International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-9, Issue-8; Aug, 2022
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.98.3

Central Nervous System Infection by SARS-CoV-2 and Neuropsychiatric Consequences Related to Disease Caused by the Virus: A Review

Ana Paula Ribeiro[1], Marcelo Benetti da Silva Junior[1], Miguel Ângelo de Marchi[1], Rogério Leone Buchaim[2], Daniela Vieira Buchaim[3,4]

[1]Department of Medicine, Medical School, University Center of Adamantina (UNIFAI), Adamantina (SP) 17800-000, Brazil
[2]Department of Biological Sciences (Anatomy), Bauru School of Dentistry, University of São Paulo (USP), Bauru (SP) 17012-901, Brazil
[3]Postgraduate Program in Structural and Functional Interactions in Rehabilitation, University of Marilia (UNIMAR), Marília (SP) 17525-902, Brazil
[4]Department of Human Anatomy and Neuroanatomy, Medical School, University Center of Adamantina (UNIFAI), Adamantina (SP) 17800-000, Brazil
*Corresponding author: rogerio@fob.usp.br

Received: 01 Jul 2022,
Received in revised form: 26 Jul 2022,
Accepted: 30 July 2022,
Available online: 06 Aug 2022

***Keywords*— Central Nervous System, Citokynes, SARS-CoV-2, Infection,**

***Abstract*—** *The COVID-19 virus infects the body, preferably by inhalation, reaching the Central Nervous System through the olfactory pathways, characterizing a primary infection. The Central Nervous System (CNS) can also be affected when the virus spreads hematogenously and crosses the blood-brain barrier. The brain tissue damage caused by the pathogen can occur directly, with the injury caused by the direct contact of the virus with neuronal cells, or indirectly, through the activation of inflammatory and thrombotic pathways due to the entry of the pathogen into the body. Endothelial dysfunction is potential for brain complications and can have neuropsychiatric consequences, both during the course of the disease and after its remission. The objective of the present literature review was to associate Central Nervous System Infection by SARS-CoV-2 with possible neuropsychiatric consequences caused by the pathological process caused by the virus. In addition to the organic factor involved, such consequences may also be related to psychosomatic processes, involving post-traumatic stress, fear and grief of individuals when facing these issues during the pandemic.*

I. INTRODUCTION

The SARS-CoV-2 presented itself in 2019 as an infection that caused mild and intermediate symptoms, such as flu and gastrointestinal symptoms, in most patients with a higher incidence in elderly patients or patients with comorbidities. In addition to these symptoms, some can also be presented by the Central Nervous System – CNS (BRITO & SILVA, 2020). Clinically, a strong feature of SARS-CoV-2 infection is the disturbance of smell (BUCHAIM *et al*., 2020). In the literature, 86% of patients showed signs of hyposmia or years of symptoms, even before symptoms of some symptoms (DOUAUD *et al*., 2022).

In April 2020, in a sample of 214 patients infected with the new coronavirus, neurological symptoms in a percentage of 36.4% were already noticed, being more common in severe cases of infection (MAO *et al*., 2020).

With the advance of the COVID-19 pandemic, the protests alert continued to grow. ELLUL *et al*. (2020) cites cases of 901 individuals, whose organic hypotheses

revolved around direct viral effects on the nervous system (attack on nervous tissue and vasculature), immune-mediated disease during and after infection, as well as systemic effects leading to neurological complications. In this retrospective study of cases in Wuhan, cerebrovascular manifestations were reported in 6% of 221 patients and as the virus spreads, evidence increases for an association with cerebrovascular disease, as well as other forms of vascular disease. In this retrospective study of cases in Wuhan, cerebrovascular manifestations were reported in 6% of 221 patients and as the virus spreads, as an association of vascular disease increases, as well as with other forms of vascular disease.

In addition, turning attention to fear, even the patient, should influence the mental health of patients, anxiety and/or post-traumatic stress, anxiety and/or more rare depression (DE OLIVEIRA *et al*., 2021). It is known that during a pandemic, the development of symptoms and quarantine led to fear and increased stress, leveraging different psychiatric disorders. It is also known that some viral syndromes harm the CNS, as they have neuropsychiatric and consequent effects on the affective, behavioral and perception domains. Dealing with the pandemic situation is a significant stressor state, as it substantially influences all areas of life, community organizations, socially and economically (MOREIRA *et al*., 2021).

Recognizing an evolving or asymptomatic neurologic neurological disease to the joint SARS-CoV-2 may be more difficult, even the infection-neurological disease ratio tends to remain minimal. However, when they do not occur, neurological sequelae may only be present as they are severe. However, considering the suffering associated with the pandemic and the pathological process that causes the virus, the effects on the CNS are still known and complementary therapies are being poorly studied, aiming at a functional and psychological recovery of the affected animals (BUCHAIM *et al.*, 2007; ROSSO *et al.*, 2020; DE MATOS *et al*., 2021).

II. MATERIALS AN METHODS

This literature review was initially prepared by searching for information in the SCIELO, PubMed/MEDLINE and MedRxiv databases, during the month of May 2022, on events associated with SARS-CoV-2 infection with an effect on the Central Nervous System. The Google Scholar website was also used to search for articles with the theme discussed, in the selected period between 2020 and 2022. The following descriptors were used: "COVID-19 and Central Nervous System", "SARS-CoV-2", "Covid long" and "cytokine storm". Initially, 21 articles were selected that provided information about the damage caused by the virus in the body, and among these, 10 were excluded because they addressed neurological repercussions superficially or because they had little data on the topic to be discussed in this study.

III. RESULTS AND DISCUSSION

According to MOREIRA *et al*. (2021), it is known that SARS-CoV-2 binds to the cell to enter it through the angiotensin 2-converting enzyme receptor as well as smooth muscle cells. In addition, an in vitro experiment showed virus replication in neuronal cells. To reach the CNS, the entry of SARS-CoV-2 occurs through the ascent of the virus through the olfactory pathways (through the olfactory bulb), precisely because it is part of the CNS not protected by the dura mater. Another form of CNS infection would be through the blood-brain barrier (BBB) crossing, hematogenous route, by contaminated leukocytes or viremia.

In a study of animal models, it was observed that SARS-CoV-2 makes use of the trans-synaptic neuronal pathway, through olfactory nerves (BUCHAIM *et al*., 2020), reaching other brain structures such as the trunk, thalamus, basal ganglia, in addition to others, this being main or additional road. This fact explains the symptoms of decreased or loss of smell in some cases. Central nervous tissue damage can be caused directly or indirectly by the infection. Directly by the virus is a possibility, but the data found do not suggest that it is highly neurovirulent - as with neurotropic viruses. The main issue would be restricted to the way in which the pathogen enters the organism (ELLUL *et al*., 2020). Even so, the neurotropism of the coronavirus can still lead to inflammation by activating glial cells (BRITO & SILVA, 2020)

An autopsy was performed on a patient who, weeks after infection with COVID-19, developed encephalopathy, identifying edema, neuronal necrosis and glial hyperplasia. In evaluating the injured tissue using immunohistochemistry, it was noted that the virus was associated with the expression of cytokines, chemokines and infiltration of defense cells. Such findings are consistent with the hypothesis that the coronavirus, upon entering the CNS, triggers immune-mediated inflammatory processes, promoting tissue damage (ELLUL *et al*., 2020). The term "cytokine storm" is used for the exaggerated immune response, which accompanies intense release of inflammatory cytokines, in which, when linked to infectious diseases, it is strongly associated with viral causes, being a hot topic after the beginning of the pandemic of COVID-19 (ALCOCK & MASTERS, 2021).

Studies show that this "cytokine storm" can break the integrity of the BBB, reaching the CNS, leading to neuroinflammation. The basis of encephalopathy caused by a toxic effect on tissue is supported by evidence of cerebral edema, as well as neuronal degeneration in patients with COVID-19 who were autopsied (BRITO & SILVA, 2020).

TAQUET *et al.* (2021) reports that cross-sectional studies formed by electronic health records covering 62,354 cases of COVID-19 were used, evaluating bidirectional associations between the aforementioned condition and psychiatric disorders. Among the sample of patients with no prior history of psychiatric disorder, illness caused by the coronavirus was associated with an increased incidence of psychiatric diagnoses within the three-month period after infection, with a 95% confidence interval and risk rate of 2.1 (1.8-2.5). Anxiety disorders increased the most, followed by depression, insomnia and dementia. Another point observed was the increased risk for COVID-19 in patients with a previous psychiatric diagnosis.

Thus, among the factors involved that explain these repercussions, when correlated with SARS-CoV-2 infection, we can mention the immune response to the virus, as discussed above, as well as psychosocial factors, such as fear related to the disease, individual and family, bereavement, and social isolation. A large part of the people who survived the disease had some type of psychiatric disorder, namely: anxiety (40%), depression (31%) and post-traumatic stress disorder (28%). In addition, disease processes have been described at the cerebrovascular level with micro ischemia caused by the virus, being related to depression (MACEDO *et al.*, 2021).

DOUAUD *et al.* (2022) describes an investigation of brain alterations using the UK Biobank database, in which 785 participants were evaluated, aged between 51 and 81 years. Therefore, brain magnetic resonance imaging (MRI) was performed at two moments, in which 401 analyzed, with a positive test for COVID-19, in the corresponding period between the two exams, had proficient images. Among these, for 351 individuals who had a diagnosis date based on antigen tests and medical records, they had an average of 141 days between diagnosis and obtaining the second image. The importance of having pre-infection imaging data available reduces the possibility of previously existing risk factors. That said, the significant effects found between the two imaging groups studied, in positive cases for COVID-19, were: gray matter reduced in thickness; contrasted orbitofrontal cortex and parahippocampal gyrus; areas with functions linked to the primary olfactory cortex (Piriformis cortex), with changes in tissue damage markers; brain with reduction in its overall size.

In view of this, in addition to the changes in the images, on average, infected individuals also evolved with greater cognitive decline in this period. When comparing a control group with SARS-CoV-2 positive participants, the differences between both were explored, based on cognitive tasks, addressing scores of patients outside the sample more susceptible to cognitive impairment and, after correction of the discovery rate false, a significant increase in the time required to perform such tasks was found (DOUAUD *et al.*, 2022).

IV. CONCLUSION

In view of the above, based on the extractions of articles presented, it is concluded that the SARS-CoV-2 virus has, albeit little, neurotropism. Even so, it is a potential cause of injury to the CNS, directly or indirectly, due to its pathogenicity, inflammation and exacerbated immune response of the infected organism. It is noted that the lesions can also lead to morphological and functional changes in the brain parenchyma, which can lead to neurological disorders. Nevertheless, with regard to the increase in diagnoses of psychiatric diseases, it is important to emphasize not only the organic cause, but also psychosocial aspects related to the entire pandemic context.

REFERENCES

[1] ALCOCK, J., MASTERS, A. (2021) Cytokine storms, evolution and COVID-19. Evol. Med. Public Health, v. 9, n. 1, p. 83-92. doi: 10.1093/emph/eoab005

[2] BRITO, W. G. F. & SILVA, J. P. D. O. (2020). Impactos neuropatológicos do COVID-19. Braz. J. Hea. Rev., v. 3, n. 3, p. 4227-4235. doi:10.34119/bjhrv3n3-026.

[3] BUCHAIM, R. L. *et al.* (2007). Biocompatibility of anionic collagen matrices and its influence on the orientation of cellular growth. Braz. Dent. Sci., v. 10, n. 3, p. 12–20. doi: 10.14295/bds.2007.v10i3.272

[4] BUCHAIM, R. L. *et al.* (2020). Loss of smell and COVID-19: Anatomical and physiological considerations. International Journal of Advanced Engineering Research and Science, v. 7, n. 5, p. 278-280. doi: 10.22161/ijaers.75.34

[5] DE MATOS, B. T. L. *et al.* (2021). Photobiomodulation Therapy as a Possible New Approach in COVID-19: A Systematic Review. Life-Basel, v. 11, n. 6, p. 580. doi: 10.3390/life11060580. PMID: 34207199; PMCID: PMC8233727

[6] DE OLIVEIRA S. M. T. *et al.* (2021). Epidemiological Study of Violence against Children and Its Increase during the COVID-19 Pandemic. Int. J. Environ. Res. Public Health, v. 18, n. 19, p. 10061. doi:

10.3390/ijerph181910061. PMID: 34639362; PMCID: PMC8507936

[7] DOUAUD, G. *et al.* (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature, v. 604, p. 697-707. doi: 10.1038/s41586-022-04569-5

[8] ELLUL, M. *et al.* (2020). Neurological associations of COVID-19. The Lancet Neurology, v. 19, n. 9, p. 767-783. doi: 10.1016/S1474-4422(20)30221-0

[9] MACEDO, L. M. *et al*. (2021). Como a covid afeta o cérebro? Brazilian Journal of Development, v. 7, n. 7, p. 74144-74153. doi: 10.34117/bjdv7n7-545

[10] MAO, L. *et al*. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology, v. 77, n. 6, p. 683-690. doi:10.1001/jamaneurol.2020.1127

[11] MOREIRA, J. *et al.* (2021). The psychiatric and neuropsychiatric repercussions associated with severe infections of COVID-19 and other coronaviruses. Progress in Neuro-Psychopharmacology and Biological Psychiatry, Elsevier, v. 106, p. 110159. doi: 10.1016/j.pnpbp.2020.110159

[12] ROSSO, M.P.O. *et al.* (2020). Photobiomodulation Therapy Associated with Heterologous Fibrin Biopolymer and Bovine Bone Matrix Helps to Reconstruct Long Bones. Biomolecules. v. 10, n. 3, p. 383. doi: 10.3390/biom10030383. PMID: 32121647; PMCID: PMC7175234.

[13] TAQUET, M. *et al*. (2021). Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. v. 8, n. 2, p. 130-140. doi: 10.1016/S2215-0366(20)30462-4