Chapter 23

Impacts of COVID-19 on the central nervous system

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Alice Borém Camargos

Ana Carolina Araújo Lage Santos

Antônio Victor Condez Alagia

Beatriz Melo de Almeida

Izabel Brito Teixeira

José Victor Mendes Milhomem

Júlia Couto Feio

Stael Fernandes Bar

ABSTRACT

Introduction: COVID-19 is an infectious disease caused by the SARS-Cov-2 virus, of the beta-coronavirus clade, which mainly affects the human respiratory system. This pathology has been the subject of high demand for studies since the beginning of its dissemination. But, despite a large number of cases related to its pulmonary involvement, the growing number of extrapulmonary and, mainly, neurological symptoms reported by a large part of the literature should not be ignored. Objective: To assess the impacts of COVID-19 on the Central Nervous System according to viral mechanisms and their long-term consequences. Material and methods: The study was carried out from a literature review based on data published in the CAPES Portal, SciELO, and PubMed using, in the research, descriptors related to COVID-19, neurological manifestations, and the Nervous System. 50 articles were collected, 26 of which were discarded. The inclusion criterion was the correlation made between COVID-19 and Central Nervous System disorders, and the exclusion criterion adopted was the language of the articles, selecting only those in Portuguese or English. Literature review: Taking into account the genomic similarities between the SARS-Cov and SARS-Cov-2 viruses, the finding of both in the cerebrospinal fluid demonstrates their undoubted ability to enter and, therefore, cause damage to the Central Nervous System. From these similarities, it was possible to determine some mechanisms of neurological invasion of SARS-Cov-2, such as the use of glycoproteins of the spike present in its structure to form bonds with ACE2 receptors of host cells, thus penetrating cells such as neurons, neuroglia, and endothelial cells, where it enters the blood-brain barrier. Furthermore, other damage caused by the virus outside the CNS, such as gas exchange disruptions and cytokine storms, can indirectly affect this system, causing some damage. Studies indicate that 40% of infected patients develop neurological symptoms, such as anosmia and ageusia, and other symptoms linked to brain dysfunction, such as headaches, dysphoria, mental disorders, and delirium. Thus, the use of neurological symptoms as signs of suspicion and isolation of individuals is a possible aid factor for reducing contagion and early diagnosis. In addition, among the rare events of the severe form of the disease, we can mention cases of cerebral hemorrhages, stroke, and even Alzheimer's, Parkinson's, and Multiple Sclerosis. However, due to the current situation of COVID-19, it is still difficult to investigate its long-term sequelae. Final considerations: Therefore, health professionals should be informed and aware of the possible involvement of this virus in the CNS, submitting affected individuals to clinical, laboratory, and radiological examinations in advance for neurological evaluation. Finally, future research on possible long-term sequelae is extremely important for the development of intervention and monitoring strategies for these individuals.

1 INTRODUCTION

COVID-19, an infectious disease caused by the virus called SARS-Cov-2, had its first cases registered in the city of Wuhan, China, in December 2019. of acute respiratory syndromes. This disease became known for its primary symptoms such as fever, dry cough, and fatigue2. In addition, its great potential for contagion has made it the target of high demand for studies around the world. And, thanks to him, in April 2020, it reached the milestone of 100 thousand deaths, after just one month of its identification as a pandemic by the World Health Organization4.

However, despite being known for the typical symptoms linked to the involvement of the respiratory system, studies indicate that 40% of patients infected with the coronavirus develop neurological symptoms and other symptoms linked to brain dysfunction2. A possible hypothesis for such a study may have arisen from the moment that some patients diagnosed with COVID-19 did not present these typical symptoms at the time of diagnosis, and, instead, manifested only neurological symptoms as initial symptoms2.

The present study aims to evaluate the impacts of COVID-19 on the Central Nervous System (CNS) of infected individuals, given the high prevalence of cases related to the new coronavirus in Brazil, where one-third of the daily deaths in the world are concentrated12. For this, knowledge about the possible access routes of this virus and its neuroinvasive potential is necessary, in addition, mainly, to the understanding of the repercussions in this system and the approach to probable future sequelae.

2 METHODOLOGY

The research was carried out from a literature review based on data published in the CAPES Portal, SciELO, and PubMed using, in the research, descriptors related to COVID-19, neurological manifestations, and the Nervous System. 50 articles were collected, 26 of which were discarded. The inclusion criterion was the correlation made between COVID-19 and Central Nervous System disorders, and the exclusion criterion adopted was the language of the articles, selecting only those in Portuguese or English. In the PubMed platform, in addition to the descriptors, filters involving the date of publication and the availability of free texts were used to obtain updated and complete studies.

3 RESULTS

The virus that causes COVID-19, named SARS-Cov-2, has been identified as belonging to the same beta-coronavirus clade as MERS-CoV, which causes Middle East Respiratory Syndrome, and SARS-Cov, related to Acute Respiratory Syndrome. serious. And, according to Abboud1 (2020), it shares a highly homogeneous sequence with SARS-Cov. These genomic similarities allowed the creation of hypotheses about the viral mechanisms of the new coronavirus and its possible damage and correlations with other diseases, which the other viruses mentioned above already have confirmed action.

Among the similar viral mechanisms of the new coronavirus and SARS-Cov, it is possible to mention the entry into host cells using the same receptor, the angiotensin-converting enzyme (ACE2). It is

a transmembrane protein expressed on the surface of several cells in the body, responsible for regulating blood pressure within the Renin-Angiotensin System, and promoting vasodilation. This protein is expressed especially in alveolar epithelial cells, small intestinal enterocytes, capillary endothelial cells, epithelial cells, and kidney cells. However, ACE2 receptors were found in cells that make up the Nervous System, such as neurons, oligodendrocytes, astrocytes, and microglia. Therefore, through the glycoproteins of the spike (S) present on the surface of the structure of the new coronavirus, it can make connections with these receptors and, from there, be encapsulated by cells, proving its ability to reach extrapulmonary organs, such as those that make up the CNS.

From the presence of ACE2 in capillary endothelial cells, the virus becomes capable of interacting with such cells and causing damage to the blood-brain barrier, entering the CNS by attacking the vascular system1. In addition to the link between the virus and cell receptors, it is possible to highlight other ways in which it manages to enter the CNS of infected patients. One of them is, according to Abboud et al.1 (2020), represented by the infection of the bulb and the olfactory nerve, which allows the virus to reach and affect the brain directly, being anosmia and/or ageusia, in the early and mild stage, suggestive of the movement of this virus through these structures.

INDIRECT EFFECTS OF THE VIRUS ON THE CNS

It is important to mention that the virus can cause CNS damage and neurological symptoms without invading the brain itself2. Such thinking is exemplified when the virus affects cells of the alveolar epithelium, it generates changes in gas exchange, causing hypoxia in the CNS, increasing anaerobic metabolism in brain cells, inducing cellular and interstitial edema, obstructing cerebral blood flow, as well as ischemia. and vasodilation in the cerebral circulation1. This would then manifest itself starting with headaches and, if left unchecked, could cause a change in the level of consciousness and even coma2.

NEUROLOGICAL MANIFESTATIONS

According to Alomari2 (2020), approximately 40% of patients infected with COVID-19 develop neurological symptoms and other brain dysfunctions. Recent studies on the new coronavirus have shown that, like its predecessors, a substantial part of its symptomatology can be explained by the cytokine storm triggered by it, leading to a Systemic Inflammatory Response Syndrome (SIRS)2. Thus, the exacerbated activation of the immune system leads to the production of a high number of mediators, such as interleukins and cytokines, which act causing damage to the tissues in which this system intended to fight the agent.

The systemic increase in inflammatory mediators, now called a cytokine storm, should explain the multi-organ damage found in some patients with COVID-19 and should also explain the effects of SARS-Cov-2 on the CNS20. In addition, this storm increases microvascular permeability in the CNS, according to Wang20 (2020), which helps the entry of the new coronavirus through the blood-brain barrier and facilitates the passage of more cytokines and chemokines towards this organ, which may amplify the

symptoms. neurological and neuroinflammatory symptoms experienced by the patient, as described by Alomari2 (2020).

Based on these thoughts, Abboud et al.1 (2020) divided the neurological symptoms manifested by patients according to their severity, namely: non-specific and systemic, moderate and severe. Following this reasoning, among the non-specific and systemic symptoms, it is possible to mention headaches, as being the most reported according to the aforementioned author. And, despite not having an exact mechanism attributed to them, for Bobker4 (2020), fever, together with endogenous and exogenous pyrogens and the results of previously mentioned cytokine storms, can be considered possible causes of these pains. Furthermore, the myalgia described during the infection with reports of muscle pain, fatigue and high levels of muscle enzymes, and dizziness is also part of this division of symptoms.

Among those called moderate symptoms, we can subdivide them according to their involvement: sensitive, intracranial, and encephalopathies.

SENSITIVE DISORDERS

Ageusia, olfactory dysfunction, including anosmia or hyposmia, and visual dysfunction are the main symptoms that make up this subgroup. In a study of 357 patients, 85.7% had olfactory dysfunction related to COVID-19 infection, 284 (79.6%) showed anosmia and 73 (20.4%) showed hyposmia23. In addition, another research demonstrated that among the 2581 patients, 1916 reported the presentation of olfactory disorders (74.2%). The prevalence of self-presentation of these disorders was 85.9%, 4.5%, and 6.9% in mild, moderate, and severe-to-critical patients respectively9.

According to Vaira19 (2020), in patients infected with the new coronavirus, ageusia, and anosmia are not accompanied by nasal obstruction or other symptoms of rhinitis, which should be explained by the direct damage of this agent to the olfactory and gustatory receptors. And in a large number of patients, ageusia and anosmia may represent the first, or only, symptomatological manifestation. Thus constituting an interesting and early neurological manifestation of SARS-Cov-2 that should help timely suspicion and isolation of the infected patient.

Added to this, given that the olfactory and sensitive nerves are supposedly the first route for invasion of this virus in the CNS, as cited by Orsini et al.15 (2020), it is predictable that nerves such as the oculomotor and optics are affected, causing visual dysfunction. However, regardless of reports of deficits in visual function and neuralgia, there are still gaps regarding this symptomatology.

ENCEPHALOPATHIES

Toxic infectious encephalopathy, also known as acute toxic encephalitis, refers to a reversible type of brain dysfunction syndrome caused by factors such as systemic toxemia, metabolic disorders, and hypoxia during the acute infection process22. According to Abboud et al.1 (2020), the basic pathological

changes include cerebral edema, without analysis of the evidence of inflammation in the cerebrospinal fluid, and its symptoms are complex, including headaches, mental disorder, delirium, and dysphoria.

In patients with COVID-19, delirium may be a manifestation of direct CNS invasion, induction of CNS inflammatory mediators, a secondary effect of other system organ failure, an effect of sedative strategies, prolonged mechanical ventilation, or environmental factors including social isolation22.

Dysphoria, a feeling of sadness and malaise, can be correlated with the ability of the virus to trigger depressive behavior in the infected patient. According to the theory presented by Wu et al.22 (2020), the pro-inflammatory cytokines responsible for the action response in the acute phase of the brain induce depression. This fact is explained by the author since the elevation of the cytokine called indoleamine 2,3 dioxygenase (IDO) is associated with alterations in neurotransmission, and with the development of depressive behaviors. Furthermore, a contingent number of patients hospitalized for COVID-19 or simply infected with SARS-Cov-2 are experiencing psychiatric symptoms such as anxiety, fear, depression, and insomnia, which can be difficult to discern from the side effects of antiviral treatment22.

INTRACRANIAL IMPAIRMENTS

For Alomari2 (2020), these conditions are rare and severe forms of encephalopathies, tending to epilepsy, paralysis, loss of consciousness, and even coma. According to Abboud et al.1 (2020), these symptoms are associated with intracranial injuries and are possibly the result of hypoxia, multiple organ failure, or metabolite and electrolyte disorder. Furthermore, in addition to requiring specific medications and neurological monitoring, the expectation of status epilepticus and acute symptomatic seizures in patients with these conditions is plausible.

SEVERE SYMPTOMS

Cases of cerebrovascular events have been reported in patients with COVID-19, among these events it is possible to highlight, according to Abboud et al.1 (2020), intracerebral hemorrhages, cerebral venous thrombosis, and ischemic strokes (CVAs). A possible explanation for the occurrence of intracerebral hemorrhages is based on the fact that ACE2 is also a cerebrovascular protective factor, and when bound to this receptor, SARS-Cov-2 can cause an abnormal increase in blood pressure. According to Abboud et al.1 (2020), this hypertension caused by the virus, associated with the presence of thrombocytopenia and bleeding disorders, is a factor that may increase the risk of intracerebral hemorrhage in patients.

Regarding strokes, the hypercoagulability evidenced by the increase in D-dimer levels added to exaggerated systemic inflammation and cardioembolism caused by the virus can be considered the potential mechanism for their occurrence in patients affected by SARS-Cov-2.

In addition to all of the aforementioned impairments, high ACE2 receptor expression in a wide variety of brain areas not only provides an initial target for SARS-Cov-2 to cause acute brain damage but

may also be the basis for neurodegenerative changes. Alzheimer's, Parkinson's, and Multiple Sclerosis are some of the diseases in which similarities between their provoked neurological changes and those of SARS-Cov-2 have been found.

But due to the short period available for studies, whether the virus causes neurodegenerative diseases or accelerates their occurrence remains unclear, and future studies are needed to, know the possible correlation between these diseases and the virus, prevent a large portion of the population is a victim of the development of such diseases.

4 CONCLUSION

Therefore, based on the premise that approximately half of the patients infected with SARS-Cov-2 develop neurological symptoms and other symptoms linked to brain dysfunction, understanding more about these manifestations and the symptoms and involvements linked to the CNS becomes extremely relevant for active or not in the health area, given that information such as early symptomatology linked to this system, for example, anosmia and ageusia, can lead to an early diagnosis in addition to reducing the chances of spreading the disease.

Furthermore, knowledge about possible developments of diseases from contact with the virus proves to be relevant so that health professionals submit affected individuals in advance to clinical, laboratory, and radiological examinations for neurological evaluations to prevent the unexpected progress of pathologies degenerative neurological.

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