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EC NEUROLOGY
Research Article

Brain and Covid-19: An Integrative Review

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Received: July 11, 2020; **Published:** July 22, 2020

Abstract

Introduction: December 2019, an outbreak of Severe Acute Respiratory Distress Syndrome started in Wuhan, China. This injury spread rapidly until, in March 2020, the World Health Organization (WHO) declared a pandemic. Although respiratory symptoms are more reported, there is also evidence of impairment of the nervous system. Among the main neurological symptoms reported, the following stand out: headache, vertigo, altered consciousness, encephalopathies, cerebrovascular disease and seizures.

Objectives: The objective of this study is to describe, based on the current literature, the main evidence of brain involvement by COVID-19 and its clinical manifestations.

Methodology: This is an integrative literature review, carried out through the following databases: PubMed, LILACS, BIREME. The searches were limited to articles from the year 2020, in English and Portuguese. For this search, were used the descriptors indexed in MESH and DeCS "BRAIN" or "CEREBRAL" or "BRAIN INJURIES" or "CENTRAL NERVOUS SYSTEM" and "COVID-19" or "SARS-CoV-2".

Results: Through crossing of descriptors in the databases, and reverse search tools, 594 articles were found. Among these, 46 were selected to compose the sample.

Discussion: Reports were found of patients with COVID-19 who had: benign intracranial hypertension, seizures, ischemic and hemorrhagic cerebrovascular diseases, acute necrotizing encephalopathy, Birkerstaff encephalitis, meningitis, and delirium. In addition, previous studies suggest that the involvement of the central nervous system by SARS-CoV-2 may induce an increase in neurodegenerative disorders in the future.

Conclusion: It is a fact that the SARS-CoV-2 virus is capable of affecting the central nervous system. The clinical manifestations resulting from this are related to the greater severity of the condition, and a greater risk of unfavorable outcomes. Thus, it is imperative that the neurological examination of these patients is done extremely carefully, and that clinical findings are reported and not disregarded.

Keywords: *Brain; COVID-19; Neurologic Manifestations*

Introduction

December 2019, an outbreak of Severe Acute Respiratory Distress Syndrome began in Wuhan, China. This injury spread quickly to different countries and continents until in March 2020 the World Health Organization (WHO) declared a pandemic [1]. The clinical manifestations caused by the virus vary, from asymptomatic patients to critically ill patients who die. Although respiratory symptoms are more frequently reported, there is also evidence of impairment of the nervous system [2].

SARS-CoV-2, the etiological agent responsible for the COVID-19 pandemic, has a genome similar to other known coronaviruses: SARS-CoV and MERS-CoV [3]. Previous studies with SARS and MERS have shown involvement of the central and peripheral nervous system [3]. Due to the similarity in the genetic material of these viruses, betacoronavirus is also believed to have neurotropic potential. The possible access routes to the brain used by coronaviruses involve access through the olfactory nerves or access through the blood-brain barrier, through hematogenous or lymphatic dissemination [4].

A study carried out in the city of Wuhan, showed that the autopsy of patients with COVID-19 showed hyperemic and swollen brain tissue, in addition to some degenerated neurons. In the same study it was evidenced that the main form of neurological injury was the symptoms of the central nervous system [5,6]. Other studies carried out in the current year evaluated some neurological symptoms resulting from infection by SARS-CoV-2 and it was noticed that most of them came from the association with hypoxemia [7]. There are also reports in the literature of meningitis, identified in cerebrospinal fluid, and of acute necrotizing encephalopathy, both associated with COVID-19 [8].

It is worth noting that patients with more severe conditions were more likely to have neurological manifestations when compared to patients with mild conditions of the disease [6]. In addition, the identification of neurological symptoms, such as delirium, is a sign of severity, given that this may appear as a prodromal symptom of hypoxia related to severe respiratory failure [9].

Objective of the Study

The objective of the present study is to describe, based on the current literature, the main evidence of brain involvement by COVID-19 and its clinical manifestations.

Methodology

It is an integrative literature review, made through articles that address the relation between COVID-19 infection and its brain manifestations. The databases used were: PubMed, LILACS, BIREME, which are considered important scientific bases of international scope. Searches were limited to articles from the year 2020, in English and Portuguese.

The inclusion criteria for the sample were: articles that addressed manifestations of the involvement of the Central Nervous System in patients infected with COVID-19. In contrast, the exclusion criteria were articles that were not in agreement with the proposed theme. For the search, the descriptors indexed in MESH and DeCS were used “BRAIN” or “CEREBRAL” or “BRAIN INJURIES” or “CENTRAL NERVOUS SYSTEM” and “COVID-19” or “SARS-CoV-2”.

The eligibility process of articles for the sample of this review followed three stages: reading of the title to suit the theme; reading of the summary to investigate the ability to answer the guiding question; and reading of the full articles in order to extract the data for later summarization of the outcomes.

All articles included in the sample addressed neurological aspects of COVID-19 infection, and the data were analyzed based on the results. Besides that, it was decided to perform the reverse search, which consists of a technique of searching for articles based on the investigation of the references of the articles selected for the sample, in order to expand the search and diversify the results.

Results

By crossing the descriptors in the databases, a total of 594 publications were found. Among these, according to the inclusion and exclusion criteria, 548 were excluded and 28 were selected to compose the sample. In addition to these, 18 articles were found through reverse search. Thus, the sample consisted of 46 articles.

Discussion

Like other previously known coronaviruses, SARS-CoV-2 is shown to have neurotropic potential [10-12]. This suggests that the risk of acute and long-term brain damage in patients with COVID-19 is high. Previous studies have described that central nervous system inoculation can occur in two ways: through hematogenous dissemination or retrograde neuronal dissemination [10,13,14]. Neuronal retrograde dissemination is correlated as responsible for early anosmia and ageusia in patients affected by the disease [15].

Different mechanisms of brain damage induced by coronaviruses have been investigated, including the massive infiltration of components of the renin-angiotensin system due to the generalized inflammatory response [16]. This imbalance promotes neuroinflammatory cascades that result in neurodegeneration and cognitive dysfunction [16,17]. Recent studies have shown that the SARS-CoV-2 virus affects the brain parenchyma through two basic mechanisms: immunomediated brain damage or direct inoculation of the virus [16,18-20].

The responses triggered by the infection of the coronaviridae family are mediated by the action of Cytotoxic T Cells, and when deregulated they can induce autoimmune encephalopathy, or side effects such as cerebral hypoxia due to metabolism dysregulation [21-24]. Viruses of the coronaviridae family can induce neurodegeneration, astrogliosis and neuroinflammation [21]. In the current literature, reports were found of patients with COVID-19 who had: benign intracranial hypertension, seizures, ischemic and hemorrhagic cerebrovascular diseases, acute necrotizing encephalopathy, Birkerstaff encephalitis, meningitis, and delirium [21,25-30]. No evidence was found of associations between COVID-19 and epilepsy [31].

In a study carried out with laboratory animals infected with coronavirus, a significant neurological disorder was observed [21,32]. This condition was associated with large amounts of the virus, especially in the hippocampus [21,32,33]. This is believed to be responsible for triggering cerebral inflammatory response with astrogliosis and neutrophil infiltration by the rupture of the blood-brain barrier [21,34]. These changes damage brain neurons, including those around the hippocampus, and can degenerate nerve cells and lead to clinical dementia or cognitive impairment [21,34].

The inflammatory process of the central nervous system by betacoronavirus can be long lasting, and cause permanent changes in its functioning [35,36]. Thus, coronavirus infection alone increases the risk of delirium [21]. In addition, patients infected with SARS-CoV-2 may manifest delirium by inducing inflammatory chemical mediators in the Central Nervous System, through the use of hypnotic and anticholinergic agents for sedation in the ICU, for a prolonged period of exposure to mechanical ventilation, as well as by the direct invasion of the Central Nervous System [21].

Of the neurological manifestations coming from the CNS, headache and dizziness stood out. Regarding the laboratory findings of patients with CNS symptoms, it can be pointed out: decreased levels of lymphocytes, platelet count and elevated levels of blood urea nitrogen [37].

Cerebral pseudotumor, also called benign intracranial hypertension, develops with headache, papilledema, arterial hypertension and clear cerebrospinal fluid [25,38]. This condition has several associated etiologies, including venous sinus thrombosis, toxicity of some substances, and sepsis [25,38]. We found a case report of a 35-year-old female patient with COVID-19, who manifested cerebral pseudotumor [25]. This patient was treated with supportive measures and nasal oxygen and evolved well and was discharged asymptomatically a few days after admission [25].

Cerebrovascular diseases are reported in the literature as complications of COVID-19. Central venous sinus thrombosis, ischemic cerebrovascular accident (CVA) and intraparenchymal hemorrhage were some of the clinical conditions described in individuals affected by the virus [39]. Although the ischemic CVA associated with the pathology is more often a late complication, this condition can also manifest itself at the beginning of the injury [39].

Countless possibilities are conjectured that would explain the connection of the virus to cerebrovascular disease. Among them, SARS-CoV-2 is considered to be linked to a pro-thrombotic state, which generates venous lesions and arterial thromboembolism [40]. In addition, the disease releases pro-inflammatory cytokines that incite the activation of mononuclear and endothelial cells with expression of the tissue factor carrying the activation of the coagulation cascade and generation of thrombin [41,42]. Even so, the pathophysiological mechanism involved in this process has not yet been elucidated.

In a recent case report, the presence of acute necrotizing encephalopathy (ANE) was evidenced in the Magnetic resonance imaging (MRI) of a patient infected with COVID-19 [30]. ANE is a rare fatal complication, resulting from a direct viral invasion that leads to an exacerbated immune response and cytokine storm, which breaks the blood-brain barrier [30,43]. MRI images showed a hemorrhagic border, lesions in the thalamus, temporal lobe and subinsular region [30]. Within this context, current evidence suggests that the cytokine storm caused by COVID-19 could be responsible for the development of ANE [30,43].

The association between brain viral infections and increased risk of developing Alzheimer's disease and Parkinson's disease has been described in different studies [44-46]. Knowing this, the involvement of the central nervous system by SARS-CoV-2 may induce an increase in neurodegenerative disorders in the future. In order to be able to estimate this correlation in the long run, it is necessary to integrate the maximum amount of information available. Thus, this study gathers the main evidence to date regarding the presence of betacoronavirus in the central nervous system, and its reported manifestations.

Conclusion

It is a fact that the SARS-CoV-2 virus is capable of affecting the central nervous system. The clinical manifestations resulting from this are related to the greater severity of the condition and a greater risk of unfavorable outcomes. Thus, it is imperative that the neurological examination of these patients is done extremely carefully, and that clinical findings are reported and not disregarded. Brain disease by COVID-19 may be a predictor of a greater number of neurodegenerative diseases in the future. However, prospective clinical studies that monitor the evolution of these patients over the long term are essential for this relation to be confirmed.

Conflicts of Interest

The authors declare no conflict of interest.

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Volume 12 Issue 8 August 2020