INFLUENCE OF COVID-19 ON THE CNS

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ABSTRACT

The pandemic caused by the novel coronavirus (SARS-Cov-2), has generated huge problems and inquiries in healthcare systems around the world. Several studies are emerging to prove the capacity of coronavirus neurotropism and its short and long-term consequences. Therefore, here, we aim to give information about the relationship between coronavirus and central nervous system in different aspects. The present study was conducted on search of the published studies available in NCBI; PubMed, MEDLINE, Scielo and Google Scholar for all kind of articles using keywords related to coronavirus and central nervous system. In addition to the most common symptoms of COVID-19 that are fever, cough, dyspnea and myalgia, anosmia and ageusia also have a high incidence in patients infected with SARS-CoV-2. Brain invasion by coronavirus, that had previously been related with glial cells, has been reported, as well as evidence that confirm the frequency and three times higher prevalence of cerebrovascular diseases in patients affected by COVID-19. Understanding the effects that the coronavirus may have on the central nervous system is essential to learn more about the possible consequences of COVID-19. It is known that the disease can cause neurological complications and the understanding of these processes may help in the detection of viral presence and in the appropriate treatment for these patients. It is hoped that soon there will be more ways to continue to deepen this knowledge.

Keywords: Coronavirus; SARS-Cov-2; COVID-19; Central nervous system; Neurological disorders; Neurons.

INFLUÊNCIA DA COVID-19 NO SNC

RESUMO

A pandemia causada pelo novo coronavírus (SARS-Cov-2) tem gerado enormes problemas e questionamentos nos sistemas de saúde em todo o mundo. Vários estudos estão surgindo para comprovar a capacidade do neurotropismo do coronavírus e suas consequências a curto e longo prazo. Portanto, aqui, pretendemos fornecer informações sobre a relação entre o coronavírus e o sistema nervoso central em diferentes aspectos. O presente estudo foi conduzido em busca dos estudos publicados disponíveis no NCBI; PubMed, MEDLINE, Scielo e Google Scholar, usando palavras-chave relacionadas a coronavírus e sistema nervoso central. Além dos sintomas mais comuns de COVID-19 que são febre, tosse, dispneia e mialgia, anosmia e ageusia também têm uma alta incidência em pacientes infectados por SARS-CoV-2. Há relatos de invasão cerebral pelo coronavírus, que já foi previamente associado a células gliais, bem como evidências que confirmam a frequência e prevalência três vezes maior de doenças cerebrovasculares em pacientes acometidos por COVID-19. Entender os efeitos que o coronavírus pode ter no sistema nervoso central é essencial para aprender mais sobre as possíveis consequências da COVID-19. Sabe-se que a doença pode causar complicações neurológicas e a compreensão desses processos pode auxiliar na detecção da presença viral e no tratamento adequado para esses pacientes. Espera-se que em breve existam mais maneiras de continuar a aprofundar esse conhecimento.

Palavras-chave: Coronavírus; SARS-Cov-2; COVID-19; Sistema nervoso central; Distúrbios neurológicos; Neurônios.

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INTRODUCTION

In December 2019, the new coronavirus (SARS-CoV-2) appeared in Wuhan, China, leading to high numbers of cases of infection and deaths. Since then, other countries have been affected, causing serious consequences for the population health. On January 30, 2020, the World Health Organization defined the situation as an epidemic of international interest, which on March 11, 2020 was declared a global pandemic. The COVID-19 disease quickly spread throughout the world, with more than 20 million people affected worldwide and more than 900 thousand deaths by September 2020 (1).

Coronaviruses are part of the *Coronavirinae* subfamily within the *Coronaviridae* family and are characterized as a group of single-stranded RNA viruses. Humans can be affected by 7 types of coronavirus. Four of them cause mild symptoms and consequences and 3 cause serious diseases. Coronaviruses have four structural proteins: spike (S), membrane (M), small envelope (E) and nucleocapsid (N). Among them, the S glycoprotein is divided into S1 subunit, responsible for binding the virus to the specific cell receptor, and S2 subunit, which is a mediator of the fusion between viral envelope and plasma membrane, with consequent release of nucleocapsid into the cytoplasm (2-5). Zhu et al. (2009) reported an involvement of spike protein in the regulation of intracellular transport of the viral genome to the endoplasmic reticulum.

There are four main genera of coronavirus, among which the betacoronavirus comprises the two most well-known types, SARS-CoV and SARS-CoV-2 (6-8). Virus-receptor interactions have been studied and offer a wide field of study for a better understanding of viral performance. Wan et al. (2020) conducted a study using previous knowledge about SARS-CoV and the involvement of ACE2 receptors (angiotensin-converting enzyme 2) to try to make possible a prediction of the behavior of new SARS-CoV-2. The binding affinity between the receptor binding domain (RBD) and ACE2 was one of the most important determinants found in the infectious process of the new coronavirus, because it is related to capacity of transmission between humans (6). This ACE2 enzyme is most expressed by lung, blood, kidney, or intestinal epithelial cells and has a positive regulation in treatments with ACE inhibitors and angiotensin receptor blockers. Individuals with *diabetes mellitus* and hypertension generally use medicines with these mechanisms of action, which therefore causes an increase in the expression of ACE2 and facilitates infection by SARS-CoV-2. For this reason, there is a hypothesis that patients with heart disease, hypertension or diabetes are at increased risk of severe COVID-19 infection. Alternative treatments that

replace this one is a possibility, however, there may be conflicts due to the therapeutic character of ACE2 in inflammatory lung diseases, cancer, among others (9).

Increasing evidence shows that coronaviruses are not only associated with the respiratory tract, but also with the central nervous system (CNS), inducing the emergence of neurological diseases (10). Several cases have been reported of individuals who showed signs and symptoms of neurological disorders, including headaches, dizziness, impaired consciousness, ataxia, epilepsy, in addition to muscle injuries (11). In this review we search to understand and define the most affected locations and most related consequences to COVID-19 in the CNS.

MATERIALS AND METHODS

The present study was conducted on search of the published studies available in NCBI; PubMed, MEDLINE, Scielo and Google Scholar for all kind of articles using the following key words: coronavirus AND central nervous system, COVID-19 AND neurological disorders, coronavirus AND brain invasion. Review papers, case reports and papers not written in English language were not included to the study. Abstracts were reviewed and relevant papers were identified. Thus, 46 articles were selected.

COVID-19 AND NEUROLOGICAL DISORDERS

The most common symptoms of COVID-19 are fever (present in 98% of cases), cough (76%), dyspnea (55%) and myalgia or fatigue (44%) (12). However, it is known that some neurological symptoms can be presented. The most found were dizziness and headaches. Other complications have been reported in some individuals, such as acute ischemic stroke, intracranial hemorrhage (13,11) and delusions (14). There are descriptions of more specific manifestations such as acute cerebrovascular diseases and seizures (15) and some symptoms have been associated with more severe cases and, in most of them, of patients who had other chronic diseases, especially hypertension (11). Symptoms such as neuralgia and impaired taste and smell were also observed (16,17). Anosmia and ageusia have a high incidence in patients infected with SARS-CoV-2 in several countries, such as Europe, Asia (18) and others, thus being considered additional symptoms of COVID-19. Loss of smell and/ or taste may indicate the need of self-isolation to reduce the spread of the coronavirus, since they may allow the identification of infected individuals who can unknowingly transmit the virus to others (19).

Among the studies that demonstrate the incidence of olfactory and gustatory problems, we can mention a comparative study between patients with COVID-19 and influenza, which showed that these disorders were significantly more frequent in patients with coronavirus and were symptoms of initial and acute manifestation (20). Another study with 59 patients testing positive for SARS-Cov-2 showed that smell and taste disorders were present in 68% of cases and 75%, respectively, compared with 16% and 17% of patients who tested negative (21). At the University Hospital in Sanssari, 73.6% of 53 patients positive for SARS-Cov-2 had chemosensitive disorders (22). A study was conducted in the United Kingdom with questions about symptoms of COVID-19 through an app called COVID RADAR. Of 579 patients positive for coronavirus, 59% had dysfunctions in smell and/ or taste and only 18% of the 1123 patients who tested negative had these dysfunctions (23). Finally, in Europe, 85.6% of 417 patients who tested positive for SARS-Cov-2, had olfactory dysfunction and 88% had taste impairment (24). It is important to note that, most of the time, majority of people did not realize these disorders until the moment they were tested (25).

Regarding the mechanisms that lead to anosmia and ageusia, studies point to three possible causes: local infection of vascular and basal cells of the olfactory epithelium and olfactory bulb, that can affect the function of bipolar neurons; damage to basal cells of the sensory epithelium that can influence the signaling pathway of sensory neurons to the brain; and damage to sustaining cells and Bowman's glands, which can lead to morphological damage to olfactory epithelium and altered olfactory perception (26). Furthermore, it is also possible to assume that the loss of smell and taste is due to inflammation of the nasal epithelium, mucosal edema, and obstruction of airflow in the olfactory cleft. Since in most cases the olfactory loss resolves within weeks, it is likely that the coronavirus causes an inflammatory response in the nasal cavity that temporarily prevents odorants from reaching olfactory receptor neurons (27). However, receptors for SARS-CoV-2, ACE2 and transmembrane serine protease 2 (TMRRSS2) are expressed in the olfactory epithelium and not in sensory neurons. Therefore, it can also be considered that when the inflammation of the olfactory epithelium due to the virus ends, the smell will return (21).

Innumerable types of viruses invade the central nervous system through cellular or pericellular transport by respiratory epithelium, such as rhinovirus, Epstein-barr and some types of coronavirus. Acute viral infections in the respiratory tract that damage this epithelium are the main cause of chronic olfactory dysfunction (25,24). Therefore, the loss of smell and

taste should be considered by the international scientific community as important symptoms of COVID-19 (24).

Although many studies point to anosmia and ageusia as symptoms in patients with COVID-19, further studies are needed about the possible mechanisms of SARS-Cov-2 entry into the central nervous system related to loss of smell and taste and their long-term implications (28). Beyond that, large-scale tests and CT scans are not widely available in all hospitals, so the detection of more symptoms that indicate the viral infection can assist on a possible diagnosis (29). In view of the facts, patients with sudden complaints of smell or taste, regardless of coexisting symptoms, should be considered suspect of COVID-19 (27).

CORONAVIRUS AND BRAIN INVASION

The exact pathway by which SARS-CoV-2 reaches the CNS is not yet completely known (10), but ACE2 expression has already been detected in the brain, through glial cells and neurons, which makes them a potential target of COVID-19 (30). Coronaviruses had previously been related to glial cells, confirming their neurotropic characteristics in humans, as well as in animals. Neurons, astrocytes, and oligodendrocytes are possible targets of the CNS for the virus, since the cell lines of astrocytomas, neuroblastomas, neurogliomas and oligodendrocytic lines were all susceptible to acute coronavirus infection in *in vitro* experiments. Factors such as route of infection, age, and host's immune system, as well as the genetic composition of the virus influence the consequences of viral infection in the CNS (2).

Histopathological examination of autopsy of individuals with SARS-CoV showed the presence of the virus in the cytoplasm of neurons in hypothalamus and cortex (31). Experimental studies with transgenic mice have shown that SARS-CoV was able to infect the brain when administered intranasally and neurons in the thalamus and brain stem were the most susceptible targets (32). In 2006, activation of an early transcription factor, Egr-1, was found in astrocytoma cells in cases of SARS-CoV infection. This indicates a correlation between the ability of the virus to induce Egr-1 expression and to cause demyelination in the CNS (4).

The slow blood flow of the microcirculation can also be a facilitating factor in the interaction between virus spike protein and ACE2 expressed in the capillary endothelium. Consequently, damage to the endothelial lining can facilitate viral access to the brain (30). CNS damage can also be mediated by the immune system with evidence of post-infectious neurological dysfunctions. The activation of immune system cells in the brain can lead to

chronic inflammation and persistent brain damage (33,34). New targets and therapeutic strategies are being studied based on the understanding of the immunopathological mechanisms of infection and it is known that high levels of three cytokines (IP-10, MCP-3 and IL-1ra) are associated with the severity of COVID-19 and worse prognosis (35).

Coronaviruses have been described as effective in tumor treatments using virotherapy, in which the epidermal growth factor receptor (EGFR) is considered a good therapeutic target due to its frequently abundant presence in most of the tumors. A study in an intracranial glioblastoma model showed that the virus redirected to EGFR was effective in eradicating the tumor, highlighting the antitumor potential of the coronavirus (36).

CEREBROVASCULAR DISEASES AND ENCEPHALOPATHIES ASSOCIATED WITH COVID-19

There are reports that confirm the frequency and three times higher prevalence of cerebrovascular diseases in patients affected by COVID-19 (37, 38). Goldberg et al. (2020) reported a case of a 64-year-old patient with a history of hypertension, anemia, and splenectomy, that had been diagnosed with COVID-19 sixteen days before returning to the emergency room with a stroke. There is evidence that the mechanism by which cerebral ischemia is established in the clinical picture of COVID-19 is related to the development of a sensitive hypercoagulable state (39,40).

The first case of encephalitis associated with coronavirus was described by Moriguchi et al. (2020) and the authors affirm the importance of detecting patients with loss of consciousness who may be infected with SARS-CoV-2. The identification of the symptoms of encephalopathies, as well as respiratory problems, can be the first step in preventing the spread of the virus and rapid referral of the individual to most appropriate treatment (41). The elderly population is more susceptible to the development of COVID-19 and is at greater risk of altering mental functions. Filatov et al. (2020) in a case report, showed a 74-year-old patient with a history of stroke who had severe symptoms, such as encephalopathy, in addition to cough and fever. This fact was important to emphasize the importance that health professionals are always attentive to the health conditions of patients with COVID-19, as they may have an acute encephalopathy during hospitalization (42).

There is evidence that some patients with severe COVID-19 may experience an intracranial cytokine storm, a factor that results in the breakdown of the blood-brain barrier and is related to the development of acute necrotizing encephalopathy (43, 44).

DISCUSSION

Since the SARS-CoV-2 outbreak was established worldwide, characterized as a pandemic, several publications have emerged bringing new studies on COVID-19 and its consequences in the organism, in an incessant search to obtain more knowledge about the viral performance, biogenesis, pathogenesis, methods of diagnosis, treatment and consequences. Through the evidence already reported in cases in several countries, the new coronavirus can be an opportunistic pathogen capable of invading the central nervous system. As the virus enters the host cell, the infection process begins and the immune response is triggered, generating a subsequent storm of cytokines and events that facilitate viral entry into the brain. The olfactory epithelium is marked by the presence of sensory olfactory neurons, in which SARS-CoV-2 can enter and quickly replicate. Although the exact pathway of the virus in the CNS is not yet fully understood, the symptoms observed are increasingly characteristic and, therefore, the physical-clinical examination is vitally important for the early identification of COVID-19 and the rapid management of patients with neurological complications (45, 46).

Understanding the effects that the coronavirus may have on the central nervous system is essential to learn more about the possible consequences of COVID-19. It is known that the disease can cause neurological complications and the understanding of these processes may help in the detection of viral presence and in the appropriate treatment for these patients. Although some of the pathways used by coronavirus in the organism are not yet completely known, studies on the neurotropism of this virus are incessant. It is hoped that soon there will be more ways to continue to deepen this knowledge.

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