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COVID–19 infection and stroke risk

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Abstract: Coronavirus disease 2019 (COVID-19), due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan city, China in December 2019 and rapidly spread to other countries. The most common reported symptoms are fever, dry cough, myalgia and fatigue, headache, anorexia, and breathlessness. Anosmia and dysgeusia as well as gastrointestinal symptoms including nausea and diarrhea are other notable symptoms. This virus also can exhibit neurotropic properties and may also cause neurological diseases, including epileptic seizures, cerebrovascular accident, Guillian barre syndrome, acute transverse myelitis, and acute encephalitis. In this study, we discuss stroke as a complication of the new coronavirus and its possible mechanisms of damage.

Keywords: COVID-19; nervous system; neurological symptoms; stroke.

Introduction

In December 2019, an outbreak of pneumonia due to an unknown cause raised intense attention in Wuhan, Hubei, China then internationally. On Jan 7th, 2020, Chinese scientists diagnosed a novel coronavirus, which was initially named 2019 novel coronavirus (2019-nCoV), leading to the Corona Virus Disease 2019 (COVID-19) from patients by deep sequencing analysis from lower respiratory tract samples in Wuhan (Hanaei and Rezaei 2020; Huang et al. 2020; Wang et al. 2020a). Based on cases, it has been confirmed that the virus can transmit from human to human (Lotfi and Rezaei 2020; Wan et al. 2020).

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Most of the symptoms of COVID-19, such as acute respiratory syndrome, are similar to the symptoms of severe acute respiratory syndrome coronavirus (SARS-CoV), which was emerged in 2002–2003, caused over 8,000 confirmed cases of human infections and about 800 deaths (Lee et al. 2003; Marra et al. 2003; Yu et al. 2004) and reemerged in 2003–2004, with 4 confirmed cases and no human-to-human transmission (Guan et al. 2003; Song et al. 2005). The clinical presentations of COVID-19 range from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction (Lotfi et al. 2020). The common clinical features include fever, dry cough, myalgia and fatigue, headache, anorexia and breathlessness (Chen et al. 2020b; Jin et al. 2020). Anosmia and dysgeusia are also notable symptoms (Lechien et al. 2020). Gastrointestinal symptoms, including nausea and diarrhea, are less common (Jin et al. 2020). In some patients, by the end of the first week, the disease can have progression to pneumonia, respiratory failure, and death due to an extreme rise in inflammatory cytokines including IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A, and TNF- α (Dong et al. 2020; Mehta et al. 2020, Ruan et al. 2020; Saghazadeh and Rezaei 2020; Yazdanpanah et al. 2020; Zhou et al. 2020a). Reported complications are lung impairment including severe respiratory failure and ARDS (Hussain et al. 2020; Huang et al. 2020; Robba et al. 2020), shock (Alhazzani et al. 2020; Li et al. 2020b; Kamali Aghdam et al. 2020), liver and kidney injury (Anders et al., 2020; Naicker et al., 2020; ten Cate 2020; Xu et al. 2020), cardiac involvement (Chen et al. 2020a; Shi et al., 2020; Liu et al., 2020), thromboembolic complications and coagulopathies (Matteo et al. 2020; Orsi et al. 2020; Simona et al. 2020; Yang et al. 2020), neurological manifestations, including acute transverse myelitis, acute encephalitis (Helms et al. 2020; Jahanshahlu and Rezaei, 2020; Mao et al. 2020; Saleki et al. 2020), epileptic seizures, the Guillain-Barré syndrome (Carod-Artal 2020; Nalleballe et al. 2020), neurological damage associated with mentioned coagulopathy, systemic and local thrombotic events which occur during this infection (Huang et al. 2020) and ischemic or hemorrhagic stroke (Ashrafi et al. 2020; Avula et al. 2020; Oxley et al. 2020). In this review, we discuss stroke as a presentation of COVID-19.

Stroke and COVID-19

Based on studies, COVID-19 patients can present with cerebrovascular accidents, including stroke. Avula et al. reported four patients with COVID-19 (aged older than 73) that presented with acute stroke in the early stages of their illness (Avula et al. 2020). In another study, Mao et al. reported a case series of 214 patients with COVID-19; 5.7% of patients with severe infection (45.5%) developed the cerebrovascular disease later in the course of disease (Mao et al. 2020). In the study by Li and colleagues the incidence of stroke in severe COVID-19 patients (median age of 71.6 years) with comorbidities, including hypertension, diabetes, coronary artery disease, and previous cerebrovascular disease, was reported about 5%; the youngest patient in that series was 55 years of age (Li et al. 2020c). In this study, it was suggested the average time of onset of stroke after COVID-19 diagnosis was about 12 days. Oxley et al. reported five cases of large-vessel stroke in patients younger than 50 years of age who presented to the health system in New York City and were diagnosed with severe SARS-CoV-2. Two of the patients had no medical history and risk factors for stroke, one patient had hyperlipidemia and hypertension, one had undiagnosed diabetes and fifth patient had diabetes and a history of previous stroke (Oxley et al. 2020). Beyrouiti and coworkers described six consecutive patients with acute ischemic stroke and COVID-19. All six patients had large vessel occlusion with markedly elevated D-dimer levels ($\geq 1000 \mu\text{g/L}$). Three patients had multi-territory infarcts, two had concurrent venous thrombosis, and in two, ischemic strokes occurred despite therapeutic anticoagulation (Beyrouiti et al. 2020).

Atherosclerotic disease in intracranial and extracranial arteries and aortic arch (Di Tullio et al. 2009; Qureshi and Caplan 2014), hypertension (Kannel et al. 1976; MacMahon et al. 1990), and atrial fibrillation (AF) (D'Souza et al. 2018) are the major causes of ischemic cerebrovascular events, such as stroke. There are studies that have suggested the occurrence of thrombosis and plaque formation in COVID-19 which will be discussed further in this manuscript. Also, it has been reported that patients with severe COVID-19 infections commonly have hypertension (Fang et al. 2020; Kreutz et al. 2020; Lippi et al. 2020; Yaghi et al. 2020; Zhang et al. 2020). So in this context, based on the major role of hypertension in stroke, its presence can be a trigger for cerebrovascular events in severe COVID-19 (Li et al. 2020c). The other usual cause of stroke, arrhythmias especially atrial fibrillation, has been also reported in the COVID-19 patients as initial symptomatology or as a comorbidity (Liu et al. 2020; Onder et al. 2020; Wang et al. 2020b). A study by

Bhatla et al. evaluated the risk of cardiac arrest and arrhythmias such as AF among 700 patients with COVID-19. The result was 9 cardiac arrests and 25 incident AF events and also they found that admission to the ICU was associated with incident AF (odds ratio [OR] 4.68; 95% confidence interval [CI] 1.66–13.18). The conclusion was that cardiac arrests and arrhythmias are likely the consequence of systemic illness and not solely the direct effects of COVID-19 infection (Bhatla et al. 2020). As it was mentioned about hypertension, AF in COVID-19 infection also can be related to stroke during infection.

Different pathophysiological processes may be responsible for an increased risk of stroke in COVID-19 (the mechanisms we aim to discuss about are shown in Figure 1). Older patients with comorbidities often experience more severe disease which can increase their risk of stroke (Berger 2020). In a retrospective study of 221 patients with COVID-19 by Li et al., it has been reported the factors for having a stroke are advanced age (mean age: 71.6 years), severe COVID-19, having a previous history of hypertension, diabetes, or cerebrovascular disease, or having a marked inflammatory and procoagulant response (increased C-reactive protein and D-dimer, respectively) (Li et al. 2020c). Based on several studies, hypercoagulability is one of the hallmarks of severe COVID-19. For example in some studies, based on the autopsies, it has been reported that in a high number of COVID-19 patients (71.4%) disseminated intravascular coagulation was detected (Colantuoni et al. 2020). This coagulation can be explained through different mechanisms. First, we describe the thrombus formation through the prism of Virchow's triad. Virchow's triad includes three essential factors needed for thrombus formation and consists of endothelial or endocardial damage or dysfunction, abnormal blood stasis, and hypercoagulability of blood (Lurie et al. 2019; Virchow 1998):

- (1) Endothelial injury: severe endothelial injury and associated disruption of cellular membranes in COVID-19 occur via the virus entrance to endothelial cells of vessels (Ackermann et al. 2020). Angiotensin-converting enzyme 2 (ACE2) is the main receptor of SARS-CoV-2 and plays an important role in the virus entry into the cell and causing infection (Hofmann et al. 2005; Li et al. 2003). The SARS-CoV-2 virus binds to the ACE2 via its spike (S) protein and also transmembrane protein serine protease 2 (TMPRSS2) is required for viral entry into cells (Zhou et al. 2020b). The ACE2 receptor is expressed in endothelial cells (Hamming et al. 2004) so SARS-CoV-2 can invade to the vessel wall (Amraei and Rahimi, 2020; Varga et al. 2020) which leads to the loss of the fibrinolytic function

of the endothelial cells (Iba et al. 2020; Suzuki et al. 2011), and release of von-Willebrand factor (vWF) from Weibel-Palade bodies that have been reported in COVID-19 (Escher et al. 2020; Kayal et al. 1998; Panigada et al. 2020; Sumiyoshi and Tanaka 1976). The complex of unusually large vWFs and platelets causes microthrombosis. As a result, multiple organ failure and stroke can take place due to the endothelial injury associated with microthrombotic disease (Sezgin et al. 2020). In a study, Varga et al. after assessing the autopsy of COVID-19 infected patients demonstrated the endothelial cell involvement of vascular beds of different organs. They detected the presence of viral elements within endothelial cells and an accumulation of inflammatory cells in the endothelium (Varga et al. 2020).

- (2) Hypercoagulability: the construction of thrombus can be aided by the inflammation. Severe COVID-19 leads to a cytokine storm as an expression of hyperactive host immune system response to the virus and the inflammation can cause coagulopathy as a consequence of sepsis (Henderson et al. 2020; Mangalmurti and Hunter 2020). This event has been termed sepsis-induced coagulopathy (SIC) and is comorbid with high D-dimer levels and elevated fibrinogen (Iba et al. 2019; Tang et al. 2020). It is because of a systemic inflammatory response toward infection after endothelial dysfunction and organ failure due to micro thrombosis (Iba et al. 2019). So, this coagulopathy may complicate COVID-19. The DIC and hypercoagulation in COVID-19 have been reported in several studies. For example in a retrospective cohort study, Zhou et al. included 191 adult inpatients (≥ 18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital and compared extracted demographic, clinical, treatment, and laboratory data between survivors and non-survivors. They demonstrated the markers of coagulation may be increased during this infection (Zhou et al. 2020a). In another study, Tang et al. have retrospectively analyzed coagulation results, medications, and outcomes of consecutive patients being classified as having severe COVID-19 in Tongji hospital and showed that DIC can be observed in this disease (Tang et al. 2020). Other components that can contribute to hypercoagulation are platelet and complement activation. Rise in the platelet-to-lymphocyte ratio, platelet hyperactivity, and also increased platelet aggregation have been postulated in severe COVID-19 (Chan and Rout 2020; Lodigiani et al. 2020; Manne et al. 2020; Qu et al. 2020; Spiezia et al. 2020). For the platelet activation and aggregation in COVID-19, AT1R in platelets can cause a rise in adherence and lead to platelet aggregation as a

response to the angiotensin II (Nagai et al. 2011). Platelets have Mas receptors that have a protective role against thrombosis via the release of nitric oxide so the loss of the angiotensin1-7/Mas pathway can also cause platelet aggregation (Fraga-Silva et al. 2008). Another pathway for platelet activation is through the altered ACE1/ACE2 function. Because of the cleavage of bradykinin by ACE1 into metabolites such as vasoactive bradykinin (1-8) and des-Arg9-bradykinin and degradation of the metabolites by ACE2, the absence of ACE2 leads to the accumulation of des-Arg9-bradykinin and des-Arg9-bradykinin can activate platelets into an inflammatory phenotype (Sodhi et al. 2018) and these activated platelets can attach to the endothelium of the vessels with a higher tendency (Afshar-Kharghan 2017). In a study, Rapkiewicz et al. by post-mortem examination, investigated the prothrombotic state in COVID-19. In seven COVID-19 autopsies, platelet-rich thrombi in the pulmonary, hepatic, renal, and cardiac microvasculature was detected even with full anticoagulation in some patients and regardless of timing of the disease course. Two cases had cardiac venous thrombosis with one case exhibiting septal myocardial infarction associated with intramyocardial venous thrombosis, without atherosclerosis. They suggested that thrombosis plays an important role early in the disease process (Rapkiewicz et al. 2020). As it is mentioned, complement activation has a role in coagulation and is a driver of the maladaptive inflammatory response in COVID-19 and also with platelets, cooperates in thromboinflammation, microvascular thrombosis, and endothelial dysfunction (Java et al., 2020; Magro et al. 2020). Complement is an essential component of the innate immune response against viruses (Li et al. 2020a). Complement is also shown to have roles in the development of adverse events in heart failure and sepsis-related cardiomyopathy (Fattahi et al. 2018; Orrem et al. 2018). It has been suggested that tissue damage leading to complement activation takes place against several viruses, such as H1N1 influenza, SARS, CoV-2, and MERS-CoV (Gralinski et al. 2018; Jiang et al. 2019; Ohta et al. 2011; Yang 2020).

- (3) Blood stasis: this is associated to the micro-circulation obstruction, irregularity in hemorheology and hyperviscosity, abnormality in hemodynamics, and abnormality in the formation of scar tissue (Chen 2012). As it has been mentioned, abnormal blood flow can be caused by hyperviscosity that occurs during infection with SARS-CoV-2 through the rise in cellular components or plasma proteins including fibrinogen or immunoglobulin (Agbuduwe and Basu 2020; Ahmed

et al. 2020; Larcan et al. 1981; Maier et al. 2020; Richardson et al. 1979). Hyperviscosity can itself cause endothelium damage and thrombus formation (Baskurt and Meiselman 2012; Forconi et al. 1987). Another factor that can lead to blood stasis is impaired microcirculation. Microcirculation consists of the smallest blood vessels including arterioles, capillaries, and venules (Ince 2005). Sepsis and inflammation can disrupt the microcirculatory function by impairment of the regulatory mechanisms that control the microcirculatory perfusion of the tissues (Ince and Sinaasappel 1999; Spronk et al. 2004). The endotheliitis associated with apoptosis leading to COVID-19 can suggest the impaired microcirculation in vascular beds (Jung et al. 2020; Varga et al. 2020). In the study by Varga et al. that was discussed earlier, the evidence of endotheliitis and induction of apoptosis and pyroptosis was found in the autopsy investigation of COVID-19 patients. They also concluded that endotheliitis could describe the occurrence of systemic impaired microcirculatory function in different vascular beds in COVID-19 patients (Varga et al. 2020).

So based on the triad of Virchow, COVID-19 can increase the risk of stroke by providing all the three essential factors for thrombosis.

Another mechanism leading to stroke during COVID-19 may be viral myocarditis. COVID-19 can affect the myocardium and cause myocarditis (Hu et al. 2020; Inciardi et al. 2020; Xu et al. 2020). In a study by Bradley et al. lymphocytic myocarditis with detected viral RNA in the tissue was reported in one patient after post-mortem examinations of 14 cases with COVID-19 (Bradley et al. 2020).

It should be mentioned that viral myocarditis may increase the risk of stroke (Madjid et al. 2020). Guo et al. reported factors associated with outcomes in 187 patients hospitalized with COVID-19 in Wuhan, China. In this study, 35% had underlying cardiovascular diseases (hypertension,

coronary heart disease, or cardiomyopathy), and 28% showed evidence of acute myocardial injury (elevated troponin T [TnT]). Patients with high TNT levels also had higher leukocyte counts, lower lymphocyte counts, and higher levels of D-dimer, C-reactive protein, procalcitonin, and N-terminal pro-brain natriuretic peptides. As for outcomes, patients with a high TNT level showed a higher incidence of acute coagulopathy (Guo et al. 2020a). Based on this evidences, we can relate myocarditis to stroke.

The next mechanism that is considered to have a role in stroke is the depletion of ACE2. As discussed ACE2 is the main receptor of SARS-CoV-2 and plays an important role in the virus entry into the cell to cause infection (Hofmann et al. 2005; Li et al. 2003). In addition to the endothelium, ACE2 has been detected in human lung, small intestine, smooth muscle cells, and the human brain, especially in both neurons and astroglia. So it can invade the neurons directly (Doobay et al. 2007; Gowrisankar and Clark, 2016). ACE2 is a homologue of angiotensin-converting enzyme 1 (ACE1), and part of the renin-angiotensin system (RAS). ACE1 has roles in angiotensin II production. ACE2 counteracts ACE1 and angiotensin II, and its action leads to angiotensin production from the cleavage of angiotensin II and angiotensin I to angiotensin which has anti-inflammatory effects and cardioprotective and neuroprotective actions (Arendse et al. 2019; Xu et al. 2011). Coronavirus causes ACE2 depletion and endocytosis in turn, over activates the classical renin-angiotensin system and this mechanism leads to a rise in ACE1 and angiotensin II and increase in lung injury and endothelial function in organs like the heart and brain then vasodilation, neuroinflammation, oxidative stress, and thrombotic response. This fact may explain the pathophysiology of stroke caused by SARS-CoV-2 (Xudong et al. 2006).

Another leading cause of stroke because of COVID can be hypoxia injury. With the entry of the virus into lung tissue cells, diffuse alveolar and interstitial inflammatory exudation, edema, and the formation of transparent membranes occur. Then results in alveolar gas exchange disorders causing hypoxia in the CNS (Abdennour et al. 2012). Hypoxia in patients with the risk of developing cerebrovascular disease may also cause acute cerebrovascular disease such as acute ischemic stroke (Wu et al. 2020). Based on studies, the patients with COVID-19 often have severe hypoxia; so, hypoxia injury can be considered as a stroke reason (Guo et al. 2020b; Kashani 2020).

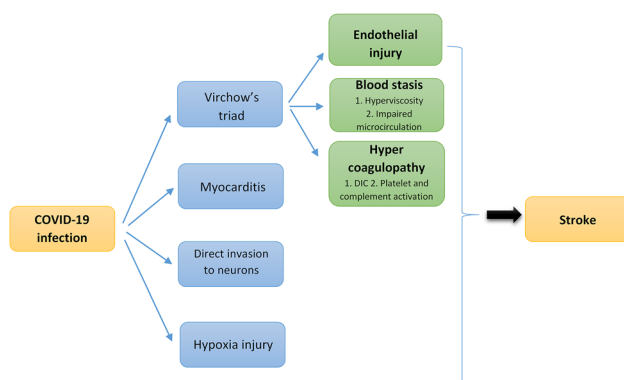


Figure 1: The pathophysiology of stroke related to COVID-19.

Conclusion

The clinical presentations of COVID-19 range from an asymptomatic state to acute respiratory distress syndrome

and multi-organ dysfunction. There are several reported complications, stroke is one of them (Ashrafi et al. 2020; Avula et al. 2020; Oxley et al. 2020). Atherosclerotic disease (Di Tullio et al. 2009; Qureshi and Caplan 2014), hypertension (Kannel et al. 1976; MacMahon et al. 1990), and atrial fibrillation (AF) (D'Souza et al. 2018) are the major causes of ischemic cerebrovascular events, such as stroke so their presence during infection can be a trigger for the occurrence of stroke. Based on this information, especial attention should be paid to this matter during the disease.

Different pathophysiological processes may be responsible for an increased risk of stroke in COVID-19 (Berger 2020): 1. the thrombus formation based on the Virchow's triad (1). Severe endothelial injury and associated disruption of cellular membranes in COVID-19 via the virus entry to endothelial cells of vessels (Ackermann et al. 2020) through ACE2 -the main receptor of SARS-CoV-2 -and causing infection (Hofmann et al. 2005; Li et al. 2003). 2. thrombus formation aided by cytokine storm due to severe COVID-19 and coagulopathy because of a systemic inflammatory response toward infection may complicate COVID-19 and cause stroke (Iba et al. 2020) 3. Blood stasis caused by hyperviscosity that occurs during infection with SARS-CoV-2 through the rise in cellular components such as fibrinogen (Agbuduwe and Basu 2020; Ahmed et al. 2020; Larcan et al. 1981; Maier et al. 2020; Richardson et al. 1979). Another factor that can cause blood stasis is impaired microcirculation which the endotheliitis associated with apoptosis leading to COVID-19 can suggest the impaired microcirculation in vascular beds (Jung et al. 2020; Varga et al. 2020).

2. Viral myocarditis is another mechanism of stroke. COVID-19 can affect the myocardium and cause myocarditis (Hu et al. 2020; Inciardi et al. 2020; Xu et al. 2020). Based on studies, myocarditis, and myocardia injury leads to a rise in TnT and D-dimer levels. As for outcomes, patients with a high TNT level show a higher incidence of acute coagulopathy (Guo et al. 2020a); 3. Another cause of stroke is depletion of ACE2 which leads to a rise in ACE1 and angiotensin II and vasodilation, neuroinflammation, oxidative stress, and thrombotic response that can promote stroke (Xudong et al. 2006); 4. Hypoxia injury also can cause a stroke. Lung tissue cell injuries diffuse alveolar, and interstitial inflammatory exudation, edema, and the formation of transparent membranes due to virus entrance result in hypoxia in the CNS (Abdenmour et al. 2012). Hypoxia in patients with the risk of developing a cerebrovascular disease may also cause acute cerebrovascular disease such as acute ischemic stroke (Wu et al. 2020).

Based on this information, SARS-CoV-2 can affect several organs and can cause significant damages; so, consideration of cerebrovascular accidents and appropriate

personal management is critical for improving the prognosis of suspected patients.

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