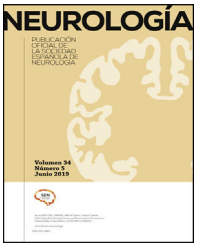
Neurología xxx (xxxx) 501944

NEUROLOGÍA

www.elsevier.es/neurologia



LETTER TO THE EDITOR

Response to ''Dysautonomia after COVID-19 infection: A case report'': The pathophysiology of COVID-19-related posterior reversible encephalopathy syndrome revisited

Respuesta a ''Disautonomía tras infección por SARS-CoV-2: reporte de un caso'': la fisiopatología del síndrome de encefalopatía posterior reversible (PRES) relacionado con la enfermedad por coronavirus de 2019 (COVID-19) revisada

Dear Editor,

We read with great interest the case report published in *Neurología* by Vera-Cáceres et al.[1] They present the case of a 64-year-old woman who experienced acute autonomic dysfunction during the parainfectious phase of coronavirus disease 2019 (COVID-19), attributed to Guillain-Barré syndrome (GBS); this is the first well-documented case of such an association. This case contributes to the growing evidence linking infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to GBS. The patient exhibited altered mental status and unusual symptoms of autonomic dysfunction, specifically posterior reversible encephalopathy syndrome (PRES), caused by blood pressure fluctuations, and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[1] Brain CT revealed diffuse occipital hypodensities within the occipital regions bilaterally.[1] The initial brain MRI scan revealed T2-weighted hyperintensities at the parietal and occipital lobes, indicative of vasogenic edema. These neuroimaging findings were suggestive of PRES, which was linked to blood pressure fluctuations (elevated blood pressure [systolic pressure >200 mmHg], requiring intravenous treatment [sodium nitroprusside, urapidil, and labetalol]).[1]

In the discussion, the authors do not address the epidemiology, pathophysiology (at least in depth), diagnosis, and management of COVID-19-related PRES. Therefore, we would like to further analyze this intriguing and potentially life-threatening association.

PRES constitutes a neurological disorder in which endothelial dysfunction is a critical factor in its underlying pathophysiology, resulting from abrupt changes in blood pressure or direct toxic effects of cytokines, leading to the breakdown of the blood—brain barrier (BBB) and cerebral edema,[2,3] with preferential hyperperfusion of the posterior circulation.[2–4]

PRES should be considered in patients with acute neurological symptoms, arterial hypertension, kidney failure, autoimmune disease, immunosuppressive therapy or chemotherapy, preeclampsia/eclampsia, severe dysautonomia, pancreatitis secondary to hypercalcaemia (primarily associated with iatrogenic vitamin D/calcium overdose, malignancy, or, infrequently, primary hyperparathyroidism),[3] or infections[2,3] (including COVID-19).[5–15] It usually presents with altered consciousness, seizures, headache, visual symptoms (which may be found at presentation),[7] and, rarely, focal neurological deficits.[2,3] Brain MRI can confirm the edema, which often involves, but is not solely restricted to, parieto-occipital cortical and subcortical structures, and resolves within days or weeks.[2,3] Notably, the presence of hemorrhage, restricted diffusion, contrast enhancement, and vasoconstriction are all suggestive of a diagnosis of PRES.[2,3]

PRES may cause substantial morbidity, and even mortality in severe forms, frequently due to intracranial hemorrhage, posterior fossa edema with brainstem compression or acute hydrocephalus, or massive diffuse cerebral edema and increased global intracranial pressure.[2] In the vast majority of cases, PRES subsides spontaneously, but therapy can be challenging and should be initiated early to reduce potential morbidity and mortality.[2,3] Persistent neurological sequelae are described in 10%—20% of patients with PRES.[2]

SARS-CoV-2 infection has been associated with several neurological complications, including COVID-19-related PRES.[5–15] PRES is considered rare in SARS-CoV-2 infections and may not be suspected when patients with COVID-19 present with neurological symptoms.[13] Nonetheless, PRES is detected in 1%—4% of neuroimaging studies of patients with SARS-CoV-2 infection.[4] One study, which included 2054 patients attended between 4 March and 9 May 2020 at 2 New York City hospitals, found that 1.1% (3/278) of patients whose cases were severe enough to undergo neuroimaging (either CT or MRI) were confirmed to have PRES.[14] Another case series, gathered from a multidisciplinary pediatric

https://doi.org/10.1016/j.nrl.2025.501944

Please cite this article as: M. León-Ruiz, C. Castañeda-Cabrero and J. Benito-León, Response to ''Dysautonomia after COVID-19 infection: A case report'': The pathophysiology of COVID-19-related posterior reversible encephalopathy syndrome revisited, Neurología, https://doi.org/10.1016/j.nrl.2025.501944

neurology clinic associated with Seattle Children's Hospital, included 2 patients who presented with MRI-confirmed PRES following hospitalization due to COVID-19.[15] Several individual cases of COVID-19-related PRES have also been documented,[9–12] with PRES symptoms manifesting between 8 and 26 days following the onset of typical COVID-19 symptoms.[6,9–12] The risk factors do not differ from those of non-COVID-19-related PRES,[4] although COVID-19-related PRES can present in the absence of arterial hypertension or significant organ damage.[13]

The exact mechanism by which COVID-19 leads to PRES is not fully clear. The most accepted hypothesis is based on the association between arterial hypertension and PRES and the failure of autoregulation at high blood pressure, leading to hyperperfusion, which causes vasogenic edema generally in the posterior brain lobes.[13] Other proposed mechanisms include: (*1*) a combination of cytokine release syndrome (decreased T-cells and natural killer cells and, most importantly, an increase in interleukin 6, leading to clinical symptoms of fever and multiorgan dysfunction) and direct SARS-CoV-2-mediated breakdown of the BBB, making patients susceptible to developing PRES (especially in case of labile blood pressure)[9]; and (*2*) cerebral endothelial dysfunction induced by the interaction of SARS-CoV-2 with host cells through angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in a wide variety of cells including neurons and vascular endothelial cells[10] (the viral S1 spike protein binds directly to the ACE2 receptor on the capillary endothelium, causing injury and increasing its permeability).[13] Once SARS-CoV-2 binds to neuronal ACE2 receptors, it can activate a self-reinforcing inflammatory response through a cytokine storm,[10] and cause an increase in blood pressure, debilitating the endothelial layer and weakening the BBB, eventually triggering dysfunction of the brain's autoregulation of cerebral circulation.[12]

It has recently been hypothesized that endothelial disruption related to SARS-CoV-2 infection may represent a promoting and synergistic agent underlying the preferential involvement of the posterior circulation, particularly due to its intrinsic hemodynamic weakness compared with the anterior circulation.[10]

The absence of viral RNA or proteins in the brain tissue indicates that neurological issues in COVID-19 can originate from brain inflammation and hypoxic-ischemic damage rather than a direct neurotropic effect of SARS-CoV-2.[13] In patients with COVID-19 associated with neurological symptoms, cerebrospinal fluid (CSF) analysis typically shows blood–CSF barrier disruption (e.g., albuminocytological dissociation) in the absence of intrathecal inflammation, a pattern compatible with cerebrospinal endotheliopathy[15] (like in the case presented by Vera-Cáceres et al.,[1] where CSF analysis revealed normal glucose and cell count, but elevated protein [70.2 mg/dL] and positive oropharyngeal SARS-CoV-2 PCR test results).

Although the most frequent presentation of COVID-19-related PRES is altered mental status (as the case reported by Vera-Cáceres et al.[1]), visual symptoms may also be found at presentation,[8] including transient cortical blindness[7] and hallucinatory palinopsia.[8] The prognosis for PRES is usually good, with complete recovery reported in 75%–90% of patients.[4] Long-term neurological sequelae are a complication for a minority of patients, and fatal outcomes are reported in only 3%–6% of cases of PRES.[4]

The diagnosis of PRES can be challenging, and neuroimaging studies (above all MRI) are crucial for diagnosis and monitoring.[13] The management of PRES in patients with COVID-19 requires a multidisciplinary approach, including neurologists, critical care specialists, and infectious disease doctors. The treatment strategy mainly focuses on controlling blood pressure, managing seizures, and addressing the underlying SARS-CoV-2 infection.[13] Furthermore, in COVID-19-related PRES, blood pressure control can prevent further damage to the BBB and reduce the risk of intracranial hemorrhage.[13] Treating COVID-19 is also essential for the management of PRES. COVID-19 treatment mainly includes supportive care, such as oxygen therapy, anticoagulation, and corticosteroids. In patients with PRES associated with COVID-19, the use of corticosteroids was shown to improve clinical outcomes by reducing inflammation and stabilizing the BBB.[13]

In summary, early recognition and intervention, as well as close follow-up and monitoring of these patients, are critical for mitigating the morbidity and mortality of COVID-19-related PRES. There is a need for larger studies to better understand the exact pathophysiology of COVID-19-related PRES, including PRES in post-COVID-19 GBS, and to identify new and effective therapeutic strategies.

Funding

This study was written freely, without funding from any company or public or private entity.

Conflicts of interest

All authors have approved the submission of this manuscript. There are no conflicts of interest.

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M. León-Ruiz[a,*], C. Castañeda-Cabrero[b], J. Benito-León[c,d,e,f]

[a] *Department of Neurology, Severo Ochoa University Hospital, Madrid, Spain*
[b] *Section of Clinical Neurophysiology, Department of Neurology, La Paz University Hospital, Madrid, Spain*
[c] *Department of Neurology, 12 de Octubre University Hospital, Madrid, Spain*
[d] *Department of Medicine, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain*
[e] *Healthcare Research Institute Hospital 12 de Octubre (i+12), Madrid, Spain*
[f] *Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*

* Corresponding author.
E-mail address: pistolpete271285@hotmail.com (M. León-Ruiz).