

# Reversible cerebral vasoconstriction syndrome in a patient with COVID-19

<sup>1</sup>Arpan Dutta MBBS MD (General Medicine), <sup>2</sup>Atanu Chandra MD (General Medicine), <sup>1</sup>Subhadeep Gupta MBBS MD, <sup>1</sup>Biman Kanti Ray MD (General Medicine) DM (Neurology), <sup>1,3,4</sup>Deep Das MD (General Medicine) DM (Neurology), <sup>5</sup>Rahul Kumar MD (General Medicine) DM (Neurology)

<sup>1</sup>Bangur Institute of Neurosciences, Institute of Post Graduate Medical Education and Research, Kolkata; <sup>2</sup>Dept. of Internal Medicine, R.G. Kar Medical College and Hospital, Kolkata, <sup>3</sup>Woodlands Multi-Speciality Hospital, Kolkata, <sup>4</sup>C K Birla Hospitals, Kolkata, <sup>5</sup>Dept of Neurology, G.S Neuroscience Clinic and Research center, Patna, India

## Abstract

COVID-19 infection is well-known to produce different neurological complications, including cerebrovascular diseases. Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by transient segmental vasoconstriction of the cerebral vasculature, has been rarely reported in association with COVID-19 infection. The causative agent, the novel coronavirus (SARS-CoV-2), binds to the angiotensin-converting enzyme 2 (ACE-2) receptors for its entry into the host cell. This leads to downregulation of the ACE-2 and increased activity of the renin-angiotensin-aldosterone (RAAS) axis resulting in sympathetic overactivity and vasoconstriction. This might be the possible mechanism of RCVS in COVID-19. We hereby report a case of RCVS occurring in a SARS-CoV-2-infected patient. This was a 38-year-old male without any comorbidities or risk factors, who presented with headache and confusion. His SARS-CoV-2 RT-PCR was positive. MRI of the brain was normal but cerebral angiography revealed segmental vasoconstriction in bilateral middle cerebral arteries and the terminal part of the internal carotid arteries, which resolved almost completely after 2 weeks. He was treated with oral nimodipine 60 mg every 6 hourly. A database search revealed 2 previous cases of RCVS associated with COVID-19. In conclusion, RCVS is a rare complication of COVID-19. It is possibly under-recognized as only a few COVID-19 patients with headaches undergo cerebral angiography especially when parenchymal brain imaging is normal.

**Keywords:** COVID-19, SARS-CoV-2, reversible cerebral vasoconstriction syndrome, angiotensin-converting enzyme 2; renin-angiotensin-aldosterone axis.

## INTRODUCTION

The novel coronavirus disease (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, is mainly associated with a wide spectrum of respiratory illness, ranging from a mild influenza-like symptom to a severe form of disease, such as acute respiratory distress syndrome and severe pneumonia.<sup>1</sup> With a better understanding of the disease pathogenesis and improved diagnostic modalities, an increasing number of patients with COVID-19 are being reported with extrapulmonary manifestations including neurological complications.<sup>2</sup> Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical condition characterized by multifocal arterial

constriction and dilation involving the cerebral vasculature, which is transient in nature and usually triggered by medications, and postpartum state with or without pre-eclampsia/eclampsia.<sup>3</sup> RCVS in association with COVID-19 has been rarely reported to date. In this report, we describe a case of RCVS occurring in the setting of COVID-19 infection and review the literature regarding similar occurrences.

## CASE REPORT

A 38-year-old gentleman presented with a complaint of mild holocranial headache and confusion for the last 2 days. There was no history of fever, cough, sore throat, diarrhea, loss of smell or taste, trauma, or recent vaccination. He had

*Address correspondence to:* Dr. Subhadeep Gupta MBBS, MD (General Medicine), Bangur Institute of Neurosciences, Institute of Post Graduate Medical Education and Research, Kolkata, India. Email- subha5713deep@gmail.com

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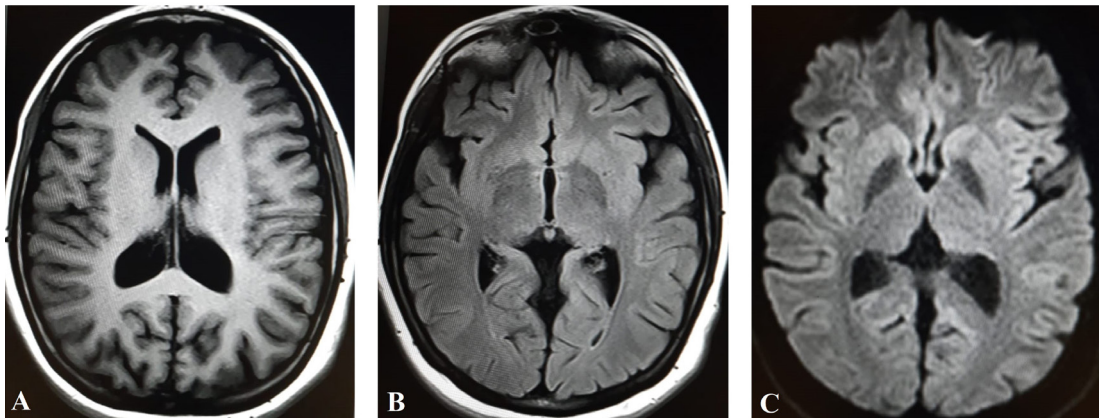


Figure 1. T1 weighted (A), T2 weighted (B) and Diffusion weighted (C) MRI Brain axial images revealed no abnormality.

no history of medications intake or recreational drug use in the recent past. The patient was non-hypertensive and non-diabetic, as well as a non-smoker and a teetotaler. His past medical history was unremarkable.

On examination, he was afebrile (temperature-98.4 F). His blood pressure was 124/84 mm Hg, pulse rate was 96/minute (regular), respiratory rate was 18/minute, and peripheral oxygen saturation was 98% on room air. He was confused, but there was no focal neurological deficit. Complete hemogram, renal function tests, liver function tests, and routine urine investigations were normal. Reverse transcriptase real-time qualitative polymerase chain reaction (RT-PCR) for SARS-CoV-2 from oropharyngeal and nasopharyngeal swabs returned as positive. Serum C-reactive

protein (CRP), interleukin-6 (IL-6), and d-dimer values were within normal limits. Arterial blood gas (ABG) and cerebrospinal fluid (CSF) analysis were normal. Electroencephalogram (EEG) showed diffuse theta waves in the background without any triphasic waves or epileptiform discharges. High-resolution computed tomography (HRCT) of the thorax did not reveal any abnormality. The coagulation profile was also normal. Contrast (gadolinium) enhanced magnetic resonance imaging (MRI) of the brain (Figure 1) and contrast MR-venogram did not reveal any abnormality or evidence of venous sinus thrombosis. (Figure 2) However, CT angiography and digital subtraction angiography (DSA) of cerebral vessels revealed narrowing of the terminal parts of both internal carotid arteries

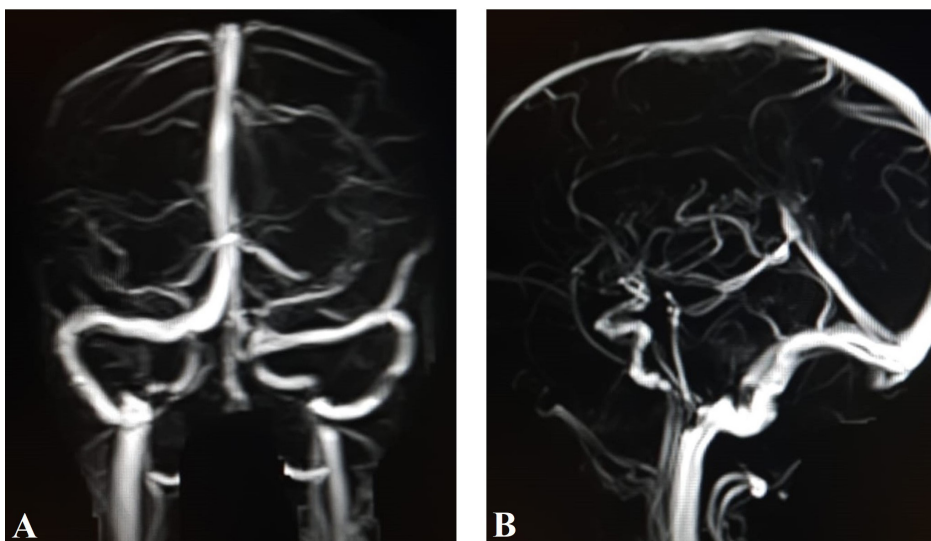


Figure 2. Antero-posterior (A) and lateral (B) contrast MR Venography revealed no abnormality.

(ICA) and bilateral middle cerebral arteries (MCA) with pruning of distal flow (Figure 3 A-C). The patient was started on oral nimodipine (60 mg 4 times a day) and simple analgesics when required for headache. The patient had significant improvement of the symptoms within the next few days. Repeat DSA and contrast CT angiography performed after 14 days, showed near-total improvement of the caliber of bilateral terminal ICA and bilateral MCA with near normalization of distal flow (Figure 3D-F). These findings suggested the diagnosis of RCVS.

## DISCUSSION

We conducted a thorough search in the Medical Subject Headings (MeSH), PubMed, and Medline databases for search terms ‘reversible cerebral vasoconstriction syndrome’ (OR ‘RCVS’) AND ‘COVID-19’ (OR ‘SARS-Cov-2’). The database search revealed 2 previously reported cases of RCVS occurring in association with COVID-19.<sup>4,5</sup> Table 1 shows the demographic, clinical, and radiological features along with the investigations and outcome of the two previously reported COVID-19 associated RCVS cases in comparison to our case.

The presenting symptom of our patient was headache and confusion, both of which could be either due to COVID-19 itself or RCVS. The cases described by Dakayet *al* and Mansoor *et al* had cough which pointed towards a respiratory involvement apart from CNS involvement.<sup>4,5</sup> However, our patient had no definite clinical features of involvement of any other system. We did the SARS-CoV-2 RT-PCR as a workup for systemic infectious. As MRI brain and CSF analysis were normal, we performed angiography to look for any vascular abnormality. Apart from RCVS, the other differentials of such angiographic findings are vasculitis due to either primary CNS angiitis (PACNS), infection, and systemic vasculitis; Moyamoya syndrome, fibromuscular dysplasia, and intracranial atherosclerotic disease.<sup>6</sup> CSF usually shows pleocytosis and elevated protein levels in PACNS and vasculitis secondary to CNS infection or systemic vasculitis.<sup>7</sup> Serum inflammatory markers such as CRP, IL-6 are frequently elevated in systemic vasculitis. Intracranial atherosclerotic disease is usually associated with cardiovascular risk factors. The reversible nature of the vasoconstriction in the absence of any cardiovascular risk factor, a normal CSF picture, and absent inflammatory

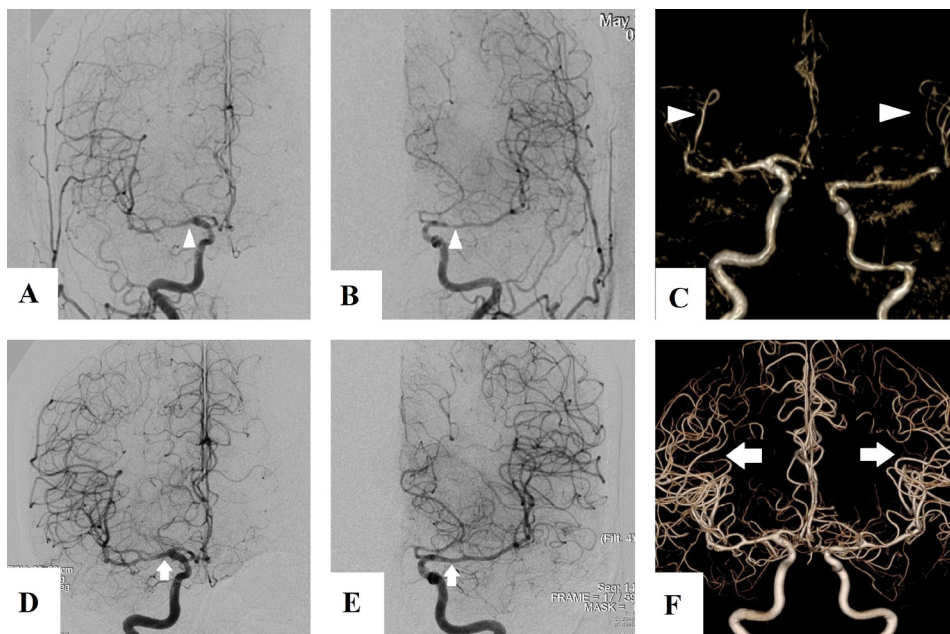


Figure 3. At presentation, Digital Subtraction Angiography (DSA) after right Internal Carotid Artery or ICA injection (A), DSA after left ICA injection (B) and contrast CT angiography image (C) shows narrowing of bilateral terminal ICA and bilateral MCA with pruning of distal flow (marked by white arrowhead). After 14 days, Digital Subtraction Angiography (DSA) after right ICA injection (D), DSA after left ICA injection (E) and contrast CT angiography image (F) shows improved caliber of bilateral terminal ICA and bilateral MCA with near normalization of distal flow (marked by white arrow).

**Table 1: Clinical and radiological characteristics of the previously published two cases and our case**

Case no.	1	2	3
Author	Dakay <i>et al.</i> <sup>4</sup>	Mansoor <i>et al.</i> <sup>5</sup>	Our case
Year	2020	2021	-
Age	Thirties	Thirties	Thirties
Sex	Female	Female	Male
Co-morbidities	Migraine	Spina bifida, thoracolumbar scoliosis	Nil
Addictions	Nil	Nil	Nil
Drugs or toxin exposure	Nil	Nil	Nil
Family history	Unremarkable	Unremarkable	Unremarkable
Presentation	Thunderclap headache	Severe headache	Mild headache, confusion
Latency from onset of COVID-19 symptoms	Few weeks (severe cough)	Not mentioned (had cough on presentation)	Presenting feature of COVID-19
SARS-COV2 RT-PCR	Positive	Positive	Positive
Severity of COVID-19	Mild	Mild	Mild
Triggers of RCVS	Nil	Nil	Nil
Brain parenchymal imaging features	Convexal sub- arachnoid haemorrhage in bilateral frontal region	Patchy gyral pattern of T2-FLAIR hyperintensity in bilateral frontal and parieto-occipital lobes	Normal
Brain angiography features	Left V2 segment vertebral artery dissection, vasospasm in left ACA and M3 segment of left MCA	Beaded appearance mainly in the basilar artery, normal venogram	Narrowing of the terminal ICA and M1 segment of the MCA on both sides, normal venogram
CSF analysis	Not done	Normal	Normal
Other investigations	Unremarkable	Unremarkable	Diffuse slowing of the background in EEG
Treatment	Verapamil, Levetiracetam, Aspirin, Analgesics	Nimodipine, Aspirin	Nimodipine, Analgesics
Outcome	Discharged	Resolution of symptoms and basilar vasospasm	Resolution of symptoms and near complete resolution of the vasospasm

ACA- anterior cerebral artery, ICA- internal carotid artery, MCA- middle cerebral artery

markers in the serum favors a diagnosis of RCVS in this case.<sup>8,9</sup> Diagnosing RCVS in the setting of COVID-19 is very challenging as highlighted by our case because headache is one of the most common symptoms of COVID-19 infection and many patients present with confusion during the course of illness.<sup>10</sup> Hence brain imaging is often not performed in COVID-19 patients who have

headaches with or without confusion and in the absence of focal neurological deficits. This may lead to the under-recognition of cerebrovascular complications such as RCVS.<sup>11-13</sup>

COVID-19 encephalopathy may also present with headache and confusion.<sup>14</sup> Brain parenchymal imaging, CSF and EEG may then be abnormal.<sup>14</sup> Apart from this entity,

hypoxia, hypercapnia, electrolyte disturbances, hypoglycemia or hyperglycemia, liver failure, and renal failure may complicate the clinical course of the disease and cause an altered level of consciousness in patients with COVID-19. Other neurological complications of COVID-19 are encephalitis/meningoencephalitis, seizure, stroke, cerebral venous sinus thrombosis, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome (PRES), acute demyelinating encephalomyelitis (ADEM), and acute hemorrhagic necrotizing myelitis (AHM) may also cause encephalopathy.<sup>15-17</sup> However, all these possible differential diagnoses were excluded by relevant investigations. Background slowing of the EEG is nonspecific and may be seen in encephalopathy due to any cause. A normal MRI brain along with normal CSF parameters favored RCVS more than COVID-19 encephalopathy.

As mentioned above, RCVS occurring in association with COVID-19 infection is extremely rare and has been reported previously in two cases only.<sup>4,5</sup> Dakay *et al.* reported a female health-care worker in her thirties with a history of migraine, who presented with severe thunderclap headache and was later diagnosed as RCVS associated with mild SARS-CoV2 infection; she was successfully managed with verapamil, levetiracetam, aspirin, and analgesics.<sup>4</sup> Another similar case was reported by Mansoor *et al.* in which they described a young female with spina bifida and thoracolumbar scoliosis who presented with severe headache, who responded well to nimodipine and aspirin.<sup>5</sup> The clinical characteristics, laboratory investigations, management, and outcome have been shown in Table 1. In contrast to the previous cases, our patient was a young male without any known comorbidity, had a normal parenchymal brain imaging, and recovered completely with oral nimodipine only.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is not a neurotropic virus and its primary target is the respiratory epithelium.<sup>1,2</sup> However, neurological complications are not uncommon and may be associated with adverse outcomes if not identified and managed early.<sup>15-17</sup> The neurological manifestations sometimes may precede classical features like fever and respiratory symptoms. The common neurological manifestations include dizziness, headache, anosmia, ageusia, large vessel stroke, acute encephalitis, Guillain-Barré syndrome, and acute transverse myelitis.<sup>11,12,16-19</sup> Among the cerebrovascular involvement is common.<sup>11-13</sup> They are ischemic stroke, intracerebral hemorrhage,

and cerebral venous sinus thrombosis. The proposed mechanisms of cerebrovascular complications include thrombosis due to hypercoagulability, vessel wall damage due to local and systemic inflammation (cytokine storm-mediated vasculitis), endothelial dysfunction due to angiotensin-converting enzyme 2 (ACE2) receptor dysregulation, cardio-embolism secondary to myocardial ischemia or arrhythmia, and intracranial bleeding due to coagulation abnormalities.<sup>2,11-13,20,21</sup>

Patients with RCVS usually present with intense headache, sometimes associated with confusion, visual blurring, vomiting, focal neurological deficit, and seizures.<sup>8,9,22</sup> Although RCVS can occur spontaneously, predisposing factors such as drugs (vasoactive agents, cocaine, amphetamine, ecstasy, alcohol, intravenous immunoglobulin, and interferon), pregnancy, post-partum state, and a few medical conditions (HELLP syndrome, thrombotic thrombocytopenic purpura, and antiphospholipid syndrome) have been identified.<sup>8,9</sup> In general, the pathological mechanism of RCVS is thought to be due to transient failure of regulation of the cerebral arterial tone with sympathetic overactivity that may occur spontaneously or precipitated by known triggers as mentioned earlier.

ACE2 receptors are present in the alveolar epithelial cells of the lung, enterocytes of the small intestine, endothelial cells of arteries and veins, and arterial smooth muscle cells.<sup>23</sup> ACE2 is a part of the renin-angiotensin-aldosterone system (RAAS) and counteracts the effects of ACE1 to maintain vascular homeostasis.<sup>20,21</sup> SARS-CoV2 binds to ACE2 receptor for host cell entry and suppresses ACE2 expression through internalization, shedding, and downregulation.<sup>12,13,20,21</sup> Reduced ACE2 expression shifts the balance towards ACE1-angiotensin interaction leading to sympathetic overactivity, increased sodium/water retention, vasoconstriction, endothelial dysfunction, and inflammation. The sympathetic overactivity and vasoconstriction secondary to ACE2 receptor downregulation thereby provide a possible mechanism of RCVS in COVID-19 infection.

The management of RCVS consists of analgesics for headaches, antiepileptic drugs for seizures, antihypertensive drugs for blood pressure control, and drugs to reduce cerebral vasospasm like nimodipine, verapamil, and magnesium sulphate.<sup>9</sup> Our patient responded well to treatment with nimodipine and simple analgesics.

**DISCLOSURE**

Informed consent for publication is obtained from the patient and husband.

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Conflicts of interest: None

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