PLOS ONE

RESEARCH ARTICLE

Ischemic stroke in COVID-19: An urgent need for early identification and management

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Citation: Jillella DV, Janocko NJ, Nahab F, Benameur K, Greene JG, Wright WL, et al. (2020) Ischemic stroke in COVID-19: An urgent need for early identification and management. PLoS ONE 15(9): e0239443. https://doi.org/10.1371/journal.pone.0239443

Editor: Muhammad Adrish, BronxCare Health System, Affiliated with Icahn School of Medicine at Mount Sinai, NY, USA, UNITED STATES

Received: June 19, 2020

Accepted: September 4, 2020

Published: September 18, 2020

Data Availability Statement: Emory University School of Medicine owns the dataset and de-identified / limited data sets could be requested via the legal/ethics committee of the University. I am giving the contact details of our legal expert - Zainab Wurie Harvey, JD, Assistant Director, Faculty Affairs Administration, Emory School of Medicine, Dean's Office | Room 416, Ph: 404-727-3407, Email: zwurie@emory.edu. Please direct any specific queries regarding this to her.

Abstract

Objective

In the setting of the Coronavirus Disease 2019 (COVID-19) global pandemic caused by SARS-CoV-2, a potential association of this disease with stroke has been suggested. We aimed to describe the characteristics of patients who were admitted with COVID-19 and had an acute ischemic stroke (AIS).

Methods

This is a case series of PCR-confirmed COVID-19 patients with ischemic stroke admitted to an academic health system in metropolitan Atlanta, Georgia (USA) between March 24th, 2020 and July 17th, 2020. Demographic, clinical, and radiographic characteristics were described.

Results

Of 396 ischemic stroke patients admitted during this study period, 13 (2.5%) were also diagnosed with COVID-19. The mean age of patients was 61.6 ± 10.8 years, 10 (76.9%) male, 8 (61.5%) were Black Americans, mean time from last normal was 4.97 ± 5.1 days, and only one received acute reperfusion therapy. All 13 patients had at least one stroke-associated co-morbidity. The predominant pattern of ischemic stroke was embolic with 4 explained by atrial fibrillation. COVID-19 patients had a significantly higher rate of cryptogenic stroke than non-COVID-19 patients during the study period (69% vs 17%, p = 0.0001).

Conclusions

In our case series, ischemic stroke affected COVID-19 patients with traditional stroke risk factors at an age typically seen in non-COVID populations, and mainly affecting males and Black Americans. We observed a predominantly embolic pattern of stroke with a higher than expected rate of cryptogenic strokes, a prolonged median time to presentation and symptom recognition limiting the use of acute reperfusion treatments. These results highlight the need

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

for increased community awareness, early identification, and management of AIS in COVID-19 patients.

Introduction

The United States has seen an exponential rise in COVID-19 infection cases recently, resulting in over 1.7 million cases and > 100,000 deaths. In the setting of the COVID-19 pandemic, there have been reports of its association with various neurological disorders including stroke [1, 2]. Stroke has been reported in 5.7% of patients with severe COVID-19 infections and 0.8% of patients with non-severe infection in an Asian study [1]. Previous studies have reported the role of infectious agents in stroke pathogenesis [3]. Based on the underlying hypercoagulability and increased incidence of thrombotic events in severe COVID-19 patients, increased risk of stroke, particularly of embolic etiology, may be predicted. A recent case series of 5 young COVID-19 patients with embolic strokes with few/no traditional risk factors supports this idea [4]. However, there are very limited data on the characteristics and frequency of stroke in COVID-19. In this case series from a large academic hospital system in the Southern United States, we report clinical and radiographic characteristics of eight acute ischemic stroke (AIS) patients with COVID-19 infection.

Methods

Study design

This is a retrospective study of adult patients aged 18 years or above admitted to Emory Healthcare hospitals in Atlanta, Georgia, USA with a diagnosis of COVID-19 and identified to have an acute ischemic stroke at initial presentation or during hospital admission. The Institutional Review Board of Emory University approved this retrospective study under the waiver of informed consent.

Inclusion and exclusion criteria

Adult patients aged 18 years or above at the time of PCR-confirmed COVID-19 admission from March 24th, 2020 to July 17th, 2020 were included. Diagnosis of acute ischemic stroke based on clinical and radiological confirmation at presentation or during admission was required for inclusion. Patients were excluded if they did not have either clinical or radiological confirmation on review of the patient records.

Study variables

We captured demographic variables including age, sex, and race. Clinical variables collected include vascular risk factors such as diabetes mellitus (DM), hyperlipidemia, hypertension, congestive heart failure (CHF) and atrial fibrillation; deep vein thrombosis (DVT) or pulmonary embolism (PE); ischemic stroke-specific features like etiology as per TOAST guidelines [5]; hemispheric laterality and location of stroke; neurological symptomatology; therapeutic interventions used including intravenous tissue plasminogen activator (iv-tPA) or mechanical thrombectomy (MT); stroke outcome measures including modified Rankin Scale (mRS at discharge), admission to the intensive care unit (ICU) and the duration of ICU stay; non-neurological presenting symptoms and diagnoses; brain imaging and laboratory characteristics in COVID-19 infection and therapies used.

Results

A total of 396 ischemic stroke patients were admitted during this time-period including 13 (2.5%) who were diagnosed with COVID-19. Mean age was 61.6 ± 10.8, 10 (76.9%) were male and 8 (61.5%) were Black Americans. History of DM was present in 9 (69.2%) patients and hypertension was present in 11 (84.6%) patients and all patients had at least one medical comorbidity (DM, hypertension, atrial fibrillation, or hyperlipidemia). The predominant pattern of ischemic stroke observed was embolic (13 of 13) and a clear cardio-embolic cause was identified for 4 cases (atrial fibrillation or flutter). Nine patients had D-dimer levels of > 3,000 ng/mL with 4 of these having a level > 60,000 ng/mL at admission, and 4 having deep venous thrombosis (DVT) or pulmonary embolism (PE).

COVID-19 patients had a significantly higher rate of cryptogenic stroke (stroke of undetermined etiology per the TOAST criteria) [5] than non-COVID-19 patients during the study period (69% vs 17%, p = 0.0001). Baseline characteristics and clinical and investigational characteristics of these 13 AIS patients with COVID-19 infection are described in Table 1.

Discussion

COVID-19 infection caused by the SARS-CoV2 virus is associated with multi-system dysfunction including neurological involvement, systemic inflammation, and hypercoagulability. Neurological involvement with stroke as a manifestation was reported in 6 (2.8%) patients with COVID-19 based on an Asian study of 214 patients. Ischemic stroke constituted a majority of these patients with 5 of the 6 having a diagnosis of ischemic stroke [1].

Infectious pathogens have been described to contribute to stroke causation via various mechanisms including accelerated atherosclerosis, vasculitis, vasculopathy, and coagulopathy [3]. Coagulopathy/hypercoagulable state specifically has been postulated to be one of the important mechanisms of COVID-19's clinical effects [6, 7]. Its possible effect on stroke causation is still unclear although some recent case reports in young patients with few/no comorbid risk factors potentially point towards an association (4). In our study, COVID-19 patients with AIS constituted 2.5% of the ischemic stroke admissions in our healthcare system. All the patients had an embolic pattern stroke noted on imaging and without a clear source of the embolism identified in 9 of the 13 (69) meeting the criteria for cryptogenic strokes that contribute to 10–30% of all stroke cases and lower in centers with advanced testing capabilities [8]. Cryptogenic strokes overall (non-COVID) constituted 17% at all our stroke centers, considerably lower than those observed in our case series. Four patients (none of whom had a diagnosis of atrial fibrillation or flutter) also had DVT or PE. All patients with DVT / PE had a D-dimer elevation of > 30,000 and 2 of them had >60,000. Based on this information, COVID-19 associated hypercoagulable state stemming from the pro-inflammatory processes [6, 7] could be hypothesized as a possible contributory mechanism for the higher prevalence of embolic cryptogenic stroke presentations in our series. Of note, a study from the New York Healthcare System also reported a high prevalence of cryptogenic strokes and suggested a possible association with hypercoagulability [9], although further prospective studies are needed to confirm these findings considering the limitations of retrospective studies.

One patient had a prior diagnosis of atrial fibrillation while three had new diagnoses of atrial fibrillation/flutter during this admission that could be causal in the stroke etiologies in these three patients. Active infectious processes triggering atrial fibrillation events have been described [10] and increasing reports suggest a cardiac involvement with COVID-19 infections [11, 12]. Of note, none of the cardiac arrhythmias were observed in patients who received hydroxychloroquine.

Table 1. Clinical and radiographic characteristics of AIS patients with COVID-19.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Demographics:													
Age	50s	60s	70s	50s	60s	60s	60s	60s	60s	20s	60s	70s	60s
Sex	Female	Male	Male	Female	Male	Male	Male	Female	Male	Male	Male	Male	Male
Race	Black	Unknown	White	Black	Black	White	Black	Black	Black	Black	Hispanic	White	Black
Stroke Risk Factors/ Associated Medical Conditions:													
Diabetes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Hypertension	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Hyperlipidemia	No	No	Yes	No	No	Yes	Yes	No	NA	Yes	No	Yes	Yes
Atrial Fibrillation or Flutter	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	No
DVT/PE	Yes	No	No	No	No	Yes	No	Yes	NA	No	No	No	Yes
Stroke Characteristics:													
Etiology	Cryptogenic	Cardio-embolic	Cryptogenic	Cryptogenic	Cardio-embolic	Cryptogenic	Cardio-embolic	Cryptogenic	Cardio-embolic	Cryptogenic	Cryptogenic	Cryptogenic	Cryptogenic
Location													
Anterior versus Posterior	Anterior	Anterior and Posterior	Anterior	Anterior	Anterior and Posterior	Anterior	Anterior	Anterior	Anterior and Posterior	Anterior	Anterior	Anterior and Posterior	Anterior
Side	Bilateral	Bilateral	Right	Left	Bilateral	Left	Left	Right	Bilateral	Bilateral	Left	Bilateral	Bilateral
Acute Therapy	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT	Yes tPA / no EVT	No tPA or EVT	No tPA or EVT	No tPA or EVT
Time from COVID-19 manifestations to stroke symptom onset or identification in days	11	6	25	0.75	7	14	2	2	15	NA	9	26	3
Last known normal (in days)	11	6	0.5	0.75	2	14	2	2	15	0.1	0.3	8	3
Primary Neurological Symptoms	Encephalopathy	Coma	Bilateral Hearing Loss	Aphasia, Right-sided Weakness	Bilateral Lower Extremity Weakness	Obtundation	Aphasia, Encephalopathy	Left-sided weakness and Right Gaze Deviation	Encephalopathy/ Obtundation	Aphasia, Encephalopathy	Right sided weakness and slurred speech	Encephalopathy, Obtundation	Encephalopathy
Cerebral Imaging Fig 1 (A to H)	A) MRI Brain: Small infarctions in the bilateral corona radiata, centrum semiovale, splenium of the corpus callosum, and left temporal lobe involving the bilateral MCA territories.	B) CT Head: Infarct in the left parietal lobe and two infarcts in the frontal and occipital lobes Involving the MCA and PCA territories.	C) MRI Brain: Right temporal lobe infarction of the insular and sub-insular cortex involving the MCA territory.	D) CT Head: Left frontal lobe infarction involving the ACA territory	E) MRI Brain: Small Infarctions involving the bilateral MCA territories.	F) CT Head: Left paramedian occipital lobe and parietal lobe infarction involving the PCA and MCA territories	G) CT Head: Left temporal and parietal lobe infarction involving the MCA territory	H) CT Head: Right frontal, temporal and parietal lobe infarctions involving the MCA territory	I) MRI Brain: Right thalamus and left superior cerebellum, as well as left capsular region involving the anterior and posterior circulations.	J) MRI Brain: Right putamen, corona radiata and left parietal lobe and posterior insula involving the right and left MCA territories.	K) CT Head: Left Frontal Lobe Infarction involving the MCA territory	L) CT head: Bilateral basal ganglia, parieto-occipital lobes, and bilateral cerebellar hemispheres involving the anterior and posterior circulations.	M) MRI Brain: Frontoparietal centrum semiovale/ corona radiata infarctions involving the bilateral MCA territories.
COVID-19 Characteristics:													

(*Continued*)

Table 1. (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Clinical Features:	Hypoxic Respiratory Failure	Respiratory and Cardiogenic Shock	Fatigue	Shortness of Breath, Encephalopath	Cough, Fever	Hypoxia, Septic Shock, Encephalopathy	Cough, Encephalopathy	Hypoxic Respiratory Failure	Hypoxic Respiratory Failure, Septic Shock	Mild Hypoxia, Fever	Abdominal pain, Nausea, Hypoxic respiratory failure	Cough, Hypoxic respiratory failure	Fevers, Encephalopathy
COVID-19 Therapy:	Hydroxychloroquine	None	None	Hydroxychloroquine	Remdesivir	None	None	None	None	None	Dexamethasone	Dexamethasone	None
General Therapeutics: ACE /ARB use	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Laboratory Parameters on initial presentation:													
WBC (10E3/mcL)	9.5	15.1	8.9	8.4	9.3	17.9	3.5	19.1	12.1	5.8	6.2	5	9.7
Platelet count (10E3/mcL)	318	302	255	291	409	337	156	466	217	154	123	162	203
CRP (mg/L)	182	27.5	3.3	236.4	126.1	104.2	59	72.9	77.6	293.7	169.3	139.3	231.7
Ferritin (ng/ml)	549	NA	433	NA	NA	NA	571	15	1191	275	NA	215	2313
Fibrinogen (mg/dl)	861	571	NA	NA	580	NA	NA	765	882	337	NA	604	587
D-Dimer (ng/ml)*	50,620	4724	781	> 60,000	2119	>60,000	833	>60,000	32530	5863	>60,000	20,322	34,671
INR	1.12	1.2	1.12	1.34	1.62	1.3	1.24	1.33	0.97	1.15	1.3	1.26	1.21
LDL (mg/dl)	46	UTC	NA	121	22	78	33	55	NA	49	59	NA	120
Triglycerides (mg/dl)	87	301	NA	178	59	94	46	232	248	332	113	114	122
HbA1c	11.3	6.1	NA	8.6	6.4	5.5	12.1	6.6	15.3	5.9	8.1	6.6	6.1
Outcomes:													
ICU Admission	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
ICU LOS (days)	21	12	-	5	1	9	-	11	25	3	-	21	-
mRS on Admission	0	0	1	0	3	3	1	0	1	0	0	4	0
mRS at Discharge*	3	6	1	3	4	5	2	6	6	4	4	6	3

DVT/PE–Deep venous thrombosis/Pulmonary Embolus; ivtPA–intravenous tissue plasminogen activator; MT–Mechanical thrombectomy; MRI–Magnetic Resonance Imaging; CT–Computed Tomography; ACA–Anterior Cerebral Artery; MCA–Middle Cerebral Artery; PCA–Posterior Cerebral Artery; ACE/ARB–Angiotensin-Converting Enzyme/Angiotensin Receptor Blocker; WBC–White blood count; CRP: C-reactive protein, INR- International Normalized Ratio, LDL- Low-density Lipoprotein; UTC = unable to be calculated; MRS–Modified Rankin Scale; ICU–Intensive Care Unit; NA = Not available, LOS–length of stay

*Highest D-dimer during admission; **At discharge or the most recent if the patient was still admitted.

https://doi.org/10.1371/journal.pone.0239443.t001

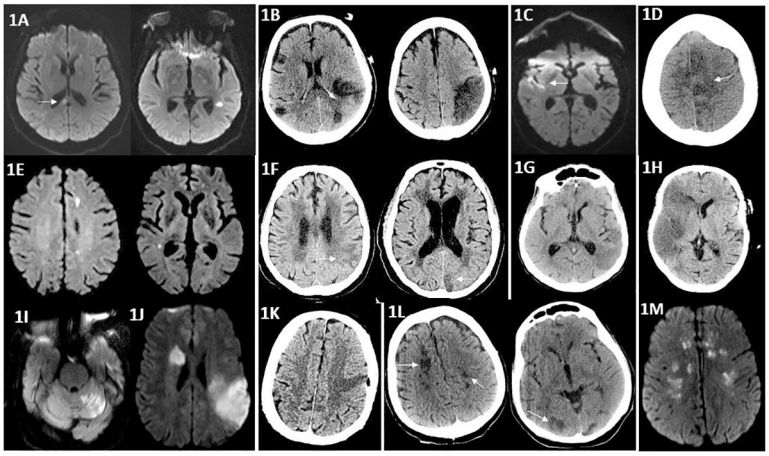

Fig 1. (A–M) Imaging characteristics of ischemic stroke in COVID-19 patients. A: MRI of the brain showing areas of infarction in the right corpus callosum and left temporal lobe on the diffusion-weighted sequence. B: CT brain showing hypodensities in the bilateral middle cerebral artery territories. C: MRI brain showing a right-sided temporal lobe infarction on the diffusion-weighted sequence. D: CT head showing hypodensity in the left anterior cerebral artery territory. E: MRI brain showing areas of infarction in the left frontal and right temporal lobes on the diffusion-weighted sequence. F: CT head showing hypodensities correlating with infarctions in the left parietal and occipital lobes. G: CT head showing a hypodensity in the left temporal lobe. H: CT head showing a large infarction in the right middle cerebral artery territory. I: MRI brain showing area of infarction in the left superior cerebellum on the diffusion-weighted sequence. J: MRI brain showing areas of infarction in the right corona radiate and left parietal lobe on the diffusion-weighted sequence. K: CT head showing a hypodensity in the left frontal lobe in the middle cerebral artery territory. L: CT head showing bilateral infarctions involving the anterior and posterior circulations. M: MRI head showing bilateral frontoparietal centrum semiovale/corona radiata infarctions on the diffusion-weighted sequence.

https://doi.org/10.1371/journal.pone.0239443.g001

All except two patients in our study had a diagnosis of either DM or hypertension (most having both), and both patients who did not have a prior diagnosis of DM were found to be pre-diabetic on testing. Although these could be argued as potential confounders from a stroke etiologic standpoint, the presence of these comorbid conditions has been associated with a higher risk of having a COVID-19 infection, and with greater disease severity [13]. In this setting, it needs to be ascertained if the presence of hypertension, DM and related upregulation of the ACE2 receptor could contribute to an increased risk of stroke in these patients. In our study, we observed that the average age of COVID-19 stroke presentation was in line with the nationwide average for ischemic stroke.

Acute ischemic stroke therapy has greatly evolved over the last two decades with excellent clinical outcomes reported in recent years with reperfusion strategies of iv-tPA and MT. Unfortunately, none of the AIS patients in our series received reperfusion therapy and with primary reasons being either delayed presentation or recognition of atypical stroke symptoms. The diverse constellation of symptoms ranging from encephalopathy, bilateral deficits, hearing loss among others compared to the typical cortical or unilateral motor findings of stroke could have contributed to this delayed stroke recognition. COVID-19 patients with cardio-pulmonary dysfunction are also generally intubated with paralytics and sedatives on board, along with strict isolation measures that could potentially cause delays in stroke recognition. There need to be protocols in place ensuring sedation holidays that can help counter this issue along with more frequent clinical monitoring. Delayed presentations could be a result of patients waiting longer due to self-isolation or quarantine precautions that have led to a general decline in acute stroke evaluations across the country [14]. This highlights the need to increase community awareness regarding stroke symptoms and the need to ensure rapid evaluation in the ED to facilitate early stroke treatments and limit disability.

Limitations

This is a retrospective case series that is limited by the small number of cases and hence, the results are mainly observational and causal association of COVID-19 infection with AIS cannot be ascertained.

Conclusion

In our case series, ischemic stroke affected COVID-19 patients at an age of stroke presentation typically seen in non-COVID populations and mainly affected males and Black Americans. We observed a predominantly embolic pattern of stroke with a higher than expected rate of cryptogenic strokes and with a prolonged median time to presentation/symptom recognition limiting the utilization of acute reperfusion therapy. These results highlight the need for community awareness, early identification, and management of AIS in COVID-19 patients. Further studies to determine the effects of COVID-19 associated coagulopathy on ischemic stroke risk as well as the interactions between COVID-19 and other known stroke risk factors are warranted.

Author Contributions

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Writing – review & editing: Dinesh V. Jillella, Nicholas J. Janocko, Fadi Nahab, Karima Benameur, James G. Greene, Wendy L. Wright, Mahmoud Obideen, Srikant Rangaraju.

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