COVID-19 Ischemic Strokes as an Emerging Rehabilitation Population

A Case Series

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Abstract: There is emerging literature that coronavirus disease 2019 infections result in an increased incidence of thrombosis secondary to a prothrombotic state. Initial studies reported ischemic strokes primarily occurring in the critically ill coronavirus disease 2019 population. However, there have been reports of ischemic strokes as the presenting symptom in young noncritically ill coronavirus disease 2019 patients without significant risk factors. Further characterization of the coronavirus disease 2019 stroke population is needed. We present four cases of coronavirus disease 2019 ischemic strokes occurring in patients aged 37–68 yrs with varying coronavirus disease 2019 infection severities, premorbid risk factors, clinical presentations (eg, focal and nonfocal), and vascular distributions. These cases highlight the heterogeneity of coronavirus disease 2019 ischemic strokes. The duration of the coronavirus disease 2019–related prothrombotic state is unknown, and it is unclear whether patients are at risk for recurrent strokes. With more coronavirus disease 2019 patients recovering and being discharged to rehabilitation, physiatric awareness of this prothrombotic state and increased incidence of ischemic strokes is essential. Because of the variable presentation of coronavirus disease 2019 ischemic strokes, clinicians can consider neuroimaging as part of the evaluation in coronavirus disease 2019 patients with either acute focal or nonfocal neurologic symptoms. Additional studies are needed to clarify prothrombotic state duration, determine prognosis for recovery, and establish the physiatrist’s role in long-term disease management.

Key Words: Coronavirus Disease 2019 (COVID-19), SARS-CoV-2, Ischemic Stroke, Neurological Manifestations

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The coronavirus disease 2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 that has resulted in 7,273,958 cases and 413,372 deaths worldwide as of June 11, 2020.1 Commonly encountered symptoms include cough, fever, myalgia, and fatigue. More severe infections can lead to pneumonia, acute respiratory distress syndrome, and multisystem organ failure.2 Recent studies have reported an increased incidence of thrombosis associated with COVID-19 infections.2–4 It is currently unknown whether this prothrombotic state is due to the virus itself, a cytokine storm with resulting systemic inflammatory response, or endovascular dysfunction.5 The most common thrombotic complication is pulmonary embolism, accounting for 87% of thrombotic events.4 However, there have been increasing reports of ischemic strokes occurring with COVID-19 infections that may be part of the hypercoagulable spectrum of this disease.2,4–9

Infection with severe acute respiratory syndrome, a closely related coronavirus, has been associated with large-vessel ischemic strokes in 2.4% of cases.10 Initial studies showed that neurologic symptoms were a feature of COVID-19 infections, with ischemic strokes reported in 3%–5% of hospitalized patients, primarily occurring in the critically ill.2,3,8 However, there have been increasing reports of COVID-19 ischemic strokes as the presenting symptom in young noncritically ill patients without significant risk factors.2,5–7 Further characterization of COVID-19 ischemic stroke patients is needed to elucidate pathophysiology, identify risk factors, and develop management strategies.

Case Presentations

We present four patients who developed acute ischemic strokes during the course of their COVID-19 infection (Table 1). The first case was a 54-yr-old man with undiagnosed hypertension who presented with dysarthria, hemiparesis, and decreased level of consciousness, found to have sustained basilar and right superior cerebellar artery infarctions (Fig. 1A). The second case was a 37-yr-old man with undiagnosed type 2 diabetes who presented with aphasia, hemiparesis, and hemisensory loss, found to have a left middle cerebral artery infarction (Fig. 1B). The third case was a 65-yr-old man with undiagnosed type 2 diabetes who presented after a motor vehicle accident with altered mental status and respiratory distress, subsequently requiring intubation because of COVID-19–related acute respiratory distress syndrome. Initial neuroimaging showed no acute intracranial abnormalities. He was unresponsive when sedation was held on hospital day 4 and magnetic resonance imaging showed bilateral multifocal subcortical infarctions (Fig. 1C). The fourth case was a 68-yr-old woman with a history of hypertension and diabetes with COVID-19 respiratory symptoms, who required intubation because of acute respiratory distress syndrome. She developed septic shock, multisystem organ failure, and decreased command following on hospital day 8, with a magnetic resonance...
TABLE 1. Clinical characteristics of four COVID-19–positive patients with ischemic strokes

|                  | Patient 1                  | Patient 2                  | Patient 3                  | Patient 4                  |
|------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Age, yr          | 54                        | 37                        | 65                        | 68                        |
| Sex              | Male                      | Male                      | Male                      | Female                    |
| Race/ethnicity   | African American           | Hispanic                  | Hispanic                  | African American           |
| Height, cm       | 189                       | 175                       | 173                       | 168                       |
| Weight, kg       | 139                       | 77                        | 82                        | 73                        |
| Medical history  | Undiagnosed hypertension  | Undiagnosed diabetes      | Undiagnosed diabetes      | Diabetes, hypertension    |
| Prehospital      | None                      | None                      | None                      | None                      |
| anticoagulant or |                           |                           |                           |                           |
| antiplatelet use |                           |                           |                           |                           |
| COVID-19 symptoms| Cough, fevers, chills     | None                      | SOB, fevers               | Cough, SOB, diarrhea      |
| COVID-19 severity| Nonsevere                 | None                      | Severe                    | Severe                    |
| Days between     | 7                         | 0                         | 4                         | 8                         |
| COVID-19 and     |                           |                           |                           |                           |
| stroke diagnosis |                           |                           |                           |                           |
| Stroke symptoms  | Dysarthria; left hemiparesis, reduced LOC | Aphasia, facial droop; right hemiparesis, sensory deficit, complete hemianopsia | Reduced LOC; unable to assess deficits further | Reduced LOC; unable to assess deficits further |
| Stroke locations | Basilar artery, right superior cerebellar artery | Left middle cerebral artery at M1 and M3 | Bilateral cerebral hemispheres, anterior circulation | Right posterior cerebral artery |
| Stroke treatment | Mechanical thrombectomy, aspirin | IV t-PA, mechanical thrombectomy, aspirin | Aspirin | Aspirin |
| Laboratories values |                         |                           |                           |                           |
| WBC              | 14.7–18.2, 2% lymphocytes | 6.4–8.0, 10% lymphocytes  | 7.4–22.4, 2% lymphocytes  | 20.2–42.9, 5% lymphocytes |
| Platelet count   | 364–244                   | 382–489                   | 87–170                    | 432–506                   |
| PT time          | 14.4–17.6                 | 14.0–18.3                 | 13.3                      | 15.2–17.3                 |
| Fibrinogen       | 520                       | 136–560                   | 210–916                   | 567–790                   |
| D-dimer          | 2802–7835                 | 1487–3918                 | 1732–6384                 | 778–2484                  |
| Ferritin         | 451                       | 583–703                   | 353–884                   | 413–1062                  |
| LDH              | 273                       | 256–313                   | 307–632                   | 376–780                   |
| CRP              | 28                        | 26–114                    | 37–310                    | 54–252                    |
| Outcome          | Intubated because of worsening infarctions; loss of brainstem reflexes; deceased on day 3 | Improved strength and aphasia; discharged home on day 9 | ARDS; sepsis, multisystem organ failure; deceased on day 42 | ARDS; sepsis, multisystem organ failure; discharged to rehabilitation on day 29 |

Reference ranges for laboratory values: white blood cell count, 4.0–11.0 × 10^9/l; lymphocytes, 20%–50%; platelets, 150–450 × 10^9/l; prothrombin time, 12.1–14.8 secs; fibrinogen, 145–490 mg/dl; D-dimer, 90–500 ng/ml FEU; ferritin, 30–400 ng/ml; lactate dehydrogenase, 120–250 U/l; C-reactive protein, 0–5 mg/l.

Minimum and maximum laboratory values as ordered during the patient’s hospital course.

ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; IV, intravenous; LDH, lactate dehydrogenase; LOC, level of consciousness; PT, prothrombin time; SOB, shortness of breath; t-PA, tissue plasminogen activator; WBC, white blood cell count.

imaging showing a right posterior cerebral artery infarction (Fig. 1D). None of the patients had a history of smoking, illicit drug use, or alcohol abuse. All patients had elevated ferritin, fibrinogen, C-reactive protein, and D-dimer levels. Stroke treatment included mechanical thrombectomy, intravenous tissue plasminogen activator, and/or aspirin. Computed tomography angiography of the head and neck showed no significant atherosclerosis, stenosis, or dissections. Cardiac telemetry showed either normal sinus rhythm or sinus tachycardia. Echocardiograms performed showed no vegetations or thrombi. Patient outcomes varied including death, discharge home, or discharge to rehabilitation.

**DISCUSSION**

The COVID-19 ischemic strokes are poorly understood with multiple proposed mechanisms for associated neurologic manifestations. Coronaviruses, including COVID-19, are thought to have direct neuroinvasive properties resulting in symptoms including encephalopathy and seizures. However, the relationship between the development of ischemic strokes and the neuroinvasive properties of viruses is unclear. Recent literature suggests that a prothrombotic state is the more likely mechanism. Autopsy findings of COVID-19 patients showed pulmonary thrombotic microangiopathy on histological evaluation. Although brain tissue was not evaluated, a similar process of thrombosis is possible within the cerebral vasculature. In addition, coagulation cascade and inflammatory marker abnormalities seen in COVID-19 patients, such as elevated C-reactive protein, ferritin, D-dimer, and fibrinogen levels, reflect a prothrombotic state. These findings, present in the previously mentioned cases, may have contributed to the
The presented cases highlight the spectrum of COVID-19 ischemic strokes. Both young and elderly patients had varying COVID-19 infection severities and infarct locations. Most of the published cases reported anterior circulation large-vessel infarctions of either the middle cerebral or posterior cerebral arteries, seen in cases 2 and 4, respectively.5-7 Posterior circulation infarctions, seen in case 1, were less frequently reported.7,8 In addition, there have been documented cases of multifocal strokes occurring in critically ill COVID-19 patients, as seen in case 3.9 Medical histories varied among the previously reported cases with all currently presented cases having either premorbid or undiagnosed medical conditions including diabetes or hypertension.5-7,10 Our cases detailed two noncritically ill patients younger than 55 yrs who presented to the hospital because of stroke symptoms, compared with the two critically ill patients older than 55 yrs who developed strokes during their hospitalization. The first and second cases had focal neurologic defects that were consistent with the involved vascular distributions. However, cases 3 and 4 experienced nonfocal, encephalopathic manifestations that led to additional neuroimaging and subsequent stroke diagnosis. The current cases also highlight the wide age range of patients susceptible to COVID-19 ischemic strokes, consistent with the current literature.5-7,9

CONCLUSIONS

With more recovering COVID-19 patients being transferred to postacute care, physiatrist knowledge of increased thrombotic risk in this population is essential. The duration of the COVID-19 prothrombotic state is currently unknown, and it is unclear whether patients are at increased risk for recurrent strokes. Therefore, clinicians have a key role in educating patients about thrombotic events associated with COVID-19 infection. In addition, a recent publication described 13 COVID-19 patients exhibiting encephalopathic features with 100% of patients showing abnormalities on magnetic resonance imaging, including acute ischemic strokes.12 This supports a role for neuroimaging in the postacute setting for COVID-19 patients with new onset of either nonfocal or focal neurologic findings. Decreased inpatient bed availability and closed outpatient facilities because of infection control measures have made access to rehabilitation challenging. However, physiatrists must advocate for appropriate rehabilitation to maximize patient recovery. This case series highlights the broad clinical spectrum of COVID-19 ischemic strokes, reported in patients aged 37–68 yrs of varying COVID-19 infection severities, clinical presentations (eg, focal and nonfocal), and vascular distributions. Prospective studies of COVID-19 stroke patients are needed to fully understand long-term risks, manifestations, and appropriate physiatric management of this emerging rehabilitation population.

This case series conforms to all CARE guidelines and reports the required information accordingly (see Supplemental Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B74).

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