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NEUROINVASION MECHANISMS ASSOCIATED WITH BRAIN INFLAMMATION IN INFECTIONS BYSARS-COV-2

Esdras Welesson Matias de Sousa*[1], Larissa Barroso Pessoa[2], Fernanda Farias Costa[1], Raissa Freitas Barbosa[1], Wilian Reis Rosário[1], Alice GabriellyLadim Lima[1],Paulo Natan Barroso Pessoa[3],Caroline Amélia Gonçalves[1],Cristiane Santos Silva e Silva Figueiredo[1] and Domingos Magno Santos Pereira[1]

[1]Department of Biomedicine, CEUMA University; [2]Department of nutrition, Empress College - Facimp Wyden; [3]Department of pharmacy, Empress College - Facimp Wyden

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Corresponding author:
Esdras Welesson Matias de Sousa

ABSTRACT

Introduction: Studies have already shown that SARS-CoV-2 can penetrate the central nervous system by different mechanisms, triggering a series of pathologies, including viral encephalitis, meningitis and necrotizing encephalopathy. Therefore, the aim of this study is to describe the neural infection mechanisms performed by SARS-CoV-2 in severe cases of COVID-19. **Methodology**: This study is a descriptive literature review, carried out by searching the following databases: Google Scholar, PubMed and WHO newsletters. **Results and Discussion**: The brain invasion mechanisms of SARS-CoV-2 can occur in different ways. One of them is through neural dissemination through peripheral nerves, where viral penetration occurs through olfactory and enteric nerves, causing the virus to reach the central nervous system (CNS); on the other hand, the hematogenic pathway is related to infected leukocytes and direct infection of brain cells that express the angiotensin-converting enzyme 2 (ACE2) receptor, such as blood vessels in the cerebral microcirculation and neurons. **Conclusion**: Brain invasion by SARS-CoV-2 causes a number of serious problems for the patient. Among them, the brain inflammation generated by the presence of the virus is directly linked to neuronal death and the development of various sequelae in survivors.

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INTRODUCTION

Severe acute respiratory syndrome virus 2 (SARS-CoV-2), which causes COVID-19 disease, was first identified after some cases of pneumonia in the city of Wuhan, China, in December, 2019, has since spread to the rest of the world leading the World Health Organization (WHO) to declare a pandemic in March, 2020 (Chu *et al*., 2020). According to WHO data, the epidemiological update on March 12, 2021, the number of confirmed cases reached 118,268,525, with an overall mortality rate around 2.21%. In addition, more than 2.7 million new cases have been reported worldwide, with a 10% increase in the Eastern Mediterranean region and Africa and a 4% increase in Europe. However, there was a decline in Southeast Asia (-2%), America (-2%) and the Western Pacific regions (- 6%) (Who, 2021). Most infected patients are asymptomatic, a fact that contributed to viral spread. On the other hand, symptomatic patients may present mild, intermediate, severe and critical clinical conditions.

The most common are: runny nose, cough, fever, sore throat, respiratory secretion and myalgia. There are also gastrointestinal ones, such as nausea, vomiting and diarrhea; in addition to more severe symptoms such as shortness of breath (dyspnea) and neurological impairment. The incubation period may vary from 2 to 14 days (Xavier *et al*., 2020). A study carried out in March 2020 showed that not all of the infected individuals present the severe forms of the disease. At about 14% of the patients need to be hospitalized, requiring specific support and treatments, such as oxygen therapy. Of this group, around 5% need intubation and intensive care (Xavier *et al*., 2020). It is noteworthy that among the laboratory methods for the diagnosis of COVID-19, the ones that stand out the most are the serological tests, such as ELISA, which is based on the detection of antibodies by enzymatic reaction, especially the immunoglobulin classes IgM, IgG; and rapid tests, which are related to high rates of false negatives, especially in the early days of the infection. In addition, performing RT-PCR (Reverse Transcription Polymerase Chain Reaction) is considered the gold standard for

diagnosis, as it is a molecular biology technique that exhibit enhanced sensitivity and specificity when compared to other ones; however, PCR is only effective in the latent phase of the COVID-19, since it looks for viral RNA (Menezez *et al*., 2020; Camargo *et al*., 2020). In addition to the respiratory system and others that may be involved in COVID-19, it is worth emphasizing that neurological manifestations can also occur. An example of this is the issue of loss of smell (anosmia) and changes in taste (augesia) that affect most infected individuals. The symptoms of hyposmia/anosmia and hypogeusia/algesia in patients who do not have nasal congestion or rhinorrhea highlight the neurological impairment directly associated with SARS-Cov-2 (Moriguchi *et al*, 2020; Mao *et al*., 2020). Reports of hospitalized patients with severe or critical symptoms show that 37% of complications are neurological in origin. These data were related to the amplitude of the immune response in the brain tissue of these patients, since the inflammation generated by the presence of the virus leads to neuron death. Encephalopathy is associated with brain inflammation, which is caused by the activation of immune system cells with production and secretion of pro-inflammatory cytokines and chemokines (Najjar *et al*., 2020; Huang *et al*., 2020). Studies have already shown that SARS-CoV-2 can penetrate the central nervous system (CNS) through several mechanisms, triggering a series of problems, including: viral encephalitis, meningitis and necrotizing encephalopathy. It is noteworthy that these neurological manifestations are not restricted to individuals in a risk group such as elderly and patients with coronary heart disease. Furthermore, studies have also shown that stroke can occur in young people diagnosed with COVID-19 (Gama *et al*., 2020; Moriguchi *et al*., 2020). Thus, considering the contemporary context of the pandemic, the present study aims to make a compilation of studies on the mechanisms of neural infection performed by SARS-COV-2 in severe cases of COVID-19.

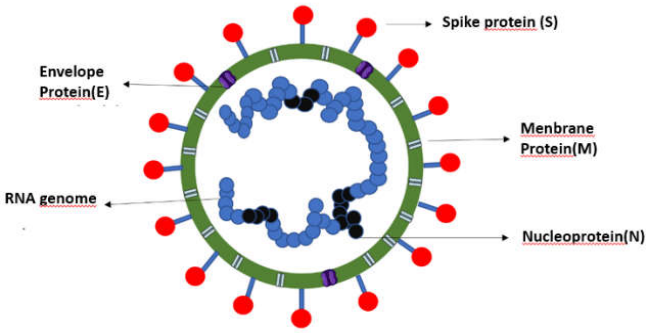
METHODOLOGY

The present study is a descriptive literature review, carried out through research and observation of scientific data related to the mechanisms of invasion of the SARS-CoV-2 virus in the CNS and the neural inflammatory response. The data collected and analyzed are published and available in databases on Google Scholar, PubMed, SciElo and WHO platforms. Due to the current research topic, the inclusion criteria for the selected articles were scientific works published between the years 2019 to 2021, which were published in english, portuguese and spanish. In addition, WHO data were also included in the bibliographic survey. The descriptors used in the research include: Central Nervous System, Immune Response, Neuroinvasion, SARS-CoV-2 and brain inflammation. Finally, articles that were not related to the proposed theme were excluded, especially scientific papers prior to the year 2019.

RESULTS AND DISCUSSION

SARS-CoV-2 structure and replication processes: Like many viruses, SARS-CoV-2 has two main structures, such as the capsid, which carries the viral RNA, and the envelope, whose main role is protection and also acts as an anchor for surface proteins, responsible for the interaction of the virus with cells. Among the RNA viruses, those of the Coronaviridae family stand out in relation to genome size, being one of the largest (Palú, 2020; Lima *et al*., 2020; Nogueira *et al*., 2020). A summary of the structure of SARS-CoV-2 and its main proteins can be seen in Figure 1.

SARS-CoV-2 is a positive-stranded RNA virus (5'3' sense), which can be read and translated directly by the host's cell structures (via ribosomes) into two polypeptides, which are subsequently cleaved by proteases, giving rise to capsid and envelope proteins of new viral particles. Virus growth causes the death of infected cells, triggering a tissue inflammatory process (Uzunian *et al*., 2020).



The structure of SARS-CoV-2 is constituted by spike proteins (S), envelope protein (E), membrane protein (M) and nuclear protein (N): The Author

Figura 1. Basic structure of SARS-CoV-2

The release of viral RNA from SARS-CoV-2 into the cell cytoplasm begins when the Spike glycoprotein (S) located on the viral surface (envelope), binds to angiotensin converting enzyme 2 (ACE2) on the cell membrane and, thus, allowing cellular infection (Souza, *et al* 2020). As an RNA virus, its mRNA encodes several proteins. For the virus to enter the cell, an interaction between the virion and the cell membrane that expresses ACE2 needs to occur, this interaction takes place through S protein, expressed on the viral envelope (Baig *et al*., 2020; Wang *et al*., 2020). The complete entry of the coronavirus into cells is also mediated by another proteins, such as the transmembrane protease serine 2 (TMPRSS2) and/or by the B and L cathepsins, which act by enabling the fusion of the envelope with the cell membrane, or entry by endocytosis, thus allowing the penetration of the nucleocapsid into the cell cytoplasm. After that, viral RNA, due to its positive polarity, is translated into two polypeptides, which, in turn, are cleaved by proteases, giving rise to structural and non-structural proteins of the virus. After the translation process, new viral particles are assembled in the Golgi complex and then released by exocytosis (Lima *et al*., 2020). It is worth noting that in addition to the lung, other tissues also have ACE2 expressed in their cells, such as the nervous system, which explains the neurological symptoms, in addition to kidney cells, blood vessels and small intestine, therefore, all these organs can be infected by SARS-CoV-2 (Brazão *et al*., 2021; Pang *et al*., 2020).

COVID-19 and the involvement of the nervous system: Reports referring to hospitalized patients affected by COVID-19, especially with severe or critical symptoms, show that 37% of the complications are of neurological origin. Furthermore, these complications have already been shown to be related to the neuronal immune and inflammatory responses, occurring as a result of the activation and recruitment of leukocytes (fromblood tobrain) and production of inflammatory mediators (mainly cytokines and chemokines) in the nervous tissue, causing inflammation with tissue loss and neuronal death(Najjar *et al*., 2020; Mehta *et al*., 2020). In addition, a study carried out recently with 214 critically ill patients with COVID-19 showed that about 88% exhibited neurological manifestations, especially impaired consciousness and acute cerebrovascular dysfunctions (Mao *et al*., 2020). Within the neurological manifestations, two categories stand out: Peripheral and central. Peripheral manifestations are related to Guillain-Barré syndrome and isolated cranial nerve dysfunction, such as loss of smell and taste. Furthermore, encephalitis, mental confusion, memory loss, delusions and post-infectious autoimmunity are manifestations related to central disorders, which are caused by the cerebral inflammatory process (Najjar *et al*., 2020; Li *et al* 2020; Baig *et al*., 2020).

Among the nervous tissue cells that can be infected by coronavirusare neurons, microglia, astrocytes and oligodendrocytes. Thus, because the surfaces of these cells present ACE2, SARS-CoV-2 is able to penetrate them and perform replication, triggering the immune response in these tissues and, therefore, generating neurological symptoms. It is worth noting that these lesions cause various

neuropathies, ranging from a simple headache to more severe symptoms such as seizures and coma. In brain tissue, several regions express ACE2, such as ventricular cells, middle temporal gyrus, substantia nigra, olfactory bulb and posterior cingulate cortex. The presence of the virus in these regions enables the activation of leukocytes and the inflammatory process in the brain, which is directly linked to neuronal death and the appearance of sometimes irreversible sequelae in survivors (Zubair *et al*., 2020; Pennisi *et al*., 2020). Previously published reports with virus similar to SARS-CoV-2 were already suggestive that the new coronavirus could infect the CNS. Within this context, in relation to the SARS-CoV-1 outbreaks during the years 2002 and 2003, there were evidences of neurological manifestations in a significant number of patients. In addition, studies have shown patients with a positive result for SARS-CoV-1 in the cerebrospinal fluid (CSF). Viral detection in the CSF of patients was performed using the polymerase chain reaction (PCR), which enabled the amplification of viral RNA. Complementarily, studies have already confirmed, through autopsies of brain tissue from patients affected by SARS-COV-1, the presence of the virus in the cytoplasm of neurons in different regions of the brain, such as in the cortex and hypothalamus (Baig *et al*., 2020). It is worth emphasizing that the SARS-CoV-1 virus is very similar to SARS-CoV-2, especially with regard to the sequentiality of its RNAs. Furthermore, both serotypes express mRNA referring to protein S translation, that is, they share the mechanisms of cell invasion. Another important factor for SARS-CoV-2 invasion is that neural tissue has been shown to be rich in ACE2, which makes viral replication in the CNS possible with subsequent activation of the brain's immune and inflammatory responses (Chen *et al*., 2020). Despite genetic similarities, it has been proven that the affinity (binding strength) of the S protein of SARS-CoV-2 is 10 to 20 times greater than that of the same protein expressed by the serotype SARS-CoV-1, in relation to binding to ACE2 expressed in host cells (Menezes *et al*., 2020). Although there is evidence of neurological manifestations resulting from COVID-19, the neuroinvasion routes, as well as the neural manifestations, are still not completely clarified. Currently, it is known that two routes of infection are important for the entry of the virus into the CNS: The hematogenous and neuronal routes (Paniz-Mondolfi *et al*., 2020).

Immune response in nervous tissue triggered by Sars-CoV-2: When SARS-CoV-2 invades the CNS, microglia residing in the nervous tissue phagocyte these viral particles, activating a cascade of immune response, with subsequent production of cytokines and chemokines. Chemokines signal the recruitment of circulating leukocytes into nervous tissue; and cytokines act by activating these cells and amplifying the immune response, which can trigger nerve tissue loss as a result of the production of free radicals during inflammation. Among the important cytokines for the virus in question, we can highlight the interleukins (IL) IL-1, IL-6, IL-8, IL-21 and tumor necrosis factor beta (TNF-β). The exacerbated increase in these pro-inflammatory cytokines is the event that characterizes the so-called "cytokine storm", which aggravates the immune and inflammatory response, since these cytokines induce an increased oxidative and nitrosative stresses, generating great nerve tissue loss and enabling the appearance of symptoms (Accorsi *et al*., 2020; Brito *et al*., 2020; Nunes *et al*., 2020). Released viral particles from infected cells are usually phagocytosed by macrophages and infected host cells are fought through a response mediated by $CD8^+$ cytotoxic lymphocytes and natural killer cells. Initially, the innate mechanisms of the immune response try to control viral growth until the development of acquired immunity, which usually occurs in the second week after infection, with the activation of responses mediated by T and B lymphocytes (Soto *et al*, 2020).

During the activation of the immune response, oxidative and nitrosative stresses, produced by leukocytes, configure two important sources of free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RNS), in the CNS. Excessive production of these molecules is intended to destroy the invading pathogen, however, ROS and RNS also react with components of nervous tissue, especially through lipid peroxidation (free radical attack onphospholipids of the membrane), injuring the cells. It is important to note that free radicals attack any biomolecule, including lipids, proteins and nucleic acids, leading to cell degradation and increasing the immune and inflammatory responses, with even greater infiltration of leukocytes in the brain (Mingoti *et al*., 2021; Vellosa *et al*., 2021). The BeijinDitan Hospital in China reported on its clinical data, evidences of encephalopathies caused by SARS-CoV-2. These results were confirmed through the analysis of the cerebrospinal fluid (CSF), which was positive for the virus, being confirmed by the sequencing of the viral genome. In addition, autopsy studies have reported the degeneration of the nervous tissue, a result of the severe cases of COVID-19, in addition to the swelling of soft tissue, which occurs due to the increase in interstitial fluid resulting from the inflammatory process in the brain region (Mao *et al*., 2020*).*

Hematogenous Pathway and Blood Brain Barrier: SARS-CoV-2 brain invasion mechanisms can occur in different ways. One is through neural dissemination through peripheral nerves, where viral penetration occurs through the olfactory and enteric nerves, causing the virus to reach the CNS; on the other hand, the hematogenous route usually occurs through infected leukocytes and also by direct infection of brain cells that express ACE2, such as blood vessels of the cerebral microcirculation and some neurons (Raony *et al*., 2020). In order to talk about the invasion of the CNS through the blood, it is first necessary to understand what the blood-brain barrier (BBB) is. This structure is made up of a semi-permeable and selective membrane that lines the blood vessels of the internal cerebral circulation. It controls everything that enters and leaves the nervous tissue, through transporters (proteins) expressed in the cells of this barrier; anatomically, the BBB is formed by occlusion junctions between the endothelial cells of the cerebral vessels, that is, the endothelial cells have binding proteins transversely and longitudinally, connecting the cells to each other on all sides, "squeezing" the paracellular spaces (between cells). In this case, this endothelium joined by tight junctions is surrounded by cells called pericytes, which are responsible for the production and support of these proteins that contract the endothelium of cerebral microvessels; among the main proteins responsible for this phenomenon are Junctional Adhesion Molecule A (JAM-A) and Claudin-5 (Kakogiannos, 2020; Aquino, 2019).

The first mechanism occurs by infection and transport through the vascular endothelium. Vascular endothelial cells found in the BBB as well as throughout the body express ACE2, which considerably increases the risk of infection by SARS-CoV-2. The beginning of this route begins when the virus arrives in the cerebral microcirculation, where the coronavirus S protein makes contact with the endothelial cells that express ACE2. The interaction of these proteins causes the viral envelope to fuse with the cell membrane, internalizing the virus RNA; yet, coronavirus can also enter the cytoplasm by endocytosis, through the action of secondary proteins as previously described (Zubair *et al*., 2020; Li *et al*., 2020). Within endothelial cells, the virus replicates using ribosomes, which translate the viral genetic material into polypeptides (2 molecules). This last one is cleaved by proteases, giving rise to structural (4 molecules) and non-structural (16 molecules) proteins that interact with each other to form new virions. It is important to remember that SARS-CoV-2 carries its own polymerase (non-structural protein 12, NSP12), enabling viral RNA replication. The new viruses are assembled and packaged into vesicles in the Golgi complex, then transported to the cell membrane, which fuses with the vesicle and releases new viruses, both into the bloodstream and into the nervous tissue (Zubair *et al*., 2020; Baig *et al*., 2020; Natoli *et al*., 2020). An illustration of the blood-brain barrier can be seen in Figure 2. The first mechanism of SARS-CoV-2 through blood routes is through the endothelium. These endothelial cells have ACE-2. So the virus is easy to invade. its penetration facilitates the multiplication of the virus. Since the central nervous system communicates with the endothelium through nerve cells, SARS-CoV-2 also contaminates these desease cells, Astrocytes for example.: The Author The new viral particles, when released from the opposite side of the bloodstream, trigger an immune response at these sites, disrupting vessels and internalizing the virus into the CNS.

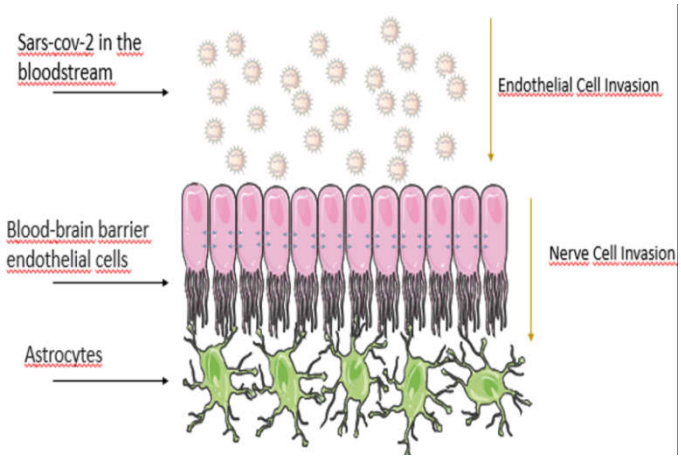


Figure 2. Blood stream, blood-brain barrier and nervous tissue

Once inside the neural tissue, viral particles can infect vessels, glias and neurons, inducing the brain tissue to inflammation. In response to the inflammatory stimulus, BBB increases its permeability, allowing the processes of chemotaxis (mediated by chemokines) and activation (mediated by cytokines) of circulating leukocytes to the CNS to occur. Blood vessel injuries also allow for a greater passage of virions, amplifying the inflammatory process and generating neurological manifestations (Zubair *et al*., 2020; Baig *et al*., 2020; Paniz-Mondolfi *et al*., 2020; Natoli *et al*., 2020). An autopsy study of cerebral and vascular tissue demonstrated viral particles of SARS-CoV-2 in capillary endothelium and neurons in the frontal lobe. This study revealed that neurons had viral particles that were packaged in dilated vesicles in the cytoplasm. It was later demonstrated by electron microscopy that viral particles were in the phase of exocytosis and endocytosis in the endothelial cells, showing the viral entry and exit of the brain tissue (Zubair *et al*., 2020; Paniz-Mondolfi *et al*., 2020). The second mechanism of neuroinvasion is mediated by the passage of infected leukocytes, such as lymphocytes and monocytes, through the BBB in chemotaxis processes, allowing and/or amplifying neuroinvasion. Studies with the new coronavirus are still limited due to the short time of disease onset, however, previous studies with SARS-CoV-1 have already shown that coronaviruses could infect granulocytes, monocytes and lymphocytes that express ACE2. Electron microscopy data have already shown the process of endocytosis and exocytosis of the virus in leukocytes, endothelial cells and also in infected neurons (Zubair *et al*., 2020; Raony *et al*., 2020; Homes *et al*., 2020). It is important to emphasize that the presence of defense cells and viral particles in the nerve tissue considerably increases the oxidative and nitrosative stresses in the brain. Reactive oxygen (superoxide anion and hydrogen peroxide) and nitrogen (nitric oxide and derivatives such as peroxynitrite) species are directly linked to brain tissue damage in new coronavirus infections (Palomino *et al*., 2021).Figure 3 shows the passage of infected leukocytes through the BBB.Another important pathway for SARS-CoV-2 penetration in the brain is the neural pathway, which will be discussed below

The second mechanism that the virus can invade the central nervous system is through the `` trojan horse `` mechanism. this mechanism is so called because of the defense cells that at first serve to defend the patient ends up contaminating the central nervous system: The Author

Neurogenic Pathways: Recent studies prove that the spread of several neuroinvasive viruses can be associated with the axonal route of peripheral and central nerves. Among them, Herpes simplex andCoronaviruses can be mentioned (Costa *et al*., 2020). Mainly through transsynaptic axonal retrograde transport, in vesicles (endocytosis) or not, SARS-CoV-2 reaches neurons, which also express ACE2, infecting them, both peripheral and central. Thus, the axonal pathway becomes an alternative for the virus to be able to invade the CNS, mainly through access to the nerves of the peripheral nervous system, which connect with the cranial nerves and thus penetrate the brain (Pennisi *et al*., 2020; Li *et al* 2020; Raony *et al*., 2020).

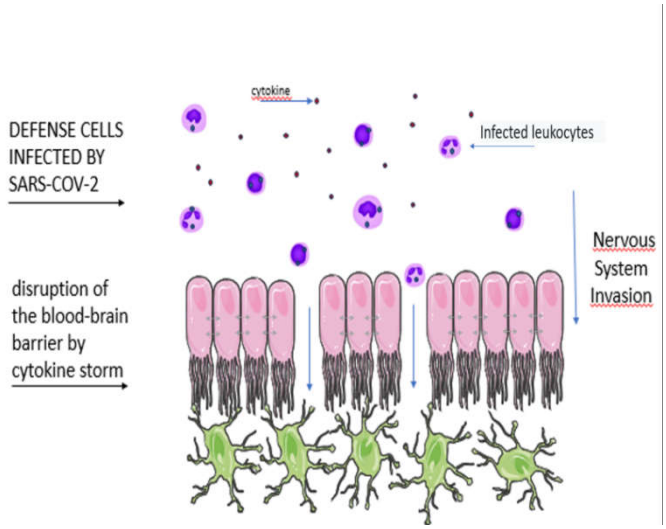


Figure 3. Increased permeability of the BBB with passage of infected leukocytes from the bloodstream to the brain

It is already evident that ACE2 is expressed in several brain structures, among them, we can highlight the brainstem, hypothalamus, cortex and striatum. Furthermore, ECA2 belongs to the cell membrane of glial cells and neurons throughout the brain. In this way, CNS becomes a vulnerable environment for infection to occur (Zubair *et al*., 2020). Since the virus remains lodged in the upper respiratory tract, a route that stands out regarding neuroinvasion is the penetration of the CNS through the terminal olfactory neurons, as they are present in an increased form in the respiratory tract, becoming the main vehicle of the SARS-CoV-2 for the brain (Nunes et al., 2020; Li *et al*., 2020 ; Almeida *et al*., 2020). In the respiratory system, infection is initiated through the invasion of dendrites of olfactory neurons, which are nerve cells that remain in the nasal cavity and in the cribriform layer of the individual's ethmoid bone. Thus, viral particles tend to move to the axons and reach the olfactory bulb of the CNS (Jarrahi *et al*., 2020). As shown in figure 4.

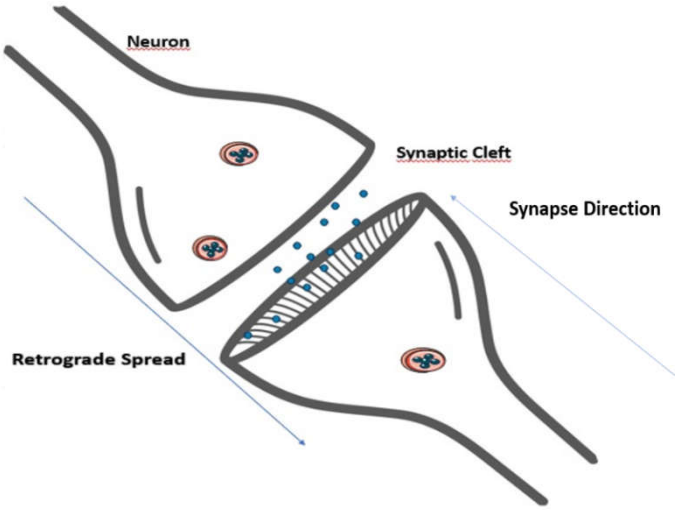


Figure 4. Transsynaptic axonal retrograde transport of SARS-CoV-2 to the brain

The main route that the virus invades the central nervous system is with the help of neurons. Through vesicles with mechanisms of endocytosis and exocytosis, the virus enters the neurons and is transported until it invades the central nervous system.: The Author

Another important factor is that SARS-CoV-2 also invades the CNS through the brainstem, this can be explained mainly by the presence of the trigeminal nerve, which basically branches into three: The

ophthalmic (V1), maxillary (V2) and mandibular (V3) ones. Neuroinvasion occurs primarily through nerves present in the larynx, lungs and trachea, which are structures linked to the respiratory system, the main site of replication of SARS-CoV-2 (Yavarpour-Bali e Ghasemi-Kasman, 2020). A case study published by Mao *et al*. (2020), with a 56-year-old male patient, affected by COVID-19, performed at the Beijing Ditan Hospital (Beijing-China), demonstrated the presence of viral RNA in the CSF, contributing to the evidences of infection of the nervous system by SARS-CoV-2. Furthermore, recent studies with a murine model have also shown that respiratory coronaviruses, such as SARS-COV-1, when inoculated in the nasal fossae of mice, can penetrate the CNS by the the disruption of the nasal epithelium, mainly through a local inflammatory process, also compromising the nerve fibers, which explains the anosmia (loss of smell), with subsequent neurological symptoms. Infection of the olfactory bulb nerves by SARS-CoV-2 has been shown to be a mechanism for olfaction loss. Studies with SARS-COV-1 are important to understand the mechanisms of SARS-COV-2, as they have similar infection processes (Paniz-Mondolfin *et al*., 2020; Zubair *et al*., 2020).

CONCLUSION

In view of the studies presented in this work, it is evident that SARS-CoV-2 is not merely a respiratory virus, but a pathogen with the potential to infect different tissues. The structure of the COVID-19 virus makes it able to infect cells that express ACE2, present in different organs. The CNS infection occurs through different pathways, including the hematogenous and synaptic ones. The hematogenous pathway is established by the infection of blood (leukocytes) and endothelial cells, contributing to the internalization of the virus in the nervous system; the neuronal pathway, on the other hand, consists of the infection of peripheral e central nerves that also express ACE2, especially the nerves of the respiratory system. When invading the CNS, the presence of virions released by infected cells triggers an immune response in the nervous tissue, with cytotoxic response, phagocytosis and brain inflammation, which can cause neuronal death and sequelae.

REFERENCES

Accorsi, DX., Santos, IAM., Accorsi, JX., Bohac, S., Chin, CM. (2020) COVID-19 and the Central Nervous System. UlakesJournalof Medicine. 1: 81-87.

Ahmad of Neurosciences (LANEU), Federal University of Fronteira Sul. 2021-10-29; 1-

Almeida, DB., Mota, SCB., Sanford, ABA., Queiroz, TC., Mesquita, DS., Honório Júnior, JER. (2021) Characteristics of Central Nervous System Involvement by SARS-COVS-2. Advanced Studies on Health and Nature. 1: 180-210

Aquino, CC (2019) Effect of low-protein and high-fat diets on markers of oxidative stress, inflammation and permeability of the blood-brain barrier in the hippocampus and anxiety behavior. Doctorate degree. Thesis in Medical Sciences. Faculty of Medicine, Federal University of Ceará (CE) Brazil.

Baig, AM., Khaleeq, A., Ali, U., Syeda, H. (2020) Evidence of the Covid-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS chemical neuroscience. 7: 995-998.

Brazão, ML., Nóbrega, S. (2021) Complications/Sequelae after SARS-CoV-2 Infection: Literature Review. Internal Medicine. 2: 184-194.

Brito, WGF., Silva, JPDO. (2020) Neuropathological impacts of COVID-19 .Brazilian Journal of Health Review. 3: 4227-4235.

Camargo, CH., Gonçalves CR., Pagnoca, EVRG., Campos, KR., Abbud, A., Bugno, A., Araujo, AC., SacchiI, CT. (2021) A year of the COVID-19 pandemic: genetic diversity of SARS-COV-2 in Brazil. São Paulo Epidemiological Bulletin (BEPA). 18: 12-33.

Chen, R., Wang, K., Yu, J., Howard, D., French, L., Chen, Z., Wen, C., Xu, Z. (2021) The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. Frontiers in neurology. 11: 1860.

Chu, H., Chan, JFW., Yuen, TTT., Shuai, H., Yuan, S., Wang, Y. (2020) Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. The Lancet Microbe. 1: 14-23.

Costa, REAR., Cardoso, AC., Martins, SAS., Amaral, AM., Campos, LNR., Martins, LRG., Sousa, LS., Paulo, AS., Cordeiro, SSA., Cunha, ELA., Silva, NA., Araújo, CRSM., Leal, JFC., Sousa, FWS., Reis, MR., Calaça, MB. (2020) Neurological complications in patients infected with coronavírus. Research, Society and Development. 8: e242985687-e242985687.

Gama, BDS., Cavalcante, KN. (2020) Covid-19 pandemic: neurological environment and brain impacts. Brazilian Journal of Health Review. 6: 19000-19006..

Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, Ballard C, Christensen H, Cohen Silver R, Everall I, Ford T, John A, Kabir T, King K, Madan I, Michie S, Przybylski AK, Shafran R, Sweeney A, Worthman CM, Yardley L, Cowan K, Cope C, Hotopf M, Bullmore E. (2020). Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. The Lancet Psychiatry. 6: 547-560.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Qi., Wang, J., Cao, B. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 395: 497-506.

Jarrahi, A., Ahluwalia, M., Khodadadi, H., Salles, ESL., Kolhe, R., Hess, DC., Vale, F., Kumar, M., Baban, B., Vaibhav, K., Dhandapani, KM. (2020) Neurological consequences of COVID-19: what have we learned and where do we go from here?. Journal of neuroinflammation. 1:1-12.

Kakogiannos, N., Ferrari, L., Giampietro, C., Scalise, AA., Maderna, C., Ravà, M., Taddei, A., Lampugnani, MG., Pisati, F., Malinverno, M., Martini, E., Costa, I., Lupia, M., Cavallaro, U., Beznoussenko, GV., Mironov, AA., Fernandes, B., Rudini, N., Dejana, E., Giannotta, M. (2020) JAM-A Acts via C/EBP-α to promote claudin-5 expression and enhance endothelial barrier function. Circulation research. 8: 1056-1073.

Li, H., Xue, Q., Xu, X. (2020) Involvement of the Nervous System in SARS-CoV-2 Infection. Neurotox Res. 38: 1-7.

Li, YC., Bai, WZ., Hashikawa, T. (2020) The neuroinvasive potential of SARS□CoV2 may play a role in the respiratory failure of COVID□19 patients. Journal of medical virology. 6: 552-555.

Lima, LNGC., Sousa, MS., Lima, KVB. (2020) The genomic discoveries of SARS-CoV-2 and their implications for the COVID-19 pandemic. Journal of Health & Biological Sciences. 1: 1-9.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., Hu, B. (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 6: 683-690.

Mehta, P., McAuley, DF., Brown, M., Sanchez, E., Tattersall, RS., Manson, JJ. (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 395: 1033-1034.

Menezes, ME., Lima, LM., Martinello, F. (2020) Laboratory diagnosis of SARS-CoV-2 by real time reverse transcriptase-polymerase chain reaction (RT-PCR). RBAC. 2: 122-130.

Mingoti, MED., Bertollo, AG., Simões, JLB., Francisco, GR., Bagatini, MD., Ignácio, ZM. (2021) Covid-19, Oxidative Stress and Neuroinflammation on the Depression Path. Proceedings II Symposium on Clinical and Experimental Neuroscience: Neurodegenerative Diseases, carried out by the Academic

League of Neurosciences (LANEU), Federal University of Fronteira Sul. 2021-10-29; 1-4.

Moriguch, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., Ueno, M., Sakata, H., Kondo, K., Myose, N., Nakao, A., Takeda, M., Haro, H., Inoue, O., Suzuki-Inoue, K., Kubokawa, K., Ogihara, S., Sasaki, T., Kinouchi, H., Kojin, H., Ito, M., Onishi, H., Shimizu, T., Sasaki, Y., Enomoto, N., Ishihara, H., Furuya, S., Yamamoto, T., Shimada, S. (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 94: 55-58.

Najjar, S., Najjar, A., Chong, DJ., Pramanik, BK., Kirsch, C., Kuzniecky, RI., Pacia, SV., Azhar, S. (2020) Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. Journal of neuroinflammation. 231: 1-14.

Natoli, S., Oliveira, V., Calabresi, P., Maia, LF., Pisani, U. (2020) Does SARS□Cov□2 invade thebrain? Translational lessons from animal models. *European journal of neurology.* 9: 1764-1773.

Nogueira, JVD., Silva, CM. (2020) Knowing the origin of SARS-COV-2 (COVID 19). *Health and Environment Magazine.* 2: 115-124.

Nunes, MJM., Silva, JCS., Oliveira, LC., Marcos, GVTM., Fernandes, ACL., Santos, WLS., Guzen, FP., Cavalcanti, JRLP., Araújo, DP. (2020) Neurological Changes at Covid-19: a Systematic Review. *Journal Neurosciences.* 28: 1-22.

Palomino, AMC. (2021) Molecular bases of ischemic damage and the effect of olive oil on it. TAUJA: Repository of Academic Works of the University of Jaén. Available online at: https://hdl.handle.net/10953.1/14537.

Palú, IA. (2021) Sars-CoV-2 virology. Connection Line-Univag Electronics magazine. 25: 95-114.

Pang, J., Wang, MX., Ang, IYH., Tan, SHX., Lewis, RF., Chen, JIP., Gutierrez, RA., Gwee, SXW., Chua, PEY., Yang, Q., Ng, XY., Yap., RK., Tan, HY., Teo, YY., Tan, CC., Cook, AR., Yap, JCH., Hsu, LY. (2020) Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus (2019-nCoV): a systematic review. J Clin Med. 3: 623.

Paniz-Mondolfi, A., Bryce, C., Grimes, Z., Gordon, RE., Reidy, J., Lednicky, J., Sordillo, EM., Fowkes, M. (2020) Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J. Med. Virol. 92: 699–702.

Pennisi, M., Lanza, G., Falzone, L., Fisicaro, F., Ferri, R., Bella, R. (2020) SARS-CoV-2 and the nervous system: from clinical features to molecular mechanisms. Int J Mol Sci. 15: 5475.

Raony, I., Figueiredo, CS., Pandolfo, P., Araújo, EG., Bomfim, PO., Wilson, S. (2020) Psycho-neuroendocrine-immune interactions in COVID-19: potential impacts on mental health. Frontiers in immunology. 11: 1170.

Santos, A. A. R.; Karen K. O. P; Bruno F. D. M.; Daniele G. C. (2021) Different aspects of the immune response in COVID-19. Research, Society and Development, v. 10, n. 14, p. e423101422531-e423101422531,

Soto, G. P.; Pastrian, S. G. (2020) Bases genéticas y moleculares del COVID-19 (SARS-CoV-2). Mecanismos de patogénesis y de respuestainmune. Int. J. Odontostomat, v. 14, n. 3, p. 331-337

Souza, JB., Farias, PCA., Oliveira, FHPC., Albuquerque, JPAS. (2020) Pharmacological approaches for the treatment of infection caused by SARS-COV-2: an integrative review. Brazilian Journal of Development. 6: 39060-39078.

Uzunian, A. (2020) Coronavirus SARS-CoV-2 and Covid-19. J BrasPatol Med Lab. 56: 1-4.

Vellosa, JCR., Biavatti, M., Françóia, PCO., Mello, BJ., Almeida, C., Buen, GE. (2021) Oxidative stress: an introduction to the state of art. Brazilian Journal of Development. 1: 10152-10168.

Wang, X., Ding, Y. (2020) Analysis of severe acute respiratory syndrome and new coronavirus infection diseases from pathogens, receptor distribution, pathological changes and treatment principles. Chinese J Pathol. 6: 647-652.

World Health Organization (2021). Atualização epidemiologica semanal - 9 de março de 2021. Disponível online em: https://www.who.int/publications/m/item/weekly-epidemiological- update-- 10-march-2021. Acesso em 17 de dezembro de 2021

Xavier, AR., Silva, JS., Almeida, JPCL., Conceição, JFF., Lacerda, GS., Salim, K. (2020) COVID-19: clinical and laboratory manifestations in new coronavirus infection. *Brazilian Journal of Pathology and Laboratory Medicine*. 56: 1-9.

Yavarpour-Bali, H., Ghasemi-Kasman, M. (2020) Update on neurological manifestations of COVID-19. Life Sci. 257: 118063.

Zubair, AS., McAlpine, LS., Gardin, T., Farhadian, S., Kuruvilla, DE., Spudich, S. (2020) Neuropathogenesis and neurological manifestations of coronaviruses in the coronavirus disease era 2019: a review. JAMA neurology. 8: 1018-1027.

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