Stroke

BRIEF REPORT

Acute Cerebrovascular Events in Hospitalized COVID-19 Patients

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BACKGROUND AND PURPOSE: Initial reports suggest a significant risk of thrombotic events, including stroke, in patients hospitalized with coronavirus disease 2019 (COVID-19). However, there is little systematic data on stroke incidence and mechanisms, particularly in racially diverse populations in the United States.

METHODS: We performed a retrospective, observational study of stroke incidence and mechanisms in all patients with COVID-19 hospitalized from March 15 to May 3, 2020, at 3 Philadelphia hospitals.

RESULTS: We identified 844 hospitalized patients with COVID-19 (mean age 59 years, 52% female, 68% Black); 20 (2.4%) had confirmed ischemic stroke; and 8 (0.9%) had intracranial hemorrhage. Of the ischemic stroke patients, mean age was 64 years, with only one patient (5%) under age 50, and 80% were Black. Conventional vascular risk factors were common, with 95% of patients having a history of hypertension and 60% a history of diabetes mellitus. Median time from onset of COVID symptoms to stroke diagnosis was 21 days. Stroke mechanism was cardioembolism in 40%, small vessel disease in 5%, other determined mechanism in 20%, and cryptogenic in 35%. Of the 11 patients with complete vascular imaging, 3 (27%) had large vessel occlusion. Newly positive antiphospholipid antibodies were present in >75% of tested patients. Of the patients with intracranial hemorrhage, 5/8 (63%) were lobar intraparenchymal hemorrhages, and 3/8 (38%) were subarachnoid hemorrhage; 4/8 (50%) were on extracorporeal membrane oxygenation.

CONCLUSIONS: We found a low risk of acute cerebrovascular events in patients hospitalized with COVID-19. Most patients with ischemic stroke had conventional vascular risk factors, and traditional stroke mechanisms were common.

Key Words: coronavirus ■ diabetes mellitus ■ hypertension ■ incidence ■ population

Increasing evidence suggests a significant risk of thrombotic events, including stroke, in patients with coronavirus disease 2019 (COVID-19).[1,2] In an early study from Wuhan, China, ischemic stroke was seen in 2.3% of 214 patients hospitalized with COVID-19.[1] More recently, a large cohort study from New York reported ischemic stroke in 0.9% of 3556 hospitalized patients with COVID-19.[3] Intracranial hemorrhage (ICH) has also been reported with COVID-19, although systematic data on incidence and clinical features are limited. We sought to determine the incidence of acute cerebrovascular events associated with COVID-19 and characterize the clinical features of these events in a racially diverse population cared for within our health system.

MATERIALS AND METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We performed a retrospective, observational study of all patients with COVID-19 (diagnosed based on positive real-time polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2) hospitalized from March 15 to May 3, 2020, at 3 Philadelphia hospitals in the University of Pennsylvania Health System. Patients with COVID-19 with an order for brain imaging were identified with a computerized search strategy, and manual chart review was undertaken in these patients. Stroke diagnosis was based on review of clinical and radiographic data by a vascular neurologist (Dr Cucchiara); stroke mechanism was assigned using the Trial of ORG 10172 in acute stroke treatment classification scheme.[4] For classification purposes, hypercoagulability

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BRIEF REPORT

Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
ICH	intracranial hemorrhage

related to COVID-19 was not considered a definitive stroke mechanism. The study protocol was approved by our local institutional review board with a waiver of informed consent.

RESULTS

We identified 844 hospitalized patients with COVID-19. Mean patient age was 59±18 years with 52% female, 68% Black, 18% White, and 14% other race. Of these, 209 (25%) had an order for brain imaging, 20 (2.4%) had confirmed ischemic stroke, and 8 (0.9%) had ICH. Detailed clinical characteristics are described in Table 1.

Table 2 shows details specific to the ischemic stroke patients. Of the 8 patients with cardioembolism, 4 had atrial fibrillation, 3 dilated cardiomyopathy, and one bacterial endocarditis. Of the 4 patients with other determined mechanism, one had antiphospholipid antibody syndrome predating COVID-19 infection, one hypercoagulability of malignancy, one multifocal severe vasculopathy of uncertain cause, and one multifocal watershed infarctions following cardiac arrest with resuscitation. Newly positive antiphospholipid antibodies were present in >75% of tested patients. These were exclusively anticardiolipin antibodies, with no patient having newly positive β-2-glycoprotein 1 antibodies or lupus anticoagulant. Brain imaging (computed tomography in 11 and magnetic resonance imaging in 9) revealed infarction in a single vascular territory in 13 patients, 2 territories in 2, and triple territory involvement in 5.

Details specific to the ICH patients are shown in Table 3. Of the 8 patients with ICH, 4 were on extracorporeal membrane oxygenation; all 4 of these were also on intravenous anticoagulation. One of these patients had a definite coagulopathic ICH based on a fluid level on computed tomography, one a large lobar ICH with associated small subdural and subarachnoid hemorrhage, one a multifocal ICH involving separate brain regions, and one a cortical subarachnoid hemorrhage; these latter three were of uncertain cause, although anticoagulation likely contributed. Of the 4 remaining patients with ICH, one had a syncopal event with possible traumatic cortical subarachnoid hemorrhage, one a cortical subarachnoid hemorrhage in the setting of disseminated intravascular coagulation, and 2 lobar hemorrhages of uncertain cause, with anticoagulation likely contributing.

Table 1. Characteristics of COVID-19 Patients With Acute Cerebrovascular Events

Characteristic	Ischemic Stroke (n=20)	Intracranial Hemorrhage (n=8)
Age (mean, SD)	64±12	57±7
<50 y old, n (%)	1 (5%)	1 (13%)
Female sex, n (%)	8 (40%)	4 (50%)
Race		
Black	16 (80%)	2 (25%)
White	2 (10%)	4 (50%)
Other	2 (10%)	2 (25%)
Mechanical ventilation, n (%)	11 (55%)	6 (75%)
ECMO, n (%)	0 (0%)	4 (50%)
Risk factor, n (%)		
Hypertension	19 (95%)	6 (75%)
Diabetes mellitus	12 (60%)	3 (38%)
Hyperlipidemia	16 (80%)	5 (63%)
Prior stroke	7 (35%)	1 (13%)
Coronary artery disease	3 (15%)	3 (38%)
Obesity	10 (50%)	3 (38%)
Current smoker	2 (10%)	0 (0%)
Time from initial COVID-19 symptoms to stroke diagnosis, d (median, IQR)	21 (7–31)	25 (17–29)
Outcomes, n (%)		
Other thrombotic events,* n (%)	2 (10%)	3 (38%)
In-hospital death	5 (25%)	6 (76%)

COVID indicates coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICH, intracranial hemorrhage; and IQR, interquartile range.

*Venous thromboembolism occurred in 2 patients with ischemic stroke and 3 with ICH; one of the latter also had myocardial infarction.

DISCUSSION

We found ischemic stroke in 2.4% of our patients with COVID-19, comparable to the rate identified in Wuhan, China, early in the course of the pandemic.[1] A similar rate was found in a subsequent report from Italy, which identified ischemic stroke in 9/388 (2.5%) hospitalized patients with COVID-19,[5] and in a report from 3 Dutch hospitals, which found ischemic stroke in 5/184 (2.5%) patients requiring intensive care.[2] However, these rates are considerably higher than found in a recent large observational study from New York of 3556 patients with COVID-19 which identified stroke in just 0.9% of the cohort.[3] This variability across studies likely reflects differences in disease severity of hospitalized patients, prevalence of vascular risk factors in the population, ability to accurately diagnose all strokes in a situation of medical services being overwhelmed, and methodological differences. For instance, the ischemic stroke cohort from the New York report was 70% White, whereas our cohort was 80% Black; our cohort also had nearly twice the rate of hypertension and diabetes. In-hospital death occurred in 43% of the patients in New York compared with 25% in Philadelphia, suggesting the New York study may have failed to capture milder strokes, possibly related to the extreme surge of COVID-19 cases in New York that overwhelmed hospitals there during the peak of the epidemic.[3]

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Table 2. Mechanistic Category, Laboratory Results, and Treatment in Ischemic Stroke Patients

Ischemic Stroke Patients (n=20)	
Large vessel occlusion, n (%)	3/11 (27%)
Stroke mechanism, n (%)	
Cardioembolism	8 (40%)
Large artery atherosclerosis	0 (0%)
Small vessel disease	1 (5%)
Other determined mechanism	4 (20%)
Cryptogenic	7 (35%)
Laboratory values	
D-dimer, µg/mL FEU,* initial (median, IQR)	1.4 (0.8–4.0)
D-dimer, µg/mL FEU,* peak (median, IQR)	4.0 (1.9–15.3)
Antiphospholipid antibodies present,† n (%)	7/9 (78%)
CRP, mg/dL,‡ initial (median, IQR)	10.6 (7.7–20.2)
CRP, mg/dL, peak (median IQR)	15.7 (9.0–22.4)
ESR, mm/h,§ initial (mean)	61±38
ESR, mm/h, peak (mean)	74±37
Ferritin, ng/mL,‖ initial (median IQR)	690 (291–1430)
Ferritin, ng/mL, peak (median IQR)	888 (467–3467)
Treatment, n (%):	
Antiplatelet therapy	16 (80%)
Anticoagulation	13 (65%)
Intravenous tPA	0 (0%)
Mechanical thrombectomy	2 (10%)

COVID-19 indicates coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEU, fibrinogen equivalent unit; IQR, interquartile range; and tPA, tissue-type plasminogen activator.

*Normal range ≤0.50 µg/mL FEU.

†Antiphospholipid antibodies considered present if either anticardiolipin IgG/IgM, β-2-glycoprotein IgG/IgM, or lupus anticoagulant positive. One patient had known antiphospholipid antibody syndrome before COVID-19 diagnosis.

‡CRP: normal range ≤0.80 mg/dL.

§ESR: normal range 0–20 mm/h.

‖Normal range 30–400 ng/mL.

Table 3. Location, Presumed Mechanism, and Coagulation Studies in ICH Patients

Intracranial Hemorrhage Patients	
Primary location of hemorrhage, n (%)	
Lobar intraparenchymal	5/8 (63%)
Subarachnoid	3/8 (38%)
Hemorrhage mechanism, n (%)	
Coagulopathy	2/8 (25%)
Syncope with head trauma	1/8 (13%)
Undetermined	5/8 (75%)
Anticoagulation at time of hemorrhage	7/8 (88%)
Anticoagulation + antiplatelet at time of hemorrhage	4/8 (50%)
Laboratory values	
Partial thromboplastin time peak, s (median, IQR)	71 (52–128)
Prothrombin time peak, s (median, IQR)	1.5 (1.3–1.6)
Platelet count nadir, thou/µL (median, IQR)	122 (102–208)
CRP, mg/dL, initial (median, IQR)	14.0 (7.8–80.7)
CRP, mg/dL, peak (median IQR)	25.4 (16.1–82.7)
ESR, mm/h, initial (mean)	96±28
ESR, mm/h, peak (mean)	112±30
Ferritin, ng/mL, initial (median IQR)	1413 (1146–2138)
Ferritin, ng/mL, peak (median IQR)	1971 (1413–3532)

CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; ICH, intracranial hemorrhage; and IQR, interquartile range.

The relatively long duration from initial COVID-19 symptoms to diagnosis of ischemic stroke (≈3 weeks) identified in our study is notable. This finding is consistent with accumulating evidence of a hypercoagulable state which evolves over the initial weeks of the disease in many patients. Also notable is that the vast majority of ischemic stroke patients in our cohort were older with vascular risk factors, and traditional stroke mechanisms were common. We confirmed a prior observation of antiphospholipid antibodies in some ischemic stroke patients with COVID-19,[6] although these were exclusively anticardiolipin antibodies in our cases. Compared with β-2-glycoprotein 1 antibodies, anticardiolipin antibodies have been reported in a number of other infectious diseases with uncertain pathogenicity in terms of increasing thrombosis risk.[7] The relatively high rate of ICH we observed is concerning given the increasing use of anticoagulant therapy in patients with COVID-19.

While the precise mechanisms linking cerebrovascular events to COVID-19 remain uncertain, it has recently been reported that severe acute respiratory syndrome coronavirus 2 directly infects endothelial cells, causing diffuse endothelial inflammation.[8] This could be a mechanism leading to either ischemic stroke or ICH. Additional mechanisms proposed to link COVID-19 and ischemic stroke include infection-induced hypercoagulability, viral cardiomyopathy, and a diffuse hyperinflammatory state. A significant limitation of the present as well as previous studies is the small overall number of stroke patients captured. Further characterization of large cohorts of stroke patients with COVID-19 should allow more precise determination of the relative contribution of these various mechanisms to stroke risk.

SUMMARY

Both ischemic stroke and ICH occur in patients with COVID-19 but are relatively infrequent. Most patients with ischemic stroke had conventional vascular risk factors, over one-third had a history of prior stroke, and traditional stroke mechanisms were common. Further observations directed at elucidating the mechanisms of hypercoagulability, determining the relative risks and benefits of anticoagulation, and exploring the potential for an infectious vasculopathy in COVID-19 are urgently needed.

BRIEF REPORT

ARTICLE INFORMATION

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None.

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