

COVID-19 Associated Large Vessel Thrombosis and Ischemic Stroke; A Case Series

Ans Alamami¹, Rabee tawel¹, Abdussalam Elgrewi¹, Anam Elarabi¹, and Ahmed Abdussalam ²

¹Hamad Medical Corporation

²Hamad Medical Corp

November 10, 2020

Abstract

The novel severe acute respiratory syndrome coronavirus (SARS-COV-2) affects different people in different ways. Most infected people will develop mild to moderate respiratory flu-like illness and recover without the need for hospitalization. However, one of the not uncommonly observed extrapulmonary associations with SARS-COV-2 is developing large-vessel acute ischemic stroke.

COVID-19 Associated Large Vessel Thrombosis And Ischemic Stroke: A Case Series

Ans Alamami¹, Rabee Tawel¹, Abdussalam Elgrewi², Ahmed L M Abdussalam¹, Anam M. Elarabi³

1 Medical intensive care Department, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar.

2 Internal medicine department, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

3 Pulmonology Department, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

Correspondence: Ans Alamami, Clinical Fellow, Division Critical Care, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar, P.O. Box: 3050.

Email : AAlamami@hamad.qa

Abstract:

The novel severe acute respiratory syndrome coronavirus (SARS-COV-2) affects different people in different ways. Most infected people will develop mild to moderate respiratory flu-like illness and recover without the need for hospitalization. However, one of the not uncommonly observed extrapulmonary associations with SARS-COV-2 is developing severe large-vessel acute ischemic stroke. Moreover, COVID-19 virus-linked cerebrovascular accidents (CVA) were more severe and resulted in a higher risk for severe disability and mortality following acute insults. Although the pathophysiology is not fully understood, the neuro-targeting nature of SARS-COV-2 due to the vascular injury and the hyperimmune response were plausible proposed mechanisms. Further research is warranted to have a deep insight into the possible mechanisms. Herein, we review the current literature and describe five patients we have encountered during the SARS-COV-2 viral pandemic.

Keywords:

Coronavirus, SARS-COV-2, COVID-19, Stroke, Hypercoagulopathy

Key Clinical Message :

-Ischemic stroke can be a presenting manifestation or a complication of SARS-COV-2.

-The pathophysiology by which SARS-COV-2 induces stroke is multifactorial and includes coagulability, immune response dysregulation, and vascular endothelial dysfunction.

-Due to the recognized hypercoagulable state, we believe thromboembolic prophylaxis has a key role in preventing such a complication.

Abbreviations:

ARDS: Adult Respiratory Syndrome.

NRBM: Non-Re breather Bag Mask

PCR: Polymerase Chain Reaction.

IL: Interleukin

TNF: Tumor Necrotizing Factor

Background:

The novel severe acute respiratory syndrome coronavirus (SARS-COV-2) is a viral respiratory illness of the coronavirus family. It was first discovered in Wuhan, China, in December 2019 and rapidly became a global pandemic of SARS-COV-2. It is transmitted primarily through respiratory droplets, but airborne transmission concerns have been raised by the World Health Organization (WHO). COVID-19 presents with widely variable clinical manifestations such as cough, fever, shortness of breath, and its complications, like pneumonia with adult respiratory distress syndrome (ARDS), circulatory shock, severe inflammatory reaction, in addition to coagulopathy and thromboembolism [1].

COVID-19-associated coagulopathy ranges from mild thrombocytopenia to severe coagulopathy, meeting the International Society on Thrombosis and Hemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC). One of the most commonly observed coagulation abnormalities of COVID-19 is the raised D-Dimer and the reduction in serum fibrinogen levels [19], which are considered a marker of disease severity and therefore have been used to monitor disease activity. The underlying pathophysiology of venous thromboembolism (VTE) is related to endothelial injury by the SARS-COV-2's direct effect on the vascular endothelium, particularly in those with well-established secondary sepsis, venous stasis [7,13] and coagulopathy, especially in critically-ill patients. [12]

Another key role in developing hypercoagulability in COVID-19 patients is the hyper-inflammatory response to the SARS-COV-2 (cytokine storm syndrome), resembling the CAR-T associated cytokine release syndrome, mainly a serial cytokine rush particularly IL1, IL6 [1,4,9,14], TNF-alpha and IL8. These inflammatory mediators directly affect the vascular endothelium concurrently with the viral insult. They together activate the coagulation cascade resulting in arterial and venous thrombosis manifested as VTE, pulmonary embolism, arterial events such as ischemic strokes [2,3], and peripheral limbs ischemia.

Herein, we report five cases of confirmed COVID-19 who developed an ischemic stroke of varying severity during their COVID-19 disease course.

Patient 1:

An 80-year-old man with a past medical history of diabetes mellitus type 2 (Type 2 D.M.), hypertension, and prostate cancer on hormonal therapy, presented to the E.D. complaining of fever, generalized fatigue, cough, and shortness of breath for three days. Upon initial evaluation, he was in respiratory distress with oxygen saturation of 92% on a non-rebreather bag-mask (NRBM). His laboratory investigations were significant for lymphopenia and elevated D-Dimer, C-reactive protein, and ferritin levels. A chest x-ray showed bilateral

perihilar infiltrates. His real-time polymerase chain reaction (PCR) from nasopharyngeal swab was positive for COVID-19; therefore, we started him was on azithromycin, hydroxychloroquine, ritonavir/lopinavir combination daily, steroids, and anticoagulation. He received tocilizumab for the significant underlying inflammatory process; then, he reported a new left-sided body weakness and tingling 24-hours after hospitalization. His physical exam revealed reduced power in the right upper and lower limbs with increased muscle tone. An urgent C.T. scan of the head ruled out acute intracerebral bleeding. MRI and MRA of the head of T2/FLAIR confirmed hyperintense acute infarct in the right parietal-frontal lobes[**Figure1**] , and smaller multifocal areas of patchy acute infarcts in the left frontoparietal lobe, right more than left insula, bilateral temporooccipital regions, left caudate head, and tiny acute lacunar infarct in the right cerebellar hemisphere in addition to the occluded right middle cerebral artery (MCA) from the origin in the neck

[**Figure 2**].

Patient 2:

A 60-year-old man diabetic and hypertensive with right nephrectomy for angiomyolipoma. We hospitalized him after testing positive for COVID-19 PCR from a nasopharyngeal swab. Initially, he was complaining of fever, cough, but he had no signs of respiratory distress. We started him on hydroxychloroquine, azithromycin, ritonavir/lopinavir, and methylprednisolone in addition to anticoagulation for mild COVID-19 pneumonia in a high-risk patient. On Day 12 of the disease course, the patient experienced an insidious onset of left-sided upper limb weakness with slurring in speech. Physical examination revealed left-side body weakness with left upper facial nerve palsy and dysarthria. His initial NIHSS was 22; however, shortly afterward, he started to become confused with a progressive deterioration in his conscious level mandating intubation and mechanical ventilation. An urgent CT-head with CT-perfusion confirmed a large area of matched perfusion defect involving the whole right MCA territory, with no clear salvageable tissue. A CT Angiogram revealed a completely occluded right MCA. We deferred thrombolysis because of a significant risk of ICH development secondary to the large area of infarction. Hence, there are matched MCA territory changes, and there are no collaterals; with an ASPECT score of 3, thrombectomy was not feasible either.

Patient 3:

A 41-year-old man was previously healthy and has been in home-based quarantine after being in close contact with a COVID-19 patient before presenting to the E.D. with complaints of severe headache, dizziness, and vomiting 1-day duration. He was drowsy but following simple commands and moving all his limbs. CT-head showed a sizable ill-defined hypodense area noted in the right cerebellar hemisphere/medulla suggestive of acute stroke in the right posterior inferior cerebellar artery (PICA) territory with corresponding edema and mild mass effect. With no evidence of hemorrhagic transformation. MRI and MRA confirmed multiple areas of late acute infarcts along with the posterior circulation territory in the right cerebellar hemisphere [**Figure 3**] .

A nasopharyngeal swab of COVID-19 real time-PCR turned out positive; we started the patient on azithromycin, hydroxychloroquine, ritonavir/lopinavir, steroid, and enoxaparin on day 3. The patient's condition deteriorated rapidly with a decreased conscious level, requiring intubation, without an interval changes on a repeat CT-head. 7-days later, his neurological deficit progressed to bilateral upper and lower limb weakness, and an MRI spine revealed spinal cord infarct at T1-T3 vertebral levels, C2-C3 disk-levels, and C4 vertebral level. Further workup to identify a possible source for the thrombus, including a transthoracic echocardiogram, was unremarkable. On day 20, and after multiple failed weaning trials, we inserted a percutaneous tracheostomy and then transferred him to a rehabilitation facility.

Patient 4:

A 42-year-old active smoker with no known past medical history. 2-days after being hospitalized for moderate COVID-19 moderate pneumonia and after receiving hydroxychloroquine, azithromycin, enoxaparin, methylprednisolone plus ritonavir/lopinavir; he developed a left-sided body weakness with facial asymmetry and slurring of speech of unknown time of onset associated with a sudden decrease in the level of consciousness

with NIHSS- 9. A CT-scan brain with perfusion and C.T. angiography showed a large area of matched perfusion defect noted in the right MCA territory with infarction involving the right front-temporoparietal region and a filling defect in the distal segment of the right common carotid artery at its bifurcation. We did not offer thrombolysis as the time of stroke onset was unclear. He was managed conservatively with IV heparin, then changed to antiplatelets and a rehabilitation program for the body weakness.

Patient 5:

EMS brought a middle-aged man with unknown past medical history after being found in a drowsy state by his neighbor. On physical exam, his Glasgow Coma Scale (GCS) was 9/15. An urgent CT-head with angiography showed a filling defect at the basilar artery's bifurcation, causing posterior circulation acute infarction with a surrounding penumbra. His routine Chest X-ray showed increased bilateral Broncho-vascular markings; however, he tested positive for the COVID-19 virus in nasal swab PCR and had a normal sinus rhythm on ECG. We did not offer him thrombolysis as the onset time is unknown, neither thrombectomy, as he already had an established infarction on the plane CT-head. The MRI head confirmed the previous C.T. findings and showed some areas of hemorrhagic transformation. Later on, the patient developed further deterioration in GCS, mandating intubation and mechanical ventilation. 6-days into his course, he developed refractory hypotension and bradycardia followed by asystole and could not be revived with cardiopulmonary resuscitation (CPR).

Discussion:

With the ongoing Outbreak of COVID-19, we noticed a significant increase in ischemic stroke incidence among patients with a severe inflammatory response to the SARS-COV-2-induced ARDS admitted to our high dependency and intensive care units [**table1**]. The authors observed SARS-COV-2's associated ischemic stroke with the ongoing recognition of the neurological manifestations of COVID-19. [**4,5,16**] Mao et al. described these manifestations in a retrospective, observational case series of 219 patients in Wuhan, China, 41.1% of which had severe pulmonary disease, 36.4% elicited a neurological manifestation of which 5.7% attributed to the cerebrovascular disease.[**16**]

In a retrospective cohort study of a 1,916 patient who visited the emergency department in two academic New York hospitals, Mekler et al. found that 36 patients had an acute ischemic stroke in SARS-COV2 infection (1.6%; 95% CI, 1.1%-2.3%) in comparison to 3 out of 1,486 patients with influenza viral infections (0.2%; 95% CI, 0.0%-0.6%).

[**18**]

The neuro-targeting nature of the virus can explain the correlation of SARS-COV-2 severity and the ischemic stroke due to the vascular injury and the hyperimmune response. These responses alter the blood-brain barrier permitting the virus to bind to the ACE2 receptor in the glial cells, which, in addition to the hypercoagulation, plays an important role in the development of ischemic stroke. [**11,15**].

Although the underlying pathophysiological process responsible for the development of stroke in COVID-19 has not yet been determined, different mechanisms related to the COVID-19 infectious process were postulated, such as the host's hyperinflammatory response with the exaggerated cytokine release. For instance, interleukins play an essential role in the inflammatory response, and COVID-19 patients; IL-1, a macrophage-secreted interleukin, is elevated, especially in severe COVID-19 cases. [**4**] Other inflammatory mediators responsible for activating acute-phase reactions like interferon-gamma[**5**], tumor necrosis factor-alpha, and IL-6 were also elevated in SARS-COV-2 infected patients [**8,9**]. IL-6 activity has a unique importance as it's considered a target for tocilizumab, an IL-6 receptor antagonist with possible alleviation of the SARS-COV2-associated cytokines storm and subsequently the severity of the infection.[**20**].

Jenny et al. has addressed the relationship between the Inflammatory cytokines and risk for ischemic stroke risk in their cohort study. They found that raised IL-6 levels were associated with increased risk of ischemic stroke (mean 4.5 vs. 3.7ng/mL; $p < 0.001$)[**14**]. Another factor supporting this association is the endothelial injury, as described by Varga et al., where the histopathology of different samples from three patients with

SARS-COV2 infection confirmed evidence of viral endothelial invasion with subsequent accumulation of the inflammatory cells attributed to the widespread of ACE2 receptors through the endothelial vascular lining [10],

A dysfunctional procoagulant state with ultimate activation of the coagulation cascade, an acceleration of the already established vasculopathy, and vascular thrombosis are keys in the cases mentioned above, explicitly numbers 1 and 2. Those patients developed strokes secondary to a large vessel disease with complete occlusion of the corresponding internal carotid artery.

About the SARS-COV-2 induced coagulopathy, the inflammatory process has been associated with an increased level of D-Dimer and fibrin degradation products. These two parameters' value was higher in severe COVID-19 cases than their milder counterparts [17]. This has subsequently led to the prolongation of P.T. and APTT and a DIC picture with increased mortality [1]. The incidence of thrombotic complications in patients with severe SARS-COV-2 infection, especially those who required critical care admission, was high, which indicates the underlying coagulation derangement correlated with the viral burden and severity. [7,13] Panigada et al. described thrombo-elastography findings in a patient with COVID-19 admitted to the intensive care unit revealed a dramatic increase in D Dimer, fibrinogen, and von Willebrand factor. Factor VIII was decreased along with antithrombin [12]

Conclusion:

The increased incidence of ischemic stroke was frequently encountered among patients with ARDS and a significant inflammatory response. We hypothesized that the underlying pathophysiology could be related to the considerable inflammation, deranged coagulation, and viral cell invasion through endothelial ACE2 receptors; this finding warranted the suggestion of a full dose of anticoagulation for the hospitalized patient with moderate to severe COVID-19 pneumonia. Such observations need further studies to define the exact mechanism by which SARS-COV-2 induces ischemic stroke.

Statement of Ethics :

informed consent was obtained from the patient/relatives for publication.

approval for publication was brought under the MRC number

MRC-04-20-1040

Availability of data and material

The data sets used or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

We acknowledge the Qatar National Library for funding the open access publication of this article. We also acknowledge the Medical Research Center at Hamad Medical Corporation for their support.

Disclosure:

The authors report no conflicts of interest in this work.

Author's Details :

Ans Alamami , Clinical Fellow, Division Critical Care, Hamad General Hospital,

Hamad Medical Corporation, Doha, Qatar

Email: AAlamami@hamad.qa

Rabee tawel , Clinical Fellow, Division of Critical Care, Hamad General Hospital,

Hamad Medical Corporation, Doha, Qatar

Email: RTawel@hamad.qa

Abdussalam Elgrewi , Internal medicine resident, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

Email: AElgrewi@hamad.qa

Anam Elarabi , Consultant Pulmonologist, Division of Respiratory medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

Email: AElarabi@hamad.qa

Ahmed L M Abdussalam , Critical Care & ECMO consultant, Division of Critical Care, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

Email: *AAbdussalam@hamad.qa*

Author's contribution:

1. Ans Alamami : manuscript writing, literature review
2. Rabee Taweel: manuscript writing, clinical management and follow up
3. Abdusalam Elgrwi: manuscript writing, clinical management
4. Anam Elarbi: manuscript writing, clinical management
5. Ahmed L M Abdussalam: manuscript writing, clinical management

References:

- 1.Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*. 2020;18(4):844–7.
- 2.Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Journal of Medical Virology*. 2020;92(7):699–702.
- 3.Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke: The Global COVID-19 Stroke Registry. *Stroke* [Internet]. 2020 Jul 9 [cited 2020 Jul 26]; Available from <https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.031208>
- 4.Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 2020 May 1;8(5):475–81.
- 5.Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020 Feb;395(10223):497–506.
- 6.Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Translational Research*. 2020 Jun;220:1–13.
- 7.Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis Research*. 2020 Jul;191:148–50.
- 8.Cheung CY, Poon LLM, Ng IHY, Luk W, Sia S-F, Wu MHS, et al. Cytokine Responses in Severe Acute Respiratory Syndrome Coronavirus-Infected Macrophages In Vitro: Possible Relevance to Pathogenesis. *Journal of Virology*. 2005 Jun 15;79(12):7819–26.

9. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis*. 2020 Jul 28;71(15):762–8.
10. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and Endotheliitis in COVID-19. *The Lancet*. 2020 May;395(10234):1417–8.
11. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020 Apr 1;11(7):995–8.
12. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *Journal of Thrombosis and Haemostasis*. 2020;18(7):1738–42.
13. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*. 2020 Jul;191:145–7.
14. Jenny NS, Callas PW, Judd SE, McClure LA, Kissela B, Zakai NA, et al. Inflammatory cytokines, and ischemic stroke risk. *Neurology*. 2019 May 14;92(20):e2375.
15. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *JAD*. 2020 Jun 30;76(1):3–19.
16. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020 Jun 1;77(6):683–90.
17. Han H, Yang L, Liu R, Liu F, Wu K, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020 Jun 25;58(7):1116–20.
18. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs. Patients With Influenza. *JAMA Neurology* [Internet]. 2020 Jul 2 [cited 2020 Aug7]; doi.org/10.1001/jamaneurol.2020.2730
19. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *Journal of Thrombosis and Haemostasis*. 2020;18(7):1559–61.
20. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *The Lancet Rheumatology*. 2020 Aug 1;2(8):e474–84.

Figure Legends:

Table 1 : patient characteristics summary

Figure 1 : MRA head with T2/FLAIR showing hyperintense acute infarct in the right parietal-frontal lobes and smaller multifocal areas of patchy acute infarcts in the left frontoparietal lobe, right more than left insula, bilateral temporooccipital regions, left caudate head, and tiny acute lacunar infarct in the right cerebellar hemisphere

Figure 2 : MRA of the head and neck showing occluded right middle cerebral artery (MCA) from the origin in the neck

Figure 3 :T2 Weighted head MRI confirmed multiple areas of late acute infarcts along with the posterior circulation territory in the right cerebellar hemisphere

Hosted file

Figures.pdf available at <https://authorea.com/users/367908/articles/492085-covid-19-associated-large-vessel-thrombosis-and-ischemic-stroke-a-case-series>