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REVIEW

The effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on ischemic stroke and the possible underlying mechanisms

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ABSTRACT

Purpose: As of November 28, 2020, COVID-19 has been reported in 220 countries with 61,036,793 confirmed cases and 1,433,316 confirmed deaths; countries became vigilant around the world. In addition to SARS-CoV-2 causing pneumonia, many studies have reported ischemic stroke in patients with COVID-19. This article describes the effects and possible underlying mechanisms of SARS-CoV-2 on ischemic stroke.

Materials and methods: A literature search was performed using PubMed, Web of Science, and other COVID-dedicated databases and the combination of the keywords 'SARS-CoV-2', 'COVID-19' and 'ischemic stroke' up to November 28, 2020.

Results: SARS-CoV-2 invades the host through angiotensin converting enzyme 2 (ACE2). ACE2 is expressed not only in the lungs, but also in the brain and vascular endothelial cells. SARS-CoV-2 infection might cause direct vascular disease or enhance the immunogenic thrombosis environment through several mechanisms. SARS-CoV-2 infection can modulate the host immune response and can cause inflammation, coagulation disorders, renin angiotensin system disorders, hypoxia, and stress disorders, which may lead to the occurrence of ischemic stroke.

Conclusions: Some patients with COVID-19 can develop ischemic stroke. Ischemic stroke has a high risk of causing disability and is associated with a high mortality rate. It is hoped that when medical staff treat patients with COVID-19, they would pay attention to the occurrence of ischemic stroke to improve the prognosis of patients with COVID-19.

Introduction

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, China with many cases in the 'South China Seafood Market' [1]. SARS-CoV-2 was previously temporarily named 2019-nCoV [2]. On February 11, 2020, the World Health Organization (WHO) announced a new name for the epidemic caused by SARS-CoV-2: coronavirus disease 2019 (COVID-19). COVID-19 was declared as a 'public health emergency of international concern' by the WHO on January 30, 2020. And COVID-19 is spreading rapidly. As of November 28, 2020, COVID-19 has been reported in 220 countries with 61,036,793 confirmed cases and 1,433,316 confirmed deaths; nowadays, countries are vigilant around the world [3].

A series of case studies showed that all six patients included showed no or mild COVID-19 symptoms, and five of the six patients (83%) had stroke symptoms as the initial and main symptoms, indicating that even mild symptoms can lead to strokes [4]. There is increasing evidence that ischemic stroke and COVID-19 are related to each other. Approximately 5% patients with severe COVID-19 infection and 1% patients with non-severe infections develop ischemic stroke [5]. In addition, stroke is associated with a 2.5-fold increase in the likelihood of severe COVID-19, with a trend for increased mortality [6]. A literature search was performed using PubMed, Web of Science, and other COVID-dedicated databases and the combination of the keywords 'SARS-CoV-2', 'COVID-19' and 'ischemic stroke' up to November 28, 2020. Therefore, this article describes the effects and possible underlying mechanisms of SARS-CoV-2 on ischemic stroke with the aim that medical staff should pay attention to the possibility of ischemic stroke when treating patients with COVID-19.

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Virology and pathogenesis

In recent years, outbreaks of coronavirus infection have occurred sporadically. Severe acute respiratory syndromecoronavirus (SARS-CoV) infection was first detected in 2002, and middle east respiratory syndrome coronavirus (MERS-CoV) infection was first detected in 2012 [7]. Coronavirus can cause respiratory and intestinal infections in animals and humans. Previous coronaviruses transmitted to humans mainly caused minor symptoms. After the outbreak of severe acute respiratory syndrome (SARS) in 2002, coronavirus was considered highly pathogenic to humans [8–10].

SARS-CoV-2 (subgenus Sarbecovirus, subfamily Orthocoronavirinae) is a new beta coronavirus containing a non-segmented, positive-sense RNA [11]. The SARS-CoV-2 viral sequence is very similar to the bat coronavirus sequence (overall genome sequence identity of 96.2%). In addition, its sequence homology with SARS-CoV is also as high as 79.5% [12]. According to the viral genome sequencing results and evolutionary analysis, SARS-CoV-2 originated from bats and may have been transmitted to humans through multiple intermediate hosts [13]. The spike glycoprotein of SARS-CoV-2 binds to host cells *via* angiotensin-converting enzyme 2 (ACE2), fuses with membranes, and releases viral RNA [14]. Viral RNA functions as a pathogen-associated molecular pattern and is detected by the pattern recognition receptors (PRRs) to induce the host immune response.

Immune response

When SARS-CoV-2 invades a host, the host's innate immune system uses PRRs, mainly Toll-like receptor (TLR), retinoic acid-inducible gene-I-like receptor, and nucleotide-binding oligomerization domain-like receptor [15], which recognize viral nucleic acids, collect specific signal adapter proteins, activate interferon-regulatory factor (IRF) 3 and IRF7, and translocate to the nucleus to promote the synthesis of type I Interferons (IFNs). IFNs then activate the downstream JAK-STAT signaling pathways and promote the expression of interferon-stimulated genes [16]. IFNs, the host's main antiviral molecule, can limit the spread of the virus, exert immunomodulatory effects, promote the phagocytosis of antigens by macrophages, and kill the infected target cells by natural killer cells.

In addition, the adaptive immunity of the patient also plays an important role in antiviral activity. Depletion of CD4+ T cells is associated with reduced recruitment of lymphocytes in the lungs and reduced production of neutralizing antibodies and cytokines, leading to strong immune-mediated interstitial pneumonia and delayed viral clearance from the lungs [17]. T helper cells produce pro-inflammatory cytokines through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway [18]. Interleukin (IL)-17 recruits monocytes and neutrophils to sites of infection and activates downstream cytokine and chemokine cascades producing IL-1, IL-6, IL-8, IL-21, tumor necrosis factor (TNF)-β, and monocyte chemoattractant protein-1 (MCP-1) [19]. C3a and C5a have strong pro-inflammatory effects, which can stimulate the recruitment of inflammatory cells and the activation of neutrophils [7]. The key to the pathogenesis of COVID-19 is related to the reduction of innate immune response-related antiviral effects and the increase in the production of inflammatory cytokines. The increase of inflammatory cytokines is related to a more serious prognosis [20].

Possible mechanisms

1. Inflammation and coagulation disorders

After SARS-CoV-2 invasion, pathogen-associated antigens not only combine with immune cells to produce inflammatory cytokines but also bind to PRRs, such as TLR4, expressed on endothelial cells and platelets, thereby triggering a series of immune and prethrombotic events [21]. A large amount of evidence indicates that patients with severe COVID-19 experience a cytokine storm and the stronger the cytokine storm, the more severe the symptoms [22, 23]. Cytokine storm refers to the excessive release of C-reactive protein (CRP) and pro-inflammatory cytokines, such as TNF-α, IL-8, IL-6, which can cause severe coagulation disorders [23, 24]. One of the characteristics of severe COVID-19 is 'sepsis-induced coagulopathy (SIC)'. SIC is associated with a systemic inflammatory response to infection and is a precursor to disseminated intravascular coagulation, which is associated with elevated prothrombin time, elevated D-dimer, and thrombocytopenia but not with hypofibrinogenemia [25–27]. SIC may also cause endothelial dysfunction, microthrombus formation, and stroke [27].

During infection, platelets, coagulation factors, and other components of the immune system can interact to form clots; this process is known as immune thrombosis (also known as thrombotic inflammation) [28, 29]. After SARS-CoV-2 infection, a large number of pro-inflammatory cytokines are produced through a series of immune responses. T lymphocytes [30], IL-6, and TNF-α may cause microvascular damage [31]. TNF-α can

promote overexpression of tissue factor (TF) on platelets and macrophages [32]. The production of anti-phospholipid COVID-19 antibodies can also upregulate TF expression [32]. TF is a transmembrane protein that can be used as a high-affinity receptor and cofactor for coagulation factors VII and VIIa [33]. It forms a part of a key step in the activation of the coagulation system during infection [34]. Proinflammatory cytokines, such as IL-1β, IL 6, and TNF-α, can promote the release of ultra-long von Willebrand factor (VWF) multimers and produce TF and coagulation factors VII/VIIa. This leads to increased thrombin generation, reduced endogenous anticoagulant levels of tissue factor pathway inhibitor, antithrombin, and activated protein C [35]. In addition, complement C3a and C5a can activate platelets and endothelial cells as well as increase the expression of TF and VWF [36]. P-selectin from storage granules is upregulated on the surface of activated platelets to promote interaction with recruited neutrophils, thereby forming platelet-neutrophil complexes [37]. SARS-CoV-2 upregulates the hfgl2 prothrombinase gene, which may further promote thrombin generation and hypercoagulability in COVID-19 [38]. In addition to causing abnormal coagulation, inflammatory cells, mainly monocytes and/or macrophages, begin to accumulate early in the walls of blood vessels to promote the formation of atherosclerosis. In the later stages of the disease, their activation can cause plaque rupture and thrombosis that increases the risk of ischemic stroke [39]. Studies show that monomeric CRP has atherogenic and thrombogenic properties, because it interacts with other immune mediators to activate platelets and complement proteins [40]. IL-6 is the main driving force that regulates the production of CRP in the liver. It also mediates the formation of atherosclerosis associated with classic risk factors such as aging, hypertension, smoking, and obesity [41]. Large-sample studies have shown that CRP and IL-6 are associated with ischemic stroke [42, 43].

2. Renin angiotensin system disorders

SARS-CoV-2 infects humans by binding with angiotensin-converting enzyme 2 (ACE2) [44]. ACE2 is widely expressed in various tissues of the human body, especially in cardiovascular system [45, 46]. ACE2 is also expressed in the brain at lower levels [47]. The expression and distribution of ACE2 suggest that SARS-CoV-2 can cause ischemic stroke indirectly by acting on the cardiovascular system and directly by acting on the brain.

Researchers have found that the cerebrospinal fluid of some patients with COVID-19 tested positive for SARS-CoV-2 by polymerase chain reaction [48], and SARS-CoV-2 was also detected in their brains by autopsy [49]. Like other respiratory viruses, SARS-CoV-2 can enter the central nervous system through blood or retrograde neuronal pathways (the fact that about 70% patients with COVID-19 have olfactory and/or taste disorders supports the latter point [50]). All components of renin-angiotensin system (RAS), including angiotensinogen, ACE, ACE2, and angiotensin II (Ang II) receptors, are expressed in the brain [47, 51]. RAS usually refers to the conversion of angiotensinogen to angiotensin I (Ang I) by renin. Later, Ang I is cleaved into Ang II by ACE to interact with Ang II type 1(AT1) and Ang II type 2 (AT2) receptors [52]. RAS is one of the most important systems in the pathogenesis of cardiovascular and cerebrovascular diseases. The distribution of ACE2 in the brain is mainly in cerebral microvascular endothelial cells and astrocytes [53]. This indicates that SARS-CoV-2 might bind to this protein in the brain and cause cerebral microvascular endothelial damage or endotheliitis. In addition, ACE2, a type I transmembrane protein composed of 805 amino acids [54], converts Ang I to Ang-(1–9) and Ang II to Ang-(1–7) [55]. This enzyme pathway that degrades Ang I and Ang II can negatively regulate the activation of RAS and reduce the harmful effects on cerebral blood vessels by inactivating Ang II and forming antagonist peptides [52, 56]. However, when SARS-CoV-2 infection occurs, the combination of SARS-CoV-2 and ACE2 activates the RAS axis, which can directly cause the loss of ACE2 and indirectly lead to the loss of ACE through proteolytic processing and shedding, shifting the balance of ACE/ACE2 towards a higher level of Ang II [57, 58]. This can greatly increase the risk of ischemic stroke in the following two ways. On one hand, increased Ang II blocks blood flow to the brain through the AT1 receptor in the brain, which leads to tissue ischemia, inflammation, oxidative stress, cell damage, and apoptosis. On the other hand, Ang-(1–7), which stimulates Mas receptors to promote cerebral angiogenesis is reduced, resulting in decreased cerebral blood flow, increased oxidative stress, neuroinflammation, and neuronal death [59].

In addition to direct interaction with cerebral blood vessels, SARS-CoV-2 can indirectly cause ischemic stroke by acting on the cardiovascular system. ACE2 receptor is abundantly expressed in myocardium, vascular endothelium, and arterial smooth muscle [60]. SARS-CoV-2 can damage cardiomyocytes through a variety of mechanisms, including direct viral damage, systemic inflammatory response, destabilized coronary plaque, and severe hypoxia, leading to cardiac

dysfunction and arrhythmias [61, 62] and predisposing to thrombogenesis and stroke risk. The baseline level of ACE2 expression in patients with hypertension, cardiovascular disease, and advanced age is reduced, which makes them more susceptible to SARS-CoV-2 mediated ACE/ACE2 imbalance [63]. ACE2 not only protects vascular endothelium and reduce atherosclerosis [64, 65] but also regulates vascular function by regulating nitric oxide release and oxidative stress [66]. When the level of ACE2 expression reduces, vascular endothelium function is impaired, and the balance of ACE/ACE2 tends to be at a higher Ang II level, which may promote thrombosis [67]. ACE metabolizes bradykinin, which causes vasoconstriction and reduces the release of tissue plasminogen activator (t-PA) [68]. Ang II induces endothelial cells to express plasminogen activator inhibitor (PAI) through the AT1 receptor resulting in PAI/t-PA imbalance and a hypercoagulable state [69, 70]. Ang II/AT1 receptor can enhance oxidative stress and inflammation by activating nicotinamide adenine dinucleotide phosphate oxidase. AT1 receptor activates NF-κB and activated protein 1 to initiate transcription of multiple pro-inflammatory genes. AT1 receptor also activates MCP-1 to induce inflammatory cell accumulation, adhesion, and infiltration [51]. Inflammation can aggravate coagulation disorders through the inflammation and coagulation mechanisms mentioned above.

3. Hypoxia

ACE2 is also expressed in the carotid body [71]. Some studies suggest that hypoxia in patients with COVID-19 may be caused by impaired oxygen sensing mechanisms in the carotid body and reduced oxygen transport capacity of the blood [72]. Decreased red blood cell count [73, 74] and low hematocrit [75] can be observed in COVID-19 patients with hypoxia. Two potential mechanisms have been identified: 1) SARS-CoV-2 interacts with hemoglobin molecules through CD147, CD26, and other receptors located in red blood cells and/or blood cell precursors; 2) The effect of hepcidin on viral spike protein can cause blockage of iron transportation [76]. Hypoxia is common in patients with COVID-19 [77–79].

Hypoxia is not only the result of vascular occlusion but local or systemic hypoxia can also stimulate thrombosis [80] and increase its incidence [81, 82]. The brain receives 15% of the total cardiac output and 20% of the body's oxygen supply. The brain is very susceptible to changes in oxygen levels. Even short-term hypoxia can affect the brain [83]. Hypoxia can increase the expression of ACE, endothelin-1 gene,

endothelin A and B receptor mRNAs, and platelet-derived growth factor chain gene in cardiac endothelial cells [84] leading to vascular function disorder. Hypoxia can activate the early growth response 1 transcription factor leading to the de novo transcription/translation of TF in mononuclear phagocytes and smooth muscle cells, which eventually causes fibrin deposition in blood vessels. Hypoxia also upregulates plasminogen activator inhibitor-1 (PAI-1), which in turn amplifies the inhibitory effect on plasmin [85]. In addition, hypoxia can increase the expression of hypoxia-inducible factor (HIF). HIF can directly activate platelets and coagulation factors, increase TF and PAI-1 expression, and inhibit anticoagulant protein S [78]. Hypoxia increases the risk of thrombosis by regulating the coagulation system and fibrinolytic system. Besides, hypoxia can also aggravate inflammation by inducing proinflammatory mediators, such as TNF-α and IL-1, and further aggravate coagulation dysfunction, thereby increasing blood viscosity and hypercoagulability [80]. ACE2 acts as a vasopressor in the lung epithelium and its homologous enzyme, ACE1, acts as a vasoconstrictor. These two enzymes form a balance under normoxic conditions. However, under hypoxic conditions, HIF-1 in pulmonary artery smooth muscle cells can upregulate ACE1 and downregulate ACE2 expression [86], which can cause pulmonary vasoconstriction and further exacerbate hypoxia.

4. Stress disorders

ACE2 in the hypothalamus can suppress stress and anxiety by inhibiting the production of corticotropin-releasing hormone [87] and increasing the production of Ang-(1–7) [88–91]. The decrease in ACE2 caused by SARS-CoV-2 infection affects this regulatory mechanism. The high expression of Ang-II caused by SARS-CoV-2 infection can bind to AT1 receptor in the brain, thereby causing stress-related behaviors, including anxiety, depression, and panic [92]. In addition, during the SARS-CoV-2 pandemic, serious mental health crises have occurred throughout the world [93]. The pressures associated with COVID-19 will continue to exist, including self-isolation, social alienation, unemployment, and disease threats [94]. The pressure and psychological crisis because of COVID-19 will exacerbate the stress disorder.

Multicenter studies have shown that acute stress conditions can cause a sudden stroke. Such patients were first observed in 1956 [95]. Psychological stress is common for up to 1 month before the onset of the illness. Studies have shown that 16.5% of the stroke patients have psychological stress [96]. Psychosocial

pressure leads to an increase in morbidity and mortality of atherosclerotic thrombotic cerebrovascular disease, that is, ischemic stroke, by 1.5 to 2.5 times [97]. Physiological prethrombotic stress response is part of the fight or flight response, but under acute stress, vulnerable individuals with cardiovascular diseases (because of their impaired endothelial function) may have excessive prethrombotic stress response and increases the risk of stress triggering atherosclerotic thrombosis [98]. Acute stress can cause changes in various procoagulant molecules, such as fibrinogen, coagulation factors, platelet activity, thrombin-antithrombin complex, and fibrin protein D-dimer leading to hypercoagulable states. The contributory factors such as advanced age, male gender, cardiovascular disease, and negative emotions, can exacerbate the above-mentioned hypercoagulation [99, 100]. Besides, acute stress increases the proinflammatory cytokines in circulation, such as IL-6, TNF-α, and IL-1. Proinflammatory cytokines can also exacerbate the hypercoagulable state. IL-6 is a strong inducer that induces the liver to produce CRP, fibrinogen, and a series of other hemostatic factors [101]. Pathological changes under acute stress greatly increases the risk of ischemic stroke.

The characteristics and pathophysiological changes of patients with coronavirus disease 2019 (COVID-19) infections

Characteristics	Pathophysiological Changes
Abnormal immune response	Inflammation; hypercoagulable state
Renin angiotensin system disorder	Vascular endothelial damage; hemodynamic disorder; hypercoagulable state; inflammation
Hypoxia	Vascular dysfunction; inflammation; hypercoagulable state
Stress disorder	Inflammation; hypercoagulable state

Results and discussions

A meta-analysis of 46,248 patients with COVID-19 showed that the most common comorbidities affecting patients are hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease, among others [102]. Hypertension (OR: 2.29, $p < 0.001$), diabetes (OR: 2.47, $p < 0.001$), chronic obstructive pulmonary disease (OR: 5.97, $p < 0.001$), cardiovascular disease (OR: 2.93, $p < 0.001$), and cerebrovascular disease (OR: 3.89, $p = 0.002$) were independent risk factors for COVID-19 [103]. Advanced age and these comorbidities were also found to be risk factors for ischemic stroke in COVID-19 patients [104]. The prevalence of ischemic stroke in COVID-19 patients was estimated to be 1.6%

(95% CI, 0.8–2.5%) based on a meta-analysis of available cohort studies [6]. Compared to that in the non-COVID-19 cohort, COVID-19-related ischemic stroke patients have increased stroke severity on admission. Studies have suggested that SARS-CoV-2 infection might cause direct vascular disease or enhance the immunogenic thrombosis environment through several mechanisms [105]. The wide range of multi-system complications of COVID-19, including acute respiratory distress syndrome, arrhythmia, shock, pulmonary embolism, cytokine storm, and secondary infection could further exacerbate the adverse consequences of stroke patients, including a higher deaths rate [105].

A study with a sample size of 20 people showed that the mechanisms of COVID-19-related ischemic stroke include cardiac embolism in 40% of cases, small vessel diseases in 5%, other established mechanisms in 20%, and cryptogenic causes in 35%. Of the 11 patients who completed vascular imaging, three (27%) had large vessel occlusion [106]. The pro-inflammatory and hypercoagulable states induced by SARS-CoV-2, which are prone to the formation of embolic stroke and large vessel occlusion-type stroke, are often described in severely ill patients with severe COVID-19 disease [107–109]. Patients with a history of vascular risk factors might have an increased risk of embolic stroke and large vessel occlusive stroke due to complications such as shock, hypotension, arrhythmia, heart failure, and diffuse intravascular coagulation [110]. In addition, studies have reported that COVID-19 patients with cardiovascular comorbidities have multiple cerebral infarctions, with no known extracerebral thrombosis. It could be that SARS-CoV-2 directly infects the cerebral arteries and causes vasculitis and vasospasms. In addition to continuous inflammation, the instability of atherosclerotic plaques and thrombosis lead to the occurrence of multiple cerebral ischemia [111, 112].

Stroke is a symptom of young patients (<50 years old) with mild COVID-19 disease, which has attracted increasing attention [107]. Compared with that in the previous year, the rate of young people suffering from large-vessel stroke has increased by seven-fold, suggesting that SAS-CoV-2 is independently associated with stroke [113]. Further, Oxley et al. recently reported five young COVID-19 patients (average age, 39 years) with no known risk factors, presenting with large vessel occlusion stroke. Arterial dissection might be one of the underlying pathological causes. One of the mechanisms is that the arterial dissection in COVID-19 patients could be secondary to excessive inflammation, which can cause endothelial

dysfunction. Another potential mechanism might be that SARS-CoV-2 directly invades vascular endothelial cells by binding to ACE2 receptors, thereby increasing the chance of vascular endothelial damage [114]. There is one case report showing that a young healthy woman developed cryptogenic stroke. The mechanism might be that SARS-COV-2 directly penetrates the endothelial cells of cerebral cortical arterioles, thereby inducing direct or immune-mediated damage [108]. There are also reports of small ischemic stroke [115], which could be caused by viral cerebral microvascular endotheliitis or systemic inflammation [116].

Limitations

We acknowledge that this review has certain limitations. Firstly, there are currently no relevant animal experiments on the molecular mechanism or pathogenic mechanisms in the context of COVID-19 and ischemic stroke. The research on the relationship between COVID-19 and ischemic stroke is mainly conducted through observational and statistical analyses, e.g. based on clinical manifestations, autopsy, blood tests, and imaging findings. This of course will be biased. Secondly, most of the included studies are case series or case reports; only a few are reports of cohorts, still with limited sizes. Additionally, most of these studies are based on relatively short follow-up times. Of note, the quality of some of the research studies is at least questionable; therefore, there is a high chance of reporting biases. Finally, many reports of ischemic stroke related to COVID-19 may be published in local languages (especially Chinese and Italian). Since this study was only based on publications indexed to PubMed, Web of Science, and other databases dedicated to COVID, biases cannot be ruled out.

Conclusions

There are currently no specific drugs for the management of COVID-19, and most patients with COVID-19 receive antiviral, anti-inflammatory, and support treatments. Many studies have reported ischemic stroke in patients with COVID-19 [5, 117–123]. Ischemic stroke has a high risk of causing disability and is associated with a high mortality rate. This article describes the effects of SARS-CoV-2 and the possible mechanisms that lead to ischemic stroke. It is hoped that when medical staff treat patients with COVID-19 (especially patients with a high risk of ischemic stroke such as the elderly and patients with hypertension, diabetes,

and cardiovascular diseases), they would pay attention to the occurrence of ischemic stroke and other thrombotic complications to improve the prognosis of patients with COVID-19.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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