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# The Many Faces of COVID-19-Associated Cerebrovascular Disease: A Case Series

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**Abstract:** The respiratory virus SARS-CoV-2, responsible for the multisystem illness known as COVID-19 that resulted in the pandemic of 2020, is increasingly recognized for its ability to cause cerebrovascular complications. This series of four cases observed during the height of the pandemic in a single institution is presented to illustrate the diverse pathophysiology of COVID-19 cerebrovascular manifestations and their corresponding clinical and radiologic manifestations.

**Keywords:** COVID-19, SARS-CoV-2, cerebrovascular disease, stroke

## Introduction

Although SARS-CoV-2 is known best for its tendency to affect the respiratory system, COVID-19's cerebrovascular manifestations have gained recognition as a serious complication. Increased rates of neurological disease in COVID-19 patients were first reported by Mao et al<sup>1</sup> in April 2020. This retrospective review of 214 patients from the pandemic's epicenter in Wuhan, China, revealed that 36.4% experienced neurologic manifestations. Of these patients, 88 experienced severe infection, with nearly 6% of patients in this population experiencing acute cerebrovascular disease such as stroke.<sup>1</sup> A more recent review of larger datasets<sup>2</sup> shows an overall incidence of stroke in the range of 0.4%-4.6%. The observation that COVID-19 increases the risk of cerebrovascular disease has since been well corroborated.<sup>3</sup> Among patients with COVID-19 who experienced stroke, most were 60 years of age or older and had other risk factors for stroke.<sup>4</sup> However, a disproportionate number of younger, otherwise healthy individuals with COVID-19 have presented with ischemic stroke,<sup>5</sup> adding to the suspicion that SARS-CoV-2 may increase the risk

## Key Points

- Primarily known for its respiratory sequelae, COVID-19 has also showed an unusual tendency for causing cerebrovascular complications.
- No imaging or clinical feature specific to COVID-19-induced cerebrovascular injury has been identified.
- A high index of suspicion should be maintained in the treatment of younger patients presenting with COVID-19-associated neurological findings.

of cerebrovascular complications either via novel virulence factors or via the immune response it induces.<sup>4</sup>

A challenge in both the identification and the management of the cerebrovascular complications of COVID-19 is its diverse pathophysiology and correspondingly varied clinical and imaging manifestations.<sup>4</sup>

The cases presented here in brief (Table) are from a single institution, where they were observed between the months of January and August 2020. These cases provide insight into COVID-19-associated cerebrovascular disease and an

opportunity to discuss some aspects of its pathophysiology and a range of clinical and imaging manifestations.

## Discussion

The advent of the COVID-19 pandemic challenged clinicians to keep pace with the rapid development of myriad presentations and novel complications of the disease. Cerebrovascular disease is now well-recognized as one of these complications, one that offers a particular challenge owing to its wide range of clinical manifestations.<sup>2</sup>

The table below describes four patients with COVID-19 and unique and overlapping cerebrovascular pathology. Although all these patients carried risk factors for vascular disease [eg, hypertension (HTN), hyperlipidemia (HL), and type 2 diabetes (T2D)], the described cerebrovascular events were first-time events that occurred without noticeable prodrome. Each of these patients experienced the sequelae of COVID-19's diverse pathophysiology, which ultimately manifested as one or more of the

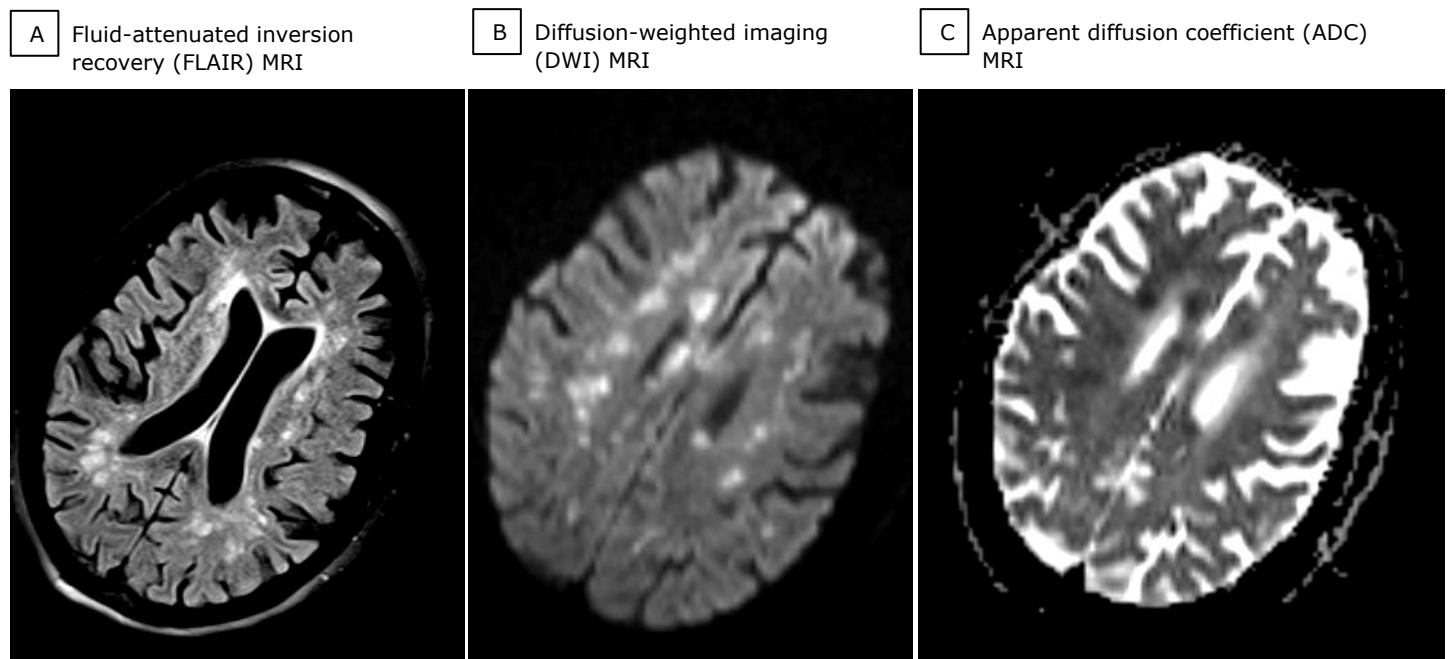
following cerebrovascular complications: (1) ischemic stroke: cerebral artery thrombosis or thromboembolism; (2) parenchymal hemorrhage; (3) cerebral venous sinus thrombosis; and (4) nonfocal cerebrovascular disease (ie, posterior reversible encephalopathy syndrome [PRES], endotheliitis, vasculitis, and hypoxia).<sup>2</sup>

The ability of COVID-19 to present with such diversity is explained in part by its unique pathogenesis. COVID-19-related cerebrovascular disease is proposed to occur via several mechanisms, including systemic coagulopathy, angiotensin-converting enzyme (ACE2) inactivation, vasculitis/endotheliitis, virus-related cardiac injury, and critical illness resulting in dysregulation of cerebral blood flow.<sup>2</sup>

COVID-19-associated coagulopathy (CAC), a coagulopathy associated with SARS-CoV-2 infection, is likely the most important of these mechanisms and is thought to play the largest role in the development of COVID-19-associated cerebrovascular complications.<sup>2</sup>

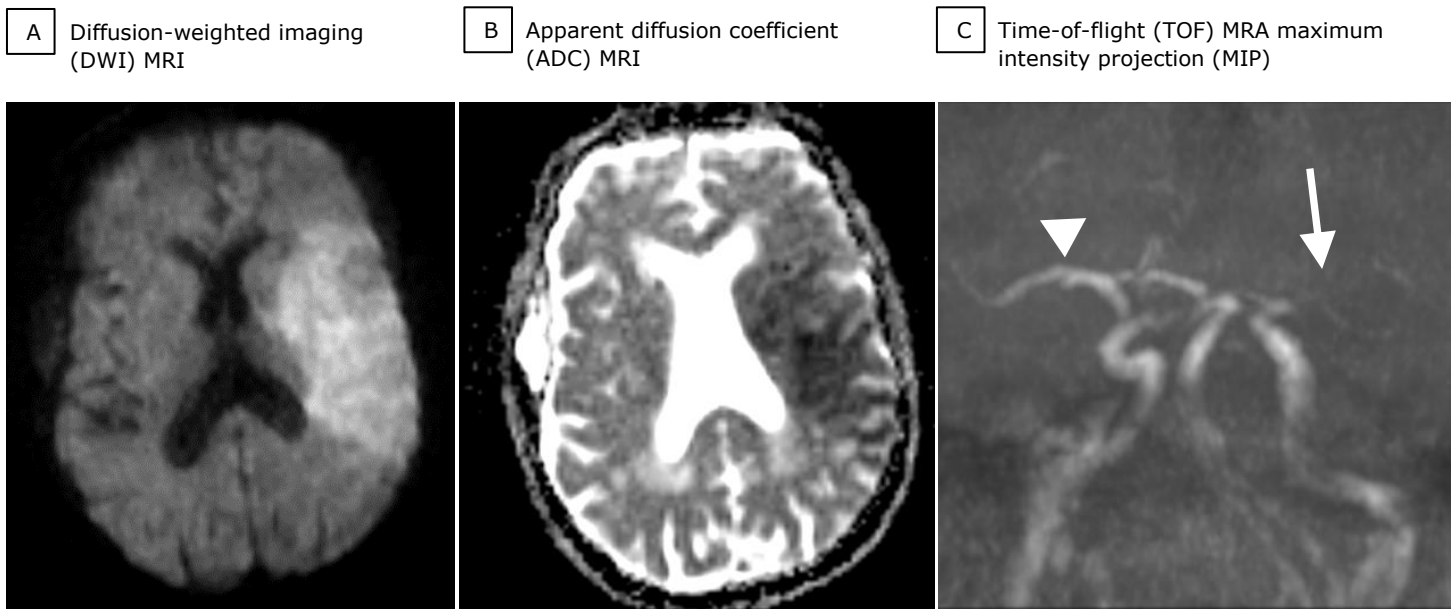
SARS-CoV-2 is also proposed to induce cerebrovascular injury through its affinity to ACE2,<sup>1,2,6,8,10</sup> which is expressed in vascular

**Figure 1.** Magnetic Resonance Imaging (MRI) of the Brain of a 70-Year-Old Woman with COVID-19 (Case 1).



(A-C) MR images show multiple periventricular and subcortical white matter hyperintensities with corresponding diffusion restriction typical of multiple small areas of acute infarction secondary to thromboembolic shower.

**Figure 2.** Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) of the Brain of a 72-Year-Old Man (Case 2).



MRI diffusion-weighted sequences of the brain (A, B) demonstrate a large area of diffusion restriction involving the left middle cerebral artery (MCA) territory consistent with recent infarction. A TOF MRA MIP of the brain (C) demonstrates a normal right MCA (arrowhead) and lack of flow within the left MCA (arrow) compatible with left MCA thrombosis. A large left ventricular thrombus was identified via echocardiogram (not shown).

endothelia throughout the body and is the target of the SARS-CoV-2 spike protein that allows viral cellular entry.<sup>6,7</sup>

Autopsy studies have supported a viral neurotropism by demonstrating viral elements within the cerebrovascular endothelium.<sup>2,5,8</sup>

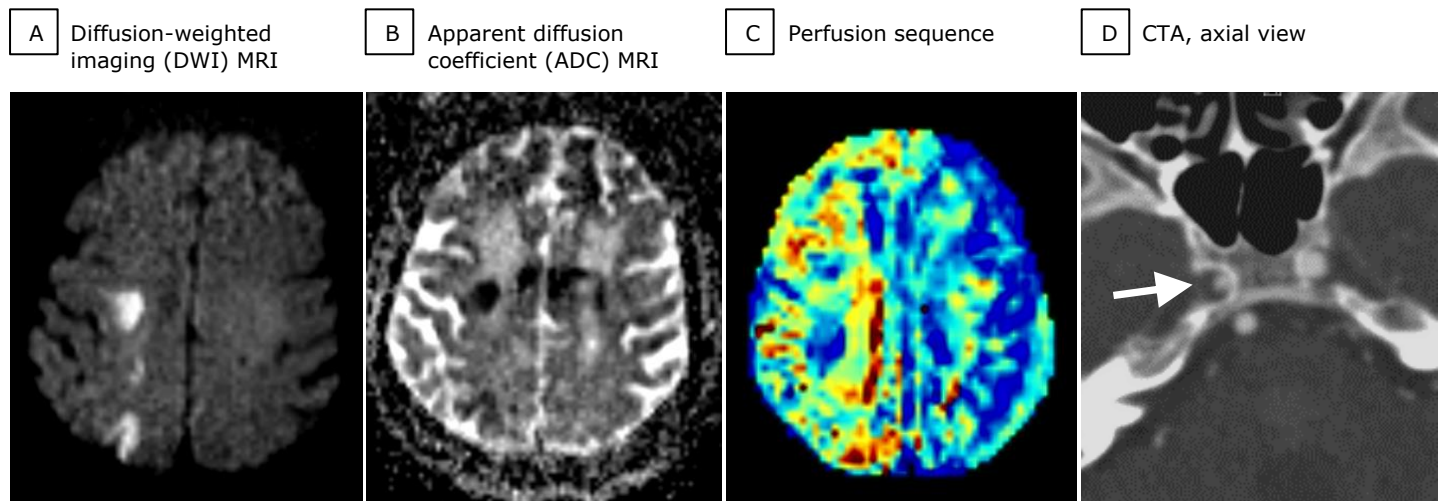
Invasion of the endothelial cells induces vasculitis/endotheliitis<sup>2,5</sup> and results in vessel wall fragility, exposure of the tissue factor and other procoagulants, and platelet aggregation.<sup>6</sup> Kaneko et al<sup>7</sup> further demonstrated that the expression of ACE2 in cerebral endothelium is regulated in a flow-dependent manner. Areas with high flow (and consequently high ACE2 expression) such as large vessels and regions with turbulent flow may then be especially sensitive to SARS-CoV-2 infection.<sup>7</sup> The result is increased endothelial damage, vasoconstriction, vessel wall fragility, and thrombosis in these susceptible regions.<sup>6,8</sup> This may help to explain the presentation of patients with COVID-19-associated large vessel thrombosis<sup>2,4,5</sup> similar to that described in Case 3 (Table) of this report.

Finally, the systemic effects of severe COVID-19—namely, inflammation,<sup>2,4</sup> hypoxemia<sup>6,8</sup> and

hypotension,<sup>2</sup> and toxemia<sup>8</sup>—should not be discounted as a significant cause of cerebrovascular disease. The exaggerated systemic inflammatory response characteristic of COVID-19, known as cytokine storm, can lead to prolonged periods of hypotension and hypoxemia, necessitating intubation, mechanical ventilation, and blood pressure support.<sup>2</sup> Hypoxic-ischemic encephalopathy (HIE) and ischemic strokes in watershed territories are commonly seen in this setting.<sup>2</sup>

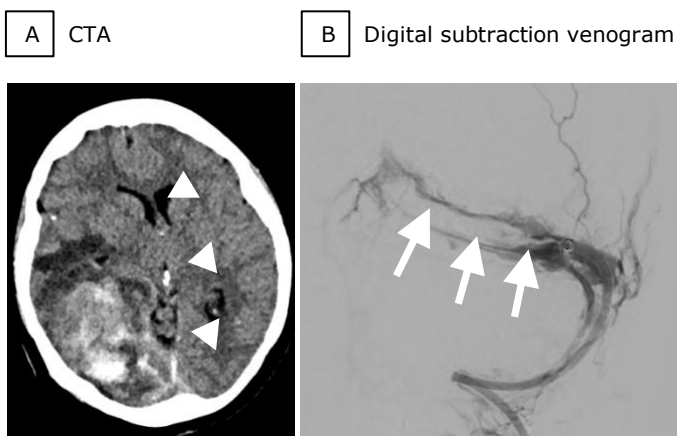
The broad spectrum of cerebrovascular pathology in patients with COVID-19 equates to a broad range of clinical and radiographic manifestations of that pathology. In a retrospective study of 64 patients who underwent brain imaging after experiencing neurological manifestations of COVID-19, 56% of the patients demonstrated central nervous system abnormalities by brain MRI. In the same cohort, ischemic stroke was by far the most common presentation, with anywhere from 11% to 27% of abnormal brain imaging identifying foci of ischemia.<sup>9</sup> According to other sources, common cerebrovascular complications also include parenchymal hemorrhage<sup>10</sup> (3.6%),

**Figure 3.** Magnetic Resonance Imaging (MRI) and Computed Tomography Angiography (CTA) of the Head of an 82-Year-Old Man with COVID-19 (Case 3).



(A) DWI and (B) ADC images show foci of diffusion restriction at the border zone of the right middle cerebral artery (MCA) and the anterior cerebral artery (ACA) territories, which indicates watershed infarcts. (C) The perfusion image shows a delayed time to peak of the entire right hemisphere, with regions of significantly delayed perfusion ( $T_{max} > 6$  seconds) in the right hemispheric territories. (D) CTA image of the head shows a peripheral filling defect (D, arrow) within the right cavernous segment of the right internal carotid artery (ICA). Angiography confirmed stenosis of the ICA, which is likely secondary to ruptured atherosclerotic plaque (not shown).

**Figure 4.** Computed Tomography Angiography (CTA) and Digital Subtraction Venogram of the Head of a 62-Year-Old Woman (Case 4).



CTA of the head (A) shows a parenchymal hemorrhage involving the right parietal, occipital, and temporal lobes with secondary edema and mass effect causing leftward midline shift (arrowheads). A digital subtraction venogram (B) shows a large filling defect within the left transverse sinus (arrows).

and PRES (1.1%), as well as venous sinus thrombosis<sup>2</sup> (0.5%-5%), leptomeningeal enhancement<sup>4,10</sup> (17%), and encephalitis<sup>4,8-10</sup> (13%). Each of these insults manifests with a breadth of clinical features ranging from a lack of symptoms to severe focal neurological defects, confusion, agitation, impaired consciousness, and death.<sup>10</sup>

Thus far, no clinical presentation or imaging finding has emerged as unique to COVID-19 cerebrovascular disease.<sup>10</sup> Therefore, a high index of suspicion for both cerebrovascular complications in those with known COVID-19 and undiagnosed infection in those with cerebrovascular disease is paramount.

### Author Contributions

Conceptualization, D.R. and N.S.; Acquisition, analysis, and interpretation of data, D.R. and N.S.; Writing – original draft preparation, D.R.; Review and editing, D.R. and N.S.; Supervision, N.S. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Disclosures

None to report.

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**Table.** Case Series in Brief.

	Medical History and presentation	Objective	Hospital course and complications	Imaging	Diagnosis	Outcome
Case 1	<b>70-year-old woman</b> <b>MH:</b> HTN, HL, T2D <b>Presentation:</b> Chest pain, shortness of breath, diaphoresis, emesis	<b>Examination:</b> AAOx4, tachypnea <b>Tmax:</b> 104.8 °F (40.4 °C) <b>D-dimer:</b> 1073 <b>FG:</b> 717 <b>PT:</b> 12.2 <b>PLT:</b> 140	<ul style="list-style-type: none"> <li>ARDS, respiratory failure, and ventilator dependence</li> <li>Obtunded upon attempt to wean from ventilator</li> <li>DIC</li> </ul>	<b>MRI of the brain:</b> Pattern of patchy restricted diffusion around the lateral ventricles, raising the possibility of thromboembolic shower with superimposed watershed infarcts (Figure 1)	Thromboembolic shower	Comatose
Case 2	<b>72-year-old man</b> <b>MH:</b> HTN, HL <b>Presentation:</b> Chest pain, shortness of breath, diaphoresis, emesis	<b>Examination:</b> AAOx4 <b>ECG:</b> Inferior STEMI <b>Troponin I:</b> 52 ng/mL (< 0.1 ng/mL) <b>D-dimer:</b> 6096 <b>PLT:</b> 195	<ul style="list-style-type: none"> <li>Cardiogenic/septic shock</li> <li>Respiratory failure</li> <li>Ischemic emboli to the extremities</li> <li>Obtunded with right-sided facial droop</li> </ul>	<b>TTE:</b> Large left ventricular thrombus, global left ventricular hypokinesia with EF of 10%. <b>MRI of the brain:</b> Acute cerebral infarct of the left MCA distribution with a clot identified in the proximal left MCA M1 segment in combination with smaller foci of acute infarction involving the left frontal lobe, the right caudate, and the left inferior cerebellum. (Figure 2)	<ul style="list-style-type: none"> <li>STEMI</li> <li>Cardioembolic ischemic stroke</li> </ul>	Deceased
Case 3	<b>82-year-old man</b> <b>MH:</b> T2D <b>Presentation:</b> Cough, fatigue, loss of appetite, ageusia, anosmia	<b>Examination:</b> AAOx4 <b>D-dimer:</b> 1131 <b>PT:</b> 15 <b>PLT:</b> 514	<ul style="list-style-type: none"> <li>COVID-19-directed therapy: remdesivir, gimsilumab, and convalescent plasma</li> <li>Improved respiratory status</li> <li>Sudden onset of acute right eye gaze deviation and left hemiparesis</li> </ul>	<b>CTA of the head and the neck:</b> Crescentic filling defect within the proximal right cavernous ICA <b>MRI of the head:</b> Acute watershed zone infarcts involving the right ACA/MCA and the MCA/PCA border zones. <b>Angiography:</b> Eccentric stenosis in the proximal segment of the right cavernous ICA, atherosclerosis of the cerebral vessels (Figure 3)	Ischemic stroke secondary to cavernous ICA thrombosis	Residual neurological defects, otherwise stable
Case 4	<b>62-year-old woman</b> <b>MH:</b> Epilepsy <b>Presentation:</b> Anhedonia, language difficulty, confusion leading to unresponsiveness	<b>Examination:</b> Obtunded, Oriented x 0, PEARLA <b>D-dimer:</b> 1059 <b>FG:</b> 631 <b>PT:</b> 14.2 <b>PLT:</b> 186	<ul style="list-style-type: none"> <li>Respiratory failure with ventilator dependence</li> <li>Labile blood pressures</li> <li>Prolonged ICU stay with ultimate stabilization and extubation</li> </ul>	<b>CT of the head from OSH:</b> Right transverse sinus thrombosis with parenchymal hemorrhage involving the right parietal, occipital, and temporal lobes. <b>Cerebral angiogram:</b> Extensive venous sinus thrombosis involving the superior sagittal sinus, the transverse sinuses bilaterally, the sigmoid sinuses, the straight sinus, the internal cerebral vein, the left cavernous sinus, and the proximal internal jugular veins. An endovascular mechanical thrombectomy was performed. (Figure 4)	Cerebral venous sinus thrombosis with parenchymal hemorrhage	Comatose

Abbreviations: AAO x 4, awake, alert, and oriented to person, place, time, and situation; ACA, anterior cerebral artery; ARDS, acute respiratory distress syndrome; CT, computed tomography; CTA, computed tomography angiography; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; EF, ejection fraction; HL, hyperlipidemia; HTN, hypertension; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; Oriented x 0, not oriented to person, place, time, or situation; PCA, posterior cerebral artery; PEARLA, pupils equal and reactive to light and accommodation; MH, medical history; SpO2, functional oxygen saturation; STEMI, ST-segment elevation myocardial infarction; T2D, type II diabetes; Tmax, max temperature; TTE, transesophageal echocardiogram; Normal ranges: D-dimer: < 500ng/mL; FG (fibrinogen): 235-490 mg/dL; PT (prothrombin time): 11.5-14.4 sec; PLT (platelets): 143-398 x 103/μL