In Reply: May Cooler Heads Prevail During a Pandemic: Stroke in COVID-19 Patients or COVID-19 in Stroke Patients?

May "Anticipation" Prevail During a Pandemic: Stroke in COVID-19 Patients Is a Reality!

To the Editor:

It is with interest and surprise that we read the correspondence entitled: "Letter: May Cooler Heads Prevail During a Pandemic: Stroke in COVID-19 Patients or COVID-19 in Stroke Patients?"[1]

Millions have been infected with COVID-19 and hundreds of thousands have died since December 2019. The current pandemic has shocked the world at all levels. With any pandemic progressing at such a rapid pace, the healthcare system has to rely on three elements to confine and limit fatalities until a sufficiently high level of scientific evidence has been compiled. The 3 elements are: (1) Previous epidemiological data (if available),[2-9] (2) sharing current unusual trends, (3) and reacting promptly to implement a change.

One aspect of this COVID-19 pandemic is the increased incidence of thrombotic events in the body in general and cerebrovascular in particular,[10-27] with unusual cases of previously healthy young individuals presenting with ischemic strokes.[28-35] While the authors[1] mention that there is currently no high-level prospective data showing an increase in stroke rates in younger patients (and we agree that this would be difficult to obtain), there is plenty of literature describing this finding.[28-35] So the authors agree that COVID-19 causes a prothrombotic state, but why is COVID-19 a bystander or incidental finding when the stroke is the initial presentation in young patients with no risk factors?

The authors say, "*The findings presented remain anecdotal and lack the methodological and statistical rigor to claim that COVID-19 infection increases stroke risk in the youth*".[1] The authors are right, at the early phase of the pandemic and when unusual trends were observed there was a paucity of evidence; however, Oxley et al[31] just described the five encounters without drawing any conclusions and they stated "*The association between large-vessel stroke and COVID-19 in young patients requires further investigation*". Currently, there is more than anecdotal evidence linking COVID-19 to stroke. The incidence of stroke in COVID-19 hospitalized patients ranges from 0.9% to 2%,[24,33,36,37] increasing to 5.7% in severe disease.[24] COVID-19 has been reported to be an independent predictor of stroke (odds ratio, 3.9; 95% CI, 1.7-8.9; P0.001),[38] and compared to influenza, it has a 7.5-fold higher rate of ischemic stroke.[37] Second, several recent publications reported a similar experience to Oxley et al[31] in terms of stroke occurrence in the young.[28-35] Two extensive multicenter studies reviewing large vessel occlusion in COVID-19 that are under review have observed that among a group of patients undergoing a mechanical thrombectomy 19% were under 50 yr,[33] and 34% under 55 (12 centers from the USA and Europe). Refuting such observations early on during the pandemic before completely understanding the full manifestations of COVID-19 should be reconsidered by the authors.[1] Along the same line of thoughts, children were perceived to be spared from COVID-19 severe manifestations.[39,40] However, later the Centers for Disease Control and Prevention based on small published observations,[41-44] issued a national health advisory to report on cases meeting the criteria for multisystem inflammatory syndrome.[45] Results of such efforts identified 186 patients with multisystem inflammatory syndrome in children and adolescents with COVID-19 disease.[21] The mortality rate was 2%, 80% receiving intensive care, 40% presenting with Kawasaki disease–like features, and 8% developing Coronary artery disease. Usually 5% of children with Kawasaki's disease present with cardiovascular shock, while in the setting of COVID-19 it was 50% (10-folds higher).

The authors[1] attributed stroke in the setting of COVID-19 to a single factor, a prothrombotic state induced by systemic inflammation[45]; however, they did not consider additional factors such as embolic events in the background of myocarditis and arrhythmia, thrombotic microangiopathy, coagulopathy and thrombocytopenia, and direct viral invasion (Central Nervous System (CNS) endothelium and cardiomyocytes).[10-21] Additionally, ACE2 viral-mediated downregulation in the CNS inhibits the neuroprotective effects of ANG-II (anti-inflammatory via its binding to the Mas receptor and vasodilator effect) and tips the balance for ANG-I (a potent vasoconstrictor) thereby increasing stroke severity.[46-55]

It is the responsibility of healthcare professionals to promptly report any noteworthy trends and being vocal in the media to reach the largest audience to spread awareness. Small case series with uncommon trends would alarm the healthcare system to be more vigilant when exposed to such presentations and alert the public to the seriousness of this disease. Whether the media coverage helped with awareness and encouraged people with stroke symptoms to present early to the hospital or resulted in just fear and anxiety among the young is yet to be determined. If the price to pay in spreading stroke awareness in the COVID-19 positive younger population is fear and anxiety in some people, maybe it is not so bad after all. Maybe the young will start taking this pandemic more seriously. Such an approach is similar to an attitude in general surgery, where they operate on 25% of negative appendectomies to avoid missing true positives.[56-60] In our case, it is not as serious because spreading awareness is not even a surgical intervention! Finally, doesn't the public know that there is a higher mortality rate with COVID-19, even among the youth? If so, which would cause more fear and anxiety, stroke or death?

Funding

This study did not receive any funding or financial support.

Disclosures

Dr Jabbour is a consultant for Medtronic and MicroVention. Dr Tjoumakaris is a consultant for Stryker. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Pascal Jabbour, MD [*]
Ahmad Sweid, MD [*]
Stavropoula Tjoumakaris, MD [*]
Michel Piotin, MD [‡]
Waleed Brinjikji, MD [§]
Kimon Bekelis, MD [¶]
Eytan Raz, MD [‖]
Nader Sourour, MD [#]
Shahid M. Nimjee, MD [**]
Demetrius K. Lopes, MD [‡‡]
Ameer E. Hassan, DO [§§]
Aditya S. Pandey, MD [¶¶]
L. Fernando Gonzalez, MD [‖‖]
Ricardo A. Hanel, MD [##]
Adnan H. Siddiqui, MD [##]
David Hasan, MD [***]
Sean D. Lavine, MD [‡‡‡]
Bernard R Bendok, MD [§§§]

[*] *Department of Neurological Surgery*
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania
[‡] *Department of Interventional Neuroradiology*
Rothschild Foundation Hospital
Paris, France
[§] *Department of Radiology*
Mayo Clinic
Rochester, Minnesota
[¶] *Department of Neurosurgery*
Good Samaritan Hospital Medical Center
West Islip, New York
[‖] *Department of Radiology*
New York University Langone Medical Center
New York, New York
[#] *Department of Interventional Neuroradiology*
Pitié-Salpêtrière Hospital
Paris, France
[**] *Department of Neurosurgery*
The Ohio State University Wexner Medical Center
Columbus, Ohio
[‡‡] *Department of Neurosurgery*
Advocate Aurora Health
Chicago, Illinois
[§§] *Department of Neuroscience*
Valley Baptist Medical Center
University of Texas Rio Grande Valley
Harlingen, Texas
[¶¶] *Department of Neurosurgery*
University of Michigan
Ann Arbor, Michigan
[‖‖] *Department of Neurosurgery*
Duke University Medical Center
Durham, North Carolina
[##] *Department of Neurosurgery and Toshiba Stroke Research Center*
School of Medicine and Biomedical Sciences
University at Buffalo
State University of New York
Buffalo, New York
[***] *Deparmtent of Neurosurgery*
University of Iowa Hospital and Clinics
Iowa City, Iowa
[‡‡‡] *Department of Neurosurgery and Radiology*
Columbia University Medical Center
New York, New York
[§§§] *Department of Neurosurgery*
Mayo Clinic
Scottsdale, Arizona

REFERENCES

1. Alawieh AM, Spiotta AM. Letter: may cooler heads prevail during a pandemic: stroke in COVID-19 patients or COVID-19 in stroke patients? *Neurosurgery*. published online: 2020 (doi:10.1093/neuros/nyaa283).
2. Kim J-E, Heo J-H, Kim H-o, et al. Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol*. 2017;13(3):227-233.
3. Arabi Y, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with middle east respiratory syndrome corona virus (MERS-CoV). *Infection*. 2015;43(4):495-501.
4. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1967-1976.
5. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1953-1966.
6. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet*. 2003;362(9380):263-270.
7. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle east respiratory syndrome. *Lancet*. 2020;395(10229):1063-1077.
8. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273.
9. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in china, 2019. *N Engl J Med*. 2020;382(8):727-733.
10. Mishra AK, Sahu KK, Lal A, Sargent J. Mechanisms of stroke and the role of anticoagulants in COVID-19. *J Formos Med Assoc*. 2020;S0929-S6646(20):30286-2.
11. Giraudon P, Bernard A. Inflammation in neuroviral diseases. *J Neural Transm*. 2010;117(8):899-906.
12. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet North Am Ed*. 2020;395(10234):1417-1418.
13. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J Exp Med*. 2020;217(6):e20200652.
14. Lorenzo C, Francesca B, Francesco P, Elena C, Luca S, Paolo S. Acute pulmonary embolism in COVID-19 related hypercoagulability. *J Thromb Thrombolysis*. 2020.50(1):223-226
15. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. 2020;58(7):1116-1120.
16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.

17. Campbell CM, Kahwash R. Will complement inhibition be the new target in treating COVID-19-Related systemic thrombosis? *Circulation*. 2020;141(22):1739-1741.
18. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
19. 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.
20. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. 2020;18(7):1752-1755.
21. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346.
22. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*. 2020;191:148-150.
23. Foley JH, Conway EM. Cross talk pathways between coagulation and inflammation. *Circ Res*. 2016;118(9):1392-1408.
24. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, china. *JAMA Neurol*. 2020;77(6):1-9.
25. Tan CW, Cheen MHH, Wong WH, et al. Elevated activated partial thromboplastin time-based clot waveform analysis markers have strong positive association with acute venous thromboembolism. *Biochem Med (Zagreb)*. 2019;29(2):020710.
26. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. published online: 2020. *Brain*. (doi:10.1093/brain/awaa240).
27. Escalard S, Maïer B, Redjem H, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19. *Stroke*. 2020;51(8):2540-2543.
28. Sweid A, Hammoud B, Weinberg JH, et al. Letter: thrombotic neurovascular disease in COVID-19 patients. *Neurosurgery*. published online: 2020 (doi:10.1093/neuros/nyaa254).
29. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J NeuroInterv Surg*. 2020;12(7):648-653.
30. Cavallieri F, Marti A, Fasano A, et al. Prothrombotic state induced by COVID-19 infection as trigger for stroke in young patients: a dangerous association. *eNeurologicalSci*. 2020;20:100247.
31. 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(20):e60.
32. Gunasekaran K, Amoah K, Rajasurya V, Buscher MG. Stroke in a young COVID-19 patient. *QJM*. 2020;113(8):573-574.
33. Mufti FA, Tiwari AT, Singla A, et al. Incidence, characteristics and outcomes of large vessel stroke in COVID-19 cohort: a multicentric international study. 2020.
34. Sweid A, Jabbour P, Tjoumakaris S. Letter to the editor: incidence of acute ischemic stroke and rate of mechanical thrombectomy during the COVID-19 pandemic in a large tertiary care telemedicine network. *World Neurosurg*. 2020;S1878-S8750(20):31311-31315.
35. Sweid A, Hammoud B, Bekelis K, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. published online: 2020. *Int J Stroke*. (doi:10.1177/1747493020937189).
36. Yaghi S, Ishida K, Torres J, et al. SARS2-CoV-2 and stroke in a new york healthcare system. *Stroke*. 2020;51(7):2002-2011.
37. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. published online: 2020. *JAMA Neurol*. (doi:10.1001/jamaneurol.2020.2730).
38. Belani P, Schefflein J, Kihira S, et al. COVID-19 is an independent risk factor for acute ischemic stroke. published online: 2020. *Am J Neuroradiol*. (doi:10.3174/ajnr.A6650).
39. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382(17):1663-1665.
40. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. published online: 2020. *JAMA pediatrics*. (doi:10.1001/jamapediatrics.2020.1467).
41. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet North Am Ed*. 2020;395(10237):1607-1608.
42. Leon MPD, Redzepi A, McGrath E, et al. COVID-19–associated pediatric multisystem inflammatory syndrome. *J Pediatric Infect Dis Soc*. 2020;9(3):407-408.
43. Simpson JM, Newburger JW. Multi-system inflammatory syndrome in children in association with COVID-19. published online: 2020. *Circulation*. (doi:10.1161/CIRCULATIONAHA.120.048726).
44. Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Child's Nervous System*. 2020:36(8):1579-1580.
45. Network CHA. Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). 2020; https://emergency.cdc.gov/han/2020/han00432.asp. Accessed July 8, 2020.
46. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112-116.
47. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879.
48. Lopez Verrilli MA, Pirola CJ, Pascual MM, Dominici FP, Turyn D, Gironacci MM. Angiotensin-(1–7) through AT2 receptors mediates tyrosine hydroxylase degradation via the ubiquitin–proteasome pathway. *J Neurochem*. 2009;109(2):326-335.
49. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci*. 2004;25(6):291-294.
50. Sampaio WO, Nascimento AAS, Santos RAS. Systemic and regional hemodynamic effects of angiotensin-(1-7) in rats. *Am J Physiol Heart Circ Physiol*. 2003;284(6):H1985-H1994.
51. Mecca AP, Regenhardt RW, O'Connor TE, et al. Cerebroprotection by angiotensin-(1-7) in endothelin-1-induced ischaemic stroke. *Exp Physiol*. 2011;96(10):1084-1096.
52. Campagnole-Santos MJ, Diz DI, Santos RA, Khosla MC, Brosnihan KB, Ferrario CM. Cardiovascular effects of angiotensin-(1-7) injected into the dorsal medulla of rats. *Am J Physiol*. 1989;257(1 Pt 2):H324-H329.
53. Xu P, Sriramula S, Lazartigues E. ACE2/ANG-(1–7)/Mas pathway in the brain: the axis of good. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(4):R804-R817.
54. Chen J, Xiao X, Chen S, et al. Angiotensin-converting enzyme 2 priming enhances the function of endothelial progenitor cells and their therapeutic efficacy. *Hypertension*. 2013;61(3):681-689.
55. Chen J, Zhao Y, Chen S, et al. Neuronal over-expression of ACE2 protects brain from ischemia-induced damage. *Neuropharmacology*. 2014;79:550-558.
56. Hong JJ, Cohn SM, Ekeh AP, Newman M, Salama M, Leblang SD. A prospective randomized study of clinical assessment versus computed tomography for the diagnosis of acute appendicitis. *Surg Infect (Larchmt)*. 2003;4(3):231-239.
57. Jones K, Peña AA, Dunn EL, Nadalo L, Mangram AJ. Are negative appendectomies still acceptable? *Am J Surg*. 2004;188(6):748-754.
58. Naoum JJ, Mileski WJ, Daller JA, et al. The use of abdominal computed tomography scan decreases the frequency of misdiagnosis in cases of suspected appendicitis. *Am J Surg*. 2002;184(6):587-589.
59. Bergeron E. Clinical judgment remains of great value in the diagnosis of acute appendicitis. *Can J Surg*. 2006;49(2):96.
60. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time?: a population-based analysis. *JAMA*. 2001;286(14):1748-1753.

10.1093/neuros/nyaa384