



Mini Review Article

Cerebrovascular Diseases: Significant Complication of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) first identified in Wuhan, China, in December 2019, and rapidly spread worldwide and turned to a human life threat pandemic. Severe respiratory illness is the main characteristic symptom of this disease, but coronaviruses are not restricted to the respiratory tract. Likewise, these viruses may invade the central nervous system and have neurologic signs, including headache, nausea, disturbed consciousness, paresthesia, and vomiting. Moreover, the infection of SARS-CoV-2 has been reported in the brains of COVID-19 infected patients. Cerebrovascular diseases are among the various defined complications of SARS-CoV-2. Also, several studies introduce COVID-19 as an independent risk factor for stroke that increases the risk of mortality. Increasing evidence shows that this neuroinvasive virus may cause these neurological insults through direct or indirect mechanisms. Understanding more about the mechanisms by which COVID-19 causes stroke and vascular damages will help prevent these damages. Accordingly, in this review, we attempt to discuss current information about the possible pathways which may mediate the deleterious effect of COVID-19 on the nervous system.

Keywords: COVID-19, SARS-CoV-2, Stroke, Cerebrovascular disease.

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Introduction

Since December 2019, the world was going to tackle a very contagious coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first emerged in Wuhan, China, and then rapidly outbreaks around the world. The infectious disease caused by this newly recognized species of coronavirus called the coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2, with a typical crown-like shape, belongs to the family of single-stranded RNA viruses (+ssRNA). To date, seven coronaviruses have been identified that infect humans, including the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), cause widespread epidemics in the last two decades. There is a 79.5% genetic similarity between SARS-CoV and SARS-CoV-2 [2]. The main clinical manifestations of COVID-19 are fever, dry cough, fatigue, and muscle pain. Moreover, in severe cases, acute respiratory distress syndrome (ARDS) and multiple organ dysfunctions are among the life-threatening complications [3]. In addition, robust findings so far showed that viruses could invade the CNS and cause severe damages to its

structure and function. Viral infections can be responsible for encephalitis, toxic encephalopathy, and demyelinating lesions in infected patients [4]. In this respect, increasing evidence shows that besides respiratory distress, neurological manifestations involved CNS, PNS, and skeletal muscles developed in 36.4% (78/214) of patients with COVID-19. Also, it has been reported that severe patients are more susceptible to develop neurologic symptoms [5]. Nevertheless, this is not an unpredictable finding before these neurological manifestations have been observed in the infected patient with other coronaviruses such as in SARS-CoV and MERS-CoV. For instance, autopsy studies confirm the presence of the SARS-CoV nucleic acid in the brain tissue and cerebrospinal fluid of those patients [6,7]. Similar to SARS-CoV, SARS-CoV-2 could induce neurological disorders such as hyposmia, weakness, headaches, altered consciousness, encephalitis, neuropathy, demyelination, and stroke [8,9]. Detection of the SARS-CoV-2 genome in cerebrospinal fluid of COVID-19 infected patients confirms this theory that SARS-CoV-2 can damage the nervous system [10]. Viruses cause brain damages through diverse mechanisms

that range from direct invasion to the brain or triggered indirect mechanisms such as the ‘Trojan horse’ mechanism (infected immune-functioning cells that cross the BBB by diapedesis) and coagulation cascade disruption [11,12].

Clinicians need to know how COVID-19 infection affects the nervous system. Thus, this review aimed to discuss the possible mechanisms by which SARS-CoV-2 causes cerebrovascular disease and stroke.

Direct neuroinvasive potential of SARS-CoV-2

Detection of the genetic material and also proteins of some viruses in cerebrospinal fluid or brain tissue specimens of some patients approves this theory that viruses can directly invade the nervous system and lead to nerve damage [13,14]. Angiotensin-converting enzyme 2 (ACE2), a cardio-cerebral vascular protection factor, has been identified in various organs, such as skeletal muscles and nervous system is known as significant the cell-entry receptor for SARS-Cov-2 and other coronaviruses [15]. Under normal conditions, this enzyme has a critical role in regulating blood pressure and anti-atherosclerosis mechanisms [16]. Coronaviruses may, through binding to this receptor, increase blood pressure and the risk of cerebral hemorrhage. Expression of ACE2 on nerve cells and vascular endothelial cells may elucidate the direct entry of SARS-CoV-2 into the CNS through hematogenous spread or retrograde transport of virus through ACE2 receptor. However, a more recent study demonstrated the probable endothelial invasion of SARS-CoV-2 in the case with posterior reversible encephalopathy syndrome (PRES)-like leukoencephalopathy [12].

CNS is protected by the blood-brain barrier (BBB), and dysfunction of this barrier can lead to the penetration of viruses to the brain. Due to the unique biological properties of the CNS, if a virus enters the CNS, it is difficult to remove, which exacerbates neurological insults. Damage to BBB and attacking the vascular system is Another scenario for the direct entrance of SARS-CoV-2 into CNS [17].

Indirect neuroinvasive potential of SARS-CoV-2

Stroke is a serious health problem that threatens the life of millions of people all over the world. Virus infections, especially respiratory tract virus infections are among the risk factors that can trigger stroke. Moreover, seasonal variation in stroke incidence emphasis the role of respiratory tract virus infections such as influenza [18]. A retrospective study conducted by Li Y et al. revealed that the incidence of stroke among hospitalized, COVID-19 infected patients was approximately 5% [19]. Moreover, the study of Mao et al. showed that about 5.7% of patients with a severe infection of COVID-19 develop the late cerebrovascular disease [20]. Most of these patients were severe cases of COVID-19 and had a higher incidence risk of underlying diseases like diabetes, hypertension, coronary artery disease, and previous cerebrovascular disease [21]. Additionally, several case reports from different countries confirm these findings [22,23]. Moreover, a recent study reports five cases of large-vessel stroke in young patients with COVID-19 [24]. This finding is following previous reports showed the association between large-vessel stroke and the 2004 SARS-CoV outbreak in

Singapore [25]. Moreover, a retrospective cohort study proposed the coagulopathy and vascular endothelial dysfunction as other complications of COVID-19 [26]. Viruses through increasing the risks of cardioembolic and arterio-arterial embolic events may cause stroke in infected patients [21]. A study demonstrated that 31% of ICU patients with COVID-19 infections develop thrombotic complications. These results proposed that COVID-19 may predispose thromboembolism due to hypoxia, excessive inflammation, immobilisation and diffuse intravascular coagulation [3]. Therefore, disruption of coagulation cascade may trigger the indirect effects of SARS-CoV2, which results in unusual thrombosis or hemorrhage occurred in strokes and acute hemorrhagic necrotizing encephalopathy [12].

In another study, Tan et al. evaluated the activated partial thromboplastin time-based clot waveform analysis (CWA) in COVID-19 patients and concluded that the rise of CWA parameters precedes and coincides with the severity of disease and ICU admission [27]. Radiologic and histopathologic evaluation of 16 patients with severe COVID-19 showed that these patients are faced with the risk for ischemic lesions and multifocal microvascular hemorrhagic in the subcortical and deep white matter [28].

Pieces of evidence from the experimental mouse model of influenza suggest that virus infection causes cytokine storm and subsequently aggravates stroke outcomes [29]. Likewise, accumulating evidence suggests that coronaviruses, especially SARS-CoV-2, trigger cytokine cascade, and probably by this way, cause cerebrovascular damages [30,31]. On the other hand, a severe reduction in platelet levels and an increase in D-dimer levels have been reported in severely SARS-CoV-2 infected patients, which may make prone these patients to acute cerebrovascular events [32]. Elevated levels of D-dimer induced hypercoagulability and exaggerated inflammatory status, which might play a critical role in the pathophysiology of stroke in patients with COVID-19 infection [19]. Mao et al.’s study reveals the correlation between the severity of COVID-19 infection and higher D-dimer levels in patients. Patients with severe infection and higher D-dimer levels were more likely to develop neurological symptoms (45.5% vs. 30.2%), particularly acute cerebrovascular disease (5.7% vs. 0.8%) [5]. Association studies shed new light on the role of the immune system in mediating the effect of viral infection on the nervous system. Multiple organs failure, which is one of the main reasons for the high mortality of COVID-19, occurs due to virus-induced systemic inflammatory response syndrome [33]. Moreover, SARS-CoV-2, like other coronaviruses, displays neurotropic properties and can invade nervous tissues and activate immune cells such as microglia, macrophages, and astrocytes in the CNS and cause chronic inflammation and brain damage [34]. There are rare brain autopsies and pathology data, but lungs and kidney autopsy findings suggest thrombotic microangiopathy in these organs [35-37]. Solomon et al., by histopathological examination of brain samples of 18 died COVID-19 patients, only observed hypoxic changes and not encephalitis or other brain changes related to the virus. Also, the level of the virus was low in brain sections of 5 patients [38]. Further brain autopsy studies are needed for the understanding of the neurological implications of COVID-19.

Conclusion

The COVID-19 causes various pathological conditions, such as ARDS, cardiovascular and cerebrovascular complications. However, the relation between COVID-19 and cerebrovascular diseases is not yet determined. Several important questions remain unknown about the pathophysiology of COVID-19 and stroke. SARS-CoV-2 can directly or indirectly tackle the nervous system described above, and healthcare professionals should be aware of these neurologic manifestations in COVID-19 patients. Numerous studies showed that patients with COVID-19 had elevated CRP, D-dimer, and platelet abnormalities, causing hyperactivation of inflammatory factors, damaged coagulation cascade. Notwithstanding the wealth of evidence supporting the possible mechanisms involved in the pathophysiology of stroke and COVID-19, further studies are needed to disclose the details.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

References

- Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents*. 2020:105924.
- Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *Journal of medical virology*. 2020;92(5):491-4.
- Klok F, Kruip M, Van der Meer N, Arbous M, Gommers D, Kant K, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research*. 2020.
- Davies NW, Sharief MK, Howard RS. Infection-associated encephalopathies—their investigation, diagnosis, and treatment. *Journal of neurology*. 2006;253(7):833-45.
- Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological examination manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. 2020.
- Desforges M, Favreau DJ, Brison É, Desjardins J, Meessen-Pinard M, Jacomy H, et al. Human Coronaviruses: Respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neurovirulent agents. 2013.
- Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *The Lancet*. 2015;386(9997):995-1007.
- Tsai L, Hsieh S, Chang Y. Neurological manifestations in severe acute respiratory syndrome. *Acta neurologica Taiwanica*. 2005;14(3):113.
- Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. *Clinical Neurology and Neurosurgery*. 2020;194:105921.
- Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS neuroscience & therapeutics*. 2020;26(5):499.
- Al-Obaidi MJ, Bahadoran A, Wang S, Manikam R, Raju CS, Sekaran S. Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. *Acta virologica*. 2018;62(1):16-27.
- Doo FX, Kassim G, Lefton DR, Patterson S, Pham H, Belani P. Rare presentations of COVID-19: PRES-like leukoencephalopathy and carotid thrombosis. *Clinical Imaging*. 2020.
- Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. *Cell host & microbe*. 2013;13(4):379-93.
- Leber AL, Everhart K, Balada-Llasat J-M, Cullison J, Daly J, Holt S, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *Journal of clinical microbiology*. 2016;54(9):2251-61.
- 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.
- Miller AJ, Arnold AC. The renin-angiotensin system in cardiovascular autonomic control: recent developments and clinical implications. *Clinical Autonomic Research*. 2019;29(2):231-43.
- 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 chemical neuroscience*. 2020;11(7):995-8.
- Lanska DJ, Hoffmann RG. Seasonal variation in stroke mortality rates. *Neurology*. 1999;52(5):984-.
- Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. 2020.
- 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 neurology*. 2020;77(6):683-90.
- Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain, behavior, and immunity*. 2020.
- Sanyasi RDLR, Pramudita EA. ISCHEMIC STROKE IN COVID-19 POSITIVE PATIENT: A CASE REPORT. *Journal of the Medical Sciences (Berkala ilmu Kedokteran)*.52(2).
- Co COC, Yu JRT, Laxamana LC, David-Ona DIA. Intravenous Thrombolysis for Stroke in a COVID-19 Positive Filipino Patient, a Case Report. *Journal of Clinical Neuroscience*. 2020.
- Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *New England Journal of Medicine*. 2020;382(20):e60.
- Umaphathi T, Kor AC, Venketasubramanian N, Lim CT, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *Journal of neurology*. 2004;251(10):1227-31.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The lancet*. 2020.
- Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically

- ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. *American Journal of Hematology*. 2020.
28. Conklin J, Frosch MP, Mukerji S, Rapalino O, Maher M, Schaefer PW, et al. Cerebral Microvascular Injury in Severe COVID-19. medRxiv: the preprint server for health sciences. 2020.
 29. Muhammad S, Haasbach E, Kotchourko M, Strigli A, Krenz A, Ridder DA, et al. Influenza virus infection aggravates stroke outcome. *Stroke*. 2011;42(3):783-91.
 30. Chen C, Zhang X, Ju Z, He W. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies. *Zhonghua shao shang za zhi= Zhonghua shaoshang zazhi= Chinese journal of burns*. 2020;36:E005-E.
 31. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. 2020;395(10229):1033.
 32. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *Journal of Medical Virology*.
 33. Yin C, Wang C, Tang Z, Wen Y, Zhang S, Wang B. Clinical analysis of multiple organ dysfunction syndrome in patients suffering from SARS. *Zhongguo wei zhong bing ji jiu yi xue= Chinese critical care medicine= Zhongguo weizhongbing jijiuyixue*. 2004;16(11):646.
 34. Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *Journal of Neurology*. 2020:1.
 35. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. medRxiv. 2020.
 36. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. Covid-19 autopsies, oklahoma, usa. *American Journal of Clinical Pathology*. 2020;153(6):725-33.
 37. Yao X, Li T, He Z, Ping Y, Liu H, Yu S, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua bing li xue za zhi= Chinese journal of pathology*. 2020;49:E009-E.
 38. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological Features of Covid-19. *New England Journal of Medicine*. 2020.