

COVID-19 Infection and Stroke

Infección por COVID-19 y accidente cerebrovascular

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ABSTRACT

The actual Coronavirus Disease 2019 (COVID-19) infection is an ongoing pandemic, characterized by high morbidity and mortality produced by SARS-CoV-2 virus. Studies reported a stroke frequency around 5-20% in infected patients; however, SNC invasion and pathophysiological mechanisms related to stroke in COVID-19 patients are still unknown. Several studies have demonstrated that SARS-CoV-2 infection is linked to a prothrombotic state causing venous and arterial thromboembolism. Also, an overstated inflammatory response with recruitment of blood cells and disproportioned secretion of proinflammatory cytokines has been reported. Finally, cardioembolism and hypoxia have been proposed as surrogate mechanisms. It is essential to define the pathophysiological mechanisms of stroke during the infection in order to apply more specific treatments to avoid further stroke complications.

Keywords: coronavirus; stroke; SARS-CoV-2; cerebrovascular diseases; neurologic symptoms.

RESUMEN

La actual pandemia de COVID-19 causada por el virus SARS-CoV-2, se caracteriza por una alta morbilidad y mortalidad. Algunos estudios han reportado que la frecuencia de ictus en pacientes infectados con el virus oscila entre un 5-20 %. A pesar de estas cifras alarmantes, las vías por las cuales el virus llega al sistema nervioso central y los mecanismos fisiopatológicos por los que puede ocurrir un ictus en estos pacientes no han sido totalmente esclarecidos. Numerosos estudios han demostrado que la infección por SARS-CoV-2 está asociada a un estado protrombótico, capaz de causar un tromboembolismo arterial y venoso. Además, se ha reportado una respuesta inflamatoria exacerbada, con reclutamiento de células sanguíneas y una secreción desproporcionada de citoquinas proinflamatorias. También la hipoxia y fenómenos cardioembólicos han sido propuestos como posibles mecanismos. Es esencial definir con exactitud los mecanismos fisiopatológicos que vincula la infección por SARS-CoV-2 con la ocurrencia del ictus, con la finalidad de aplicar tratamientos más específicos y evitar futuras complicaciones.

Palabras clave: coronavirus; ictus; SARS-CoV-2; enfermedad cerebrovascular; síntomas neurológicos.

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Introduction

Coronaviruses belong to the family Coronaviridae and are large enveloped non-segmented positive-sense RNA viruses. Their genome is approximately 31 Kb, making these viruses the largest known RNA viruses.⁽¹⁾ Briefly, coronaviruses infecting humans (hCoVs) can be classified in two groups according to their virulence degree: low pathogenic, which include HCoV-229E, HCoVOC43, HCoV-NL63, HCoV-HKU and highly pathogenic CoVs such as: severe acute respiratory syndrome CoV (SARSCoV), Middle East respiratory syndrome CoV (MERSCoV)⁽²⁾ and the recent discovered SARS-CoV-2.

The actual Coronavirus Disease 2019 (COVID-19) infection is an ongoing pandemic, characterized by high morbidity and mortality produced by SARS-CoV-2 virus. This virus causes acute, highly lethal pneumonia with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV previous infections.^(3,4) Based upon the first-hand evidence from Wuhan, the most common symptoms of COVID-19 infection were fever and dry cough at the onset of illness.⁽³⁾

In a recent study of COVID-19 infected patients, neurologic symptoms were found in 36.4% (78/214 cases) of the subjects and the most common symptoms identified were dizziness (16.8%), headache (13.1%), and anosmia (5.1%).⁽⁵⁾ In addition, neurological symptoms were more frequent in patients with more severe disease, denoting the appearance of acute cerebrovascular events (6%), impaired consciousness (15%), and muscle injury (19%).⁽⁵⁾ In relation to stroke; all cases, except one, occurred in the group with more severe infection (6% vs 1%, $p < 0.05$), and it was related to advanced age, cardiovascular risk factors and more severe pneumonia⁽⁵⁾. Similar results were published by *Li Y et al.*, who found an incidence of stroke of approximately 5% in COVID-19 patients.⁽⁶⁾ However, a recent report from the Spanish Society of Neurology (SEN), published 131 neurologic events in COVID-19 patients, and the most prevalent syndromes were: confusional syndrome or mild-moderate encephalopathy (28.3%) and stroke (22.8%). Instead of this stroke percentage, the exactly pathophysiological mechanisms linking SARS-CoV infection and stroke in COVID-19 patients are not defined.⁽⁷⁾

Neuroinvasion mechanism of SARS-CoV-2

Many viruses are capable to reach the central nervous system (CNS) such as: herpes virus, arboviruses, measles, influenza and HIV, among others.^(8,9) There is no doubt that coronavirus are capable to infiltrate the CNS and CoV RNA has been detected in the central nervous system of patients with neurological diseases.⁽¹⁰⁾ Recently researchers confirmed the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing.⁽¹¹⁾

Central nervous system involvement has been previously reported in patients with SARS-CoV and MERS-CoV infections. A study in Saudi Arabia found that 25.7% of the MERS patients developed confusion and 8.6% experienced seizures.⁽¹²⁾ In addition, acute disseminated

encephalomyelitis, stroke and encephalitis have been reported for patients with MERS.⁽¹³⁾ During the SARS-CoV outbreak in 2002-2003, neurological symptoms were also described, although frequency was found low and in remote cases.⁽¹⁴⁾ However, during the course of hospitalized patients with SARS-CoV-2 infection, more than a third of the patients develop neurologic manifestations, which could be divided in central nervous system involvement, such as: dizziness, headache, impaired consciousness, ataxia, acute cerebrovascular disease, seizures; and peripheral nervous system symptoms: taste impairment, smell impairment, vision impairment, nerve pain, and skeletal muscle injury.⁽⁵⁾ Most of these symptoms are more frequent in severely affected patients, and stroke could be present in 6% to 23% of them.^(5,7)

The exact neuroinvasive route of SARS-CoV-2 is still unknown,⁽¹⁵⁾ however two ways have been proposed: via cribriform plate of the ethmoid bone and through the blood-brain barrier (BBB) after systemic circulatory dissemination.⁽¹⁶⁾ In the hematogenous route the virus could infect the endothelial cells of the BBB and pass through it, due to the affected permeability of the barrier as a result of the infection. In the other pathway, the virus could reach the CNS through the olfactory or trigeminal nerves.⁽¹⁷⁾ This is supported by the appearance of peripheral symptoms as anosmia (5.1%) and dysgeusia (5.6%) in COVID-19 infected patients.⁽⁵⁾ Also, in past outbreaks SARS-CoV has been isolated from brain tissue with the use of immunohistochemistry techniques, confirming the entry of the virus to the brain.^(10,18) Other authors have proposed that CoVs may first invade peripheral nerve terminals, and then gain access to the CNS via a synapse-connected route,^(19,20) however as anosmia and dysgeusia are early neurological symptoms in many COVID-19 patients, this route is less plausible.

It has been extensively reported that angiotensin-converting enzyme 2 (ACE2) facilitates SARS-CoV-2 cellular invasion in the different organs.⁽²¹⁾ This enzyme is a carboxypeptidase that lowers blood pressure by the catalysis of angiotensin II (vasoconstrictor) into angiotensin^(1,2,3,4,5,6,7) vasodilatador. As a transmembrane protein, ACE2 serves as the main entry point into cells for SARS-CoV2 and other coronavirus, and neurovirulence could be related to the ACE2 expression in the SNC. The brain has a high expression of this receptor, and it can be found in neurons and glial cells of cerebral cortex, striatum, hypothalamus and brainstem.⁽²²⁾ Also it has an extensive location in endothelial cells around the brain^(15,21). Previous studies have showed a positive correlation between ACE2 expression and *in vitro* SARS-CoV infection⁽²³⁾ and neuroinvasive

propensity of CoVs has been documented almost for all betacoronaviruses, including those with epidemic outbreaks: SARS-CoV⁽²⁴⁾ and MERS-CoV.⁽²⁵⁾

During the entry to the cells through ACE2 receptor, coronavirus spike S1 protein binds to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells. This entry process also requires priming of the S protein by the host serine protease TMPRSS2.⁽²⁶⁾ Overexpression of the ACE2 receptor in the brain capillary endothelium could favor the interaction between both proteins, increasing the risk of stroke.⁽²⁷⁾

Physiopathological mechanisms linking SARS-CoV-2 infection to stroke

There is previous published evidence that respiratory-related infection is an independent risk factor for acute cerebrovascular disease.⁽²⁷⁾ A number of potential mechanisms by which COVID-19 might increase stroke risk have been identified, but they have not been proven yet. These include exaggerated systemic inflammation or a “cytokine storm”,⁽²⁸⁾ hypercoagulability,⁽⁵⁾ cardioembolism from virus related cardiac injury⁽²⁹⁾ and hypoxia.⁽²¹⁾

Cytokine storm and a hipercoagulable state will be briefly discussed, as two of the most outstanding mechanisms related to stroke occurrence.

Exaggerated systemic inflammation or a “cytokine storm”

The innate immune response is the first line of defense against SARS-CoV-2 infection; however, if the immune response is deregulated, an extreme inflammation response will appear. It began with the recruitment of blood cells (monocytes and macrophages) after the virus infiltrates the lung parenchyma and begins to proliferate.⁽³⁰⁾ The following inflammatory response include: vasodilation, endothelial permeability and leukocyte recruitment, leading to a further pulmonary damage, hypoxemia and cardiovascular stress. If this exaggerated inflammation continues (even with diminishing viral loads), the result is a generalized systemic inflammation, which is extremely toxic and has the potential to injure several distant organs.⁽³⁰⁾

This exaggerated systemic inflammation or cytokine storm correlate with lymphocytopenia and is a hallmark of severe SARS-CoV-2 infection.⁽²⁸⁾ This include raised levels of several inflammatory markers such as: interleukin (IL)-6, IL-2, IL-7, tumor necrosis factor (TNF)- α , interferon- γ , inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP) 1- α , granulocyte-colony stimulating factor (G-CSF), C-reactive protein (CRP), procalcitonin, and ferritin.^(28,31) This overload of inflammatory mediators propagates from the initial organ injury (lungs) to other organs as heart and brain.

In addition, the infection of hematopoietic cells such as dendritic cells by SARS-CoV-2 induces low-level expression of anti-inflammatory cytokines (IFN- $\alpha\beta$) and up-regulation of pro-inflammatory cytokines such as: TNF, IL-6 and other chemokines (CCL3, CCL5, CCL2, and CXCL10).⁽³²⁾ Together with these, macrophages express elevated levels of IFN and other pro-inflammatory cytokines;⁽³²⁾ and infected airway epithelial cells by the virus also produce large amounts of chemokines CCL3, CCL5, CCL2, and CXCL10.⁽³³⁾

In a cohort of confirmed COVID-19 patients in Wuhan, China an increasing in neutrophil-to-lymphocyte ratio (NLR) and a decreasing in CD4+ T cells was reported; however no significant change in the number of CD8+ cells and B cells were found.⁽³⁴⁾ The increase of NLR was consistent with the findings from *Wang et al* that patients with SARS-CoV-2 infection had a rising neutrophil count and a falling lymphocyte count during the severe phase.⁽³⁵⁾ The consumption of CD4+ and CD8+ T cells, and the decrease of regulatory T cells, leads to a cytokine storm, which might result in aggravated inflammatory response to SARS-CoV-2 infection.⁽³⁴⁾

Similar inflammatory response patterns have been reported in previous coronavirus epidemic.^(36,37) For example in SARS-CoV infection, patients with a more severe disease had higher serum levels of pro-inflammatory cytokines (IFN- γ , IL-1, IL-6, IL-12, and TGF β) and chemokines (CCL2, CXCL10, CXCL9, and IL-8), with very low levels of the anti-inflammatory cytokine, IL-10 than patients with less severe infection.^(36,37) Also, in MERS infection, studies showed elevated levels of serum pro-inflammatory cytokines (IL-6 and IFN- α) and chemokines (IL-8, CXCL-10, and CCL5) in individuals with severe infection compared to those with mild to moderate disease.⁽³⁸⁾

Several factors have been associated with this cytokine storm: 1) Rapid virus replication, which could lead to enhanced cytopathic effects and production of higher levels of proinflammatory

cytokines and chemokines by infected epithelial cells;⁽³⁹⁾ 2) Delayed IFN responses which postpone innate immune response; 3) Monocyte-macrophages and neutrophil accumulation, which are a reservoir and source of cytokines and chemokines;⁽⁴⁰⁾ and 4) Lower levels of regulatory T cells, which are vital in maintaining immune homeostasis and the prevention of excessive inflammation after infection.⁽⁴⁰⁾

This exaggerated inflammatory response, with the recruitment of cells, the disproportioned secretion of proinflammatory cytokines and chemokines, an endothelial cell apoptosis with further vascular leakage and altered tissue homeostasis, is closely linked to the occurrence stroke.

Hypercoagulability state

Mao et al found that patients with severe SARS-CoV-2 infection had higher D-dimer (DD) levels than that of patients with non-severe infection and also severe platelet reduction; and both could be linked to the occurrence of stroke in cases of severe infection.⁽⁵⁾ High levels of DD are a sign of excessive coagulation activation and hyperfibrinolysis. This state of hypercoagulability increases the risk of arterial thrombosis through the formation of thrombus and platelets aggregation, and it is related to inflammation, with endothelial and smooth muscle cell activation; macrophage stimulation and tissue factor expression.⁽⁴¹⁾ This state of hypercoagulability is accompanied with high levels of FVIII, fibrinogen, plasminogen, VWF, FX and FXIII, and leads the haemostatic balance towards thrombus formation, increasing the risk of arterial thrombosis.^(41,42) In addition, a hypercoagulable state is associated with unbalanced endothelial function that facilitates intravascular coagulation in the venous or arterial bed, which may towards to cerebral artery occlusion and stroke.⁽⁴¹⁾

Previous studies have demonstrated that other virus (eg. *Mycoplasma pneumonia*) can affect the vascular walls of brain circulation by the induction of proinflammatory cytokines and chemokines;⁽⁴³⁾ which may cause local vasculitis and thrombotic vascular occlusion. In addition, leukocyte activation under septic state may also induce the release of TNF and IL-1, which may in turn induce endothelial organ activation, and likely alter the normal anticoagulant state of the endothelium tissue. The recent explained cytokines storm could support this hypercoagulability state, because inflammatory cytokines can promote the activation of blood coagulation pathways.⁽⁴⁴⁾ Also, sepsis, which is commonly found in patients with SARS-CoV-2 infection, could cause disseminated intravascular coagulation.⁽⁴⁵⁾

A recent report published by *Beyrouti et al*, demonstrated in six COVID-19 infected patients large vessel ischemic occlusion elevated D-dimer levels ($\geq 1000\mu\text{g/L}$).⁽⁴⁶⁾ Increased levels of serum ferritin and high-sensitivity C-reactive protein were visualized in 5 patients.⁽⁴⁶⁾ Higher levels of ferritin and lactate dehydrogenase have been previously reported in severe COVID-19 infected patients.⁽⁴⁷⁾

It is important to remember that virus might enhance the production of antibodies such as: IgM anticardiolipin antibodies and antiphospholipid antibodies, which could increase the risk of cerebral thrombosis. *Zhang et al* recently published three COVID-19 cases with antiphospholipid antibodies, -type Anticardiolipin IgA, anti- β 2-glycoprotein I IgA and IgG- and multiple cerebral infarcts.⁽⁴⁸⁾ These antiphospholipid antibodies are the hallmark for the diagnosis of the antiphospholipid syndrome; and they probably cause lymphocytic infiltration, necrosis of smooth muscle and occlusion of the vessel wall in brain capillaries, improving the risk of stroke.^(48,49)

Final comments

Peripheral and central nervous system involvement have been demonstrated in patients infected with SARS-CoV-2 virus,⁽⁵⁾ and stroke could be presented in almost 20% of those patients.⁽⁷⁾ However, until date the exact mechanisms of neuroinvasion of the virus and the causal relation between etiopathogenic agent and stroke is unknown.

Several studies have demonstrated that SARS-CoV-2 infection is linked to a prothrombotic state causing venous and arterial thromboembolism with elevated D-dimer Levels^(5,46,50). Additionally, an overstated inflammatory response, with recruitment of blood cells and disproportioned secretion of proinflammatory cytokines and chemokines, will exacerbate endothelial and mononuclear cell activation with expression of tissue factor leading to coagulation activation and thrombin generation,^(5,46) which are known as leading causes of ischemic stroke.

However, patients with COVID-19 usually carry vascular risk factors, which are strongly associated to stroke occurrence, such as: advanced age, hypertension, diabetes, obesity and others. Cardioembolism and hypoxia as a result of heart and lung injuries during infection could cause or even facilitate stroke in these patients.

It is crucial to evaluate the risk of stroke in COVID-19 patients and consider the possible mechanisms involved to apply more specific treatments in order to avoid stroke progression.

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Conflict of interest

The authors declare no conflicts of interest.

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