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Thematic Dossier
COVID-19: POLICIES, PRACTICES AND REPERCUSSIONS IN HEALTH

THE RELATIONSHIP BETWEEN THE BRAIN STROKE AND COVID-19: A NARRATIVE REVIEW

A RELAÇÃO ENTRE O ACIDENTE VASCULAR CEREBRAL E A COVID-19: UMA REVISÃO NARRATIVA

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Abstract
Objective: To review the literature on the theories that seek to explain the possible relationship between COVID-19 and stroke. **Method:** The scientific databases were searched in the following databases: SciELO, Virtual Health Library (VHL), Pubmed and Google Sholar. The descriptors used in the research were: COVID-19, Stroke, Interrelation and Prognosis. **Results:** The findings of this research include the relationship between COVID-19 and its risk factors, the connection of the Sars-Cov-2 virus with the Angiotensin-Converting Enzyme (ACE), and also, the inflammatory responses triggered by the virus in its clear relationship with the onset of stroke. **Conclusion:** The relationship between the presence of COVID-19 in the human organism and a greater predisposition to develop stroke is evident, however, further studies are necessary to be able to deepen the knowledge on this topic, as well as to consolidate the theories involving its mechanism.

Keywords: Coronavirus; Stroke; Comorbidity; Interrelation.

Resumo
Objetivo: Revisar a literatura acerca das teorias que buscam explicar a possível relação entre a COVID-19 e o AVC. **Método:** Realizou-se busca na literatura científica nas seguintes bases de dados: SciELO, Biblioteca Virtual de Saúde (BVS), Pubmed e Google Sholar. Os descritores utilizados na pesquisa foram: *COVID-19*, *Stroke*, *Interrelation* e *Prognosis*. **Resultados:** Os achados desta pesquisa incluem a relação da COVID-19 com os seus fatores de risco, a ligação do vírus Sars-Cov-2 com a Enzima Conversora de Angiotensina (ECA), e ainda, as respostas inflamatórias desencadeadas pelo vírus em sua clara relação com o desencadeamento do AVC. **Conclusão:** É evidente a relação entre a presença do COVID-19 no organismo humano e a maior predisposição para se

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desenvolver o AVC, no entanto, novos estudos são necessários para que seja possível aprofundar o conhecimento neste tema, bem como consolidar as teorias envolvendo seu mecanismo.

Palavras Chave: Coronavirus; Acidente Vascular Cerebral; Comorbidade; Inter-Relação.

INTRODUCTION

On December 31, 2019, in Wuhan, a village located in China, outbreaks of atypical pneumonia were reported in correlation to the seafood and animal Market [1], what would later be identified as the first registred case of infection by the new coronavirus (Sars -Cov-2), the potential causer agent of a severe acute respiratory syndrome. The high virulence of SARS-CoV-2, combined with a great reach of respiratory transmission via aerosols, allowed a fast geographic spread across all continents, characterizing it as a global public health problem on the rise. Therefore, on March 11, 2020, the general director of the World Health Organization (WHO) officially classified the state of contamination as a pandemic [2,3].

After recognizing the seriousness of the infection, each country took the necessary measures to prevent the spread of the viral pathogen, and each one followed a different rate of application. They were formal governmental policies aligned with recommendations to the population's behavior: social isolation, closure of businesses, distancing from person to person, implementation of the use of masks in public places, among others. However, due to its high virulence, associated with the absence of a specific medication, unavailability of a vaccine and the unequal public policies, SARS-CoV-2 was able to infect around 29 million people around the globe, causing 926,544 deaths only in the first six months of the pandemic [4]. A year after the pandemic, Brazil registered 12,051,619 cases and 295,685 deaths by Sars-Cov-2 [5].

The new coronavirus (Sars-Cov-2), causing the disease COVID- 19, is categorized as a ribonucleic acid virus of the *Coronaviridae* family. The survival of this zoonotic pathogen depends on a human host, through the following life cycle: viral replication is initiated through the binding between a molecule present on the surface of the viral particle and the host cell membrane receptors (adsorption),

which allows the entry of the microorganism through membrane fusion, or by endocytosis (penetration). With the entry of the virus into the cytosol, the capsid is removed by the action of lysosomes (denudation), exposing the RNA which will be used in the synthesis of viral proteins (viral synthesis). Finally, there is formation of a complete viral particles (morphogenesis/maturation) and the exit of the pathogen from the cell-by-cell lysis or budding [6, 7, 8].

Symptomatic repercussions are the evidence that arise according to the spread of the virus throughout the human body. Sars-Cov-2 is mainly known for its respiratory and gastrointestinal manifestations, such as fever, dyspnea, diarrhea, cough and fatigue. This disease, however, exhibits a wide range of symptoms, ranging from mild symptoms to complications, such as severe acute respiratory syndrome, pneumonia, cardiac and kidney damage, sepsis, intravascular coagulation, metabolic disorders [9, 10] and neurological disorders [11]. Among the most common neurological signs are: headache, syncope, motor loss, anosmia and ageusia, even more severe conditions such as stroke, viral encephalitis, acute hemorrhagic necrotizing encephalopathy and Guillain Barré syndrome are also correlated to this pathology [12]. The reason for this is presented in the studies about the viral replication process of Sars-Cov-2, in which there are reports of high affinity and replication in neuronal cells, explaining the number of neurological symptoms and sequelae caused by this disease [13, 14, 15].

The cerebral or brain accident, equivalent to the English word *stroke,* [16] is a serious medical emergency classified as a focal neurologic deficit due to an acute vascular focal cause injury in the central nervous system [17]. This disease has an incidence of 3.7 to 5% in patients affected by COVID-19, making it a problem with notable rates of morbidity and mortality, deficits andan unfavorable prognosis for the patient [18,19]. Despite this information, the relationship between them is still poorly established, showing the need for more capable studies to better elucidate the link between stroke and COVID-19, and its clinical repercussions for the patient.

METHODS

This study is classified as a narrative literature review, a study method based on the analysis and review of the existing literature on the subject in question, which the purpose is to synthesize the different results of primary studies on the issue addressed [20].

The question that guided the search strategy was: “Is there a relationship between COVID-19 and stroke?”. The evaluation of the scientific articles was done by accessing the platforms PubMed and SciELO. To this purpose, the following descriptors were used: *COVID-19, Stroke*. The association of these keywords in both databases was the following: *COVID-19 AND Stroke*. Only primary studies and original articles published in other languages on any of the mentioned databases and with no time restrictions were considered eligible. It were considered as exclusion criteria: books and documents, opinion articles, review articles, systematic review articles, letters to the editor, book reviews and conference proceedings. The numerical data about COVID-19 in Brazil and in the world was obtained from the internet homepages of the Unified Health System (UNA -SUS), G1 News Portal and the World Health Organization (WHO), with the most recent date being June 9, 2021.

In all databases, 57 articles were found, based on the mentioned keywords. The results obtained from this research were analyzed from the critical perspective of the authors, who discussed and selected those that would be used as sources for such a review. With the inclusion and exclusion criteria, and, after a cautious reading of the title, resume and, when necessary, the reading of the entire article, were considered 26 articles to compose this study.

THE PATHOPHYSIOLOGICAL PROCESS OF SARS-COV-2

As it is a viral etiological agent, Sars-Cov-2 will have the same transmission and infection mechanism as other organisms, such as the measles-generating *Morbilivirus*. The difference lies in the ability of these agents to contaminate, being the cause of COVID-19 characterized by low infectivity

rate when present in the environment [21]. However, the emergence of new viral variants, from spontaneous genetic mutations in the pathogen, can directly affect the infectious process, enabling an increase in the rate of contamination depending on where such modification of the viral genome has occurred [22].

The main way of spreading the virus is through aerosols: small droplets in suspension in the air indefinitely, resulting in the transportation of numerous viral agents in just one of these droplets [21]. The means for generating these small drops include coughing, sneezing and speaking [22].

The possible ways that a healthy individual can be contaminated by such suspended droplets are through breathing and contact with the patient or a surface presented with such elements [21]. After that, the virus will enter the individual's organic system, and if not neutralized by the immune system, it will start a new infection. Although the pathogenesis has not been fully understood, it is noted that the virus has a preference for Converting Enzyme Angiotensin receptor type 2 (ACE2), cells present in lungs, kidneys, brain and other organs [23]. After establishing contact with one of these receptors, the virus uses a small molecular structure called the S - glycoprotein to attach to that structure, while using the hemagglutinin-esterase protein to recognize the sialic acid exposed by the receptor, so that process allows its entry into the cell via endocytosis [23, 24].

Although the cell tries to destroy the virus located inside the vesicle by lowering its pH, this organism manages to escape because this process induces a structural change of the hemagglutinin-esterase, inducing a fusion with the structure membrane and the consequent exit of the virus [23, 24]. From then on, the viral agent uses its proteins to fuse its genetic material to the one from the cell, using its machinery and organelles to synthesize new structures that will compose new pathogens which, at the end of the entire process, will be released to infect more cells [23, 24].

THE RELATIONSHIP WITH THE STROKE

Stroke (CVA) is configured as a disease with a multifactorial cause, which causes a lack of blood supply necessary to maintain the functional mechanism of a certain area of neural tissue. Depending on how it manifests itself, the stroke can be classified in two ways: ischemic, when the necessary blood flow to supply the metabolic demands of a part of the brain tissue is suddenly interrupted by some type of obstruction; and hemorrhagic, which induces a leakage of intravascular fluid into the interstitium, which also results in lack of blood supply[25].

Although it has not yet been proven that the presence of the SARS coronavirus-2 can promote the onset of stroke in sick individuals, it is known that the both conditions keep mutual relations [26, 27]. Studies conducted in the Chinese city of Wuhan indicated that patients with comorbidities that were risk factors for stroke, such as hypertension, diabetes, obesity and heart disease, had a more severe clinical course for COVID-19 [27]. Another factor that points to a possible relationship between COVID-19 and stroke is the Sars-Cov-2 action mechanism itself. In binding in with the receptor ACE2, which is also present in brain tissue, the SARS coronavirus-2 reduces the action of this enzyme, directly interfering in system renin-angiotensin-aldosterone system (RAAS) and inducing a tissue injury in the brain, which is a major risk factor for stroke [26 ,28, 29].

All RAAS homeostasis are maintained by keeping the balance of action of its enzymes, including ECA1 and ACE2. When the action of ACE2 is inactivated, the conversion of Angiotensin II into Angiotensin I-VII , a potent vasodilator , will not occur . However, the balance of a functional balance will lean towards the increase of the action of ACE1, which converts Angiotensin I into II. However, as type II angiotensin is naturally capable of inducing vascular pro-inflammatory cytokines, such as IL-6 and TNF-α, in addition to being vasoconstrictor and potentially damaging to organs, when in high concentration, the risk of brain damage will increase considerably [26 ,27].

The UTRA theory indicates that a formation of blood thrombi induced by a variety of intravascular inflammatory responses would have a key role in this

metter. Such a process would occur as follows: by presenting tropism for the central nervous system, due to the high amount of receptor ACE 2 located in such tissue, the virus is spread in the bloodstream and induce a series of inflammatory responses by the contact with the endothelial cells of brain vasculature, this is because such structures can exhibit specific binding with the virus receptor [28, 29]. As a result, a brain inflammation induces the aggregation of several white blood cells in an attempt to contain the virus. Likewise, platelets and fibrin molecules agglomerate at the site, characterizing the vasculitis picture. Finally, the presence of such pro-inflammatory cells induces the formation of a thrombus, which can dislocate and, by obstructing smaller capillaries, induce thromboembolism, or remain in the vasculitis site, interrupting the blood flow responsible for the nutrition of the brain tissue, in a situation known as ischemic stroke [28, 29].

Therefore, although further studies are required for a clarification in the existing relation between the infection with SARS-Cov-2 and a increased risk of developing stroke, several hypotheses already show promise to prove this fact. A wide coverage of exams is necessary to guarantee, in advance, the prevention of the possible development of stroke in patients with COVID-19.

CONCLUSION

The infection SARS-Cov-2 establishes a direct relationship in triggering vascular conditions necessary for the emergence of a stroke. Although there is no consensus on how such a viral disease exerts this cause-consequence relationship, several theories have been established, requiring further studies to better understand this relationship. In any case, all healthcare professionals should be aware of the risk of developing a stroke in patients with COVID-19, especially those patients with the most severe form of the disease. In addition, it is of fundamental importance that the medical centers responsible for offering hospital support to patients affected by COVID-19 are prepared with the necessary supports, such as thrombolytic drugs, imaging tests, anticoagulants and antiplatelet agents, to control the possible trigger of this disease vascular.

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