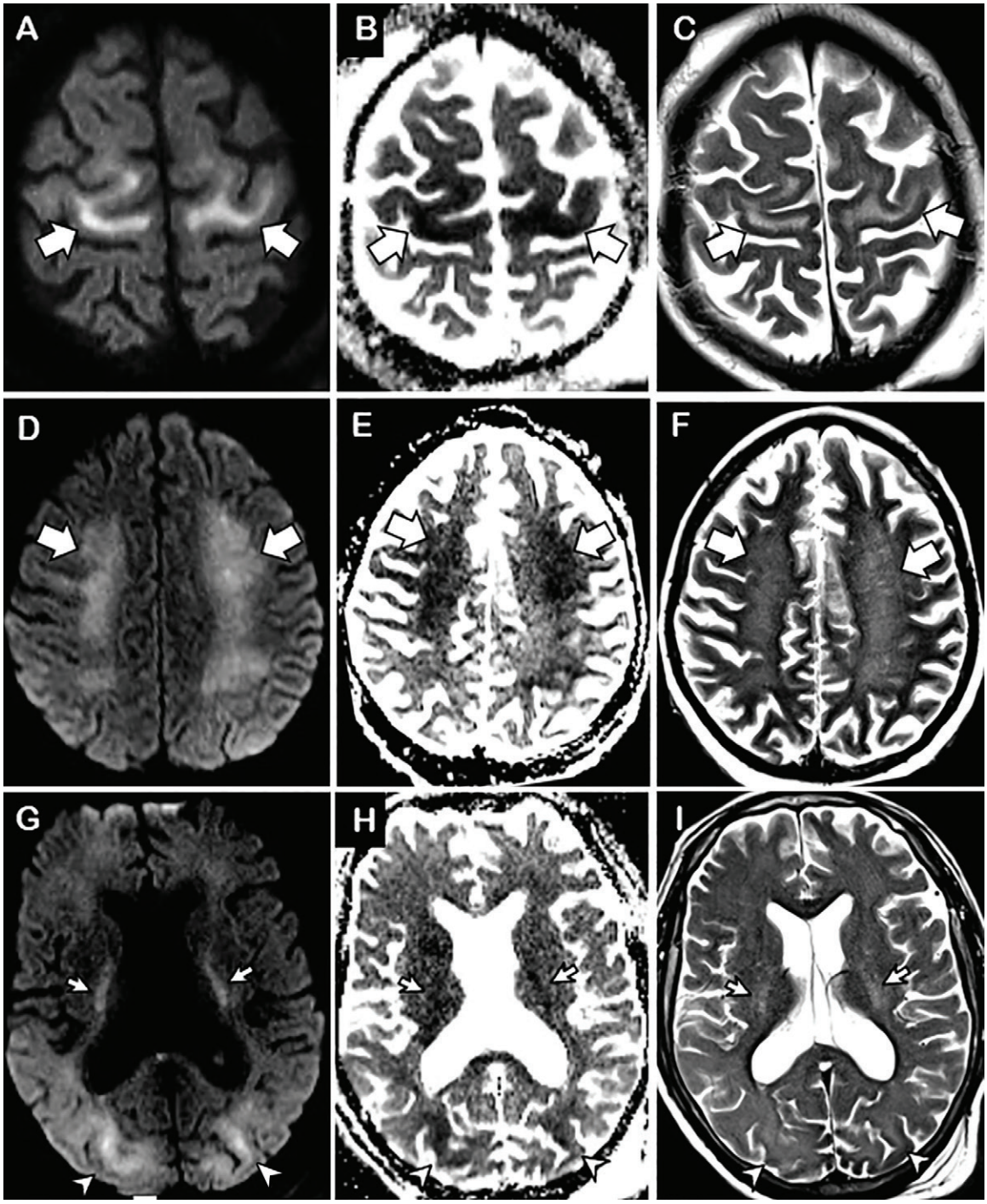

Figure 2: Axial brain MRI scans in a 63-year-old woman who was critically ill due to coronavirus disease 2019. The patient had persistently diminished mental status after 27 days of mechanical ventilation. *A, D, G,* Diffusion-weighted images, *B, E, H,* apparent diffusion coefficient maps, and, *C, F, I,* T2-weighted images at the levels of, *A–C,* paracentral lobule, *D–F,* centrum semiovale, and, *G–I,* corona radiata demonstrate confluent symmetric T2 hyperintensity and restricted diffusion extending from the juxtacortical and subcortical white matter of the precentral gyrus (arrows in *A–C*) down to the centrum semiovale (arrows in *D–F*) and down through the posterior limbs of the internal capsules (arrows in *G–I*) and occipital lobe juxtacortical and subcortical white matter (arrowheads in *G–I*).

involved the juxtacortical white matter (in five of seven patients) (Fig 4, *A*) and/or corpus callosum, particularly the splenium (in four of seven patients) (Fig 4, *B*).

Only one patient with microhemorrhages had previous brain MRI scans available for comparison. The scans had been obtained 7 days before the current hospital encounter (during workup for headache) and revealed that all microhemorrhages present on the current study were new (Fig 5). Four of seven patients had undergone brain CT 3–7 days before MRI. CT, even upon retrospective review, did not reveal punctate microhemorrhages. All seven patients with microhemorrhages were, at least temporarily, on closely monitored anticoagulation therapy

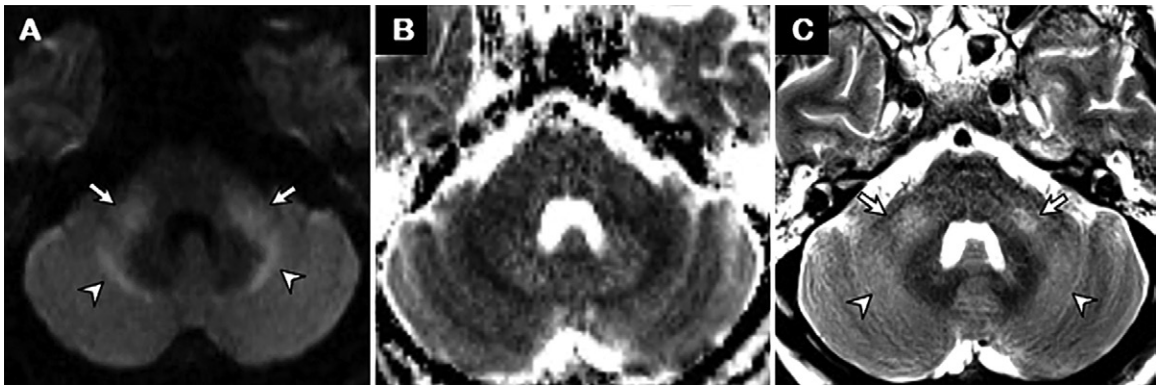

Figure 3: Axial brain MRI scans in a 64-year-old man who was critically ill due to coronavirus disease 2019. Images were obtained after 28 days of mechanical ventilation. *A*, Diffusion-weighted image, *B*, apparent diffusion coefficient map, and, *C*, T2-weighted image demonstrate patchy faint areas of restricted diffusion and T2 hyperintensity in the middle cerebellar peduncles (arrows) and in the white matter lateral to the deep cerebellar nuclei (arrowheads). The remaining parts of the brainstem and cerebellum are normal.

with no supratherapeutic coagulation indexes, and no patient had concomitant intracranial hemorrhage larger than 4 mm or known bleeding in other organs.

Discussion

We report on two neuroimaging features observed in critically ill patients with COVID-19: *(a)* diffuse leukoencephalopathy, with symmetric confluent white matter T2 hyperintensity and restricted diffusion with relative sparing of juxtacortical and infratentorial white matter, and *(b)* punctate microhemorrhages with predominant involvement of juxtacortical and callosal white matter. In a series of 11 critically ill patients with COVID-19 who underwent brain MRI for a persistently depressed mental status, four patients had only diffuse leukoencephalopathy, one patient had only punctate microhemorrhages, and six patients had a combination of both. Physicians who manage patients with COVID-19 should consider these findings during work-up for persistently diminished mental status.

Although initial reports of brain imaging findings in patients with COVID-19 showed ischemic and hemorrhagic complications (2,5), there are now increasing reports of other findings such as patchy demyelinating lesions (6) and acute hemorrhagic necrotizing encephalopathy involving the thalami and medial temporal lobes (3). Our report comprises 11 patients in a single 3-week period in April 2020, with all patients having been critically ill and on mechanical ventilation for a mean duration of 26.5 days. We believe the diffuse leukoencephalopathy and microhemorrhages described herein are late complications of critically ill patients with COVID-19 and likely related to hypoxemia. Previously, we reported brain imaging findings in 242 consecutive patients with COVID-19 seen at

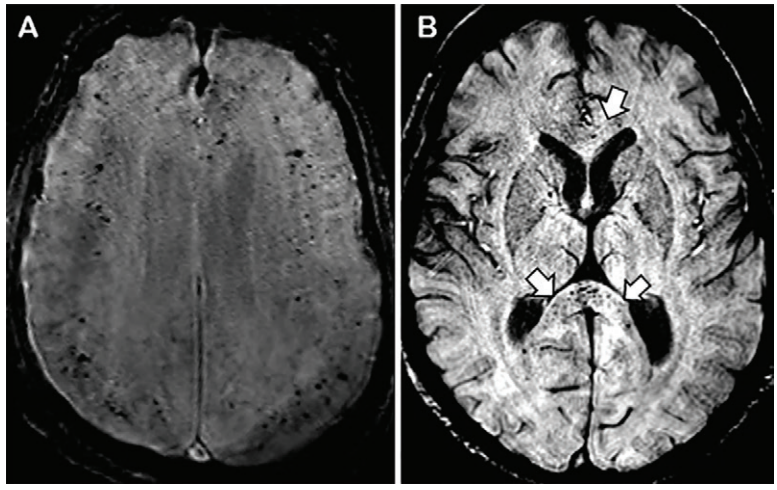

Figure 4: Axial susceptibility-weighted images in two critically ill patients with coronavirus disease 2019. *A*, Image obtained in a 45-year-old man after 23 days of mechanical ventilation. *B*, Image obtained in a 56-year-old man after 17 days of mechanical ventilation. Images demonstrate numerous punctate microhemorrhagic foci within the juxtacortical white matter, particularly near the depth of the sulci (*A*), and multiple punctate microhemorrhages within the corpus callosum, particularly in the splenium (arrows in *B*).

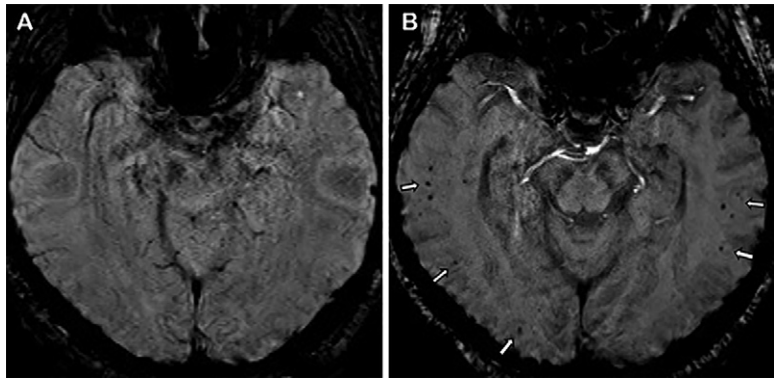

Figure 5: Axial susceptibility-weighted images in a 64-year-old man. *A*, Image obtained 1 week before the current hospital encounter, during work-up for headaches. *B*, Image obtained after 23 days of mechanical ventilation in the hospital intensive care unit due to coronavirus disease 2019 show multiple juxtacortical punctate microhemorrhages in bilateral temporal and right occipital lobes (arrows) that were not on the previous MRI scan.

our institution in March 2020 (2). None of those patients demonstrated these diffuse patterns of white matter involvement that we describe here. This suggests that these findings are not typical of earlier stages of COVID-19.

The diffuse white matter T2 hyperintensity and restricted diffusion reported herein may relate to delayed posthypoxic leukoencephalopathy (DPHL), for which a similar pattern of involvement has been described in patients approximately 10–14 days after a hypoxic insult (7). DPHL was previously described in victims of carbon monoxide poisoning, drug overdose, and cardiopulmonary arrest (8,9) and is believed to relate to oligodendroglial cell death and subsequent demyelination occurring preferentially in the deep interarterial boundary zones (10). Observed mild restricted diffusion can be related to acute demyelination. The predominant involvement of the deep white matter, sparing of juxtacortical white matter (except in precentral and occipital regions), and sparing of deep gray nuclei are typical of DPHL and in contrast to acute hypoxic ischemic injury (11).

The leukoencephalopathy observed in our critically ill patients is, however, nonspecific and the exact cause is not clear. Other potential causes of diffuse leukoencephalopathy in critically ill patients include direct cerebral infection (although this was not supported by negative viral cerebrospinal fluid assay in one patient), sepsis-associated encephalopathy (12,13), postinfectious demyelinating or hemorrhagic encephalitis, toxic and metabolic causes, and posterior reversible encephalopathy syndrome.

White matter microhemorrhages with predominant distribution in juxtacortical white matter and corpus callosum are also nonspecific and similar to DPHL, are thought to be related to hypoxia (7). Similar microhemorrhages have been reported in high-altitude exposure, possibly relating to hypoxemia and disruption of the blood-brain barrier (14). Multiple hemorrhages can alternatively be related to a small vessel vasculitis. Although the imaging distribution is reminiscent of traumatic axonal injury, none of our patients presented with severe head trauma. Of note, none of our patients fulfilled diagnostic criteria for disseminated intravascular coagulation (4).

Limitations of the current report include small sample size, retrospective nature, lack of quantification of MRI findings, and lack of histopathologic determination of underlying cause. Clinical follow-up to determine longer-term outcome in these patients should be further investigated.

In conclusion, herein we describe two neuroimaging findings, leukoencephalopathy and microhemorrhages, in critically ill patients with COVID-19 that affect white matter diffusely in characteristic patterns. We believe that both findings are related to hypoxia but have different pathogeneses: demyelination versus disruption of blood-brain barrier. It is important to recognize these findings as potential late central nervous system complications of COVID-19, particularly in patients with persistently diminished mental status.

Author contributions: Guarantors of integrity of entire study, A.R., A.D., M.H., G.M.F.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.R., A.D., E.R., M.J.B., E.Z., G.M.F.; clinical studies, A.R., A.D., Y.W.L., E.R., J.P.L., M.H., M.J.B., E.Z.; experimental studies, A.R., E.R.; and manuscript editing, A.R., A.D., Y.W.L., E.R., M.H., M.J.B., E.Z., G.M.F.

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