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Nervous system complications of COVID-19 with a focus on stroke

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Abstract. – As a severe and highly contagious infection, coronavirus disease (COVID-19) affects all aspects of society and has become a global public health problem. Because of the complexity of the pathology of COVID-19, it is difficult to treat. An increasing number of reports have indicated that COVID-19 may have neurological complications, including stroke. The nervous system complications of COVID-19 have gradually attracted research attention. In this review, we summarize the latest findings related to COVID 19, elaborate on the possible mechanism of COVID 19 related onset of stroke, and summarize current treatment options because an improved understanding and appropriate treatments may improve the prognosis of patients with COVID-19-related stroke.

Key Words:
SARS-CoV-2, COVID-19, Stroke, Nervous system complications.

Introduction

Since December 2019, coronavirus disease (COVID-19) has spread globally. Approximately 28 million people have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and this number continues to increase. COVID-19 affects all aspects of society and has become a global public health problem. The World Health Organization declared COVID-19 a pandemic in March 2020[1]. From an epidemiological perspective, the incubation period is estimated to be 1 to 14 days, with a median of 5 to 6 days. However, it has been reported that the incubation period may be as long as 24 days[2]. At present, the basic reproduction number (R_0) value of COVID-19 is estimated to be between 2 and 3, which indicates that the infectivity of COVID-19 is higher than that of severe acute respiratory syndrome (SARS), which is caused by an associated coronavirus. In addition, the transmission of SARS-CoV-2 by asymptomatic carriers makes the prevention and treatment of COVID-19 more difficult.

The most common clinical manifestations of COVID-19 are respiratory symptoms, such as cough and expectoration, and fever, although an increasing number of atypical clinical manifestations are being reported, which increases the difficulty of diagnosing and treating COVID-19. In a recent case review of 55,924 laboratory-confirmed cases of SARS-CoV-2 infection, symptoms and signs included headache (13.6%) and myalgia or joint pain (14.8%)[3]. In another recent study of 214 patients with COVID-19, 78 (36.4%) developed neurological symptoms such as headache, dizziness, neurological deficits, and disturbances of consciousness, and these symptoms were more common in patients with severe disease[4], which increased the difficulty of treatment.

In this review, we focus on the neurological symptoms associated with COVID-19, especially acute cerebrovascular disease, and summarize its possible causes, as well as its treatment methods. Early treatment can greatly reduce the morbidity and mortality rate of patients with COVID-19 complicated by acute cerebrovascular disease.

Stroke and Other Neurological Complications of COVID-19

Coronavirus infection has been reported in patients with encephalitis, optic neuritis, multiple sclerosis, and Parkinson's disease. Viruses, including human coronavirus 229e (HCoV-229e), HCoV-293, and HCoV-oC43, have also been isolated from cerebrospinal fluid and the brains of patients with multiple sclerosis. However, the significance of these findings is unclear because these viruses are common, and

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their pathogenic role in these diseases has not been determined[5-7]. SARS-CoV has been reported in the cerebrospinal fluid of patients with encephalitis and acute respiratory distress syndrome (ARDS)[8]. Middle East respiratory syndrome coronavirus can cause severe acute disseminated encephalomyelitis and vascular disease. Post-infectious brainstem encephalitis and Guillain-Barré syndrome have also been reported[9]. In recent COVID-19 case reports, neurological symptoms were among the most common symptoms after respiratory symptoms, including headache, nausea, vomiting, dizziness, myalgia, and fatigue[3]. Anosmia, taste disorder, and stroke are also possible neurological symptoms[10]. However, there are not many cases of COVID-19-related nerve injuries. Viral RNA of another novel human coronavirus, HCoV-OC43, has been detected in the cerebrospinal fluid of a 15-year-old child with acute demyelinating encephalomyelitis[11]. SARS coronavirus has also been detected in the serum and cerebrospinal fluid of two patients with persistent epilepsy and SARS[12]. Wang et al[13] showed that SARS-CoV-2 RNA was detected in the cerebrospinal fluid, indicating that SARS-CoV-2 has the potential to attack and damage the nervous system. An analysis of the clinical data of 214 patients with SARS-CoV-2-related ARDS who were hospitalized in Wuhan, China revealed that 78 patients (36.4%) had central nervous system symptoms or signs, including headache, dizziness, disturbance of consciousness, ataxia, acute cerebrovascular disease, and seizures. Nineteen patients (8.9%) had symptoms of neuropathy, such as hypofunction, hyposmia, or neuropathic pain, and seven patients (23%) had skeletal muscle symptoms[14]. The study found that the incidence of acute cerebrovascular disease was 5.7% in patients with severe disease but only 0.8% in those with mild disease[14]. There is also evidence that COVID-19 may be associated with arterial and venous thromboembolic complications, including venous thromboembolism, ischemic stroke, acute coronary syndrome, and myocardial infarction. Lodigiani et al[15] found that the incidences of COVID-19 combined with ischemic stroke and acute coronary syndrome or myocardial infarction were 2.5% and 1.1%, respectively, in a hospital in Milan, Italy. Furthermore, ischemic stroke is a possible complication of COVID-19[16]. Oxley et al[17] recently reported that five patients with COVID-19 who were younger than 50 years were admitted to their hospital with macrovascular strokes. Notably, of the five patients, only one had a history of diabetes and mild stroke; two patients, a 33-year-old woman and a 37-year-old man, had no significant risk factors of cerebrovascular disease, and the source of thrombosis was not found on stroke screening. Based on these findings, we hypothesize that their strokes may have been associated with COVID-19. A patient with COVID-19 hospitalized in the Philippines developed dysarthria and weakness of the right upper and lower limbs. Computed tomography (CT) suggested that the cause was an acute ischemic cerebrovascular disease. The patient's symptoms improved after undergoing recombinant tissue plasminogen activator (rtPA) intravenous thrombolytic therapy[18]. Saggese et al[19] reported a 62-year-old patient with COVID-19 with stroke who had ischemic injuries and venous thrombosis at different intracerebral sites; this patient underwent rtPA treatment, which improved the respiratory and neurological conditions. There have been several reports on COVID-19 combined with cerebral hemorrhage, besides stroke. Sharifi-Razavi et al[20] reported a case of COVID-19 complicated by intracranial hemorrhage. Skull CT showed that the patient, a 79-year-old man, had a large amount of bleeding, and the location was atypical of hypertensive hemorrhage. Notably, the patient had no history of hypertension or anticoagulant drug use. It could not be determined whether his intracranial hemorrhage was caused by COVID-19 or was coincidental. Degeneffe et al[21] described three patients with COVID-19 who developed acute hemorrhage after intracranial biopsies. Of 31 patients who underwent brain surgery, three were confirmed to have acute SARS-CoV-2 infection. All three patients with COVID-19 had signs of diffuse intraparenchymal hemorrhage postoperatively after intracranial biopsy. The exact cause of these postoperative complications could not be determined, although the SARS-CoV-2 infection may have led to an increased risk of bleeding. Therefore, it is important to pay greater attention to the cerebrovascular manifestations of COVID-19. The new American Heart Association/American Stroke Association guidelines[22] state that 5.9% of COVID-19 patients had a stroke on an average of 10 days after the onset of symptoms. Therefore, the possibility of stroke should be recognized in patients with COVID-19 because early intervention and treatment may greatly reduce the possibility of stroke-related complications.

Etiology of COVID-19-Related Stroke

The etiology and pathogenesis of COVID-19-related stroke are unknown, although several possible mechanisms have been proposed. Some studies have shown that patients with COVID-19 experience a transient increase in serum inflammatory cytokines[23]. The levels of pro-inflammatory cytokines, such as interleukin-2, interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor-alpha, have been reported to be substantially increased in fatal cases[24]. These inflammatory factors may cause vascular endothelial dysfunction, increase blood procoagulant activity, and thus contribute to the formation of occlusive thrombus in arterial plaques, leading to the occurrence of stroke[25].

Some studies have found that the incidence of ischemic stroke in patients with severe COVID-19 is much higher than that in patients with mild symptoms. Many patients with severe COVID-19 develop sepsis-induced coagulopathy (SIC), with high D-dimer and fibrinogen levels. SIC is the precursor state of disseminated intravascular coagulation, which is associated with prothrombin time, high D-dimer, and thrombocytopenia. It is also associated with systemic inflammation, endothelial dysfunction, microthrombosis, and organ failure caused by infection[26,27]. In a retrospective study comparing the clinical characteristics of 113 patients who died owing to COVID-19, the D-dimer level in fatal cases was significantly higher than that in recovered cases. This is another possible pathogenic mechanism whereby strokes may occur in patients with COVID-19[24].

The third possible mechanism causing COVID-19 is SARSCoV2, which binds to the angiotensin-converting enzyme 2 (ACE2) through its spike protein[28]. ACE2 is expressed in endothelial cells and smooth muscle cells of the lung, small intestine, and brain. Overexpression of ACE2 in nerve cells or endothelial progenitor cells can reduce the risk of ischemic stroke[29]. SARS-CoV-2 may block ACE2 receptors and thus lead to functional underexpression of ACE2, thereby increasing the risk of stroke.

The underlying mechanism whereby hemorrhagic stroke may be associated with COVID-19 is unclear. A case report of patients with COVID-19 with cerebral hemorrhage showed that COVID-19 may be associated with an increased risk of intracerebral hemorrhage[13]. As mentioned elsewhere in this review, SARS-CoV-2 binds to ACE2 via its spike protein, which causes symptoms in the lungs and extrapulmonary organs. ACE2 antagonizes ACE1 and angiotensin II. ACE2 directly cleaves angiotensin II to angiotensin (1-7), angiotensin I to angiotensin (1-9), and then further to angiotensin (1-7). Angiotensin (1-7) produces vasodilation and anti-inflammatory effects by binding to Mas receptors[30]. Therefore, ACE2 can reduce blood pressure. Because of the decreased expression of ACE2 in patients with hypertension, the ability of ACE2 to reduce blood pressure also decreases. After SARS-CoV-2 infection, the expression and function of ACE2 protein are decreased. Because of the low expression of ACE2 in patients with hypertension, SARS-CoV-2 infection may be more likely to induce cerebral hemorrhage[13]. A second possible mechanism that may lead to cerebral hemorrhage in COVID-19 patients is coagulopathies and a prolonged prothrombin time[31], both of which increase the risk of cerebral hemorrhage.

Recommendations for the Treatment of COVID-19-Related Stroke

At present, there are a limited number of case reports and clinical studies on COVID-19-related stroke. Therefore, there is still a lack of guidance on the effective treatment for patients with COVID-19 with cerebrovascular complications. According to one case report, the symptoms of neurological deficit were reduced in two patients treated early with rtPA[18,19]. Moreover, the rescue application of tissue plasminogen activator (tPA) can improve the recovery rate of patients with ARDS, thus reducing COVID-19-related mortality[32]; therefore, rtPA may be beneficial for patients with COVID-19, particularly for those with ischemic stroke. It is worth considering tPA therapy in patients with COVID-19 who experience an ischemic stroke within the thrombolytic treatment time window after assessing their risk of hemorrhage. Further large clinical studies are needed to confirm this. To select an antithrombotic regimen, the Ministry of Health of Iran recommends the following anticoagulant regimen for patients with COVID-19: (1) all hospitalized patients diagnosed with COVID-19 should receive subcutaneous injection of enoxaparin 40 mg/day or subcutaneous injection of 5,000 units of heparin two to three times a day for prevention or (2) patients in whom anticoagulants are contraindicated, mechanical prevention methods, such as compression socks, are recommended. In the updated fourth edition of the COVID-19 management guidelines, the World Health Organization also suggested that low molecular weight heparin

should be used to prevent venous thrombosis in adults and adolescents without contraindications. For patients with contraindications, an intermittent pneumatic compression device can be used if low molecular weight heparin cannot be used[33]. In a retrospective multivariate analysis of 440 patients with severe COVID-19 in Wuhan, heparin administration (mainly low molecular weight) for 7 days or more was associated with better prognosis among patients with severe COVID-19 who met the SIC criteria or had a significant increase in D-dimer levels[27]. Anticoagulant therapy may reduce the incidence of stroke in patients with COVID-19, particularly in patients with severe infection. However, the risk of bleeding needs to be completely assessed, and the blood pressure should be strictly controlled to prevent the possibility of secondary bleeding.

Moreover, because of the SARS-CoV-2 infection pathway, which binds to ACE2 via its spike protein[34], therapies targeting the renin-angiotensin system (RAS), such as angiotensin (1-7), have shown promise in preclinical models of stroke and for treating patients with COVID-19[30]. Furthermore, angiotensin type 1 receptor blockers (ARBs), such as losartan, may have a protective effect on stroke. Although there is concern that ARBs and ACE inhibitors may be harmful to patients with COVID-19 because they increase the expression of ACE2 and SARS-CoV-2-binding proteins, some researchers consider that it is not advisable to withdraw ACE inhibitors and ARBs in the treatment of COVID-19 patients[35]. The joint statement issued by the American Heart Association and the American Heart Failure Association also recommends the continued use of ARBs and RAS antagonists in patients with COVID-19[30].

Conclusions

Cerebral hemorrhage and infarction appear to be among the neurological complications of COVID-19. For patients with a high risk of coagulopathy, anticoagulant therapy with low molecular weight heparin should be considered, although this needs to be weighed against the risk of bleeding. In addition, it is important to maintain strict blood pressure control in patients with COVID-19. Thrombolytic therapy should be considered in patients with COVID-19 who develop acute cerebral infarction. Large studies are required to gain a better understanding of the treatment and prevention of cerebrovascular complications of COVID-19. Paying attention to the neurological features of COVID-19, especially stroke, and providing appropriate interventions can greatly improve the prognosis of patients with COVID-19 and reduce associated mortality and long-term disabilities.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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