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# Acute ischemic stroke and COVID-19

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## ■ ABSTRACT

Ischemic stroke may be a presenting feature of COVID-19. Its etiology remains unclear, but severe COVID-19 disease might increase the risk of large-artery strokes. More evidence is needed to substantiate the current reports and provide insights for optimal management.

## ■ INTRODUCTION

Although COVID-19 mostly causes lung injury, there are emerging data on related neurologic complications, including acute cerebrovascular disease.

## ■ INCIDENCE AND RISK FACTORS

A stroke incidence of 2.5% to 6% has been reported in retrospective studies of European and Chinese hospitalized COVID-19 patients.<sup>1–3</sup>

In a study that has not yet been peer-reviewed,<sup>4</sup> among 221 hospitalized COVID-19 patients in Wuhan, China, those with acute stroke were more likely to be older, to present with severe infection, and to have cardiovascular risk factors such as hypertension, diabetes, and a history of prior stroke. In this report, intracranial hemorrhage appeared to be much less common than acute ischemic stroke.

Acute ischemic stroke was also reported during the earlier severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics.<sup>5,6</sup> Of 206 patients hospitalized for SARS in Singapore, 5 patients (2.4%) had large-artery strokes.<sup>5</sup> Three had no traditional cerebrovascular risk factors and 4 were critically ill, suggesting an association with infection itself or its treatment. Potential causes of acute ischemic stroke in these patients included low ejection fraction from cardiac dysfunction, disseminated intravascular coagulopathy, and marantic

(nonbacterial thrombotic) endocarditis.

A recent case series from New York City supports this study's findings, as large-vessel ischemic strokes occurred in 5 COVID-19 patients younger than 50 years.<sup>7</sup> Each presented with acute stroke symptoms and lymphopenia and elevated inflammatory markers on admission laboratory testing, but 2 had no COVID-19 symptoms.

## ■ REVIEW OF PROPOSED ETIOLOGIES

### Coagulopathy

Severely infected COVID-19 patients might be at risk of thromboembolic events from COVID-associated coagulopathy.<sup>2,3,8,9</sup> Hospitalized COVID-19 patients have been reported to have increased coagulation activity, marked by increased D-dimer concentrations.<sup>3,8,10</sup> In one study, a D-dimer value greater than 1 µg/mL was associated with fatal outcome of COVID-19.<sup>9</sup> In another study, patients with both cerebrovascular disease and SARS-CoV-2 had higher D-dimer levels than SARS-CoV-2 patients without cerebrovascular disease (6.9 mg/L vs 0.5 mg/L,  $P < .001$ ).<sup>4</sup>

At this time, it is unclear if elevated D-dimer values in COVID-19 are directly associated with either arterial or venous ischemic stroke, or both. There is only 1 recent report of cerebral venous sinus thrombosis in a 32-year-old with severe COVID-19, who was successfully managed with therapeutic anticoagulation.<sup>4</sup>

### Antiphospholipid antibodies

Lupus anticoagulants and prolonged activated partial thromboplastin time are also frequently found in hospitalized COVID-19 patients, in whom the prevalence of lupus anticoagulant is 45% to 91%.<sup>9–12</sup> There is no clear association between lupus anticoagulant and thrombosis in these studies, but a case series reported the finding of antiphospholipid antibodies in 3 critically ill COVID-19 patients with bilateral cerebral infarcts in multiple vascular territories.<sup>12</sup> Laboratory investigations showed increased antiphospholipid antibodies, including anticardiolipin immunoglobulin A (IgA) IgA and beta-2 glycoprotein IgM

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and IgG, but without lupus anticoagulant.

This case series<sup>12</sup> suggested an acquired antiphospholipid syndrome was the underlying etiology, but unlike in the reported series of large-artery strokes in 5 young patients, these patients with antiphospholipid antibodies were over 60 years of age. The study did not provide information on other arterial or venous thromboembolism nor did it report the laboratory values or whether the patients had IgM or IgG antiphospholipid antibodies. In addition, 2 patients had prior strokes, and the underlying etiology for these prior events was not discussed. Finally, the questionable association of thrombosis with IgA antiphospholipid makes it difficult to determine a causal relationship.

These reports indicate the presence of antiphospholipid antibodies at variable frequencies, but likely higher than expected in the general population. Since their clinical significance is not yet known, these laboratory tests should not be routinely checked in COVID-19 patients without thrombosis.

### Vasculitis

Other etiologies of ischemic stroke, such as virus-induced central nervous system vasculitis, were proposed when MERS and SARS patients had brain lesions in vascular patterns without a clear cerebrovascular etiology.<sup>13,14</sup> Postmortem histologic analysis of 3 COVID-19 patients revealed lymphocytic endotheliitis within the endothelial cells of multiple organs, including the lungs, heart, kidneys, small intestine, and liver.<sup>15</sup>

Endotheliitis can cause microcirculatory vasoconstriction and endothelial dysfunction with consequent ischemia and apoptosis.<sup>15</sup> Direct viral infection of endothelial cells via angiotensin-converting enzyme 2 receptors, along with the host inflammatory response, may contribute to the wide spectrum of clinical sequelae of COVID-19.<sup>15</sup> Histopathologic analysis of the central nervous system is needed to determine if SARS-CoV-2-related central nervous system vasculitis can occur due to lymphocytic endotheliitis.

### MANAGEMENT

Standard acute ischemic stroke management should be pursued, including reperfusion therapy with intravenous alteplase and mechanical thrombectomy.

Stroke imaging findings in COVID-19 have not revealed a single mechanism with evidence of small-vessel infarction, large-artery strokes, and cardioembolism. In addition, imaging is likely limited, given

the disease severity and limited access to magnetic resonance imaging (MRI).

A study reported unusual MRI findings in 13 COVID-19 patients with encephalopathy.<sup>16</sup> Imaging revealed leptomeningeal enhancement in 8 patients, and 3 patients were found to have silent cerebral ischemic strokes. Interestingly, all 11 patients that underwent perfusion imaging showed bilateral frontotemporal hypoperfusion. This study suggests that cerebral ischemia and meningoencephalitis might be underreported in COVID-19 patients with encephalopathic presentations.

Close monitoring of characteristic laboratory findings of COVID-associated coagulopathy, such as elevated D-dimer and fibrinogen, shortened prothrombin time and augmented partial thromboplastin time, and low international normalized ratio should be considered in suspected COVID-19 cases.

Appropriate diagnostic workup and antiplatelet agents for secondary stroke prevention should be considered.

Although prophylaxis of venous thromboembolism would be recommended for all nonambulatory hospitalized COVID-19 patients, including those with ischemic strokes, therapeutic anticoagulation for prevention of stroke remains uncertain. Current practices encourage an individualized decision based on imaging, timing, clinical context, and risk-benefit discussions.

Management strategies for anticoagulation in COVID-19 stroke patients may change with emerging data.

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