COVID-19–related posterior reversible encephalopathy syndrome: insights from a clinical case

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In the present case report, a 50-year-old female presented with hemiparesis and blurred vision and was subsequently diagnosed with posterior reversible encephalopathy syndrome (PRES) associated with coronavirus disease 2019 (COVID-19). Magnetic resonance imaging revealed cortico-subcortical edema with hyperintensities bilaterally in the frontoparietal and bi-occipital regions. Although PRES is a neurotoxic disorder that typically affects white matter of the brain and often is associated with hypertension, renal failure, and autoimmune disorders, recent studies have suggested that COVID-19 increases the risk of PRES. This case report presents a unique instance of COVID-19–related PRES. Unlike most previously reported cases occurring during the acute phase of severe COVID-19, our patient experienced PRES during the recovery phase with mild initial symptoms, such as fatigue and mild fever. The article discusses the pathophysiology of PRES, the potential mechanisms by which COVID-19 leads to PRES, and the treatment and outcome of the patient.

Keywords: COVID-19, Cytokine release syndrome, Posterior leukoencephalopathy syndrome, Vascular endothelium
Case Report

A 50-year-old female with a history of COVID-19 infection and a positive SARS-CoV-2 reverse-transcription polymerase chain reaction test on a nasopharyngeal specimen presented to our center with sudden onset of left hemiparesis and blurred vision, which were suspected to be indicative of a stroke.

The patient previously experienced mild symptoms associated with COVID-19 during the early phase of her infection, including fatigue, mild fever, and a sore throat. These initial COVID-19 symptoms were self-limiting and resolved without the need for hospitalization or specific COVID-19 treatments.

The patient’s COVID-19 infection was categorized as mild because she did not experience dyspnea or require intensive medical intervention during her illness. Notably, an approximate 6-day gap existed between the presentation of her COVID-19 symptoms and the emergence of PRES-related symptoms.

The patient reported experiencing left-sided weakness involving the arm and leg. She described the weakness as affecting her entire left side, from her left hand down to her left foot. In addition, her blurred vision was characterized as a sudden, painless loss of clarity in both eyes, with no associated eye pain, redness, or discharge. The nature of her blurred vision was not suggestive of homonymous hemianopsia or palinopsia but a generalized reduction in visual acuity, preventing her from distinguishing objects clearly. She did not report any other neurological symptoms, such as headaches, altered mental status, seizures, or speech disturbances. No prior history of hypertension was documented.

Upon admission, a comprehensive examination was conducted. The neurological examination revealed flaccid left-sided hemiparesis involving the upper and lower limbs. Muscle strength in the left arm and leg was notably reduced compared with the right side, with a Medical Research Council grade of 3/5 in the affected limbs. Sensory examination did not reveal any significant abnormalities. In addition, the vision examination using Snellen charts indicated a bilateral reduction in visual acuity, with both eyes affected equally. The patient was conscious, oriented, and followed verbal commands. Her body temperature was 36.8 °C, heart rate 102 beats/minute, noninvasive blood pressure 135/72 mmHg, respiratory rate 19 breaths/minute, and oxygen saturation 98%, with no signs or complaints of dyspnea. Blood pressure measurements performed throughout the admission period consistently indicated normotensive levels. Laboratory test results showed highly elevated C-reactive protein (CRP) level. A computed tomography (CT) scan of the brain was performed and showed no evidence of recent ischemia or suspicious hyperdense areas suggestive of bleeding (Figure 1A). In addition, there were no acute intracranial findings. Due to the unremarkable observations on CT, magnetic resonance imaging (MRI) was planned. Laboratory results showed no signs of infection.

MRI of the skull was performed using transverse diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR) MRI sequence, T2 fast field echo (FFE) sequence, coronal T1 spin echo (SE) sequence, and axial and coronal T2 FFE sequences after intravenous contrast administration. The MRI revealed diffuse and symmetric diffusion abnormalities without a reduction in apparent diffusion coefficient (ADC) (Figure 1B), as well as edematous brain parenchyma with symmetric cortico-subcortical hypersignal on weighted FLAIR (Figure 1C). These hyperintensities were observed bilaterally in the high-frontoparietal to occipital regions as well as in the bilateral dorsal cerebellar regions. Following intravenous administration of contrast medium, nodular leptomeningeal enhancement was observed in these areas due to disruption of the blood-brain barrier. Susceptibility artifacts or any evidence of post-hemorrhage was not detected.

The patient was diagnosed with PRES and treated with supportive therapy. She received comprehensive supportive care that primarily focused on close neurological and general medical monitoring throughout her admission. Specific therapies such as blood pressure control and seizure management were not required due to the absence of hypertension or seizures. Follow-up MRI 6 days later revealed regressing cortico-subcortical edema bilaterally in the frontoparietal and bi-occipital regions, as well as near-total regression of the cerebellar edema with hypersignal on weighted FLAIR (Figure 1D). There were no acute diffusion abnormalities. The patient showed complete regression of blurred vision, and the hemiparesis was improved upon discharge. A follow-up MRI 2 weeks after discharge showed substantial improvement. Cortico-subcortical edema in the frontoparietal and bi-occipital regions had significantly regressed (Figure 1E). New acute diffusion abnormalities were not observed, confirming neurological recovery.

Discussion

PRES is a neurological disorder characterized by a variety of
Comprehensive insights from CT, MRI, DWI, and ADC maps. (A) Axial view of the brain CT scan showing no evidence of recent ischemia or suspicious hyperdense areas suggestive of bleeding. There were no acute intracranial findings observed. (B) DWI and ADC maps; MRI at admission showing diffuse and symmetric diffusion abnormalities in the posterior circulation without a reduction in ADC. (C) Weighted FLAIR MRI at admission showing edematous brain parenchyma with symmetric cortico-subcortical hypersignal. Bilateral hyperintensities observed in high-frontoparietal to occipital regions and bilateral dorsal cerebellar regions. (D) Follow-up weighted FLAIR MRI 6 days after admission, showing regressing cortico-subcortical edema bilaterally in the frontoparietal and bi-occipital regions. Notably, near-total regression of cerebellar edema is evident, with residual hypersignal on weighted FLAIR. (E) Follow-up weighted FLAIR MRI 2 weeks after discharge showing significant improvement with substantial regression of cortico-subcortical edema in the frontoparietal and bi-occipital regions compared with the prior MRI. CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery MRI.

COVID-19 has been associated with a range of neurological complications, including PRES [8]. The exact mechanism by which COVID-19 leads to PRES is not fully understood. However, numerous pathological models have been proposed to explain the pathogenesis of PRES. The most widely accepted model is based on the well-known association between hypertension and PRES and posits that autoregulation failure at high blood pressure leads to hyperperfusion, which causes vasogenic edema in the posterior regions of the brain [7]. In another model, endogenous or exogenous toxic damage to the vascular endothelium was suggested to result in disruption of the blood-brain barrier and increased vessel permeability, leading to the characteristic edema of PRES [9]. Although hypertension is a reported risk factor in some cases, most PRES patients do not have hypertension. These findings support the model involving endothelial dysfunction for COVID-19–related PRES. The cytokine storm syndrome, a well-known mediator of COVID-19 disease [10], damages the capillary endothelium of the cerebral vasculature, leading to endothelial dysfunction. T-cells and macrophages, which contribute to the proinflammatory cytokine storm that drives endothelial dysfunction, are markedly elevated following COVID-19 infection [11]. In addition, the S1 spike protein of the virus binds directly to the angiotensin-converting enzyme 2 receptor on the capillary endothelium, causing injury and increasing its permeability [12]. This increased permeability may be one reason for the association between COVID-19 and PRES.

When exploring the possibility of direct brain invasion by the SARS-CoV-2 virus, recent systematic review of deceased COVID-19 patients revealed that neurological symptoms correlated with brain edema, hypoxic-ischemic lesions, and inflammatory infiltrates. Notably, the absence of viral RNA or proteins in brain tissue indicates that neurological issues in COVID-19 may stem from brain inflammation and hypoxic-ischemic damage rather than a direct neurotropic effect of SARS-CoV-2 [13].

In addition, it is important to acknowledge the potential value of cerebrospinal fluid (CSF) analysis in understanding the mechanisms of COVID-19–related neurological complications. Prior research has indicated that, in COVID-19 patients
with neurological symptoms, CSF analysis typically reveals blood-CSF barrier disruption in the absence of intrathecal inflammation, a pattern compatible with cerebrospinal endotheliopathy [14]. Although CSF analysis could provide valuable insights, we did not conduct CSF analysis in this case, which should be considered a limitation of the present study.

In our case study, we report a 50-year-old female with a history of COVID-19 infection who presented with an atypical presentation of PRES syndrome, with sudden onset of hemiparesis and visual disturbance instead of the more common symptoms of headache, altered mental status, and visual disturbances. The patient did not have a history of hypertension, but laboratory results showed a highly elevated CRP level, a marker of inflammation. MRI revealed diffusion abnormalities without a reduction in ADC, as well as edematous brain parenchyma with symmetric cortico-subcortical hypersignal on weighted FLAIR. These findings are consistent with the diagnosis of PRES.

However, unlike most reported cases that occurred in the acute phase of severe COVID-19, our case occurred during the recovery phase. The patient initially experienced only mild symptoms such as fatigue, mild fever, and pharyngitis, which later progressed to the atypical presentation of hemiparesis and blurred vision. This unique aspect of our case highlights the variable clinical presentations of PRES syndrome associated with COVID-19. To the best of our knowledge, there are few reported cases of COVID-19–associated PRES syndrome presenting with hemiparesis as the primary symptom [15-17]. Therefore, our case adds to the growing body of literature suggesting that PRES syndrome can have a wide range of clinical presentations and that healthcare providers should be aware of atypical presentations, particularly in the setting of COVID-19.

In addition, investigations to identify known associated medical disorders and triggering agents for PRES yielded negative results [18]. Regarding systemic conditions and metabolic disturbances, laboratory tests, including kidney function and electrolyte levels, did not reveal any signs of infection or abnormalities at the time of admission.

The diagnosis of PRES syndrome can be challenging, and imaging studies such as MRI are crucial for the diagnosis and monitoring of the condition [19]. The management of PRES in COVID-19 patients involves a multidisciplinary approach, including neurologists, critical care specialists, and infectious disease experts. The treatment strategy mainly focuses on controlling blood pressure, managing seizures, and addressing the underlying COVID-19 infection [9].

Controlling blood pressure is a crucial step in the management of PRES. In patients with hypertension, aggressive blood pressure control can prevent the progression of PRES. In COVID-19–associated PRES, blood pressure control can prevent further damage to the blood-brain barrier and decrease the risk of intracranial hemorrhage [20].

Addressing the underlying COVID-19 infection is also crucial for the management of PRES. COVID-19 treatment mainly involves supportive care, such as oxygen therapy, anticoagulation, and corticosteroids. In PRES patients with COVID-19, the use of corticosteroids was shown to improve clinical outcomes by reducing inflammation and stabilizing the blood-brain barrier. In our case, the decision against corticosteroid administration was based on mild symptoms, including left-sided hemiparesis and visual disturbances, without severe neurological issues such as altered mental status or seizures as well as limited brain edema. Due to the potential risk of hypertension, the multidisciplinary neurology team opted for a conservative approach, leading to clinical improvement [21,22].

In conclusion, this case report highlights the importance of considering PRES syndrome in patients with COVID-19 who present with neurological symptoms. COVID-19–related cytokine storm and coagulopathy can contribute to the development of neurological complications, including PRES, and early recognition of PRES is crucial for favorable outcomes. However, this case presented an atypical feature of PRES syndrome, with hemiparesis being the dominant clinical manifestation instead of the more common symptoms of headache, altered mental status, and visual disturbances [20].

The clinical presentation of PRES syndrome can vary, and the diagnosis should not be overlooked in the absence of typical symptoms [3]. As previously noted, PRES is considered rare in COVID-19 infections and may not be immediately suspected when COVID-19–infected individuals present with neurological symptoms. Notably, PRES can occur in COVID-19 infections even in the absence of hypertension or significant organ damage.

Further research is needed to better understand the pathophysiology of PRES in COVID-19 and to identify effective treatment strategies. In addition, due to the potential long-term neurological sequelae of COVID-19 infection, close follow-up and monitoring of patients with PRES syndrome asso-
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Associated with COVID-19 are essential [23,24].

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization, Investigation: Dehdab R; Supervision, Validation: Afat S; Project administration: Dehdab R, Afat S; Writing–original draft: Dehdab R; Writing–review & editing: Afat S

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