REVIEW
Pathophysiological mechanisms of covid-19 cerebrovascular accident in young adults


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Abstract
Introduction: COVID-19 is an infection caused by the SARS-CoV-2 virus, which was originated in the city of Wuhan (China) and spread rapidly to other countries and continents until the World Health Organization (WHO) declared a pandemic situation. Among the serious conditions resulting from the pathology, it was observed that certain patients had systemic neurological symptoms, such as cerebrovascular accident (CVA). Objective: The objective of this study is to propose a discussion about the current knowledge about the pathophysiology of CVA in young adults with COVID-19. Methods: A search was carried out in the main databases: Lilacs, Bireme, Pubmed in Portuguese and English, for articles of the current year. The choice had taken place at random, obviously, following a line of reasoning of the authors involved. The keywords searched were: COVID-19, Cerebrovascular accident, Pathophysiology, Coagulopathy. Results: It is conjectured countless possibilities that would explain the connection of the virus to the cerebrovascular disease. SARS-CoV-2 is considered to instigate an inflammatory process in the arterial wall and this is responsible for the CVA. Although the correlation between these two clinical conditions is notorious, there are still no studies that clearly determine the pathophysiological mechanism involved in the process. Conclusion: Neurological manifestations in the COVID-19 are reported, including cerebrovascular accident. The state of hypercoagulability generated by the cytokine storm seems to be related to the pathophysiological mechanism of this condition. Still, there is no clear evidence in this regard and studies are needed in order to elucidate its physiopathogenesis.

Keywords: coronavirus infections, stroke, pathophysiology, coagulopathy.

Resumo
Mecanismos fisiopatológicos do acidente vascular encefálico por COVID-19 em adultos jovens

Introdução: A COVID-19 é uma infecção causada pelo vírus SARS-CoV-2, que se originou na cidade de Wuhan (China) e se propagou rapidamente para outros países e continentes até que a Organização Mundial da Saúde (OMS) declarasse situação de pandemia. Dentre as condições
graves decorrentes da patologia, observou-se que determinados pacientes apresentaram sintomatologias neurológicas sistêmicas, como acidente vascular encefálico (AVE). **Objetivo**: O objetivo do presente trabalho é propor uma discussão acerca dos conhecimentos atuais sobre a fisiopatologia do AVE em adultos jovens com COVID-19. **Métodos**: Foi realizada uma busca nas principais bases de dados: Lilacs, Bireme e Pubmed nos idiomas português e inglês, de artigos publicados no ano vigente. A escolha ocorreu de forma aleatória, obviamente, seguindo uma linha de raciocínio dos autores envolvidos. As palavras-chave pesquisadas foram: COVID-19, Acidente Vascular Encefálico, Fisiopatologia, Coagulopatia. **Discussão**: Conjetura-se inúmeras possibilidades que explicariam a ligação do vírus à doença cerebrovascular. É considerado que o SARS-CoV-2 instiga um processo inflamatório na parede arterial e isso seja responsável pelo AVE. Embora a correlação entre essas duas condições clínicas seja notória, ainda não existem estudos que determinem claramente o mecanismo fisiopatológico implicado no processo. **Conclusão**: Manifestações neurológicas na COVID-19 são relatadas, incluindo o acidente vascular encefálico. O estado de hipercoagulabilidade gerado pela tempestade de citocinas parece estar relacionado ao mecanismo fisiopatológico desta condição. Ainda assim, não existem evidências claras quanto a isso e estudos são necessários a fim de elucidar sua fisiopatogenia. **Palavras-chave**: infecção por coronavírus, acidente vascular enCEFálico, fisiopatologia, coagulopatia.

**Resumen**

**Mecanismos fisiopatológicos del accidente cerebrovascular por COVID-19 en adultos jóvenes**

**Introducción**: El COVID-19 es una infección desencadenada por el virus SARS-CoV-2, que se originó en la ciudad de Wuhan (China) y se extendió rápidamente a otros países y continentes hasta que la Organización Mundial de la Salud (OMS) ha declarado pandemia. De entre las condiciones graves decorrentes de la patología, se observó que ciertos pacientes presentaban síntomas neurológicos sistémicos, como el Accidente cerebrovascular (ACV). **Objetivo**: El objetivo del presente trabajo es proponer una discusión acerca de los conocimientos actuales sobre la fisiopatología del ACV en adultos jóvenes con COVID-19. **Métodos**: Se hizo una búsqueda en las principales bases de datos: Lilacs, Bireme, Pubmed en los idiomas portugués e inglés, de artículos comprendidos en el año actual. La elección se había realizado al azar, obviamente, siguiendo una línea de razonamiento de los investigadores involucrados. Las palabras clave buscadas fueron: COVID-19, Accidente cerebrovascular, Fisiopatología, Coagulopatía. **Discusión**: Se conjeturan innumerables posibilidades que explicarían la conexión del virus con la enfermedad cerebrovascular. Es considerado que el SARS-CoV-2 incita un proceso de inflamación en la pared arterial y eso sea responsable por el ACV. Aunque la correlación entre las dos condiciones clínicas era notoria, aún no hay estudios que determinen claramente el mecanismo fisiopatológico involucrado en el proceso. **Conclusión**: Manifestaciones neurológicas en la COVID-19 son relatadas, incluyendo el accidente cerebrovascular. La condición de hipercoagulabilidad generada por la gran cantidad de citocinas puede estar relacionada con el mecanismo fisiopatológico de esta condición. Sin embargo, no existen evidencias claras sobre eso y estudios son necesarios a fin de aclarar su fisiopatogenia. **Palabras-clave**: infecciones por coronavirus, accidente cerebrovascular, fisiopatología, coagulopatía.

**Introduction**

COVID-19 is an infection caused by the SARS-CoV-2 virus, which was originated in the city of Wuhan (China) and spread rapidly to other countries and continents until the World Health Organization (WHO) declared a pandemic. The clinical condition of the pathology varies from asymptomatic individuals to severe conditions that culminate in death. Among the serious conditions resulting from the pathology, it was observed that certain patients had systemic neurological symptoms, such as cerebrovascular accident (CVA) [1].

Although little is known about the new Coronavirus, there is evidence of tropism by the Nervous System (neuropotism). The inflammatory process and the vascular lesions generated by it can increase the permeability of the blood-brain barrier, promoting adverse effects on the Central Nervous System (CNS). Many are the ways of transporting the virus against the blood-brain barrier, highlighting the transcellular, retrograde and paracellular axonal transport along the entire length of the olfactory and sensory nerves [1,2].
The axonal transport of SARS-CoV-2 is pointed out, through the cribiform plate adjacent to the olfactory bulb to the brain, as a possible cause of the loss of smell. The anosmia, which appears early in most cases, can be associated with this mechanism [1,2]. The slowed microcirculation in the capillary compartment can contribute to the binding of the peak glycoprotein of the virus with the Angiotensin-Converting Enzyme 2 (ACE2) in the cell membranes, which favors the penetration of SARS-CoV-2. The ACE2 is expressed on the surface of several cells in the body such as: gastrointestinal tissue, epithelium of the respiratory system and brain [3].

SARS-CoV-2 can deregulate the Angiotensin-Converting Enzyme 2, which leads to the over activation of the Renin-Angiotensin-Aldosterone System (RAAS). In addition, it reduces the activation of the alternative RAAS pathway in the brain. The RAAS imbalance associated with disharmony in vasodilation, oxidative stress, thrombotic response and neuroinflammation may be fundamental factors in the pathophysiology of Cerebrovascular accident throughout the SARS-CoV-2 infection [1]. The aim of the present study is to propose a discussion about the pathophysiological mechanisms involved in the genesis of cerebrovascular accident caused by COVID-19 in young adults, based on a brief review of the current literature.

Methods

The purpose of this article is, based on current literature, to produce and update reflections about the ongoing pandemic context. To this end, a search was carried out in the main databases: Lilacs, Bireme, Pubmed in Portuguese and English, for articles included in the current year. The choice had taken place at random, obviously, following a line of reasoning from the authors involved. The keywords searched were: COVID-19, cerebrovascular accident, pathophysiology, coagulopathy.

Results and discussion

The ischemic cerebrovascular accident (ICVA) is reported as a complication of COVID-19, however, the mechanisms that govern this pathology have not yet been elucidated. It is known that the ICVA associated with the clinical entity is usually a late complication, however, it can happen both in the beginning and in the final course of the disease. Cerebral venous sinus thrombosis, ischemic cerebrovascular accident and intraparenchymal hemorrhage were some of the clinical conditions described in individuals affected by the virus [4]. In addition, it was found that the involvement of smell and taste predicts COVID-19 infection.

The SARS-CoV-2 infectious process is linked to a pro-thrombotic state, which generates venous lesions and arterial thromboembolism, in addition to an increase in D-Dimer levels. In addition, the disease releases pro-inflammatory cytokines that incite cell activation mononuclear and endothelial cells with tissue factor expression, carrying the activation of the coagulation cascade and generation of thrombin. The lack of control of circulating thrombin by anticoagulants can activate platelets and promote thrombogenesis [5,6].

Countless possibilities are conjectured that would explain the connection of the virus to cerebrovascular disease. SARS-CoV-2 is considered to instigate an inflammatory process in the vessel wall, and this is responsible for the occurrence of a cerebrovascular accident. It is also believed that SARS-CoV-2 has a function analogous to the herpes simplex virus, which has been shown to minimize the binding to anti-thrombin III, heparan sulfate, thrombomodulin, prostacyclin and ultimately potentiate the formation of thrombin, expression of tissue factor and platelet bonding [7,8].

Recently, The New England Journal of Medicine published an informative study, reporting five cases of cerebral vascular accident in young adults, all younger than 50 years of age. Symptoms such as headache, coughing and chills lasting for a week have been mentioned. Among the participants in this study, a 33-year-old woman reported not having previous pathologies [9]. This study suggested as explanations for the possible cases of cerebral vascular accident from COVID-19, endothelial dysfunction and coagulopathy [10].

The cells of the epithelium of the respiratory and gastrointestinal systems are the focus of infection of SARS-CoV-2, however, their impact is not limited to just the afore mentioned cells and the nervous system can also be compromised. Considerably, the presence of the virus was found in the cerebrospinal fluid [7], and pathologies such as seizures, leukoencephalopathy, refractory mal-epileptic status, encephalitis, Guillain-Barré syndrome (GBS) and myopathy were found in patients with COVID-19 [8]. Neurological signs such as dizziness, headache and altered
level of consciousness have been documented in 8%, 11%, 9% of infected patients, respectively [11,12].

A study, carried out in Singapore, described 5 patients who had cerebrovascular accident of major vessels after infection by SARS-CoV-2. In this study, it was proposed that embolisms located proximally, such as in the heart and severe hypotension, could have been precursors to CVA. The supposed relation between COVID-19 and CVA can be simultaneous, however, about one third of the cases had pulmonary thromboembolism [13-15]. It is also worth noting that some studies suggest that COVID-19 stimulates the production of antiphospholipid antibodies (aPL), as a mechanism of ischemic cerebral vascular accident, even though the post-infection aPL are generally transient and not related to thrombosis [16].

Certain patients with the severe form of COVID-19 have Disseminated Intravascular Coagulation (DIC) or total consumption of coagulation factors and activation of the coagulation cascade. Current literature indicates that patients infected with SARS-CoV-2 are subject to developing coagulopathy due to acute systemic inflammatory response. The COVID-19-induced coagulopathy is determined by an increase in blood clotting markers, such as: D-dimer and fibrin or fibrinogen breakdown products, in addition to an increase in peripheral inflammatory markers, such as C-Reactive Protein, and mild thrombocytopenia [17,18]. Furthermore, the virus can bind to Toll-like receptors and trigger the synthesis and release of interleukin 1 [19].

It is a fact that COVID-19 inflammatory mechanisms generate a state of hypercoagulability, and the number of CVA cases in young adults associated with the pathology tends to increase as it spreads. Although the correlation between these two clinical conditions is notorious, there are still no studies that clearly determine the pathophysiological mechanism involved in the process. Therefore, research related to the damage caused by the virus in the Cerebral Vascular System is necessary in order to elucidate the pathophysiology of the CVA in these patients.

**Conclusion**

The clinical conditions of patients infected with COVID-19 range from asymptomatic to severe conditions. Among these, neurological manifestations are reported, including cerebral vascular accidents. Epidemiological statistics on the incidence of CVA cases during the COVID-19 pandemic have not yet been published, however, informal observations suggest an increase in the number of cases of thromboembolic CVA among young adults. The state of hypercoagulability generated by the cytokine storm seems to be related to the pathophysiological mechanism of this condition. Still, there is no clear evidence for this. Thus, research related to the damage caused by the virus in the cerebral vascular system is necessary in order to elucidate its pathophysiology.

**Conflicts of interest:** The authors declare no conflict of interest.

**References**

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