Bihemispheric ischemic strokes in patients with COVID-19

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Abstract:
BACKGROUND: There is emerging evidence that COVID-19 can trigger thrombosis because of a hypercoagulable state, including large-vessel occlusion ischemic strokes. Bihemispheric ischemic stroke is uncommon and is thought to indicate an embolic source. Here, we examine the findings and outcomes of patients with bihemispheric stroke in the setting of COVID-19.

METHODS: We performed a retrospective cohort study at a quaternary academic medical center between March 1, 2020, and April 30, 2020. We identified all patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who presented with simultaneous bihemispheric ischemic strokes.

RESULTS: Of 637 COVID-19 admissions during the 2-month period, 13 had a diagnosis of acute ischemic stroke, including 5 who developed bihemispheric cerebral infarction. Three of those 5 (60%) were female, median age was 54 (range 41–67), and all five were being managed for severe COVID-19-related pneumonia complicated by acute kidney injury and liver failure before the diagnosis of cerebral infarction was established. Five presented with elevated ferritin, lactate dehydrogenase, and interleukin-6 (IL-6) levels, and four had lymphopenia and elevated D-dimer levels. All patients underwent neuroimaging with computed tomography for persistent depressed mentation, with or without a focal neurologic deficit, demonstrating multifocal ischemic strokes with bihemispheric involvement. Outcome was poor in all patients: two were discharged to a rehabilitation facility with moderate-to-severe disability and three (60%) patients died.

CONCLUSIONS: Stroke is implicated in SARS-CoV-2 infection. Although causality cannot be established, we present the imaging and clinical findings of patients with COVID-19 and simultaneous bihemispheric ischemic strokes. Multifocal ischemic strokes with bihemispheric involvement should be considered in COVID-19 patients with severe infection and poor neurologic status and may be associated with poor outcomes.

Keywords: Coronavirus disease 2019, embolism, ischemic stroke, neurologic complications, severe acute respiratory syndrome coronavirus 2

Introduction

The coronavirus disease 2019 (COVID-19) global outbreak commenced in Wuhan, China, in December 2019 and was designated a pandemic on March 11, 2020, by the World Health Organization.[1,2] COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with several manifestations of varying degree including asymptomatic disease, mild upper respiratory tract illness, severe viral pneumonia, respiratory failure, and death with 26%–32% of patients warranting intensive care unit (ICU) admission.[3,5] Although COVID-19 predominantly causes pulmonary injury,
there is emerging evidence on COVID-19-related neurologic complications, of which stroke has a reported incidence of 2.5%–2.8%.[6–8] Given that preexisting vascular risk factors are prevalent in COVID-19 patients, the association between stroke and COVID-19 may be unrelated; however, there is overwhelming evidence suggesting a high risk for coagulopathy and thromboembolic events in patients with COVID-19, primarily in the acute phase of the infection.[6,7,9] A recent case series reported large-vessel ischemic stroke in 5 patients with COVID-19 under the age of 50, each with minimal to no preexisting vascular risk factors and presenting with elevated markers of inflammation on laboratory testing.[10] In addition to the prevalence of stroke in COVID-19 patients, stroke is highly suggestive of severe infection and poor outcomes.[8] Ischemic stroke with bihemispheric involvement is generally indicative of an embolic source and is associated with increased death and disability.[11] Herein, we present 5 cases of acute multifocal ischemic stroke with bihemispheric involvement in the setting of COVID-19 infection.

Methods

Study population
We retrospectively reviewed 46 charts of patients with acute ischemic stroke admitted between March 1, 2020, and April 30, 2020 to Westchester Medical Center, a large quaternary medical center in Valhalla, NY. These patients were identified using our ischemic stroke database. We identified 13 charts of patients with acute ischemic stroke and concomitant COVID-19. A confirmed case of SARS-CoV-2 infection was defined by a positive result on reverse-transcriptase polymerase chain reaction assay on nasopharyngeal swab. Among the patients with acute ischemic stroke and concomitant COVID-19, we identified 5 patients with bihemispheric involvement. These patients were identified by reviewing neuroimaging with either noncontrast computed tomography (CT) of the head or magnetic resonance imaging of the brain. All radiology reports were reviewed. We defined bihemispheric stroke as acute infarcts involving both cerebral hemispheres.

Data collection
Demographic data, preexisting vascular risk factors (for example, hypertension, diabetes mellitus, hyperlipidemia, cardiac disease, peripheral vascular disease, obesity, and habitual smoking), initial COVID-19 symptoms, neurologic symptoms warranting brain imaging, laboratory values, and neuroimaging modality and results for stroke diagnosis were recorded retrospectively. We looked at outcomes including discharge location and discharge disability score as measured via the modified Rankin scale (mRS). The mRS is a general assessment of function in which a score of 0 indicates no symptoms and a score of 5 indicates severe disability), and mortality.

Clinical management
All patients with COVID-19 admitted to our center are graded based on disease severity and assessed for risk for progression. COVID-19 disease severity ranges from asymptomatic to critical illness, with critical illness defined as acute hypoxic respiratory failure with shock and/or multiorgan failure. High risk for progression is defined by having any of the following: absolute lymphocyte count <0.8, lactate dehydrogenase (LDH) >250, C-reactive protein >1, ferritin >300, creatine phosphokinase > twice the normal limit, D-dimer >1, and positive troponin level. All patients with bihemispheric stroke and concomitant COVID-19 admitted to our center within the study period were critically ill and managed in an ICU. At our institution, infectious disease (ID) consultations are obtained for all critically ill COVID-19 patients for antiviral and adjunctive therapy recommendations. Prophylactic anticoagulation for venous thromboembolism (VTE) prevention is initiated in all COVID-19 patients unless otherwise contraindicated. Management of ischemic stroke was determined by patient-specific variables and are described in the results below.

Ethical approval
The research received IRB approval from the New York Medical College Institutional Review Board (IRB#14130). Due to the retrospective nature of the chart review, written informed consent was waived for this study.

Results
We provided care for 637 patients with COVID-19 infection between March 1, 2020, and April 30, 2020. During this time, patients with acute ischemic stroke were diagnosed, 13 of whom had associated COVID-19 infection. Of these 13 COVID-19 patients with acute ischemic stroke, five with bihemispheric ischemic strokes were identified [Table 1]. Three were females and the median age was 54 (range 41–67) years. Four patients had preexisting vascular risk factors. All five patients were managed for severe COVID-19-related pneumonia warranting critical care support after presenting with varying combinations of fever, cough, dyspnea, and fatigue. All five patients required mechanical ventilation. All five developed lymphopenia, leukocytosis, and progressive thrombocytopenia, all had elevated serum ferritin, LDH, d-dimer, and interleukin-6 (IL-6) levels, all experienced acute kidney injury and transaminitis, and four developed hyperfibrinogenemia. All five patients underwent neuroimaging with CT for persistently depressed mentation despite discontinuation of sedating agents for a median of 16 (range 5–27) days.
Table 1: Clinical Characteristics of 5 patients with coronavirus disease 2019 and bihemispheric ischemic strokes

| Variable                                      | Case 1                  | Case 2                  | Case 3                  | Case 4                  | Case 5                  |
|-----------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Age (years)                                   | 41                      | 67                      | 67                      | 47                      | 52                      |
| Sex                                           | Female                  | Male                    | Female                  | Female                  | Male                    |
| Preexisting stroke risk factors               | None                    | Hyperlipidemia DM type 2| Hypertension DM type 2  | DM type 2 morbid obesity| Hyperlipidemia DM, CAD, PVD morbid obesity|
| COVID-19 symptoms on admission               | Fever, cough, dyspnea   | Fever, cough, dyspnea   | Dyspnea, fatigue        | Fever, dyspnea          | Fever, cough, dyspnea   |
| Reason for neuroimaging                       | Depressed LOC, left hemiparesis | Depressed LOC          | Depressed LOC, diminished brainstem reflexes | Depressed LOC, diminished brainstem reflexes |
| NIHSS*                                        | 22                      | 29                      | 35                      | 23                      | 28                      |
| Imaging modality                             | CT/CTA                  | C/CTA                   | CT                      | CT                      | CT                      |
| Time from admission to imaging (days)         | 9                       | 18                      | 5                       | 27                      | 15                      |
| Stroke etiology                               | Mechanical ventilation Disseminated intravascular coagulation | Atrial fibrillation | Mechanical ventilation Presumed hypercoagulable state | Mechanical ventilation Presumed hypercoagulable state | Atrial fibrillation |
| Treatment for stroke                          | Heparin infusion followed by aspirin 81 mg daily | Eliquis 5 mg twice daily | Heparin infusion followed by aspirin 81 mg daily | Heparin infusion | Heparin infusion |
| White cell count (k/mm$^3$)                   | Initial: 21.3            | 7.4                     | 11.4                    | 8.6                     | 10.6                    |
|                                              | Peak: 51.3               | 30.4                    | 34.3                    | 23.0                    | 31.1                    |
| Lymphocyte count (%)                          | Initial: 2.5             | 8.6                     | 6.0                     | 30.0                    | 4.7                     |
|                                              | Trough: 0.0              | 0.0                     | 3.0                     | 4.0                     | 3.5                     |
| Platelet count (k/mm$^3$)                     | Initial: 216             | 103                     | 406                     | 133                     | 257                     |
|                                              | Trough: 27               | 23                      | 258                     | 4                       | 124                     |
| PT (s)                                        | Initial: 12.6            | 10.5                    | 10.7                    | 11.0                    | 10.4                    |
|                                              | Peak: 15.0               | 26.6                    | 12.0                    | >143.7                  | 12.1                    |
| PTT (s)                                       | Initial: 36.7            | 29.0                    | 30.7                    | 25.8                    | 28.9                    |
|                                              | Peak: 83.2               | 72.3                    | >133.6                  | >133.6                  | 89.6                    |
| D-dimer (mg/L-FEU)                            | Initial: 0.54            | 1.62                    | 3.68                    | 6.35                    | 19.17                   |
|                                              | Peak: >35.20             | >35.20                  | >35.20                  | >35.20                  | >35.20                  |
| Fibrinogen (mg/dL)                            | Initial: NT              | NT                      | NT                      | 322                     | 641                     |
|                                              | Peak: 280                | 624                     | >960                    | 871                     | 798                     |
| Ferritin (µg/L)                               | Initial: 261.5           | 903.7                   | 750.5                   | 216.4                   | 3082.2                  |
|                                              | Peak: 2454.1             | 5200.5                  | >40,000.0               | 34,563.2                | 3082.2                  |
| LDH (U/L)                                     | Initial: 296             | 502                     | 579                     | 380                     | 726                     |
|                                              | Peak: 6127               | 1857                    | 5143                    | 2373                    | 774                     |
| Creatinine (mg/dL)                            | Initial: 0.51            | 1.16                    | 1.06                    | 0.79                    | 8.31                    |
|                                              | Peak: 6.99               | 7.74                    | 3.05                    | 1.56                    | 15.81                   |
| Dialysis                                      | Yes                      | Yes                     | No                      | No                      | Yes                     |
| AST/ALT (U/L)                                 | Initial: 89/59           | 63/44                   | 43/29                   | 51/79                   | 273/442                 |
|                                              | Peak: 589/246            | 106/106                 | 2400/1934               | 1028/795                | 273/442                 |

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Kurian, et al.: Bihemispheric stroke in COVID‑19

Brain Circulation - Volume 8, Issue 1, January‑March 2022 13

after admission. Neuroimaging revealed multifocal acute‑to‑subacute ischemic strokes with bihemispheric involvement [Figures 1‑5]. All the infarcts were territorial and appeared to be embolic except for patient 4, who developed a combination of branch occlusions and bilateral capsular penetrator infarcts. CTA was completed in two patients and did not demonstrate a large‑vessel occlusion or severe vessel stenosis. All patients were ineligible for acute thrombolysis or endovascular intervention as they presented outside of the therapeutic time window for acute stroke intervention. Outcome was poor in all patients. Two patients were discharged to rehabilitation facilities (1 acute and 1 subacute) with mRs scores of 4 and 5, respectively. Three patients died, of whom two patients with do‑not‑resuscitate code status died from cardiopulmonary arrest and one patient was declared brain dead.

**Discussion**

We report 5 cases of patients hospitalized for primary SARS‑CoV‑2 infection and discovered multifocal ischemic strokes with bihemispheric involvement during their hospital course. All patients warranted critical care support for severe COVID‑19‑related pneumonia with evidence of multiorgan failure. All patients underwent neuroimaging with CT primarily for persistent depressed mentation despite discontinuation or tapering of sedation, plus or minus focal neurologic deficits. The average time from admission to CT was 15 days. CT demonstrated multifocal ischemic strokes with bihemispheric in all patients, likely contributing to poor clinical status. All patients were under 70 years of age, and although they had vascular risk factors, they all had severe COVID‑19 infection with significant elevations in D‑dimer, ferritin, and IL‑6 suggestive of hyperinflammation response. All patients had poor outcomes with death or severe disability. There are emerging data on COVID‑19‑related neurologic complications and its implication of severe disease and poor outcomes. A recent case series of patients with COVID‑19 in Wuhan, China, reported an incidence of stroke of 5.7% in severe infection versus 0.8% in nonsevere infection. It is known that systemic inflammatory processes impact patient susceptibility for stroke and that patients with stroke and systemic inflammation typically have poorer outcomes given exacerbation of cerebral damage through interleukin (IL) and neutrophil‑dependent mechanisms.

The incidence of bihemispheric involvement in patients with acute ischemic stroke is 1.4%–6.1% and bihemispheric...
strokes are associated with poorer outcomes. We found bihemispheric involvement in 5 (38%) patients with acute ischemic stroke and concomitant COVID-19, which is higher than reported. Outcomes in our study group were similar with increased death and disability. Given involvement of multiple vascular distributions, a central embolic source typically involving the heart, aorta, or a hypercoagulable state should be considered. The underlying mechanism for cerebral ischemia in COVID-19 patients is unclear. The relationship between stroke and COVID-19 may be coincidental, given the prevalence of traditional vascular risk factors within this population. Nevertheless, there are significant data demonstrating high risk for coagulopathy and venous and arterial thromboembolic complications in patients with COVID-19. Patients with COVID-19 are reported to have abnormal coagulation represented by higher D-dimer and fibrin degradation product levels, suggestive of recent, or acute clot development. In one study, an 18-fold increase in odds of death was noted in patients with COVID-19 and admission D-dimer levels >1 µg/L.

Transient causes of thromboembolism associated with critical illness may play a role in the mechanism of cerebral ischemia in COVID-19 patients. Multiple infarcts, significant coagulopathy and antiphospholipid antibodies (aPL), primarily anticardiolipin immunoglobulin (Ig) A and beta-2 glycoprotein IgM and IgG, have been described in patients with COVID-19 in China. Lupus anticoagulant and prolonged aPTT have also been reported in hospitalized patients with COVID-19. It is known that aPL antibodies can transiently arise in patients with various viral illnesses and that in some cases the presence of aPL antibodies is associated with thrombosis. However, the difficulty remains differentiating from other causes of multiple thrombotic events in critically ill patients, such as disseminated intravascular coagulation, which was reported in 71.4% of nonsurvivors in the late stages of COVID-19 pneumonia. Furthermore, arrhythmias such as atrial fibrillation is prevalent in acute illness and is associated with thromboembolism.

Vasculopathy due to direct vascular endothelial injury is another proposed mechanism of cerebral ischemia in patients with COVID-19. It is known that SARS-CoV-2 infects cells by the binding of COVID-19 virus spike with angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in multiple organs and endothelial cells. Postmortem analysis in patients with COVID-19 have reported direct viral infection of the endothelial cells and accumulation of inflammatory cells from host inflammatory response leading to diffuse endothelial dysfunction and cell death. Endothelial dysfunction results in vasoconstriction and subsequent ischemia, and procoagulant state. Furthermore, patients with preexisting atherosclerotic disease may be prone to plaque disruption and thrombosis due to activation of immune and inflammatory pathways.

Cytokine storm as a hyperinflammatory response secondary to COVID-19 has been examined as a cause of critical illness in this patient population, implicated in: Acute respiratory distress syndrome, ischemic stroke, myocardial infarction, and more. Patients who died from severe infection were found to have higher levels of cytokine storm markers as well as evidence of systematic binding of the SARS-CoV-2 S protein to endothelial cells of the body. While the damage of healthy cells is usually initially isolated to the lungs, it often spreads to other organs including the vasculature and the brain. COVID-19 patients have higher risk of hypercoagulability and arteriovenous thrombosis.

Figure 3: Computed tomography brain noncontrast of case 3 demonstrating (a) infarcts within the bilateral cerebellum and left paramedian inferior frontal lobe (green arrow), (b) infarcts within the left paramedian frontal lobe and left occipital lobe, (c) infarcts within the bilateral paramedian frontal lobes (Green arrow) and (d) infarcts within the left paramedian frontal lobe and left occipital lobe.

Figure 4: Computed tomography brain noncontrast of case 4 demonstrating (a) small infarct within the right temporal lobe, (b) small infarct within the left occipital lobe, (c) small infarcts within the bilateral internal capsule, (d) and infarcts within the right frontal and parietal lobes (Infarcts demonstrated by green arrow)
As in our present study, patients with COVID-19 and stroke have been found to have elevated acute phase reactants including D-dimer, which were correlated with negative outcome.[29,34]

Given proposed mechanisms of cerebral ischemia in patients with COVID-19, management goals may include early treatment to minimize viral replication, stabilize endothelium and decrease clot formation, especially in patients who carry risk factors for severe infection and adverse outcomes. Anti-inflammatory anticytokine agents, medications that target ACE2 and its ligand-COVID-19 spike protein, statins and anticoagulants may be beneficial but warrant further studies including clinical trials.[35-40]

Limitations of the present study include small sample size and involvement of a single center. Though one can examine the associated clinical and imaging findings in this cohort, this prevents the establishment of causality between COVID-19 and bihemispheric stroke. The number of patients with ischemic stroke in the setting of COVID-19 may be underestimated, as some patients were hemodynamically unstable and therefore could not safely undergo neuroimaging. Furthermore, some patients may have received paralytics confounding the neurological examination resulting in delay to diagnosis of stroke.

Conclusions

Neurologic complications including stroke is implicated in SARS-CoV-2 infection. Multifocal ischemic stroke with bihemispheric involvement should be considered in COVID-19 patients with severe infection and poor neurologic status and may be associated with poor outcomes.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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