COMMENTARY



COVID-19-Related Stroke

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Abstract

The COVID-19 pandemic is associated with neurological symptoms and complications including stroke. There is hypercoagulability associated with COVID-19 that is likely a "sepsis-induced coagulopathy" and may predispose to stroke. The SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) present on brain endothelial and smooth muscle cells. ACE2 is a key part of the renin angiotensin system (RAS) and a counterbalance to angiotensin-converting enzyme 1 (ACE1) and angiotensin II. Angiotensin II is proinflammatory, is vasoconstrictive, and promotes organ damage. Depletion of ACE2 by SARS-CoV-2 may tip the balance in favor of the "harmful" ACE1/angiotensin II axis and promote tissue injury including stroke. There is a rationale to continue to treat with tissue plasminogen activator for COVID-19-related stroke and low molecular weight heparinoids may reduce thrombosis and mortality in sepsis-induced coagulopathy.

Keywords COVID-19 · SARS-CoV-2 · Stroke · Sepsis · Coagulopathy · Angiotensin-converting enzyme 2 (ACE2)

Although the precise incidence is not known, stroke is emerging as a complication of the COVID-19 pandemic. The clinical course of COVID-19 is most severe in elderly patients, in men, and in patients with comorbidities such as hypertension, diabetes, heart disease, and obesity, all risk factors for stroke. [1]. Neurological symptoms are common in COVID-19 including anosmia and hypogeusia, seizures, and strokes. In a retrospective study of 214 hospitalized COVID-19 patients from Wuhan, China, 5.7% of the severe patients suffered a stroke [2].

Coagulopathy

One of the emerging hallmarks of severe COVID-19 is a coagulopathy that has been termed "sepsis-induced coagulopathy" (SIC) with high D-dimer levels and elevated fibrinogen [3, 4]. SIC is a precursor state to DIC and associated with

☐ David C. Hess Dhess@augusta.edu elevated prothrombin time (PT), elevated D-dimer, and thrombocytopenia, but without hypofibrinogenemia. It is related to an infection-induced systemic inflammatory response with endothelial dysfunction and microthrombosis with organ failure and usually no bleeding [4]. In a multivariate analysis of a retrospective series of 440 severe COVID-19 patients, the predictors of 28-day mortality were age, prothrombin time, D-dimer levels, and thrombocytopenia. Patients with elevated D-dimer or SIC score had lower mortality when treated with heparin (mostly low molecular weight) compared with those not treated with heparin. A case series of 3 patients with respiratory failure and high D-dimer levels reported transient improvement in respiratory parameters with the use of tissue plasminogen activator [5]. The lung pathology in one COVID-19 patient revealed microvascular thrombosis suggesting that the lung microvascular thrombosis in COVID-19 patients may contribute to respiratory failure and ARDS [5].

Antiphospholipid antibodies (aPL) were reported in 3 COVID-19 patients. aPL are antibodies directed to phosphoproteins and associated with both arterial and venous thrombotic events. All 3 patients suffered multiple cerebral infarcts and one had multiple limb ischemia. All had elevated IgA anticardiolipin antibodies and elevated IgA and IgG beta 2 glycoprotein I antibodies with prolonged activated partial thromboplastin times and prothrombin times but no lupus anticoagulant. Two of the 3 patients had thrombocytopenia and



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all had high C-reactive protein levels [6]. It is not clear if the strokes and thrombotic events were related to SIC or the aPL. There is an association of aPL with viral infections especially HIV-1 and hepatitis C and a subgroup of these are associated with thrombotic events [7, 8].

Depletion of ACE2 and Endothelial Dysfunction

The COVID-19 pandemic is caused by the SARS-CoV-2 virus, a member of the coronavirus family. The SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) via its spike (S) protein [9]. Transmembrane protein serine protease 2 (TMPRSS2) is also required for viral entry into cells [10]. Similarly, the virus that caused the SARS pandemic in 2003, SARS-CoV-1, also binds to ACE2 [11, 12]. ACE2 is a dipeptidyl carboxydipeptidase, a homologue of angiotensinconverting enzyme 1 (ACE1), and part of the renin angiotensin system (RAS). Renin secreted from juxtaglomerular cells in the kidney cleaves angiotensingen produced by the liver to angiotensin I. Angiotensin I is cleaved by ACE1 to angiotensin II. Angiotensin II binds to angiotensin 1 (AT1) and angiotensin 2 (AT2) receptors and its binding to AT1 leads to vasoconstriction, aldosterone secretion with sodium and water retention, proinflammatory and procoagulation effects, and elevated blood pressure. Angiotensin II worsens heart failure and worsens ARDS. AT1 blockers are widely used antihypertensive drugs and have beneficial effects in organ protection including the brain.

ACE2 counteracts ACE1 and angiotensin II. ACE2 directly cleaves angiotensin II to angiotensin (1-7) and cleaves

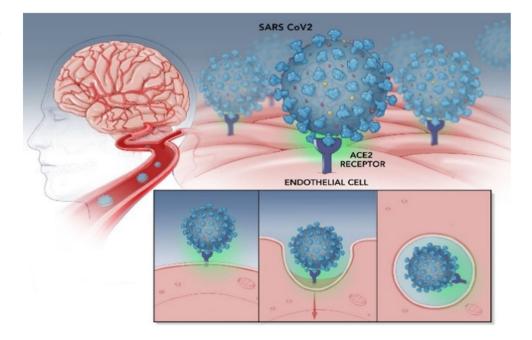
angiotensin I to angiotensin (1-9) which is then further cleaved to angiotensin (1-7). Angiotensin (1-7) produces vasodilatation and has anti-inflammatory effects via its binding to the Mas receptor. Activation of ACE2/Ang (1-7)/Mas axis leads to beneficial cardioprotective and neuroprotective actions that counter-regulate the harmful actions of ACE1/angiotensin II/AT1 axis (reviewed in [13, 14]). In rodent models of stroke, angiotensin (1-7) is neuroprotective and anti-inflammatory [15–17].

ACE2 is expressed in human lung, small intestine, and endothelial and smooth muscle cells in the human brain [18]. ACE2 is also expressed in neurons in mice [18]. Overexpression of ACE2 in neuronal cells or endothelial progenitor cells protects the brain from ischemic stroke [19, 20].

SARS-CoV-1 and 2 viruses deplete ACE2 through receptor endocytosis upon viral entry, leaving ACE1 unopposed with generation of angiotensin II. Angiotensin II worsens lung injury and also worsens endothelial function in organs like the heart and brain. ACE2 in the lung declines with age and the decrease in males with age is greater than that in females [21]. Meanwhile, the ACE1-angiotensin II system activity increases with age [22]. The depletion of ACE2 by the SARS-CoV-2 virus coupled with the age-related decline in ACE2 and increase of ACE-1-Ang II tips the balance in favor of ACE-1/angiotensin II with proinflammatory and organ damaging effects. This may explain the higher mortality in the elderly and in men seen in the COVID-19 pandemic.

One of the obstacles to COVID-19 research is the lack of rodent models. SARS 1 and 2 bind to ACE2 but mouse and rat ACE2 does not avidly bind the spike protein and mice do not develop severe illness. A humanized ACE2 transgenic mouse developed after the SARS pandemic is associated with severe

Fig. 1 ACE2 is expressed in human brain endothelium. SARS-CoV-2 binds ACE2, depleting ACE2 on the endothelium





SARS infection in the lung that models human disease [23]. Working with SARS-CoV-1 and 2 requires a BSL-3 facility. Stroke models in rodents will need to use humanized ACE2 mice or move to other animals such as ferrets that are commonly used in influenza models of disease.

Treatments

For patients with COVID-19 and stroke, it seems reasonable to treat with tPA. It is not clear if other anticoagulants such as low molecular weight heparin (LMWH) or full dose heparin should be used. There is some evidence that LMWH may be useful in SIC. For a more "targeted" COVID-19 therapy, one promising treatment is to supply exogenous ACE2 by administering human recombinant soluble ACE2 (hrsACE2) which inhibited SARS-CoV-2 infections in engineered human blood vessel organoids [24]. Recombinant human soluble ACE2 was safe in a pilot clinical trial in ARDS [25] and is entering clinical trial for COVID-19. (ClinicalTrials.gov number NCT04335136).

Recombinant ACE2 may work primarily in two ways: (1) competing with the SARS S protein for binding to lung and endothelial endogenous ACE2 thereby acting as a decoy to reduce infection of host cells; (2) preventing the ACE2 depletion by the SARS2 virus. Since ACE2 is expressed by brain endothelium and neurons, it is likely that viral mediated depletion of ACE2 impairs endothelial function and predisposes to or worsens acute stroke (Fig. 1).

Other treatments that target the RAS system such as angiotensin (1-7) and that have already shown promise in stroke preclinical models may also be promising therapies for COVID-19. Angiotensin (1-7) is in clinical trial for COVID-19 (Clinical Trials.gov NCT04332666). Moreover, blockers of the AT1 receptor (ARBs), such as losartan, may be protective in stroke. While there has been some concern that ARBs and ACE inhibitors may be harmful in COVID-19 patients by increasing expression of ACE2 and SARS-CoV-2 binding, a joint statement from the American Heart Association, American College of Cardiology, and Heart Failure Society of American has recommended ARBs and antagonists of the RAS system be continued in COVID-19 patients as they may be effective. https://www.acc.org/latest-in-cardiology/articles/ 2020/03/17/08/59/hfsa-acc-aha-statement-addressesconcerns-re-using-raas-antagonists-in-covid-19

Summary

Strokes are being reported as a complication of COVID-19. The cause is not clear but SIC is associated with COVID-19 and may contribute to endothelial dysfunction,

microthrombosis, and stroke. The role of aPL, likely triggered by the viral infection, is unclear and may be related to SIC.

Binding to and depletion of ACE2 may tip the RAS balance in favor of the ACE-1-angiotensin II-AT1 axis and contribute to endothelial dysfunction, organ damage, and stroke.

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Compliance with Ethical Standards

Conflict of Interest David C Hess MD is a consultant for Aruna Bio, Inc and receives fees for consultation and receives royalty payments from Athersys, Inc. Wael Eldahsahn PhD has no conflicts of interest/competing interests. Elizabeth Rutkowski has no conflicts of interest/competing interests.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62. https://doi. org/10.1016/S0140-6736(20)30566-3.
- Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. SSRN Electron J. 2020. https://doi.org/10.2139/ssrn.3544840.
- 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. https://doi.org/10.1111/jth.14817.
- Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989–94. https://doi.org/10.1111/jth.14578.
- Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost. April 2020. https://doi.org/10.1111/jth. 14828.
- Zhang Y. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382:e38.
- Sène D, Piette JC, Cacoub P. Antiphospholipid antibodies, antiphospholipid syndrome and infections. Autoimmun Rev. 2008;7:272–7. https://doi.org/10.1016/j.autrev.2007.10.001.
- Abdel-Wahab N, Lopez-Olivo MA, Pinto-Patarroyo GP, Suarez-Almazor ME. Systematic review of case reports of antiphospholipid syndrome following infection. Lupus. 2016;25:1520–31. https://doi.org/10.1177/0961203316640912.
- Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3. https://doi.org/10.1038/ s41586-020-2012-7.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and



- TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:1–10. https://doi.org/10.1016/j.cell.2020.02.052.
- Li W, Moore MJ, Vasllieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426:450–4. https://doi.org/10.1038/nature02145.
- Kuhn JH, Li W, Choe H, Farzan M. Angiotensin-converting enzyme 2: a functional receptor for SARS coronavirus. Cell Mol Life Sci. 2004;61(21):2738–43. https://doi.org/10.1007/s00018-004-4242-5.
- 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):804–17. https://doi.org/10.1152/ajpregu. 00222.2010.
- Arendse LB, Jan Danser AH, Poglitsch M, et al. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. Pharmacol Rev. 2019;71(4):539–70. https://doi.org/10.1124/pr.118.017129.
- Mecca AP, Regenhardt RW, O'Connor TE, Joseph JP, Raizada MK, Katovich MJ, et al. Cerebroprotection by angiotensin-(1-7) in endothelin-1-induced ischaemic stroke. Exp Physiol. 2011;96(10): 1084–96. https://doi.org/10.1113/expphysiol.2011.058578.
- Regenhardt RW, Desland F, Mecca AP, Pioquinto DJ, Afzal A, Mocco J, et al. Anti-inflammatory effects of angiotensin-(1-7) in ischemic stroke. Neuropharmacology. 2013;71:154–63. https://doi. org/10.1016/j.neuropharm.2013.03.025.
- Regenhardt RW, Mecca AP, Desland F, Ritucci-Chinni PF, Ludin JA, Greenstein D, et al. Centrally administered angiotensin-(1-7) increases the survival of stroke-prone spontaneously hypertensive rats. Exp Physiol. 2014;99(2):442–53. https://doi.org/10.1113/expphysiol.2013.075242.
- Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol. 2007;292:R373– 81. https://doi.org/10.1152/ajpregu.00292.2006.

- Chen J, Xiao X, Chen S, Zhang C, Chen J, Yi D, et al. Angiotensin-converting enzyme 2 priming enhances the function of endothelial progenitor cells and their therapeutic efficacy. Hypertension. 2013;61(3):681-9. https://doi.org/10.1161/HYPERTENSIONAHA.111.00202.
- Chen J, Zhao Y, Chen S, Wang J, Xiao X, Ma X, et al. Neuronal over-expression of ACE2 protects brain from ischemia-induced damage. Neuropharmacology. 2014;79:550–8. https://doi.org/10. 1016/j.neuropharm.2014.01.004.
- Xudong X, Junzhu C, Xingxiang W, Furong Z, Yanrong L. Ageand gender-related difference of ACE2 expression in rat lung. Life Sci. 2006;78(19):2166–71. https://doi.org/10.1016/j.lfs.2005.09. 038.
- Wang M, Monticone RE, Lakatta EG. Proinflammation of aging central arteries: a mini-review. Gerontology. 2014;60:519–29. https://doi.org/10.1159/000362548.
- Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82(15):7264–75. https://doi.org/10.1128/jvi. 00737-08.
- Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. 2020. https://doi.org/10. 1016/j.cell.2020.04.004.
- Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017;21(1):1–9. https://doi.org/10.1186/s13054-017-1823-x.

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