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Posterior Reversible Encephalopathy Syndrome in Patients with Coronavirus Disease 2019: Two Cases and A Review of The Literature

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Introduction: Encephalopathy is a common complication of coronavirus disease 2019. Although the encephalopathy is idiopathic in many cases, there are several published reports of patients with posterior reversible encephalopathy syndrome in the setting of coronavirus disease 2019. *Objective:* To describe the diverse presentations, risk factors, and outcomes of posterior reversible encephalopathy syndrome in patients with coronavirus disease 2019. *Methods:* We assessed patients with coronavirus disease 2019 and a diagnosis of posterior reversible encephalopathy syndrome at our institution from April 1 to June 24, 2020. We performed a literature search to capture all known published cases of posterior reversible encephalopathy syndrome in patients with coronavirus disease 2019. *Results:* There were 2 cases of posterior reversible encephalopathy syndrome in the setting of coronavirus 2019 at our institution during a 3-month period. One patient was treated with anakinra, an interleukin-1 inhibitor that may disrupt endothelial function. The second patient had an underlying human immunodeficiency virus infection. We found 13 total cases in our literature search, which reported modest blood pressure fluctuations and a range of risk factors for posterior reversible encephalopathy syndrome. One patient was treated with tocilizumab, an interleukin-6 inhibitor that may have effects on endothelial function. All patients had an improvement in their neurological symptoms. Interval imaging, when available, showed radiographic improvement of brain lesions. *Conclusions:* Risk factors for posterior reversible encephalopathy syndrome in patients with coronavirus disease 2019 may include underlying infection or immunomodulatory agents with endothelial effects in conjunction with modest blood pressure fluctuations. We found that the neurological prognosis for posterior reversible encephalopathy syndrome in the setting of coronavirus disease 2019 infection is favorable. Recognition of posterior reversible encephalopathy syndrome in this patient population is critical for prognostication

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and initiation of treatment, which may include cessation of potential offending agents and tight blood pressure control.
Key Words: PRES—COVID-19—Immunosuppression

Background

Central nervous system (CNS) manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection include encephalopathy, encephalitis, meningitis, acute disseminated encephalomyelitis, and stroke,[1] both as a result of direct viral invasion of the central nervous system[2–5] and as a consequence of critical illness and systemic infection.[6] Coronavirus disease 2019 (COVID-19) may also cause significant changes in endothelial morphology, including disruption of intercellular junctions, cell swelling, and a loss of contact with the basal membrane.[7] However, posterior reversible encephalopathy syndrome (PRES), which may result from such endothelial dysfunction, has rarely been reported in patients with COVID-19.[8–11] The diverse etiologies and risk factors of PRES in this unique population warrant close examination, as they may elucidate strategies to prevent or treat the syndrome in select patients with COVID-19.

Methods

This study protocol was approved by the Boston Medical Center's Institutional Review Board. Two cases were identified through surveillance of patients admitted to the neurocritical care service between April 1, 2020 and June 24, 2020 with positive nasopharyngeal swab testing for SARS-CoV-2 and a clinical diagnosis of PRES.

A literature review for published cases of PRES in patients with COVID-19 was conducted on July 20, 2020 by searching PubMed and Medline using the terms "posterior reversible encephalopathy syndrome AND COVID" and "PRES AND COVID".

Results

Case 1

A previously healthy 61-year-old woman presented with one week of dyspnea, headaches, fever, and cough. She was diagnosed with COVID-19 based on a positive nasopharyngeal PCR for SARS-CoV-2 and was treated with remdesivir and anakinra. Her hospital course was complicated by worsening respiratory failure requiring intubation on hospital day 5, subsequent proning for respiratory distress syndrome, ventilator dyssynchrony requiring significant sedation and periodic paralysis, and septic shock with hypotension requiring vasopressors. On hospital day 15, a head CT was obtained because of persistently poor mental status in spite of weaning sedation and revealed significant posterior cortical paramedian hypodensity consistent with cerebral edema (Fig. 1A). Blood pressure range was 152−187/79−98 mmHg, with no metabolic derangements. CT venogram showed no evidence of venous sinus thrombosis. In order to conserve personal protective equipment and limit healthcare worker exposure and risk, a lumbar puncture was not performed.

A subsequent brain MRI on hospital day 18 revealed symmetric white matter T2 hyperintense signal abnormalities involving the parietal and occipital lobes without diffusion restriction consistent with PRES, as well as a focus of susceptibility artifact in the right frontal lobe (Fig. 1B-C). On hospital day 18, she had a clinical seizure characterized by rightward gaze deviation and right arm and leg shaking. She was treated with levetiracetam and valproic acid. Subsequent 24 h continuous video electroencephalography (EEG) revealed rare bursts of repetitive sharp waves and spikes noted over the right hemisphere with a broad field, more prominent over the right frontal-parietal region with no clear ictal evolution. She was extubated on hospital day 21, but was re-intubated on hospital day 24 because of worsening hypoxemia, ultimately undergoing a tracheostomy. Her mental status improved over the subsequent weeks. At time of discharge on hospital day 48, she was alert, oriented, and following commands consistently.

Case 2

A 52-year-old woman with a history of HIV infection (CD4+ lymphocyte count 699/μL, viral load undetected) presented with fever and respiratory distress requiring intubation in the emergency department. Admission labs were remarkable for hyperglycemia to 450 mg/dL with an anion gap of 23 mEq/L, and her course was complicated by oliguric renal failure with a maximum creatinine of 4.33 mg/dL requiring continuous hemodialysis. She was diagnosed with COVID-19 based on a positive nasopharyngeal PCR for SARS-CoV-2 but did not receive specific therapies for COVID-19 because of her renal failure. Her respiratory status continued to worsen, and she underwent proning for respiratory distress syndrome. She subsequently developed ventilator dyssynchrony requiring significant sedation and periodic paralysis. Tracheostomy was placed on hospital day 23 because of an inability to extubate, and her course was further complicated by septic shock with hypotension requiring vasopressors.

On hospital day 34, she had a 2 min clinical seizure characterized by leftward gaze deviation and generalized

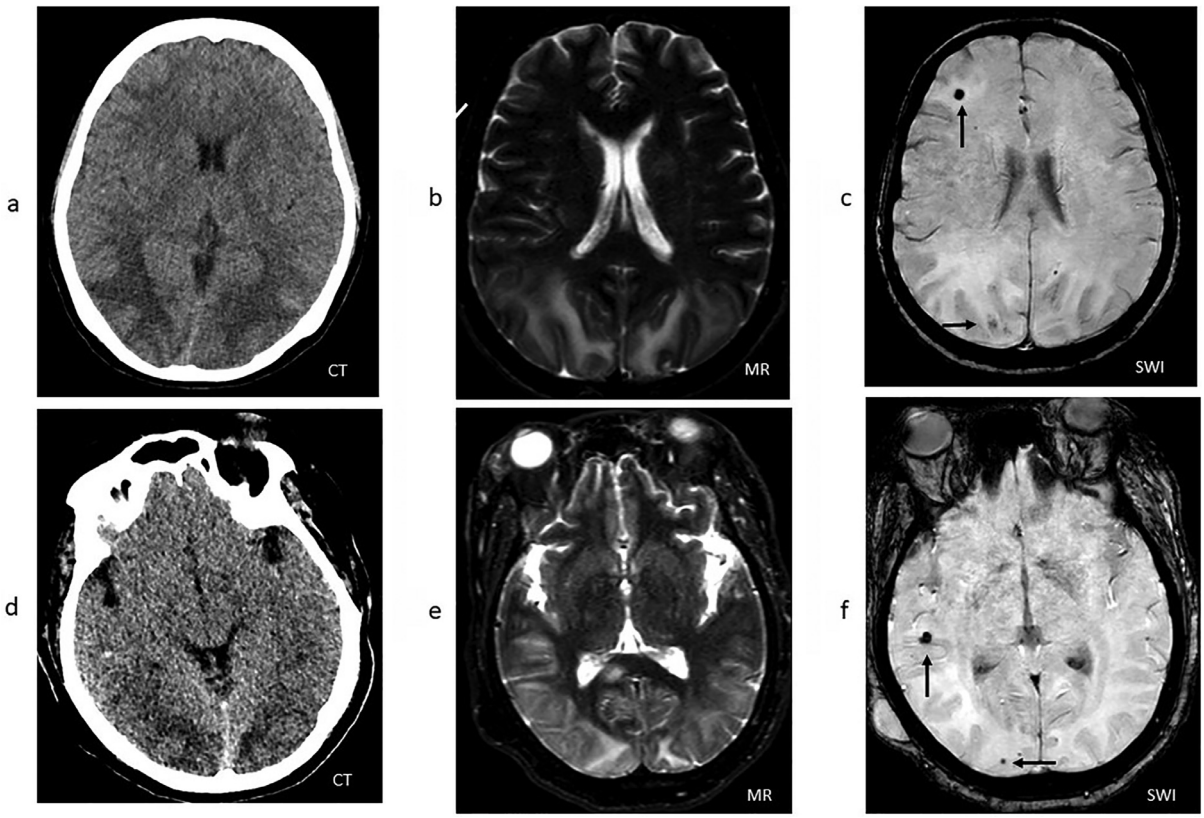

Fig. 1. *Patient 1: (a) Head CT demonstrating hypodensities involving the subcortical white matter of the bilateral parietal and occipital lobes. (b) Hyperintensities in the same anatomic distribution as the CT on T2-weighted MRI sequences. (c) Multiple foci of susceptibility artifact in the right parietal and frontal lobes (arrows) on susceptibility-weighted MRI sequences. Patient 2: (d) CT hypodensities involving the cortical and subcortical white matter of the bilateral occipital and temporal lobes. (e) Hyperintensities in the same anatomic distribution as the CT on T2-weighted MRI sequences. (f) Multiple foci of susceptibility artifact in the right.*

tonic-clonic movements. Blood pressure range was 140−180/70−97 mmHg. Her head CT revealed bilateral occipital hypodensities (Fig. 1D). A 24 h continuous video EEG revealed a reactive and continuous background without epileptiform discharges. Brain MRI on hospital day 35 revealed diffuse T2 hyperintensities involving the white matter of the bilateral parietal, occipital, frontal, and temporal lobes, with partial sulcal effacement. Similar to case 1, there were punctate microhemorrhages in the temporal and occipital lobes. (Fig. 1E-F). Cerebrospinal fluid (CSF) analysis revealed an elevated protein of 95 mg/dL, glucose 78 mg/dL, elevated total nucleated cell count of 28/μL (89% polymorphonuclear), red blood cell count of 223/μL, and negative infectious studies including a meningitis and encephalitis PCR panel and a cryptococcal antigen. Her mental status gradually improved over the next several days. On hospital day 43, 9 days after onset of symptoms attributable to PRES, she was alert and oriented and began to follow commands consistently. Follow-up head CT demonstrated significant improvement in the hypodensities of the bilateral occipital, parietal, temporal and frontal lobes.

Literature search

We found 13 cases of PRES in patients with COVID-19 in the literature.[8,9,11–14] There was an additional case of PRES identified via virtuopsy (post-mortem imaging) but this was excluded from our results due to limited clinical details.[10] The included patients all had positive nasopharyngeal PCR for SARS-CoV-2. Relevant clinical details for these cases are summarized in Table 1 along with the 2 patients in our series for comparison.

Discussion

We cared for 2 patients with COVID-19 and PRES at our institution and identified additional cases through a literature search, finding variable risk factors for developing the syndrome. Although the exact mechanisms underlying PRES are unclear, contributing factors are thought to include hypertension with subsequent cerebral hyperperfusion and endothelial dysfunction.[15] SARS-CoV-2 has been found to bind directly to angiotensin-converting enzyme 2 receptors, which can dysregulate the endothelial layer, increase blood pressure, and disrupt cerebral blood flow autoregulation.[16] The mechanism by which

Table 1. *Summary of 13 cases of posterior reversible encephalopathy syndrome in patients with COVID-19. Patients 1 and 2 are described in this case series while patients 3 through 13 are cases reported in the literature. CT: computed tomography; CTA: computer tomography angiography; FLAIR: fluid attenuated inversion recovery; HIV: human immunodeficiency virus; ICU: intensive care unit; MRI: magnetic resonance imaging; PRES: posterior reversible encephalopathy syndrome; SWI: susceptibility weighted imaging.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Age	61	52	48	67	38	58	67	64	64	73	65	74	74
Gender	Female	Female	Male	Female	Male	Male	Female	Female	Male	Male	Female	Female	Male
Comorbidities	None	HIV	Obesity	Hypertension, diabetes, coronary artery disease, gout, asthma	None	Hyperlipidemia	Hypertension, diabetes, obesity	Hypertension, gastroesophageal reflux disease, hyperuricemia, dyslipidemia, obstructive sleep apnea, paroxysmal atrial fibrillation	Unknown, none reported	Unknown, none reported	Hypertension, diabetes	Hypertension, diabetes, hyperlipidemia	IgG kappa multiple myeloma
Blood pressure (mm Hg)	152-187/79-98	140-180/70-97	70-180/30-90	115-178/72-83	"high levels for few hours"	86−189/52−122	79-193/44-97	150/70 on admission, no others reported	SBP 187, MAP 128 (maximum values)	SBP 212, MAP 135 (maximum values)	SBP 180, MAP 138 (maximum values)	SBP 237, MAP 150 (maximum values)	SBP 140-150 at the time of diagnosis
Presentation of COVID-19	Fever, dyspnea, cough, malaise	Fever, dyspnea, chest pain	Fever, dyspnea, cough	Altered mental status (no respiratory symptoms)	Fever, dyspnea	Fever, dry cough, malaise	Fever, dyspnea, myalgia, vomiting, diarrhea	Fever, dyspnea	Unknown, not described	Dyspnea, cough	Dyspnea, cough	Fever, cough	Fever, dry cough
Mechanical Ventilator Status	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	Unknown, not reported
Chest Radiologic Findings	CT chest with peripheral diffuse ground glass opacities. No pleural effusions.	Chest X-ray with bilateral diffuse airspace opacities	Unknown, not reported	CT chest with bilateral, multifocal ground-glass opacities	CT chest with bilateral multiple, multilobar, peripheral ground glass opacifications	Unknown, not reported	Unknown, not reported	Chest X-ray with reduction of parenchymal transparency in the basal region of right lung	Unknown, not reported	Unknown, not reported	Unknown, not reported	Unknown, not reported	Unknown, not reported
Treatment for COVID-19	Anakinra 200mg IV q12h x 3 days Remdesivir 200mg IV followed by 100mg IV x 4 days	None administereds	Unknown, none reported	Unknown, none reported	Hydroxychloroquine 400mg followed by 200mg/d x 4 days Azithromicin 500mg/d Osetalmivir 150mg/d	Tocilizumab 400mg IV Hydroxychloroquine (dose not reported) Azithromicin (dose not reported)	Hydroxychloroquine (dose not reported) Azithromicin (dose not reported)	Unknown, none reported	Hydroxchloroquine (dose not reported)	Hydroxychloroquine (dose not reported)	Hydroxychloroquine (dose not reported)	Hydroxychloroquine (dose not reported), tocilizumab	Hydroxychloroquine 200 mg q12, lopinavir / ritonavir 400/ 100 mg q12, dexamethasone 20 mg q12
Symptoms attributable to PRES	Altered mental status	Altered mental status and clinical seizure	Altered mental status	Altered mental status	Bilateral vision loss, apathic, impaired ability to follow commands	Altered mental status	Altered mental status	Altered mental status, blurred vision	Altered mental status, global aphasia	Left gaze preference, subclinical seizures	Stuporous	Persistent confusion with intermittent agitation	Clonic movement of the left limb, focal motor seizures
MRI findings	T2 hyperintensities in parietal and occipital lobes; SWI with focus of susceptibility artifact in right frontal lobe	T2 hyperintensities involving right side of splenium of corpus callosum	T2/FLAIR hyperintensities in posterior regions; SWI with extensive petechial hemorrhages throughout corpus callosum	Restricted diffusion with associated edema most extensive in posterior regions; SWI with extensive superimposed hemorrhages in parieto-occipital region	T2/FLAIR hyperintensities and diffusion restriction on DWI in bilateral, especially left occipital, frontal cortical white matter and splenium of corpus callosum	T2/FLAIR hyperintensities in subcortical white matter of bilateral occipital and posterior temporal lobes; SWI with subarachnoid hemorrhage	T2/FLAIR hyperintensities in subcortical white matter of right occipital lobe and left cerebellar hemisphere; SWI with petechial hemorrhage	T2/FLAIR vasogenic edema; GRE with right temporal lobe hypointensity	T2/FLAIR hyperintensities include the white matter of the bilateral occipital lobes, thalamus, and internal capsule	T2/FLAIR bilateral subcortical occipital lobe hyperintensity compatible with vasogenic edema	T2/FLAIR mild subcortical bilateral occipital lobe edema	T2/FLAIR hyperintensities in the white matter of the occipital lobes susceptibility weighted images with signal loss in the right occipital lobe	T2/FLAIR hyperintensities in the parietal lobe and right frontal lobe white matter
Cerebrovascular Imaging	CTA/CTV, normal vasculature	None	None	None	None	None	None	CTA without vascular malformation, posterior vessel caliber suggestive of vasoconstriction	None	None	None	None	None

Table 1 (*Continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Risk factors for PRES	Sepsis	HIV Renal failure	None mentioned	Hypertension	None mentioned	Hypertension Sepsis	Acute kidney injury requiring hemodialysis Sepsis	None mentioned	None mentioned	None mentioned	None mentioned	None mentioned	Multiple myeloma
Onset of PRES from hospitalization	Less than 15 days	34 days	18 days	0 days	5 days	26 days	25 days	25 days	Not reported	6 weeks	Not reported	Not reported	15 days
SOFA	6	7											
Outcome	Mental status gradually improved, discharged 33 days after onset of symptoms attributable to PRES	Mental status gradually improved, became interactive and started following commands 9 days after onset of symptoms attributable to PRES	Insufficient data Mental status gradually improved, transferred from ICU to medical floor six days from onset of symptoms attributable to PRES	Insufficient data Mental status gradually improved and discharged	Insufficient data Visual impairment resolved two days after onset following corticosteroid administration, neurocognitive assessment on day 10 of hospitalization was normal, brain MRI two weeks after symptom onset showed complete resolution of prior lesions	Insufficient data Mentation slowly improved to baseline, discharged 7 days after onset of symptoms attributable to PRES	Insufficient data Mentation slowly improved to nearly baseline, discharged 22 days after onset of symptoms attributable to PRES	Insufficient data Alert, fully oriented; blurry vision normalized	Insufficient data Alert, oriented, inattentive, right homonymous hemianopsia	Insufficient data Alert, following commands, no focal neurological deficits	Insufficient data Mild cognitive deficit, no focal neurological deficit	Insufficient data Alert and oriented to person and time (not to place), consistently following commands	Insufficient data Not reported
Reference	n/a	n/a	Franceschi et al (2020)[10]	Franceschi et al (2020)[10]	Kaya et al (2020)[7]	Kishfy et al (2020)[8]	Kishfy et al (2020)[8]	Cariddi et al (2020)[2]	Parauda et al, (2020)[15]	Parauda et al, (2020)[15]	Parauda et al (2020)[15]	Parauda et al (2020)[15]	Gomez-Enjuto et al (2020)[14]

COVID-19 may be associated with PRES is unclear, although it is notable that neuropathological studies of patients with COVID-19 and central nervous system dysfunction have identified only hypoxic changes without specific brain changes attributable to the virus.[17]

By contrast to the majority of published cases of PRES,[8,9] the patients described here had relatively modest blood pressure fluctuations before developing the syndrome. Similar to guidance offered by other authors,[8] we advocate for tight blood pressure control in patients with COVID-19 and risk factors for PRES, including renal failure, uncontrolled hypertension, or HIV infection. Two patients who developed PRES in the setting of COVID-19 were treated experimentally for the infection with interleukin inhibitors, one with the interleukin-6 inhibitor tocilizumab and one with the interleukin-1 inhibitor anakinra, which have known effects on endothelial function.[18–20] In particular, the interleukin-6 inhibitor tocilizumab has been described in association with PRES.[21] Our findings suggest that caution may be warranted when considering interleukin inhibitors to treat COVID-19 in patients with underlying PRES risk factors, that anakinra may also be associated with an increased risk of PRES in patients with COVID-19, and that these agents should be discontinued if PRES is diagnosed.

One of the patients presented here also had well-controlled HIV. Multiple reports in the literature describe PRES in HIV-infected patients, most often in those with advanced immunodeficiency, though it has been rarely described in patients with well-controlled HIV.[22–25] Possible mechanisms include impaired cerebrovascular reactivity even in virally suppressed patients and long-term exposure to antiretroviral therapies that may lead to mitochondrial damage in endothelial cells.[25] The HIV-infected patient presented here had a CSF profile with elevated protein and neutrophilic pleocytosis. The latter finding is rare in PRES and may be associated with a higher risk of ischemic or hemorrhagic events, consistent in this case with the small area of restricted diffusion on imaging.[26]

The majority of patients had severe respiratory manifestations of COVID-19 requiring intensive care, with just one patient (Patient 4)[11] whose primary manifestation of COVID-19 was altered mental status secondary to PRES. Although chest CT findings were concerning for viral pneumonia, she had subclinical respiratory involvement, suggesting that development of PRES is possible without obvious pulmonary manifestations, and that COVID-19 should be considered in patients presenting with PRES without other obvious risk factors.

Five of 7 patients had foci of susceptibility artifact on imaging consistent with various degrees of hemorrhage. In general, PRES is associated with hemorrhage at an estimated rate of 10-30% in patients. Risk factors for developing hemorrhage include bone marrow or solid-organ transplantation and coagulopathy.[27,28] Reversible cerebral vasoconstriction syndrome, which shares findings of

blood-brain barrier breakdown and cerebral edema with PRES, has also been described in association with both subarachnoid and parenchymal hemorrhage.[29,30] Patients 1 and 8 underwent computed tomography angiography (CTA) of the head and neck to evaluate for underlying vascular abnormalities with no alternative etiologies of hemorrhage found. Patients 2, 3, 4, 6, 7, 8, and 12 all had evidence of hemorrhage on MRI susceptibility sequences but no additional work-up was performed to evaluate for alternative etiologies of hemorrhage. Our observations suggest that hemorrhage may be more likely seen with PRES in patients with COVID-19, but additional study is required to determine the clinical significance of this finding.

Although hemorrhage and cytotoxic edema are risk factors for poor outcome in PRES,[31] all seven patients described here had marked clinical recovery. In general, 70−90% of patients with PRES have clinical recovery and resolution of edema on neuroimaging.[32] It is unclear if patients with COVID-19 may have a higher likelihood of a favorable outcome following PRES due to its potentially distinct pathophysiology.

Conclusions

Similar to other reports on neurologic complications of COVID-19, ours is limited by a lack of long-term follow-up. It is important, however, to describe cases early to add to the scarce literature on central nervous system injury potentially related to COVID-19. Here, we describe the diverse presentations, risk factors, and outcomes of PRES in patients with COVID-19. Based on these cases, we advocate for tight blood control for patients with COVID-19 and risk factor for PRES, and advise caution regarding the use of interleukin inhibitors in these patients. We also offer hope that COVID-associated PRES may have high likelihood of clinical recovery.

Declaration of Competing Interest

None

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