Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Case Report

Acute Cerebrovascular Disorders and Vasculopathies Associated with Significant Mortality in SARS-CoV-2 Patients Admitted to The Intensive Care Unit in The New York Epicenter

Fawaz Al-Mufti, MD,*′†′‡ Christian Becker, MD,§ Haris Kamal, MD,† Hussein Alshammari, MD,* Vincent Dodson, MD,¶ Rolla Nuoman, MD,* Katarina Dakay, MD,† Jared Cooper, MD,† Edwin Gulko, MD,*′†′‡′§′¶′‖ Gurmeen Kaur, MD,*′†′‡′§′¶′‖ Ramandeep Sahni, MD,* Corey Scurlock, MD,§ Stephan A. Mayer, MD,*′† and Chirag D. Gandhi, MD*′†′‡

The current Coronavirus pandemic due to the novel SARS-Cov-2 virus has proven to have systemic and multi-organ involvement with high acuity neurological conditions including acute ischemic strokes. We present a case series of consecutive COVID-19 patients with cerebrovascular disease treated at our institution including 3 cases of cerebral artery dissection including subarachnoid hemorrhage. Knowledge of the varied presentations including dissections will help treating clinicians at the bedside monitor and manage these complications preemptively.

Key Words: Cerebrovascular disorders—Vascular dissection—COVID19, Ischemic stroke, Venous sinus thrombosis

Introduction

The current Coronavirus pandemic due to the novel SARS-Cov-2 virus has proven to have systemic and multi-organ involvement alongside typical respiratory symptoms.[1] Among neurological manifestations, multiple reports reflect emerging evidence for neurotropism of the novel SARS-CoV-2 virus, including frequent complaints of anosmia, seizures and less common reports of acute inflammatory demyelinating polyneuropathy, acute necrotizing encephalitis etc.[2] A hypercoagulable state has also been reported in many patients, characterized by thrombocytopenia, elevated fibrinogen and d-dimer levels leading to unusual cases of multifocal pulmonary thrombosis as well as acute ischemic strokes.[3–6] SARS-CoV-2 virus has also been implicated in autoimmune and auto-inflammatory disease leading to a vasculopathy and/or vasculitides[1] among mounting reports of spontaneous coronary artery and cerebral artery dissection in COVID-19 patients without any history of antecedent trauma or connective tissue disorder.[7–11] Here, we describe a subset of consecutive COVID-19 patients with acute cerebrovascular disease (CVD) including 3 unique cases of spontaneous cerebral artery dissection. As our knowledge of the different afflictions of this virus grows, it is important for clinicians to be aware of the far reaching

From the *Department of Neurology, Westchester Medical Center at New York Medical College, Valhalla, NY USA; †Department of Neurosurgery, Westchester Medical Center at New York Medical College, Valhalla, NY USA; ‡Department of Radiology, Westchester Medical Center at New York Medical College, Valhalla, NY USA; §Department of Internal Medicine −Division of Pulmonary and Critical Care, Westchester Medical Center at New York Medical College, Valhalla, NY USA; ¶Department of Surgery, Rutgers University New Jersey Medical School, Newark, NJ USA; and ‖Department of Neurosurgery, Westchester Medical Center, Valhalla, NY 10595 USA.

Received August 14, 2020; revision received September 21, 2020; accepted October 24, 2020.

Address correspondence to Haris Kamal, MD, Department of Neurosurgery, Division of Neuroendovascular surgery, Westchester Medical Center at New York Medical College,100 Woods Road, Valhalla, NY 10595, USA. E-mail: haris.kamal@wmchealth.org.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105429

clinical consequences they may be faced with while providing optimal care to our patients. To our knowledge, this is the largest number of reported cases of cerebral artery dissection among COVID-19 patients from a single center.

Methods

We report a prospectively followed cohort of all hospitalized cases with confirmed COVID-19 infection (SARS-CoV-2 RT-PCR positive) and CVD (ischemic and hemorrhagic stroke) between March 26th and April 12th, 2020 treated at our comprehensive stroke center located in the New York City Metropolitan area. Diagnosis of CVD was confirmed on neuroimaging with CT, CTA and/or MRI of the brain. Baseline demographics, clinical, laboratory, diagnostic and imaging findings were extracted by a board-certified or board-eligible neurologist. Stroke etiology, according to the TOAST criteria for ischemic stroke, was determined based on available workup.

Results/case series

We cared for approximately 600 COVID-19 patients between March 26th and April 12th, 2020, of whom 127 were admitted to the ICU. We admitted a total of 48 patients with acute ischemic stroke during the study period, 8 of whom had concomitant COVID-19 and were managed in the COVID Intensive care unit.

Ischemic stroke patients

Of the eight COVID-19 positive patients, seven (87%) patients presented with acute ischemic stroke (AIS) (Table 1,2). Five patients were adjudicated to have embolic stroke of undetermined source (ESUS) as defined by the Cryptogenic Stroke/ESUS International Working Group consensus 2014 statement outlining the diagnostic guidelines to ischemic strokes without clear etiology. With regards to infarct location, all of the ESUS strokes had bilateral middle cerebral artery involvement and either anterior or posterior cerebral artery territory infarctions. One of the ESUS patients also developed cerebral venous thrombosis (CVT) involving the right transverse sinus and jugular bulb. Of note, all of these patients experienced their neurological symptoms within 4-10 days of the onset of their respiratory symptoms (Table 2).

Cerebral artery dissections

Three of the eight COVID-19 positive patients were found to have extracranial and/or intracranial dissections seen on CTA/MRA and confirmed with diagnostic cerebral angiography. Two patients had extracranial dissections involving the cervical segment of the internal carotid artery, and one had concomitant dissection of the supraclinoid segment of the internal carotid artery with associated diffuse subarachnoid hemorrhage. One of these patients had presented with a non-aneurysmal convexity subarachnoid hemorrhage and was found to have concomitant dissections of the middle cerebral artery and extracranial V2 segment of the vertebral artery. This patient subsequently developed delayed ischemic injury due cerebral vasospasm (Table 1, 2). None of the patients with cerebral dissections had any known risk factors such as connective tissue disorders, vasculopathy, recent history of trauma or cervical manipulations to explain the dissections.

APACHE IVa score and disease severity

The average age, presenting APACHE IVa scores as well as severity of the COVID-19 in patients with cerebrovascular disorders was similar to those with no cerebrovascular disorders (Table 3). The average APACHE IVa Score for ICU deaths of the COVID-19 patients with no cerebrovascular involvement compared to COVID-19 patients with cerebrovascular involvement was similarly high in both groups (97.5 vs 89.5). One patient was discharged from the intensive care unit, and five patients (63%) required intubation with mechanical ventilation per the ARDSNet protocol. None of the COVID-19 patients with cerebrovascular involvement were extubated compared to a 19% (25/127) extubation rate in the COVID-19 ICU patients with no cerebrovascular involvement. Of the

Table 1. *Demographics, Comorbidities and Symptomatology of Covid-19 Patients with Acute Cerebrovascular Disorders*

Male: Female	3:5
Hypertension – no. (%)	5 (63%)
Type II Diabetes Mellitus – no. (%)	3 (38%)
Coronary Artery Disease/Cardiovascular Disease – no. (%)	1 (13%)
History of Malignancy – no. (%)	2 (25%)
Chronic Kidney Disease – no. (%)	1 (13%)
Fever – no. (%)	4 (50%)
Cough – no. (%)	7 (88%)
Acute Ischemic Stroke – no. (%)	7 (88%)
Subarachnoid Hemorrhage	2 (25%)
Sinus Thrombosis – no. (%)	1 (13%)
Stroke Etiology – Extracranial Dissection – no. (%)	3 (38%)
Stroke Etiology – Intracranial Dissection – no. (%)	2 (25%)
Stroke Etiology – ESUS – no. (%)	5 (63%)
Median NIHSS	8
Median GCS	13
Required Intubation – no. (%)	5 (63%)
Severe ARDS – no. (%)	5 (63%)
Headache – no. (%)	1 (13%)
Altered Mental Status – no. (%)	6 (75%)
Ataxia – no. (%)	2 (25%)

Table 2. *Clinical and laboratory characteristics of the Patients COVID-19 and acute cerebrovascular syndromes.*

Characteristics	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7	Patient-8
Age	31	57	81	72	67	47	60	72
Acute Cerebrovascular Syndrome Characteristics	RCVS with Convexity SAH in setting of intracranial and extracranial Dissection	Large vessel occlusion stroke secondary to extracranial dissection with status post mechanical thrombectomy	Extracranial and intracranial dissection with diffuse subarachnoid hemorrhage	Embolic stroke of undetermined source (ESUS) followed by acute onset cerebral venous thrombosis (CVT) in the right transverse sinus and jugular bulb.	Embolic stroke of undetermined source (ESUS)	Embolic stroke of undetermined source (ESUS)	Embolic stroke of undetermined source (ESUS)	Embolic stroke of undetermined source (ESUS)
Gender	Female	Female	Male	Female	Female	Male	Male	Female
WBC	7.2	13.8	7.4	0.2	11.4	10.1	6.4	8.6
Neutrophils	59	15.7	86.7	85	84	70.9	52.9	65.4
Lymphocytes	29.8	76.4	6.9	10	6	17.4	32	22.3
Platelets	242	270	205	9	406	323	262	124
C- Reactive Protein	1.5	38	17		34	<0.1		5.2
Creatinine	0.79	0.72	2.26	0.85	2.19	1.87	0.81	0.68
BUN	22	10	49	71	85	25	18	17
Creatine Kinase	66	62	173	189	1561	270		1919
LDH	316	527	334	779	896			303
AST	17	64	16	139	461	57	33	33
ALT	13	23	10	189	534	55	73	19
D-Dimer	1.27	7.79	>35	>35	>35	0.19		
Ferritin	151.4	4311.3	772.8		10941	77.6		773.9
Covid19 Severity	Mild	Severe	Severe	Severe	Mild	Mild	Severe	Severe
Procalcitonin	Negative	0.93	Negative	Negative	7.85	Negative	Negative	Negative
Fibrinogen	491	732	440	856	836	666	499	519

WBC (White Blood Cells) RCVS (Reversible cerebral vasoconstriction syndrome); SAH (Subarachnoid Hemorrhage); ESUS (Embolic stroke of undetermined source); ALT (alanine aminotransaminase); AST (aspartate transaminase); LDH (lactate dehydrogenase).

Table. 3. *Comparison between All COVID patients and Covid-19 Patients with Acute Cerebrovascular Disorders admitted to the ICU*

COVID positive ICU pts	All COVID-19 Patients	COVID Patients with Acute Cerebrovascular Disorders
COVID positive ICU pts (n)	127	8
Avg ICU LOS (days)	8.1	5.1
Avg MV Duration for vented pts (days)	10	4
Avg Age	62	60
Median Age	61	67
Average APACHE IVa Score for ICU deaths	97.5	89.5
Pts successfully extubated (n)	25	0
Pts died (n)	31	3
Pts discharged home/ transferred alive (n)	44	5

COVID-19 patients with cerebrovascular disease, 3(37.5%) died in the ICU while on mechanical ventilation, while the other 4(50%) could not be weaned off mechanical ventilation and were transferred to long term care facilities with tracheostomy on ventilators.

Outcomes and ICU mortality

Of the 8 patients with COVID-19 with cerebrovascular involvement, 3 patients progressed to a Glasgow Coma Scale of 3 with evidence of cerebral edema as well as severe ARDS and eventually died. One patient was discharged home independent while the other 4 were discharged to long term care facility on mechanical ventilation needing full time care. In addition, the average duration to progression to a modified Rankin Score (mRS) of 5/6 was 2 days with an average length of stay of 5.1 days for the COVID-19 patients with CVD compared to 8.1 days for the patients with no cerebrovascular symptoms. The rate of mortality or end-of-life in the ICU in the COVID-19 patients with CVD was 37.5% (3/8), compared to 24% (31/127) in the COVID-19 patients with no cerebrovascular involvement.

Discussion

As the incidence of COVID-19 exponentially multiplies around the world, there is mounting evidence for its association with cerebrovascular disease as well as a predisposition for a hypercoagulable state secondary to a DIC-like condition and alteration of the coagulation pathways.[4,12] Our COVID-19 patients with spontaneous dissections and SAH or AIS fared worse than others which further added to the morbidity and mortality of these patients already dealing with multi-organ failure. While the mechanism of action leading to a vasculopathy remains multifactorial, our case series adds important literature to the growing volume of case reports describing spontaneous coronary,[8,9] aortic[10] and carotid[11] dissections among patient afflicted with COVID-19. Viral illnesses have been linked to cranial and cervical dissections in prior studies with viral replication causing direct vascular injury or vascular damage as a result of immune response activation secondary to proinflammatory cytokines, free radicals, and proteases.[12,13] SARS-COVID-2 causes damage to endothelial cells, activating inflammatory and thrombotic pathways.[14] It can be postulated that a vasculitic process similar to that seen with varicella zoster virus,[15] in which viral replication in the cerebral arterial wall triggers local inflammation may be responsible for causing spontaneous dissections.[15–17] Additionally, virus binding to the CNS ACE II receptors may lead to disruption of its autoregulatory function causing blood pressure elevations leading to vessel wall damage predisposing to dissections.[18,19]

Implicated mechanisms for ischemic stroke in COVID-19 patients include inflammation, prothrombotic coagulopathy and endothelial injury. The strong inflammatory response alongside elevated D-dimer levels and often noted anti-phospholipid antibodies leads to high rates of coagulopathy leading to embolic strokes which fits with the stroke sub-type seen in our patient cohort.[3–5] Empiric low dose anticoagulation has been considered to be effective in preventing strokes in critically sick patients with COVID-19.[20]

As our understanding of the multiple pathways of action of COVID-19 continues to improve, knowledge and awareness of these added complications will help clinicians to pro-actively monitor and perhaps manage these conditions better.

There are several limitations to these observations. This is a single center report and while it may not be generalizable, our study represents the first series of reported dissections among COVID-19 patients. While it is possible that the association of severity of COVID and cerebral dissections may or may not be a direct one, further reporting of cases and larger cohort registries will help elucidate the natural history of these spontaneous infectious dissections and add to the literature.

Conclusion

In conclusion, based on the presumption that the infection with the COVID-19 virus results in a hyperinflammatory cascade, and consequently hypercoagulability, intensivists should have a high index of suspicion for cerebrovascular complications in the setting of this pandemic. Our institution's preliminary experience suggests a higher incidence and mortality of acute cerebrovascular disease in COVID-19 patients admitted to the ICUs. Further studies exploring the use of antiplatelets early in the course of COVID-19 related cerebrovascular disorders and specifically cerebrovascular dissections are needed as this contributes to a significant percentage of the overall ICU mortality.

Declaration of competing interest

None of the Authors have any relevant conflict of interest or disclosures.

References

1. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol 2020;16:413-414 https://doi.org/10.1038/s41584-020-0448-7.
2. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurol Neurosurg 2020 Jul;194:105921. https://doi.org/10.1016/j.clineuro.2020.105921. Epub 2020 May 15. PMID: 32422545; PMCID: PMC7227498.
3. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020;220:1.
4. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738.
5. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020;18:1747.
6. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382:e60. https://doi.org/10.1056/NEJMc2009787.
7. Dakay K, Kaur G, Gulko E, Santarelli J, Bowers C, Mayer SA, Gandhi CD, Al-Mufti F. Reversible cerebral vasoconstriction syndrome and dissection in the setting of COVID-19 infection. J Stroke Cerebrovasc Dis 2020 Sep;29(9):105011.
8. Courand PY HB, Bonnet M, Lantelme P. Spontaneous coronary artery dissection in a patient with COVID-19. JACC: Cardiovasc Interv 2020.
9. Remo Albiero, Giuseppe Seresini, Atherosclerotic spontaneous coronary artery dissection (A-SCAD) in a patient with COVID-19: case report and possible mechanisms, European Heart J Case Rep, https://doi.org/10.1093/ehjcr/ytaa133
10. Fukuhara S, Rosati CM, El-Dalati S. Acute Type A aortic dissection during COVID-19 Outbreak. Ann Thorac Surg 2020.
11. Patel P, Khandelwal P, Gupta G, Singla A. "COVID-19 and cervical artery dissection- a causative association? J Stroke Cerebrovasc Dis 2020 Oct;29(10):105047. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105047. Epub 2020 Jun 13. PMCID: PMC7293449.
12. Cheng W, Wang Y, Lian Y, Zhang J, Zheng Y, Hu Y, Chen Y, Wu S, Huang Z, Shi Y, Cheng W, eds. A case-control study of the determinants for cervicocerebral artery dissection, 266, J Neurol; 2019 Jan:119-123. https://doi.org/10.1007/s00415-018-9096-0.
13. Smedly LATonnesen MGSandhaus RA, et al. Neutrophil-mediated injury to endothelial cells: enhancement by endotoxin and essential role of neutrophil elastase. J Clin Invest 1986;771233-:1243.
14. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19 Lancet. 2020; 395: 1417-1418
15. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009;8:731-740.
16. Schievink WIWijdicks EFKuiper JD Seasonal pattern of spontaneous cervical artery dissection. J Neurosurg 1998;89101-:103.
17. Gherardi R, Belec L, Mhiri C, Gray F, Lescs MC, Sobel A, et al. "The spectrum of vasculitis in human immunodeficiency virus-infected patients. A clinicopathologic evaluation". Arthritis Rheum 1993;36(8):1164-1174.
18. Pober JS. Cytokine-mediated activation of vascular endothelium: physiology and pathology. Am J Physiol 1988;133426-:43.
19. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect 2020;35:100669.
20. F.A. Klok, M. Kruip, N.J.M. van der Meer, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19 Thromb Res (2020)