

Correlation, causation, or illusion: SARS-COV-2 infection and stroke

Abstract

Several studies have explored the association between SARS-CoV-2 infection, COVID-19 (or symptomatic illness), and stroke. In vitro studies of other coronaviruses suggest that SARS-CoV-2 infection could lead to an increase in the incidence of vascular thrombosis and, in turn, acute ischemic stroke (AIS). We performed a review of recent literature in hopes of providing a reliable, evidence-based position on this matter.

Volume 11 Issue 6 - 2021

Jonathan T Grossman DO, Asia Filatov MD
Florida Atlantic University, Charles E Schmidt College of
Medicine, USA

Correspondence: Asia Filatov, Florida Atlantic University,
Charles E. Schmidt College of Medicine, Boca Raton, Florida,
Email jgdoneuro@gmail.com

Received: November 15, 2021 | **Published:** December 21,
2021

Background

Stroke is an acute neurological event caused by reduction or interruption of blood flow to the brain, hindering delivery of nutrients and oxygen to brain tissue. Common symptoms of stroke include sensory loss or weakness affecting the face, arm or leg, speech difficulties, incoordination, and visual abnormalities. COVID-19 is an acute respiratory illness caused by a strain of coronaviruses, SARS-CoV-2, and spread by inhalation of respiratory droplets produced during talking, coughing or sneezing.¹ Patients infected with SARS-CoV-2 are believed to be at increased risk for coagulopathy due to either the presence of pathologic antibodies e.g. lupus anticoagulant or antiphospholipid antibodies² or endothelial injury.³ In vitro studies of other coronaviruses suggest that SARS-CoV-2 infection could lead to an increase in the incidence of vascular thrombosis and, in turn, acute ischemic stroke (AIS).

Literature review

Studies have explored AIS in both symptomatic illness and asymptomatic seropositivity. Variable conclusions have resulted including an apparent increase in AIS during convalescence⁴ and a relative infrequency of stroke in COVID-19 patients.⁵ For our purposes, we will focus primarily on the incidence and prevalence of stroke in those infected with SARS-CoV-2.

One of the early studies conducted by Belani et al.⁶ determined COVID-19 to be an independent risk factor for stroke. After controlling for traditional vascular risk factors, nearly ½ of the 41 patients found to have AIS were also positive for SARS-CoV-2; this compared to approximately 18% in the control group. Unfortunately, this was a small population (n = 123) and has yet to be reproduced on a larger scale.

Merkler et al.⁷ found that COVID-19 patients have an elevated risk of developing clinical complications like myocarditis, atrial arrhythmias, venous thromboses, heart failure, and myocardial infarction, all of which can increase acute ischemic stroke risk.¹ Increased CRP and D-dimer levels observed in COVID-19 patients increase suspicion that infection may play an active role in stroke pathophysiology.⁸ Additionally, SARS-CoV-2 has been isolated from both cerebrospinal fluid and neural tissue which could suggest a potential contribution to the evolution of cerebrovascular disease with consequential increased susceptibility to stroke.

Factors such as impaired organ function, systemic inflammation, and inappropriate activation of the coagulation cascade are linked to an increase in risk of arterial or venous thromboembolisms.⁴ Both arterial and venous clots can lead to stroke.

There are numerous studies to support an elevated risk of AIS in the setting of respiratory infection. While a causal role of infection in AIS remains to be proven, infection may serve as a trigger for increase in incidence of large vessel and cardioembolic stroke.⁹ This is thought to be a product of a multitude of mechanisms including increased platelet aggregation, variations in lipid metabolism, variable prothrombotic states, plaque rupture and instability, and altered endothelial function.¹⁰ Research conducted in Wuhan confirmed that viral infections, like COVID-19, are risk factors for thrombotic and embolic infarcts.⁶ The study examined 221 COVID-19 patients, 5% of whom were found to have stroke. The patients examined were older and a large proportion were found to have “severe” COVID-19.

A more recent systematic review carried out by Markus & Martins¹¹ found that 1106 of 108,571 COVID-19 patients analyzed experienced hemorrhagic or ischemic stroke. Elevated serum fibrinogen and D-dimer levels are thought to portend an evolving coagulopathy. The study revealed that COVID-19 can heighten stroke risk by more than seven times compared to other viral illnesses such as seasonal influenza. This study also concluded that stroke in COVID-19 patients is associated with an increased risk of long-term disability and higher rates of morbidity and mortality.¹¹ This finding parallels an analysis of 41,971 patients from 458 hospitals which found that AIS appeared to be more severe in those with COVID-19.¹²

In conclusion, there is considerable evidence to support an association between incident COVID-19 infection and AIS. Anticipating an increase in AIS in COVID-19 patients seems almost intuitive when we consider how a systemic inflammatory response can lead to a hypercoagulable state. Further, the lone observation of increased large vessel occlusions increases the risk of consequential stroke.

While causation remains to be established, it does appear that stroke incidence is increased in both asymptomatic seropositive patients as well as COVID-19 patients. Whether or not this is due to the presence of traditional vascular risk factors, comorbidities, viral infection itself, or a combination of factors remains to be determined. It goes without saying that pre-hospital management of modifiable

risk factors is paramount in reducing stroke risk in any population. What may be undervalued is the timely and appropriate management of complications of COVID-19 (e.g. myocarditis, atrial arrhythmias, venous thromboses, heart failure, myocardial infarction) in reducing stroke risk. At the present time, we believe that there is a paucity of literature to support the routine use of anticoagulation in COVID-19 patients and that the most effective means of reducing incident stroke is by addressing traditional risk factors and prompt management of disease-related complications.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Shahjouei S, Tsvigoulis G, Farahmand G, et al. SARS-CoV-2 and stroke characteristics: a report from the multinational COVID-19 Stroke Study Group. *Stroke*. 2011;52(5):e117–e130.
2. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med*. 2020;382(17):e38.
3. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7(8):e575–e582.
4. Tu TM, Seet CYH, Koh JS, et al. Acute Ischemic Stroke During the Convalescent Phase of Asymptomatic COVID-2019 Infection in Men. *JAMA network open*. 2021;4(4):e217498.
5. Qureshi AI, Baskett WI, Huang W, et al. Acute Ischemic Stroke and COVID-19: An Analysis of 27 676 Patients. *Stroke*. 2021;52(3):905–912.
6. Belani P, Schefflein J, Kihira S, et al. COVID-19 is an independent risk factor for acute ischemic stroke. *American Journal of Neuroradiology*. 2020;41(8):1361–1364.
7. Merkler A E, Parikh N S, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA neurology*. 2020;77(11):1366–1372.
8. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. *Brain, behavior, and immunity*. 2020;87:115–119.
9. Paganini-Hill A, Lozano E, Fischberg G, et al. Infection and risk of ischemic stroke: differences among stroke subtypes. *Stroke*. 2003;34(2):452–457.
10. Stein LK, Mayman NA, Dhamoon MS, et al. The emerging association between COVID-19 and acute stroke. *Trends in Neurosciences*. 2021;44(7):527–537.
11. Markus H S, Martins S. COVID-19 and stroke—Understanding the relationship and adapting services. A global World Stroke Organisation perspective. *International Journal of Stroke*. 2021;16(3):241–247.
12. Srivastava PK, Zhang S, Xian Y, et al. Acute Ischemic Stroke in Patients With COVID-19: An Analysis From Get With The Guidelines-Stroke. *Stroke*. 2021;52(5):1826–1829.