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Posterior reversible encephalopathy syndrome (PRES) is a spectrum of radiologic and clinical findings unified by acute neurological symptoms and associated cerebral vasogenic edema. PRES is thought to occur from disordered cerebrovascular autoregulation and is associated with acute renal failure, acute hypertension, inflammatory and autoimmune conditions, select immunomodulatory medications, and endothelial injury [1,2]. Many of these processes, as well as ischemic stroke, have been observed in SARS-CoV-2 infection [3,4], yet little is known about the occurrence of PRES in this context. We present clinical and radiographic characteristics of four patients with PRES and SARS-CoV-2 infection. The Weill Cornell Medicine Institutional Review Board approved this study and waived the requirement for informed consent.

2. Case 1

A 64-year-old man presented with hypoxic respiratory failure requiring intubation and neuromuscular blockade five days after symptom onset. He was treated with hydroxychloroquine. He developed acute renal failure with a peak serum creatinine of 5.67 mg/dL requiring continuous veno-venous hemodialysis, and had acute hypertension with peak mean arterial pressure 128 mmHg and peak systolic pressure of 187 mmHg (Fig. 1A Table). He had a right internal jugular deep vein thrombosis treated with heparin anticoagulation. He also had ongoing encephalopathy initially characterized by global aphasia and then by obtundation and minimal spontaneous movements despite extubation and improving respiratory status. Computed tomography (CT) of the head and lumbar puncture were unremarkable. 72 h of continuous video electroencephalogram (EEG) showed diffuse slowing but no seizures. A repeat CT six days later demonstrated new bilateral occipital confluent white matter hypodensities and patchy lucencies in the bilateral frontoparietal white matter and posterior limb of the left internal capsule. He had a generalized tonic-clonic seizure several hours later. Repeat EEG showed focal non-convulsive status epilepticus arising from the left posterior quadrant. His seizures were controlled. MRI on day 32 of hospitalization confirmed confluent T2 hyperintensities without diffusion restriction or susceptibility.
hypointensity in the locations of hypodensity on the prior CT (Fig. 1A). At discharge, he was alert and oriented, though inattentive, and had a right homonymous hemianopsia.

**3. Case 2**

A 73-year-old man presented with a five-day history of dyspnea and cough and was found to have hypoxic respiratory failure requiring intubation and neuromuscular blockade. He was treated with hydroxychloroquine. His hospitalization was complicated by multiple infections and acute renal failure with creatinine peak of 2.04 mg/dL (Fig. 1B Table), and myocardial infarction. He was encephalopathic and treated for presumed alcohol withdrawal with benzodiazepines and for delirium with antipsychotics. Six weeks into his hospitalization, he was noted to be persistently hypertensive with a maximum mean arterial pressure of 135 mmHg and a maximum systolic pressure of 212 mmHg (Fig. 1B Table). He had a left gaze preference on exam. CT head showed confluent hypointensation in the bilateral parietooccipital white matter. MRI showed confluent T2 hyperintensity in the same regions (Fig. 1B) without diffusion restriction or susceptibility hypointensity. A five-day EEG showed subclinical focal seizures arising from the right posterior quadrant; these stopped after 24 h with treatment, and his level of arousal and attention improved. At the time of discharge, he was alert and oriented and followed all commands, with no focal neurologic deficits.

**4. Case 3**

A 65-year-old woman with hypertension and diabetes was admitted and intubated with hypoxic respiratory failure after two weeks of dyspnea and cough. She was treated with hydroxychloroquine. She developed bacterial pneumonia with mean arterial pressure as high as...
1.38 mmHg, systolic blood pressure up to 190 mmHg, and a peak serum creatinine of 2.48 mg/dL (Fig. 1C Table). Although her respiratory failure improved, she remained stuporous with repetitive blinking after sedation was weaned. CT showed symmetric hypodensity involving the bilateral occipital subcortical white matter. MRI showed corresponding non-enhancing T2 hyperintensities without diffusion restriction (Fig. 1C). Routine EEG did not demonstrate any epileptiform activity. Blood pressure was controlled with improvement in her level of arousal and radiographic findings at discharge. She did not have focal neurologic deficits, but she had mild cognitive deficits and temporal disorientation on formal neuropsychologic testing.

5. Case 4

A 74-year-old woman with hypothyroidism, diabetes, and hyperlipidemia presented with eight days of cough, fever and progressive dyspnea. She required endotracheal intubation and mechanical ventilation for two weeks. Her hospitalization was notable for mild transaminitis, an elevated creatinine that peaked at 1.61 mg/dL, persistent respiratory failure requiring paralysis and proning, acute hypertension with a maximum mean arterial pressure of 150 mmHg, and maximum systolic blood pressure of 237 mmHg, and encephalopathy (Fig. 1D Table). She was treated with hydroxychloroquine and tocilizumab (Fig. 1D, blue arrow). Her course was complicated by persistently confusion with intermittent agitation. She followed commands inconsistently. A CT of the head performed for new onset right arm weakness showed hypodenuation in the parietooccipital white matter bilaterally (Fig. 2A). MRI showed T2 hyperintensity in the bilateral parietooccipital lobes (Fig. 1D) with corresponding diffusion restriction and foci of susceptibility hypointensity within the areas of T2 hyperintensity (Fig. 2B and C). A 48-h EEG was negative for epileptiform activity. Her blood pressure was controlled, and her confusion and right arm weakness improved. On discharge, she was alert and oriented to person and time but not place and followed commands consistently.

6. Discussion

We describe four cases of PRES in critically ill patients with SARS-CoV-2 infection. All four patients had acute kidney injury (AKI) with elevated blood pressure preceding the diagnosis of PRES. Of note, in Case 1 and 2, maximum mean arterial pressure occurred on the day of diagnosis (Fig. 1A and B). Neurological findings improved with blood pressure control, and in Case 1 and 2, with seizure control. Three of the four patients were discharged to acute rehabilitation, and the fourth to subacute rehabilitation.

Recent reports in patients with COVID-19 and persistent confusion and lethargy have demonstrated diffuse leukoencephalopathy and numerous cerebral microbleeds [5]. PRES in SARS-CoV-2 infection has not yet been well described, though it appears that COVID-19 is associated with multiple risk factors that have been seen in PRES.

Renal failure is a common complication of COVID-19, with 13.3% of those intubated requiring new renal replacement therapy [3]. Among our four patients, all had AKI with elevated blood pressure, though only Case 1 required dialysis. It has been suggested that renal failure is the strongest predictor of the development of PRES, seen in up to 55% of cases [2].

Another hallmark of critical illness in COVID-19 has been "cytokine storm" with fevers, elevated ferritin, IL-6, and TNF-α [3]. In this regard, ferritin levels were elevated in our patients as were LDH and CRP which are also nonspecific markers of inflammation. IL-6 levels, however, were elevated only in Case 4, although IL-6 was not checked regularly in COVID-19 cases in our institution. D-dimer levels were extremely high as is often the case in association with COVID-19 and with activation of the proinflammatory cytokine cascade in general [6].

The cytokine storm of COVID-19 may be related to the development of PRES in our patients. TNF-α (not specifically measured in our patients) has been associated with cytokine storm in COVID-19 patients and is implicated in PRES because it increases vascular permeability and upregulates vascular endothelial growth factor (VEGF) in the setting of hypoxia [2,7]. Elevated levels of VEGF have been found in disease states associated with PRES, most notably SLE [8]. Endothelial injury, which has also been implicated in PRES and in conditions associated with it such as pre-eclampsia [9], is prominent in COVID-19; viral inclusion structures have been found on autopsy in the endothelial cells in lungs, heart, kidneys, and liver. Virus is thought to enter cells through the ACE2 receptor [10].

Immunomodulatory medications such as cyclosporine and tacrolimus are known to induce PRES. Similar treatments used for SARS-CoV-2 infection, such as tocilizumab, which was given to one patient in our series, has also been implicated [11]. Hydroxychloroquine, which was given to all of the patients in our case series, has been implicated in PRES; though it is unclear if this is an independent risk factor or simply a consequence of the fact that it is used commonly in patients with SLE [12]. The use of hydroxychloroquine in our patients does not distinguish them from other patients with COVID-19 since this drug was used uniformly at our institution in COVID-19 patients during the time period studied here.

The imaging characteristics of PRES have been well described, with the hallmark finding of bilateral hemispheric subcortical and cortical edema. While there is usually a predominance of edema in the bilateral parietooccipital lobes, other areas commonly affected are the frontal lobes, temporo-occipital junction and cerebellum [13,14]. Involvement of the thalamus and internal capsule, as seen in Case 1, has also been reported. Diffusion restriction, which was present in Case 4, has been reported in up to 16% in one series [14], and may reflect cytotoxic edema rather than vasogenic edema, indicating ischemia. Studies suggest that diffusion restriction may portend a worse prognosis in PRES [15], and that apparent diffusion coefficient reduction, which was reported in 17% of cases in another series, may be an independent predictor of poor outcome [16].

7. Conclusion

Cerebrovascular complications are emerging as an important cause of morbidity and mortality among patients with COVID-19. Here we present four cases of critically ill patients with COVID-19 who developed neurological findings including seizures, focal neurological deficits, and encephalopathy and were found to have PRES. All patients had renal injury and new acute hypertension, and had been treated with hydroxychloroquine. One patient was treated with tocilizumab. Based on these initial cases at our institution, we suggest that COVID-19 represents a “perfect storm” for PRES given the high rates of acute renal insufficiency, inflammation, and endothelial injury. Whether the virus confers an independent increase in risk of PRES is not known, but clinicians should consider the possibility of PRES early in the
appropriate circumstances, particularly given its reversible nature with appropriate treatment.

Declaration of Competing Interest

Dr. Merkler has received personal fees for medicolegal consulting on stroke. Dr. Leifer has received personal fees for medicolegal consulting on Neurology. Dr. Navi serves as a DSBM member for the PCORI-funded TRAVERSE trial and has received personal fees for medicolegal consulting on stroke. Dr. Segal has received personal fees for medicolegal consulting on stroke. No other authors have conflicts of interest to disclose.

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