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Study of neuroanatomical sequelae associated with post-COVID-19 syndrome

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ABSTRACT: Objective: To point out the neuroanatomic repercussions that the Post-COVID Syndrome triggers in individuals and address the pathophysiology of SARS-CoV-2 infection. Literature review: COVID-19 is an acute viral respiratory disease. Post-COVID-19 Syndrome gets its name because it is a set of clinical manifestations that persist for longer than two or three weeks after the onset of symptoms. Among the related disorders, neuroanatomical sequelae stand out, such as injuries with the ability to generate significant morbidity and mortality. Final considerations: It is concluded that this syndrome is associated with relevant sequelae, such as in the Central Nervous System. There were descriptions of different neurological manifestations such as stroke, ageusia, headache, Guillain-Barré syndrome, encephalopathy, anosmia, and dizziness. It is essential to further studies to support patient management with the best evidence to reduce morbidities.

Keywords: Post-COVID Syndrome, SARS-CoV-2, Nervous System Diseases, Neuroanatomy

INTRODUCTION

On January 30, 2020, the outbreak of a new coronavirus - COVID-19 - was declared by the World Health Organization (WHO), consisting of a Public Health Emergency of international relevance, having been considered the highest alert level. of the WHO, following the International Health Regulations. Due to the rapid spread of the disease in several countries, several types of research were and continue to be carried out in the search for a cure, as well as the laboratories worked exhaustively to create a vaccine that was able to treat and/or prevent this disease.

Brazil was in 2nd place in the ranking of countries with the highest number of disease cases, having registered 7,753,752 confirmed cases and 196,561 confirmed deaths, according to data from the Interactive Panel of the Unified Health System (2020) on January 4, 2020. 2021.

COVID-19 is a disease caused by the single-stranded, enveloped RNA virus and the junction of the virus's spike protein with Angiotensin-Converting Enzyme 2 (ACE2) that causes the development of SARS-CoV-2 infection. This enzyme has considerable expressiveness, mainly in the heart and lungs. Therefore, respiratory symptoms may be linked to elevated ACE2 secretion in patients with comorbidities. In addition, the virus predominantly affects alveolar epithelial cells (ZHENG et al., 2020).

Although the clinical perceptions of the diseases have a predominance of respiratory symptoms, the neurological manifestations were confirmed in studies in which ageusia, impaired consciousness, headache, dizziness and anosmia were detected (3). The Central Nervous System (CNS) has ACE2 receptors, which are located on glial cells and neurons. This fact can make understandable how the CNS becomes a target of the disease (ACCORSI et al., 2020).

Post-COVID 19 Syndrome consists of clinical manifestations that persist for two or three weeks after the onset of symptoms. Among the related disorders, neuroanatomical sequelae stand out, such as injuries with the ability to generate significant morbidity and mortality. However, as it is an incipient condition, there is still no standardized treatment for the management of sequelae (BRAGATTO et al., 2021).

Thus, the present study aims to address the pathophysiology of SARS-CoV-2 infection and point out the neuroanatomical repercussions that the Post-COVID Syndrome triggered in individuals.

This study is relevant to understanding the relationship of the virus' tropism to the Central Nervous System and the hypotheses about the mechanism used by SARS-CoV-2 to penetrate this system. It is important to present the neurological manifestations that usually start between the first and fourteenth day after the onset of respiratory symptoms, more frequently in the severe or critical person, with anosmia, ageusia and headache as the most common reports. ; PINTO, 2020). It is pertinent to address the post-COVID syndrome regarding the neuroanatomical changes generated by the disease (CAROD-ARTAL, 2020).

LITERATURE REVIEW

At the end of 2019, a group of individuals was infected by the Coronavirus in Wuhan, China. These cases happened in live animals and a seafood market. As the transmission of the virus is from person to person, there were many people infected worldwide, among health professionals, families and the population in general, which made the World Health Organization (WHO) declare a pandemic of Covid-19 on March 11, 2020.

Guan W et al. (2020) describe COVID-10 as a respiratory condition caused by the severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2). This clinical condition has dry cough, dyspnea, fever, and fever, although other symptoms are frequently reported. Both women and men seem to be affected equally and the age group with the highest prevalence is around 40 years old. It is known that older people who have comorbidities such as heart disease, diabetes, lung disease, kidney disease, and hypertension may have a worse prognosis.

According to the Coronavirus Panel (2021), until June 21, 2021, the disease had already affected 17,927,928 individuals and recorded 501,825 deaths throughout Brazil. Due to the rapid spread of this disease and high contamination, the World Health Organization (WHO) declared a public health emergency of international concern in March 2020, and the Brazilian Ministry of Health recognized the pandemic.

Coronaviruses are considered part of the Coronaviridae family, identified because of their surface when observed under a microscope. Some of these pathogens are related to respiratory system diseases of a more lethal nature. They are the main ones responsible for triggering Severe Acute Respiratory Syndrome outbreaksSevere Acute Respiratory SyndromeSevere Acute Respiratory Syndrome outbreaks, which are related to SARS-CoV and Middle East Respiratory Syndrome, which MERS causes. -CoV SARS-CoV-2 consists of a beta coronavirus that has RNA-like genetic material and has proteins called spike (S) on its surface that are responsible for allowing the binding to the host cell receptor and enabling the virus to enter this cell (HUANG Y et al., 2020; MURRAY P, et al., 2016).

According to Huang Y et al. (2020). Protein S, which is present in the outermost area of the virus, is considered a determining factor for infection. The spike proteins are considered class I trimeric transmembrane glycoproteins and consist of a transmembrane domain anchored in the viral membrane, an extracellular N-terminus, and a short intracellular C-terminal segment. What can be observed in these proteins are the polysaccharides that they keep in their final portions in the quest to pass without being noticed by the infected person's immune system.

Huang T et al. (2020) and Zhang H et al. (2020) state that S proteins act as an inactive precursor in the body so that, during the course of infection, the proteins undergo activation and cleavage in their S1 and S2 subunits. This phase is critical for fusing the

virus membrane with that of the target cell. The S1 subunit plays an essential role in the initiation of viral infection. This subunit recognizes the angiotensin-converting enzyme 2 (ACE2) receptor and is bound to this receptor on the host cell surface through the interaction of the receptor-binding domain in the N region. The S2 subunit demonstrates the heptapeptide repeat region (HR) with the HR 1 and HR2 domains, which have a close relationship with the virus fusion. This subunit is responsible for allowing the fusion between the host cell membrane and the virus, allowing it to enter the target cell.

According to Huang Y (2020), Zhang H et al. (2020) and Wan Y et al. (2020), the angiotensin-2 converting enzymes, which correspond to the virus receptor in the cell, is located on the surface of organs such as the intestine, kidney, heart and lung, mainly, presenting the greater expression of this enzyme in epithelial cells. type II alveolar

Through the study carried out by Li MY et al. (2020) the presence of the ACE 2 receptor in 31 human tissues was identified. Some of the tissues showed higher expression of this receptor, such as the testes, heart, adipose tissue, small intestine, kidneys and thyroid, while others demonstrated moderate to low grades, such as the colon, bladder, blood, bone marrow, muscles, brain, blood vessels, spleen, adrenal gland, liver, and lungs. It is possible to understand, from this study, that SARS-CoV-2 infection is not limited only to the tissues of the respiratory tract, as it can affect noble tissues, such as the brain.

Given the widespread distribution of this receptor in human cells and considering its presence in neural tissues, it is understood that it is useful to study the relationship between coronavirus infection and the neurological sequelae identified in patients affected by the disease (LI MY, et al., 2020; PATEL AB and VERMA A, 2020).

According to Abboud et al. (2020), studies have shown that the vast majority of the symptoms of COVID-19 have their explanation based on the cytokine storm that the virus triggers, leading to Systemic Inflammatory Response Syndrome (SIRS). This exaggerated response of the immune system causes the production of many inflammatory mediators whose primary purpose is to fight the infection caused by SARS-CoV-2. However, at the same time, it generates significant tissue damage.

Alomari et al. (2020) point out that it is possible to highlight fatigue and dry cough, which are linked to the respiratory system, among the most common symptoms presented. However, research has been carried out that pointed to the development of neurological symptoms in about 40% of those infected by the virus, making it evident that SARS-CoV-2 has to affect the nervous tissue. , more precisely. Some of the respiratory symptoms may be a consequence of the involvement of the Central Nervous System, the Respiratory Center. In addition, the virus can cause infection of neuronal cells of the brainstem, especially the medulla, causing respiratory symptoms, a consequence of the involvement of the respiratory and cardiovascular centers.

In this way, neurological damage can be associated with the development of acute respiratory failure, which is a feature of patients with COVID-19. Considering the invasive potential SARS-CoV-2 has on the nervous system, neurological manifestations can be classified according to their severity as severe, moderate and non-specific (ALOMARI, et al., 2020; JASTI et al., 2020). Among the systemic and non-specific symptoms, the most common are headaches, probably provoked by exposure to fever associated with the components of the immune response. Among moderates, olfactory disorders such as anosmia or hyposmia, visual disturbances, and ageusia were reported more frequently (ALOMari et al., 2020). Alomari et al. (2020) state that the loss of smell after infection is believed to be due to initial nasal congestion, which leads to dysfunction of the terminals of the olfactory receptor cells, causing them to lose their efficiency in capturing odor molecules. The virus appears to be highly concentrated in the infected person's nostrils, entering through the cribrosa plate and producing inflammation in the olfactory nerves and damaging the structure of the receptors, causing anosmia. .

Some studies have pointed out that the tongue is full of ACE2 receptors, which can be considered a potential site of virus binding, causing damage to taste receptors and leading to ageusia. However, in most cases, anosmia and ageusia are the first or even the only symptomatic manifestation presented by the disease, which can be considered essential affections to assist in diagnosing and suspicion of infection in individuals (VAIRA, et al., 2020). ; JASTI, et al., 2020).

Delirium, dysphoriamoderate involvement, and mental disorder can be considered signs of toxic, infectious encephalopathies, another moderate involvement since they are representations of direct manifestations of the virus in the Central Nervous System. Direct infiltration into the CNS can trigger a neuroinflammatory reaction that leads to the activation of microglia, which causes demyelinating processes, being considered one of the main causes of encephalopathies. However, if this infiltration is not present, a neuroinflammatory response is triggered by the cytokine cascade, generating the disruption of the blood-brain barrier with the consequent transmigration of immune cells from the periphery to the CNS, producing a lack of neurotransmission balance. Even though they are severe and rare, some cases of encephalopathies can lead to paralysis, loss of consciousness and epilepsy, reaching coma in some situations (WU et al., 2020; ABBOUD et al., 2020; JASTI et al., 2020; JASTI et al., 2020; ABBOUD et al., 2020; JASTI et al. al., 2020).

The most severe symptoms included cerebrovascular events such as intracerebral hemorrhage, ischemic stroke and cerebral vein thrombosis. Although the involvement of the virus in the circumstances is still not specific, neurodegenerative diseases such as

multiple sclerosis, Guillain-Barr syndrome and Alzheimer's have been reported, which require further studies in the future to establish a correlation with these events (ABBOUD, et al ., 2020). ; WANG, et al., 2020b).
Post-COVID-19 Syndrome eventually received multiple nominations such as: It is understood that attacks lasting more than two or three weeks after the onset of the disease are classified as part of the post-COVID-19 syndrome. Therefore, much of the literature is devoted to the acute involvement and pathophysiology of the disease. However, since many survivors and some of them have symptoms that last longer than expected, some authors end up considering the post-COVID-19 syndrome as the second pandemic, which justifies the need to deepen this topic (MALTEZOU et al., 2021; FERNNDEZ-DELAS-PEAS et al., 2021).

According to Fernández-de-las-Peñas et al. (2021), based on a meta-analysis and a systematic review, it was estimated that about 60% of people who survived COVID-19 had at least one symptom more than 30 days after the onset of illness or hospitalization. Dyspnea and fatigue are the most frequently presented symptoms. Other symptoms such as anosmia, chest pain, headache, palpitations or ageusia had a lower prevalence and high variation. Lopez-Leon et al. (2021) performed another meta-analysis in the preprint stage. This study points out that headaches, hair loss, attention disorders, dyspnea, and fatigue prevailed in the syndrome.

COVID-19 generates neuroanatomical repercussions. The PNS and CNS are severely affected by SARS-CoV-2, generating neuronal sequelae that may be related to long-term chronic degenerative diseases. It was thought that the virus would have great difficulty in crossing the blood-brain barrier (BBB). Afterward, it was found that the SRAS-CoV-2 spike protein binding receptor (s), ACE2, is well expressed in the microvascular endothelial cells of the brain. This S protein can also cause damage at different levels to the integrity of the BBB and induce the inflammatory response of endothelial cells that modify the function of the BBB. Such findings proved the action of SARS-CoV-2 on BBB and, therefore, entry into the brain ends up contributing to the occurrence of encephalitis and microthrombi in association with the disease (WANG et al., 2020a).There is a report of a patient with the disease who had fever, cough and change in his mental status. The diagnosis was acute necrosis encephalopathy. A non-contrast tomography was performed on this patient, which showed symmetrical hypoattenuation in the bilateral medial thalamus with normal venogram and angiography. In addition, magnetic resonance imaging showed lesions whose characteristics enhance the hemorrhagic edge in the subinsular regions, in the medial temporal lobes and the thalamus (POYIADJI et al., 2020).

Maltezou et al. (2021) stated that the pathogenesis of post-COVID-19 syndrome is still largely unknown. However, prolonged inflammation plays an essential role in the genesis of most syndrome images. This may present an example given that the inflammatory process associated with viruses can compromise gamma-aminobutyric acid (GABA), possibly representing the basis of cognitive and neuromotor fatigue, explaining executive deficits and apathy. Studies suggest that the hippocampus appears to be vulnerable to infection, which would contribute to the memory deficit after infection.

It has been proposed by Wostyn (2021) the possibility that post-COVID-19 fatigue syndrome may result in damage to olfactory sensory neurons, generating a lower flow of cerebrospinal fluid through the cribriform plate and leading to congestion of the lymphatic system with toxic accumulation in the CNS. The direct neuroinvasion of the virus can lead to persistent neuropsychiatric complications. Sher (2021) conducted a study in which he agrees with other authors. He considers that stroke, ageusia, headache, Miller Fisher syndrome, encephalopathy, anosmia, dizziness, skeletal muscle myalgia and Guillain-Barré syndrome are neurological manifestations. Epileptic conditions have been observed in patients with the disease, such as seizures, status epilepticus, recent-onset seizures, refractory recent-onset status epilepticus, and myoclonic seizures.

Neurological symptoms related to the disease may persist for a long time after the acute illness, being identified in the post-COVID-19 syndrome. There is also a considered significant probability that neurological diseases, inflammatory brain damage, psychiatric symptoms and physical illness in subjects with the syndrome maximize suicidal ideation and behavior. However, subjects who did not have the syndrome may also have a higher risk of suicide. The treatment of the disease and its neurological manifestations is much debated, and there is still no systematic protocol. The recommended management to treat symptoms that are less severe about the CNS, such as headache and fever, is with paracetamol due to the reported relief of symptoms and the reduced probability of complication. The other anti-inflammatory drugs are considered a potential therapy, especially for the most complicated symptoms. Concerning blocking viral activity and, ultimately, manifestations in the Central Nervous System, furin inhibitors are useful in a possible treatment, since they make it impossible for viral spike proteins to bind at their cellular site of action. However, its use has relevant limitations, since furin has an essential function in the normal physiology of nervous tissue (FIANI et al., 2020). Countless neurological changes are related to COVID-19. It is not feasible to determine all possible manifestations. There is no global treatment capable of stopping all possible injuries.
The best option to control the disease remains vaccines, and until vaccination begins, efforts need to be focused on preventing organ failure, respiratory failure, immune dysregulation and hypercoagulable state. There is no specific treatment, and neurological manifestations must be treated according to the standard protocol (IADECOLA et al., 2020). However, as neurological complications occur, especially in severe systemic disease, it is essential to reduce hypoxia and protect against cytokines and thromboembolic complications, which are important therapeutic goals. Immunosuppression with steroids improves mortality in subjects with severe disease, but not in people with milder forms. Differentiated approaches are being tested for neutralizing immune dysregulation, such as targeting inflammatory pathways or specific cytokines. A conclusion has not yet been established as to whether these interventions reduce long- and short-term psychiatric and neurological complications (IADECOLA et al., 2020).

Furthermore, appropriate additional surveillance of intracranial infection in subjects with the disease would provide more information about the neurological prognosis. Magnetic resonance imaging of the skull and lumbar puncture procedures for cerebrospinal fluid collection would highlight the neuroinvasive association of the pathogen. For subjects with definite intracranial infection, suggested treatment techniques are control of cerebral edema, treatment and prevention of seizures, and treatment of psychotic symptoms. For issues who had symptoms associated with muscle damage, it is essential to strengthening nutritional support and actively treat and actively treat the virus (FIANI et al., 2020).

The SARS-CoV-2 pandemic has created an inevitable need for health professionals to search for symptoms, prophylaxis, pathophysiology and other knowledge that can support their therapy. Although there is no consensus in several aspects regarding the disease's involvement, today, there is already a consensus among scholars that a new pandemic arises, that of Post-COVID-19 Syndrome. It is pointed out by the neuroanatomical repercussions of how much the CNS ends up being affected by SARS-CoV-2 in the acute phase and the chronic phase. Understanding the impairments and neuroanatomical manifestations is an essential factor in mitigating the neurological damage resulting from the disease. Thus, conducting new studies focusing on post-COVID is essential and contributes to a more comprehensive approach to the patient infected by the disease because of the disease itself and its immediate repercussions.

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CONFLICT OF INTEREST:

The authors confirm no conflict of interest.

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