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Reversible cerebral vasoconstriction syndrome related to extracranial dissection associated with COVID-19: an immunological trigger?

Ícaro Araújo de Sousa[1], Elizeu Pereira dos Santos Neto[2], Matheus Rodrigues Corrêa[3], Arthur de Oliveira Veras[1], Octávio Marques Pontes-Neto[1]

[1] Department of Neuroscience and Behavior Sciences, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.
[2] Institute of Radiology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo SP, Brazil.
[3] Department of Neurology, Faculdade de Medicina, Universidade Federal do Piauí, Teresina, PI, Brazil.

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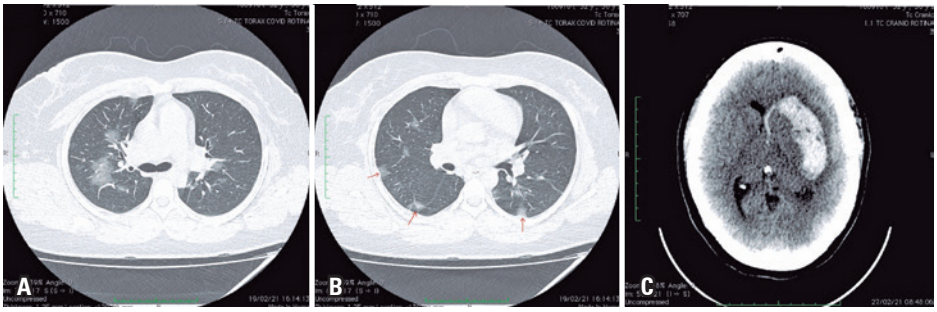

Figure 1. Computerized tomography. Chest scan showing peripheral (red arrows) and central (white arrows) ground glass opacities compatible with viral pneumonia (A and B). Head scan showing left basal ganglia hematoma with ventricular extension (C)

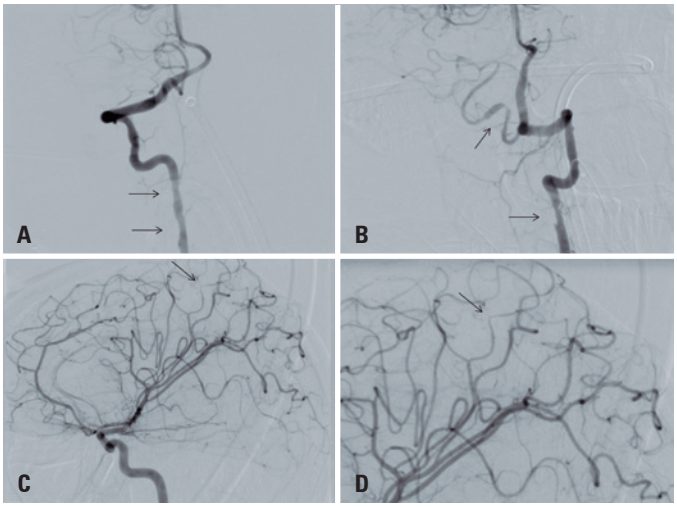

Figure 2. Digital subtraction angiography. Segmental narrowings (black arrows) followed by dilations on right and left vertebral arteries compatible with dissection (A). Subtle segmental narrowing (black arrow) followed by normal appearance in left posterior inferior cerebellar artery compatible with vasoconstriction (B). Subtle segmental narrowing (black arrow) followed by normal appearance in the left distal branch from middle cerebral artery – artery of central sulcus – compatible with vasoconstriction (C and D)

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Corresponding author:
Ícaro Araújo de Sousa
Department of Neuroscience and Behavior Sciences
Rua Tenente Catão Roxo, 2,650 - Vila Monte Alegre
Zip code: 14051-140 - Ribeirão Preto, SP, Brazil.
Email: icaroas@hcrp.usp.br

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A 30-year-old woman had respiratory symptoms and a positive RT-PCR SARS-CoV-2 test. Chest computed tomography (CT) revealed 30-50% lung parenchymal involvement (Figures 1A and B), suggestive of viral pneumonia. Six days later, she presented with a thunderclap headache, right hemiplegia, and decreased consciousness. CT of the head revealed a large left parenchymal intracerebral hemorrhage (ICH) (Figure 1C), and the patient underwent a decompressive craniotomy. Cerebral angiography showed segmental narrowings followed by dilations in the V2 and V3 segments of the right and left vertebral arteries, suggesting bilateral vertebral artery dissection (VAD). No history of trauma or connective tissue disorders was noted. Furthermore, a mild segmental narrowing followed by a normal appearance in both the left posterior inferior cerebellar artery and distal branches of the left middle cerebral artery was observed, which, in this context, was suggestive of reversible cerebral vasoconstriction syndrome (RCVS) (Figure 2). She had received corticosteroid therapy for COVID-19 and was not taking any anticoagulant or antiaggregant medications. She had a poor outcome and was classified with modified Rankin Scale 5 at discharge.

There is only one similar reported case involving hemorrhagic stroke, RCVS, and VAD in the context of COVID-19 infection;[1] however, unlike the present case that featured convexity subarachnoid hemorrhage (cSAH) and a benign course, we report a typical clinical course of parenchymal ICH with acute neurological deterioration. Moreover, the most exuberant vascular findings were observed in a territory far from the hemorrhage site (Figures 1C and 2).

Reversible cerebral vasoconstriction syndrome is characterized by the sudden onset of severe headache and reversible diffuse segmental vasoconstriction of the cerebral arterial vasculature, which resolves spontaneously within 3 months. Patients often report a trigger for RCVS-associated headaches, which is usually vasoactive agents. Regarding the spectrum of complications, hemorrhage occur in 43% of RCVS cases, including 38% with cSAH and 13% with ICH (mostly lobar). Furthermore, hemorrhagic lesions occur within the first week and manifested earlier than the infarcts.[2]

Despite its rarity, the association between RCVS and cervical artery dissection (CeAD) has been described in a prospective cohort.[3] Regarding the pathophysiological connection, it has been suggested that a more generalized underlying arterial vulnerability exists that may lead to vascular diseases. Therefore, the literature precludes us from stating whether CeAD may induce RCVS, or vice versa.[4]

An association between arterial dissection and COVID-19 has been suggested in some case reports, and it has been hypothesized that arterial dissection is one of the mechanisms involved in strokes in young patients with COVID-19 infection.[5] The underlying pathophysiology is still uncertain, but systemic mechanisms, such as exaggerated inflammation by cytokine storm and endothelial dysfunction, and local disruption of connective tissue in the intimal layer due to COVID-19, have been suggested.[6]

Current literature suggests a possible association between COVID-19 and RCVS. The pathophysiology of RCVS remains unknown; however, considering the proposed mechanisms of endothelial dysfunction, cerebral arterial tone dysregulation, and sympathetic hyperactivity, it has been inferred that COVID-19 may specifically contribute to an increased risk for the development of RCVS.[7] In the present case, it was not possible to define which vascular pathology occurred first. Therefore, given the intersection between the proposed mechanisms for the association between VAD and COVID, as well as between RCVS and COVID, we propose that viral infection and its systemic effects are independent triggers for both vascular pathologies.

RCVS, either alone or in combination with posterior reversible encephalopathy syndrome (PRES), has been associated with immune dysfunction.[8-10] These two conditions share similar triggers and clinical features. Accordingly, common pathophysiological mechanisms have been proposed because of their frequent overlap.[11] PRES was recently associated with COVID-19, and cytokine storms play a significant role in its pathophysiology. The cytokine storm is an inflammatory response induced by COVID-19, leading to the release of a large number of cytokines, proinflammatory products, and vasoconstrictor agents such as thromboxane A2, which can lead to the onset of PRES.[12]

Therefore, considering the available information regarding the pathophysiology of RCVS and PRES as well as the mechanisms common to both diseases, it can be concluded that in the present case, the cytokine storm could be an immunological trigger for RCVS.

AUTHORS' CONTRIBUTION

Ícaro Araújo de Sousa: study writing and concept. Elizeu Pereira dos Santos Neto: study concept. Matheus Rodrigues Corrêa and Arthur de Oliveira Veras: study writing and image designing. Octávio Marques Pontes-Neto: study supervision.

AUTHORS' INFORMATION

Sousa IA: http://orcid.org/0000-0002-9452-1207
Santos Neto EP: http://orcid.org/0000-0002-8791-4440
Corrêa MR: http://orcid.org/0000-0001-9696-1786
Veras AO: http://orcid.org/0000-0001-8865-177X
Pontes-Neto OM: http://orcid.org/0000-0003-0317-843X

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