

Influence of COVID-19 on Cerebrovascular Disease and its Possible Mechanism

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Abstract: The global spread of COVID-19 has caused a substantial societal burden and become a major global public health issue. The COVID-19 elderly population with hypertension, diabetes, cardiovascular, and cerebrovascular diseases are at risk. Mortality rates are highest in these individuals if infected with COVID-19. Although the lungs are the main organs involved in acute respiratory distress syndrome caused by COVID-19 infection, COVID-19 triggers inflammatory and immune mechanisms, inducing a “cytokine storm” that aggravates disease progression and may lead to death. Presently, effective drugs are lacking, although current studies have confirmed that drugs with therapeutic potential include redacivovir, lopinavir/ritonavir combined with interferon- β , convalescent plasma, and monoclonal antibodies. Currently, the most reasonable and effective way to prevent COVID-19 is to control the source of infection, terminate routes of transmission, and protect susceptible populations. With the rise of COVID-19 in China and worldwide, further prevention, diagnosis, and treatment measures are a critical unmet need. Cerebrovascular disease has high incidence, disability rate, and fatality rate. COVID-19 patient outcomes may also be complicated with acute stroke. This paper summarizes the influence of COVID-19 on cerebrovascular disease and discusses possible pathophysiological mechanisms to provide new angles for the prevention and diagnosis of this disease.

Keywords: novel coronavirus pneumonia, 2019-nCoV, SARS-CoV-2, cerebral vascular disease

Introduction

In December 2019, a group case of unexplained pneumonia occurred in Wuhan, Hubei Province, China.¹ With the spread of the epidemic, cases have consecutively appeared in other parts of China and abroad. On April 10, 2020, the number of countries involved has tripled with 1,521,252 cases worldwide and 85,054 deaths.² The epidemic has resulted in serious negative effects on health and socioeconomic development. On March 11, 2020, WHO declared COVID-19 as a pandemic.³ The agent of the disease is a novel coronavirus. On February 11, 2020, the International Committee on Virus Classification officially termed the virus “SARS-CoV-2”. It was formerly temporarily named 2019-nCoV, and the disease caused by novel coronavirus was termed Corona Virus Disease 2019 (COVID-19). Pneumonia caused by novel coronavirus was uniformly named “novel coronavirus pneumonia” by the National Health Commission of the people's Republic of China. The virus is the seventh member of envelope RNA coronavirus (sarbecovirus subgenus, coronavirus subfamily). Novel coronavirus belongs to novel coronavirus of β genus, with enveloped, round, or oval particles, often pleomorphic and 60–140 nm in diameter.⁴ Novel

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coronavirus is most similar to bat SARS-like coronavirus from the Chinese chrysanthemum-headed bat, with nucleotide homology of 84%, 78%, and 50% with bat SARS-like coronavirus, human SARS virus, and MERS virus, respectively.⁵ The most primitive host of novel coronavirus is the Chinese chrysanthemum-headed bat.⁶ Diseases are caused by spread from pangolin hosts to humans. Of the first 41 confirmed cases, 27 reported contact with the South China seafood market.¹ Therefore, at present, it is believed that the original source of novel coronavirus was the South China Seafood Market in Wuhan, and the source of infection was patients infected by novel coronavirus. Further, asymptomatic infections and incubation periods are considered potential sources of infection.⁷ The route of transmission is droplet, contact, aerosol, fecal-oral, and/or mother-to-child transmission.^{8–12} The average incubation period was 5.2 days, and the basic regeneration number (R_0) in the early stage of the epidemic was 2.2.¹³ Clinical symptoms include fever, cough, myalgia, or fatigue; atypical symptoms include expectoration, headache, hemoptysis, and diarrhea, approximately half of patients have dyspnea; complications include acute respiratory distress syndrome, acute heart injury, and secondary infection.¹ Chest CT revealed that the most common radiological manifestations on admission were ground glass shadow and bilateral patchy shadow.¹⁴ Novel coronavirus cases are often complicated with high risk of cerebrovascular diseases, such as cardio-cerebrovascular disease, hypertension, and diabetes,¹⁵ or death, occurring mainly in elderly and chronically ill patients.¹⁶ According to the influence of novel coronavirus on cerebrovascular disease and the clinical manifestations of COVID-19 patients, this paper expounds on the pathophysiological hypothesis of COVID-19's effect on cerebrovascular disease.

Increased Susceptibility and Poor Prognosis

Based on the current epidemiological data, people of all ages are generally susceptible to novel coronavirus. The latest findings published in the Chinese Journal of Epidemiology are based on the findings of 72,314 cases of COVID-19.¹⁷ The majority of confirmed cases are between the ages of 30 to 79 years (86.6%), mainly middle-aged and elderly individuals. The proportion of patients with hypertension, diabetes, and cardiovascular disease is 12.8%, 5.3%, and 4.2%, respectively, indicating that middle-aged and elderly individuals with chronic

diseases may be more likely to be infected. Compared with healthy individuals, stroke patients are mainly middle-aged and elderly individuals, with a higher proportion of diseases such as hypertension and diabetes. Thus, the elderly, individuals with chronic diseases, and individuals with poor resistance may be more susceptible to infection. A recent study on the clinical characteristics of 138 patients with novel coronavirus infection in Wuhan¹⁵ revealed that the median age was 56 years old, with a higher proportion of middle-aged and elderly people. Of cases, 64 were complicated with underlying diseases, including 14 cases of diabetes, 43 cases of hypertension, 27 cases of cardio-cerebrovascular diseases, and 10 cases of cancer. This study demonstrated that elderly patients with cerebrovascular diseases and risk factors such as hypertension and diabetes may be at the highest risk of infection. Zhong Nanshan's team reported that the median age of critical recombination was 52 years old, and that of the non-critical group was 45 years old. Males accounted for 58.10%, females accounted for 41.90%, and patients under 15 years old accounted for 0.9%, suggesting that the rate of infection is higher in males than in females, and infection in children is rare. Approximately a quarter of patients have hypertension, diabetes, coronary heart disease, and other diseases. Further, the proportion of patients with smoking history is less than 15%.¹⁸ Collectively, these data suggest that the elderly with cerebrovascular diseases may be more infectious than other groups. When these patients were admitted to the hospital, only 43.1% of the patients had a fever, and more patients presented with a fever while in hospital. Conversely, almost all patients with SARS and Middle East respiratory syndrome (MERS), both caused by coronavirus, had symptoms of fever at the time of diagnosis, and only 12% of the patients had no fever. The case fatality rate of COVID-19 is lower than that of SARS and MERS. COVID-19 is associated with a mortality rate of approximately 2.1%.¹ The case fatality rates of SARS and MERS were 9.6% and 34%, respectively.^{19,20} The study reported that elderly patients with cardiovascular and cerebrovascular diseases, diabetes, and hypertension had a higher case fatality rate than other populations. Blackburn et al²¹ reported that respiratory virus infection is associated with an increased risk of stroke in hospitalized stroke patients. The existing studies suggest that novel coronavirus is not conducive to the prognosis of patients with cerebrovascular diseases, and special attention should be paid to changes in their clinical condition.

Possible Mechanisms

Lymphocyte counts are low, prothrombin time is prolonged, and lactate dehydrogenase levels are significantly increased in all COVID-19 patients. White blood cell and neutrophil counts in severely infected patients are significantly increased, further, D-dimer, creatinine, and creatine kinase levels are also increased.¹⁵ More patients require oxygen therapy and may even require extracorporeal membrane oxygenation (ECMO) to provide respiratory support. It is suggested that the patient's body is in a state of hypoxia, inflammation, and hypercoagulability. These pathophysiological changes may underpin the development of stroke.

Inflammatory Mechanisms

Hematological reports of COVID-19 patients often include counts of white blood cells and neutrophils, and high C-reactive protein. Common complications include the presence of inflammatory reactions. COVID-19 patients with cerebrovascular diseases often present with complications such as hypertension, diabetes, hyperlipidemia, and other stroke risk factors. These risk factors are associated with pro-inflammatory changes, including leukocyte activation and cerebrovascular thrombosis under inflammatory stimulation. Inflammatory cells begin to accumulate in the vascular wall in the early stage of atherosclerosis, increase blood-brain barrier permeability, destroy brain cells, and activate the formation of atherosclerosis in the anterior and internal cerebral arteries. Endothelial dysfunction affects the automatic regulation of cerebral circulation. These processes may lead to plaque rupture and thrombosis, increasing the risk of stroke. Inflammatory markers such as leukocytes, fibrinogen, and C-reactive protein are independent predictors of ischemic stroke.²² Long-term chronic infection can increase the risk of stroke. In a case-control study,²³ acute infection in the previous week was reported to be a trigger for ischemic stroke. Acute and aggravated chronic infections may play a role by activating blood clotting and chronic infection and may lead to atherosclerosis. Inflammatory reactions in patients with COVID-19 may be a critical common determinant of atherosclerosis and stroke risk.

Immune Mechanisms

When an individual is infected with novel coronavirus, individuals with immune function may experience excessive systemic immune responses and even die of acute

respiratory distress syndrome and septic shock.²⁴ This mechanism is termed immunopathogenicity, in which the virus stimulates immunity and causes the immune system to attack itself. Currently, it is critical to avoid excessive immune responses in the whole body as well as improve the immune function of individuals with weak immunity. Cytokine storm is an over-activation of the immune system caused by infection, which leads to massive accumulation and exudation of inflammatory substances, leading to multiple organ failure and acute respiratory distress. This may be an important cause of death in severe and critical patients with COVID-19.²⁵ Accumulating evidence suggests that severe COVID-19 patients might present with cytokine storm syndrome.²⁶ Although the symptoms of most patients with coronavirus infection are mild at present, some patients present with milder symptoms in the early stage which rapidly worsen in the later stage; these patients eventually die of multiple organ failure, which is mainly due to the "cytokine storm". Cytokines include interferon (IFN), interleukin (IL), chemokine (chemokines), colony stimulating factor (CSF), and tumor necrosis factor (TNF) which are secreted by immune cells. Cytokines can have either pro-inflammatory or anti-inflammatory effects. When SARS swept through China in 2003, the cytokine storm was also a direct cause of death in many patients.²⁷ In 2009, excessive inflammation was observed in patients with acute respiratory distress syndrome caused by H1N1A infection.²⁸ The toxicity of the virus depends on the severity of the induced immune response. However, different viruses trigger cytokine storms via various mechanisms. As such, they cause different cytokine changes. For example, SARS-related cytokine storms are mainly related to interleukin (IL)-1 β , IL6, IL12, interferon (IFN)- γ , inducible protein (IP)-10, and monocyte chemoattractant protein-1 (MCP-1).²⁹ In contrast, cytokine storms caused by MERS coronavirus are mainly associated with IFN γ , tumour necrosis factor (TNF)- α , IL15, and IL17.³⁰ In the above-mentioned study, doctors at Wuhan Zhongnan Hospital observed that the blood levels of IL2, IL7, IL10, granulocyte colony stimulating factor (GSCF), MCP1, macrophage inflammatory protein (MIP)-1 α , and TNF- α in critically ill patients were significantly increased, suggesting that the cytokine storm was associated with disease severity.¹ Low levels of CD4+T and CD8+T and higher levels of IL-6 and IL-10 were observed in severe patients. In this regard, T cell subsets and cytokines are positively correlated with the severity of COVID-2019 symptoms.³¹

On January 25, the Lancet published an online paper on novel coronavirus.³² Coronavirus shows neuroinvasive characteristics secondary to peripheral organ replication in humans and animals. The invasion of the blood-brain barrier by coronavirus is related to the destruction of tight junctions of brain microvascular endothelial cells induced by coronavirus, which leads to blood-brain barrier dysfunction and enhanced blood-brain barrier permeability.³³ Researchers detected SARS-CoV nucleic acid in the cerebrospinal fluid of patients with SARS.³⁴ After invading brain tissue, SARS virus attracts CD68+ monocytes/macrophages and CD3+T lymphocytes to infected tissues through mixed cells to participate in the immune process. However, a large number of cytokines/chemokines are released after a viral infection, which induces an inflammatory cascade reaction and promotes atherosclerosis, plaque rupture, and thrombosis.³⁵ Toll-like receptor (TLR) is activated after coronavirus infection, which plays an important role in the mechanism of innate immunity and can promote atherosclerosis and accelerate the occurrence of ischemic stroke.^{9,36} Cytokine cascade aggravates ischemic brain damage and increases the risk of intracerebral hemorrhage after tissue plasminogen activator treatment.³⁷ IL-6 can contribute to increased probability of a thrombotic event, induction of platelet production, and promotion of plaque disruption.³⁸

Angiotensin-Converting Enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV and SARS-CoV-2, the spike protein S1 interacts with the host ACE2 receptor for adherence of viral particles to the cell membrane.^{39–41} In SARS, ACE2 signaling plays an important role in the pathogenesis of severe lung failure after viral infection.⁴² ACE2 is highly expressed in vascular endothelial cells, heart, kidney, liver, digestive tract, and other organs.⁴³ Tissues and organs expressing ACE2 may be sites of interaction between novel coronavirus and immune cells. ACE2 is a negative regulator of renin-angiotensin system (RAS), which can balance many functions of ACE. By targeting angiotensin II (Ang II), ACE2 shows protective effects in the cardiovascular system and many other organs.⁴⁴ ACE2 deficiency impaired endothelial function in cerebral arteries in adult mice and augmented endothelial dysfunction during aging,⁴⁵ indicating that ACE2 provides endothelial protection. ACE2 inactivates Ang II while generating angiotensin (Ang) 1–7 and exerts potent vasodilator effects via activation of the Mas receptor.⁴⁶

ACE2 is an important metabolic enzyme in RAS, which plays a central role in maintaining heart and brain homeostasis.⁴⁶ SARS-CoV infections and Spike protein of SARS-CoV reduce ACE2 expression.⁴⁷ A decrease in ACE2 is associated with a decrease in Ang 1–7 which has vasoprotective effects. The balance between the classical RAS ACE-Ang II-angiotensin 1 receptor (AT1R) regulatory axis and the ACE2-Ang 1–7-MasR counter-regulatory axis in the RAS system is disturbed, leading to higher Ang II levels in the blood. AngII levels in COVID-19 patients are markedly elevated and linearly associated with viral load and lung injury.⁴⁸ Ang II stimulates nuclear factor- κ B (NF- κ B) activation in human monocytes. NF- κ B participates in most signaling pathways involved in inflammation of atherosclerosis, which may contribute to the pathogenesis of atherosclerosis.⁴⁹

Angiotensin 1/7 stimulates Mas receptors to promote angiogenesis in brain tissue, inhibit oxidative stress, resist neuroinflammation, improve cerebral blood flow, and resist apoptosis.⁵⁰ Therefore, ACE2 as a target receptor can inhibit the beneficial effects of the RAS system in the brain. Due to ACE2 involvement in blood pressure regulation, a subset of hypertensive patients with COVID-19 may present with an abnormal increase in blood pressure and increased risk of cerebral hemorrhage. In addition, critically ill patients with COVID-19 are often associated with severe thrombocytopenia, which may be risk factors for acute cerebrovascular events in these patients. Therefore, we assume that Angiotensin-converting enzyme inhibitors (ACEI) and AT1R inhibitors may be used to reduce pulmonary inflammation and mortality in patients with COVID-19 pneumonia under conditions of controlled blood pressure.^{51,52} However, experiments in animals revealed that ACEI and angiotensin receptor blockers increase the number of ACE2 receptors in the cardiopulmonary circulation, which increases the risk of severe disease outcomes.⁵³

Hypercoagulable State

Clinical studies have demonstrated that blood of COVID-19 patients contained higher levels of D-dimer and prolonged prothrombin time,¹⁵ reflecting a hypercoagulable state of blood. Pulmonary infection is related to platelet aggregation and activation of the coagulation system.⁵⁴ Significantly increased levels of D-dimer in severe COVID-19 patients were observed,^{55,56} indicating that a hypercoagulable state may be an important marker of critical illness in COVID-19 patients. A clinical study demonstrated that anticoagulant therapy may be associated

with superior prognosis in severe COVID-19 patients with markedly elevated D-dimer levels.⁵⁷ Decreased blood oxygen saturation leads to the release of inflammatory factors.⁵⁸ One possible explanation for the increase in blood coagulability is that a decrease in blood oxygen triggers inflammatory factors, catecholamine, increased plasma levels of tissue factors, and platelet aggregation, which alter capillary blood flow due to increased sympathetic activity and more widespread micro-endothelial damage, resulting in blood coagulability.⁵⁹ If COVID-19 patients remain in a prolonged state of hypoxia, production of erythropoietin may increase, causing secondary polycythemia, increased hematocrit levels, increased blood viscosity, and slowing of blood flow.⁶⁰ More of these patients are concurrently complicated with risk factors of cerebrovascular disease,^{15,32} making them more prone to embolic vascular events and increasing the probability of acute ischemic stroke.

Hypoxemia

COVID-19 patients often present with hypoxemia due to respiratory dysfunction,^{15,61} the features of severe patients is acute respiratory distress syndrome.⁶² When bodily oxygen content changes, the brain is the first organ to be affected,⁶³ resulting in a series of pathophysiological changes. Hypoxia can dilate intracranial blood vessels and increase intracranial blood flow, cerebral capillary pressure, tissue fluid production, brain free radicals, membrane lipid peroxidation, and endogenous inhibitors; these effects may impact cell energy metabolism.^{64,65} Anaerobic glycolysis in the brain produces increased lactic acid and oxygen free radicals and lipid peroxides, weakened antioxidant system, and blood-brain barrier dysfunction.⁶⁶ Metabolic acidosis caused by hypoxia increases cerebral vasospasm and permeability, leading to interstitial brain edema, intracranial hypertension,⁶⁷ and decreased ATP production caused by hypoxia. This initiates an injury cascade encompassing intracellular Ca^{2+} overload, glutamate excitotoxicity, and oxido-nitrosative stress, culminating in neuronal and astroglial necrosis, apoptosis, and neurocognitive deficits.⁶⁸

Diagnosis of SARS-CoV-2

The diagnosis of the confirmed case should be based on suspected cases and provide any one of the following pathogenic or serological evidence: (1) Real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) for SARS-CoV-2 (2) Genome sequencing of the coronavirus showed highly homogeneity with the SARS-CoV-2. (3)

positive for the specific IgM antibody and IgG antibody to SARS-CoV-2 in serum test; or SARS-CoV-2 specific IgG antibody changes from negative to positive, or titer rising ≥ 4 times in the recovery phase above that in the acute phase.⁶⁹

Prevention

At present, there is a lack of effective treatments for COVID-19 virus infection. Clinical research is underway for an effective therapeutic, but the most effective immediate action involves scientific prevention and isolation. People of all ages are not resistant to novel coronavirus and may be infected if transmission conditions are satisfied. However, the elderly and individuals with cerebrovascular diseases are at risk; therefore, prevention and control in these populations are particularly important. Presently, the most effective way to treat the disease is to control the source of infection, use personal protective measures to reduce the risk of transmission, and protect vulnerable groups. It is suggested that the elderly and individuals with cerebrovascular diseases should reduce their outdoor activities, ensure good personal protection and hygiene, maintain good living habits, take the initiative to monitor the health of individuals and family members, ventilate and disinfect their rooms frequently, take medicine regularly, eat healthily, and maintain a positive mindset. If symptoms such as fever, cough, sore throat, chest tightness, and muscle soreness are present, individuals should undergo timely diagnosis, isolation, and treatment. When treating and nursing patients, medical staff have closer contact with patients and hence a higher risk of infection. Among the 138 consecutive patients admitted to Zhongnan Hospital of Wuhan University from January 1 to 28, the proportion of medical staff was as high as 29%.¹⁵ A retrospective analysis of 1,099 patients diagnosed with COVID-19 from 552 hospitals in 31 provinces revealed that the proportion of medical staff was 2.09%.¹⁸ When providing medical services for diagnosed patients or individuals suspected of infection, medical staff should wear goggles, protective clothing, and other additional protective measures to strengthen their own protection and prevent cross-infection.^{70,71}

Treatment

There is currently a lack of specific antiviral drugs for novel coronavirus. Clinically, most patients are mainly treated with empirical antiviral, anti-infective, glucocorticoid drugs, and/or supportive care for the most critically ill patients.^{16,72} Nevertheless, none of these approaches

have resulted in curative effects. Therefore, for COVID-19 patients with cerebrovascular diseases, personalized medication should be used according to the individual factors of the patients. In addition to COVID-19 symptoms, it is necessary to concurrently strengthen treatments for basic cerebrovascular diseases to effectively reduce COVID-19-associated mortality and improve prognosis. The main treatment principle of cerebrovascular disease is to treat reversible etiology, control risk factors, and reduce complications. General treatment includes bed rest, monitoring vital signs, finger oxygen saturation, symptomatic support treatment, and maintaining water, electrolytes, acid-base balance, and stability of the internal environment. The negative psychological impact of quarantine is evident,⁷³ and psychological support may be conducive to symptom improvement of this disease. Antiviral therapies⁷⁴ such as interferon-alpha (5 million U per dose or equivalent for adults, 2 mL of sterilized water for injection, twice a day nebulized inhalation), lopinavir/ritonavir (two tablets per administration, twice a day for no more than 10 days), ribavirin (recommended in combination with interferon or lopinavir/ritonavir, 500 mg for adults, two to three times a day, intravenous infusion, course of treatment no more than 10 days), chloroquine phosphate (500 mg, twice a day for adults, no more than 10 days), and abidol (200 mg, three times a day for adults, no more than 10 days) have been indicated. Nevertheless, it is not recommended to use three or more antiviral drugs concurrently, and the use of related drugs should be stopped if intolerable side effects are experienced. Convalescent plasma therapy is suitable for patients with rapid progression, severe, and critical illness. Shufeng jiedu capsule (SFJDC, a traditional Chinese medicine) may also improve the condition^{74,75} Recently, a retrospective study of influenza, SARS, and MERS published in the *Lancet* reported that the use of glucocorticoids in patients with SARS and MERS viral infection did not improve prognosis but caused problems such as delayed cure, secondary infections, and osteoporosis. Therefore, it is recommended that glucocorticoids should not be used in the treatment of new coronary pneumonia.⁷⁶ Redacivovir holds the most potential for the treatment of 2019-nCoV at present.⁷⁷ The results of animal experiments have demonstrated that compared with the control treatment, redacivovir effectively reduced viral titer in lung tissue of MERS-CoV-infected mice and improved lung tissue injury. Further, its curative effects were superior to those of lopinavir/ritonavir combined with

interferon- β treatment. After the first case of novel coronavirus was diagnosed in the United States, after entering a critical state, the symptoms of dyspnea were significantly improved after the use of redcevir, and oxygen therapy was no longer required. However, research and development companies and physicians state that the effectiveness and safety of the drug have not been proven, and further clinical research is needed. The drug is currently in clinical trials⁷⁸ in China. Anticoagulant therapy is recommended for secondary prevention of stroke in patients with acute cerebrovascular disease with an abnormal increase in D-dimer. After treatment, patients are admitted to the isolation ward of the infection department, and concurrent rounds by neurologists in the isolation ward should occur daily to assist doctors with patient management.

Conclusion

COVID-19 may cause respiratory diseases as well as other primary and secondary nervous system diseases. At present, neurological symptoms have been reported in COVID-19 patients: acute cerebrovascular symptoms such as sudden speech confusion and limb paralysis; symptoms of intracranial infection such as headache, epilepsy, and disturbance of consciousness; symptoms of muscle damage such as soreness and weakness of limbs; and occasionally symptoms such as neuralgia, abnormal sensation. In this period of high incidence of COVID-19, neurologists need to pay attention to this patient population, especially patients with nervous system symptoms. Indeed, differential diagnosis of COVID-19 and early detection, diagnosis, treatment, prevention, and countermeasures are warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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