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REVIEW

Covid-19 and the repercussions to the nervous system: a literature narrative review

Covid-19 e suas repercussões no sistema nervoso: uma revisão narrativa da literatura

Abdeel Roberto Alves da Silva[a], Anna Myrna Jaguaribe de Lima[b*]

[a] Departamento de Biologia, Universidade Federal Rural de Pernambuco, Recife - PE, Brazil.

[b] Departamento de Morfologia e Fisiologia Animal. Universidade Federal Rural de Pernambuco, Recife - PE, Brazil.

* Correspondence: anna.myrna@ufrpe.br

ABSTRACT

Introduction: COVID-19, caused by the SARS-CoV-2 virus, belongs to the family of beta-coronaviruses, and its symptoms are similar to those of influenza virus flu, with the lungs being the main affected organ. **Objective:** To conduct a literature review on the pathophysiology of COVID-19, its repercussions, and sequelae in the nervous system. **Data sources**: The research was conducted on the PubMed, ScienceDirect, Scielo, and Web of Science databases between July and October 2020. The keywords used were: "nervous system and COVID-19," "nervous system and COVID-19 physiopathology," "neurological complications and COVID-19," "neurological associations and COVID-19." **Data synthesis:** Symptoms and involvement of the nervous system emerged in patients after SARS-CoV-2 infection. These symptoms were commonly divided into central nervous system (CNS) involvement, peripheral nervous system involvement, and skeletal muscle involvement. Studies indicate headache as the main neurological manifestation, as well as impaired taste and smell. **Conclusion**: Despite evidence of neuroinvasion and neurotropism resulting from SARS-CoV-2 infection, further studies are needed to better determine the central and peripheral neurological manifestations associated with COVID-19.

RESUMO

Introdução: A COVID-19, causada pelo vírus SARS-CoV-2, pertence à família dos betacoronavírus, e seus sintomas são semelhantes aos da gripe causada pelo vírus influenza, com o pulmão sendo o principal órgão afetado**. Objetivo**: Realizar uma revisão da literatura sobre a fisiopatologia da COVID-19, suas repercussões e sequelas no sistema nervoso. **Fonte de dados:** A pesquisa foi realizada nas bases de dados PubMed, *ScienceDirect*, Scielo e *Web of Science* entre julho e outubro de 2020. As palavras-chave utilizadas foram: "sistema nervoso e COVID-19", "sistema nervoso e COVID-19 e fisiopatologia", "complicações neurológicas e COVID-19", "associações neurológicas e COVID-19". **Síntese de dados:** Houve o surgimento de sintomas e comprometimento do sistema nervoso em pacientes após a infecção por SARS-CoV-2. Esses sintomas foram comumente divididos em: comprometimento do sistema nervoso central (SNC), do sistema nervoso periférico e da musculatura esquelética. Estudos apontam a cefaleia como a principal manifestação neurológica, assim como o comprometimento do paladar e olfato. **Conclusão:** Apesar de existirem evidências de neuroinvasão e neurotropismo decorrentes da infecção por SARS-CoV-2, são necessários estudos complementares para uma melhor determinação das manifestações neurológicas centrais e periféricas associadas à COVID-19.

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Introduction

The first case of Severe Acute Respiratory Syndrome caused by the coronavirus type 2 (SARS-CoV-2) was documented in late December 2019 in the city of Wuhan, China[1]. Since then, the virus has infected approximately 765 million people and caused over 6 million deaths by mid-May 2023 when it was classified as a pandemic by the World Health Organization (WHO) in March 2020. The pandemic persisted until May 2023 when the WHO declared it to be over worldwide[2].

The SARS-CoV-2 virus belongs to the family of beta-coronaviruses, with its origin associated with bats. It is similar to the virus responsible for Severe Acute Respiratory Syndrome (SARS-CoV-1), which affected around 8,000 individuals with a mortality rate of 10%. Another type of coronavirus was responsible for Middle East Respiratory Syndrome (MERS-CoV), infecting 2,500 individuals with a mortality rate of 35%[3]. COVID-19 presents flu-like symptoms, with the lungs being the main affected organ. Infected patients commonly experience symptoms such as fever, cough, and shortness of breath. Additionally, it is now known that the respiratory system is not the only one affected[4], [5]. COVID-19 symptoms involve the nervous, circulatory, renal, gastrointestinal, hepatic systems, among others. Recent studies show that the coronavirus family has a certain tropism for the central nervous system[6].

The aim of this study was to conduct an analysis of the pathophysiology of COVID-19, its potential consequences, and neurological sequelae.

Methods

The study is a narrative review with the objective of identifying scientific articles about the impact of SARS-CoV-2 on the nervous system. The research was limited to articles written in English, Portuguese, and Spanish. Databases such as Pubmed, Science Direct, Scielo, and Web of Science were consulted. The following keywords were used: "nervous system and COVID-19," "nervous system and COVID-19 and physiopathology," "neurological complications and COVID-19," and "neurological associations and COVID-19." Additionally, some studies were manually identified to include additional research. The article collection period ranged from July 2022 to May 2023.

Initially, a total of 144 articles were identified. In a second analysis, 124 articles referring to the years 2021 to 2023 were found. The articles were then read, focusing on those that presented samples or data related to patients who manifested one or more neurological

conditions. Reviews found in the used databases were excluded. The inclusion criteria were: samples with individuals aged eighteen years or older, data related to neurological symptoms or complications, and qualitative data related to neurological complications.

Results

Pathophysiology

Several studies indicate that SARS-CoV-2 infection can affect the nervous system, although it is not a neurotropic virus. Neurological symptoms and disorders have been reported in these studies. Encephalitis resulting from SARS-CoV-2 infection has been highlighted in some isolated reports, demonstrating the virus's potential for neuroinvasion[7, 8, 9].

Abnormalities in brain magnetic resonance imaging (MRI) have been observed in 12 out of 27 patients, showing increased cortical fluid signal during fluid-attenuated inversion recovery (FLAIR) MRI, as well as FLAIR abnormalities in the subcortical and deep white matter[10]. Another study with 27 critically ill and mechanically ventilated individuals found that 11 patients underwent MRI, and 10 of them presented with leukoencephalopathy. Additionally, microhemorrhages with a maximum size of 3mm were also observed[11].

Table 1. Main pathophysiological aspects related to the SARS-CoV-2 virus.

Authors	Year	Pathophysiology
De Felice, et al[4]	2020	Summarizes understanding of the impact of SARS-CoV-2 on the CNS.
Butowt & Bilinska[6]	2020	Olfactory epithelium of the nasal cavity as a probable site of major binding of SARS-CoV-2; rapid immune responses from olfactory receptor neurons in the early stages of the disease.
Corad-Artal[8]	2020	Mutations in specific genes that enhance the virulence of SARS-CoV-2, neurotropism with the nervous system, and interaction between the virus and the host.
Straburznński	2023	Headache (cefaleia) as the most prevalent symptom in COVID-19, relating to the main pathophysiologies associated with the symptom.
Heneka, et al[15]	2020	Summarizes the understanding of symptoms and pathophysiology up to the time of its publication.
Ng Kee Kwong, et al[16]	2020	Relates recent evidence on the pathophysiology of COVID-19 and its relationship to the nervous system.
Chigr, et al[17]	2020	Investigates the role of brainstem structures that are located in the spinal medulla involved in food intake and possible pathways that SARS-CoV-2 uses to reach the brainstem.
Kulakowska	2023	Most common neurological and psychiatric disorders in patients with COVID-19 and their pathophysiology.
Kotfis el al[19]	2020	SARS-CoV-2 as a neuroinvasive potential in cases of delirium.
Abboud et al[21]	2020	Suggests movement of the virus to the brain through the olfactory bulb and possible use of ACE2 to enter the cell from the spike protein of SARS-CoV-2 Ability to infect macrophages and glial cells.
Baig, et al[22]	2020	It points out the density of ACE2 expression in the CNS and the interaction that exists between host-virus and relates them to pathogenesis.
Serrano-Castro et al[23]	2020	Cytokine storm caused by SARS-CoV-2; neurodegenerative disease of neuroinflammatory origin.

Symptoms

Patients report: headaches, confusion, total or partial loss of taste, total or partial loss of smell, among others, as well as some neurological disorders such as encephalopathy, stroke, seizures, and others. The most commonly mentioned symptom by patients or reported in studies is headache, classified as acute headache attributed to systemic viral infection, affecting approximately 22% to 72% of individuals, with most prospective studies reporting a prevalence of 60% to 70%[12].

A study evaluating data from 905 individuals with COVID-19-related headaches showed that 31.1% of patients still had headaches after one month, 16.8% after three months, and 16% after nine months. These numbers were slightly lower in a recent meta-analysis: 47.1% during the acute phase, 10.6% at three months[13].

Several studies indicate that SARS-CoV-2 infection can affect the nervous system, triggering neurological symptoms and disorders, despite not being a neurotropic virus. Encephalitis resulting from SARS-CoV-2 infection has been highlighted in some isolated reports, demonstrating the virus's potential for neuroinvasion[7, 8, 9].

In Wuhan, a study conducted with 214 patients highlighted the main neurological manifestations in patients diagnosed with COVID-19. Among the total, 78 (36.4%) had one or more neurological manifestations[5]. The symptoms were classified into central nervous system (CNS) involvement, peripheral nervous system (PNS) involvement, and skeletal muscle involvement. Symptoms such as anxiety, headache, drowsiness, taste impairment, among others, were reported and investigated.

In another study with 417 patients, severe olfactory and gustatory dysfunctions related to SARS-CoV-2 were emphasized. Among them, 357 (85.6%) had olfactory dysfunction related to the virus, with 284 (79.6%) experiencing partial loss of smell. Regarding gustatory dysfunctions, a total of 342 patients (88.8%) reported deficiencies in four taste modalities: salty, sweet, bitter, and sour[14].

In a study with 304 SARS-CoV-2 positive patients in China, a low incidence of seizures was observed[15]. Despite isolated reports of patients presenting this clinical picture, there is also a low incidence of acute cerebrovascular diseases, such as stroke and cerebral hemorrhage.

Table 2. Main symptoms and complications described in patients infected with SARS-Cov-2.

Authors	Year	Study setting	Sample	Gender	Symptoms	Complications
Mao et al[1]	2020	Wuhan, China	214	Male and female	• Dizziness • Headache • Impaired conscience • Slight impairment of taste • Slight impairment of smell • Nerve pain	• Acute cerebrovascular diseases (stroke and cerebral hemorrhage) • Ataxia • Convulsions • Immunosuppression
Filatov et al[3]	2020	EUA	1	Male	• Headache • Cough • Fever	• Encephalopathy
Kandemirli et al[5]	2020	~	749	Male and female	• Altered mental state	• Restriction of cortical diffusion • Leptomeninges • Subcortical abnormalities • Stroke • Encephalitis
Moriguchi et al[7]	2020	Japan	1	Male	• Headache • Fatigue • Fever • Pharyngitis	• Viral meningitis/encephalitis
Duong et al[10]	2020	Los Angeles, United States	1	Female	• Headache • Fever	• Encephalopathy
Lu et al[11]	2020	Hubei, Sichuan and Chongqing, China	304	Male and female	• Delirium • Altered level of consciousness (coma)	• Acute cerebrovascular diseases
Radmanesh et al[24]	2020	New York, United States	27	Male and female	• Not informed	• Diffuse leukoencephalopathy • Microhemorrhages
Oxley et al[25]	2020	New York, United States	5	Male and female	• Cough • Headache	• Ischemic stroke

Sequelae

In a first study, five individuals had ischemic stroke, and one had a hemorrhagic stroke, representing approximately 3% of the evaluated patients[5]. In a second study, three out of thirteen (23%) patients had ischemic stroke[16].

It is important to highlight the occurrence of encephalopathy in patients diagnosed with COVID-19, as there are reported cases indicating the development of this condition during viral infection. In one study, a 74-year-old man with a history of atrial fibrillation, stroke, Parkinson's disease, and chronic obstructive pulmonary disease underwent examinations after experiencing altered mental status. He was diagnosed with encephalopathy, presenting speech impairment and unresponsiveness to commands[17].

There are also isolated reports of complications resulting from COVID-19 infection. For example, a case of a 41-year-old woman who experienced worsening encephalopathy with disorientation and hallucinations[8], and a case of a 24-year-old man who presented characteristic symptoms such as fever, headache, general fatigue, and pharyngitis, and had worsening due to meningitis/encephalitis[9]. Seizures, although uncommon, have also been reported as a complication of SARS-CoV-2 infection.

Discussion

There have been reports from patients regarding headaches, confusion, total or partial loss of taste, total or partial loss of smell, among others, demonstrating that COVID-19 may increase the risk of developing neurological symptoms[14,15]. There is a higher frequency of symptoms related to the central nervous system (CNS), occurring early in the disease, with an average time of one to two days for the onset of the first symptoms[15].

As for olfactory disorders, they are commonly observed in patients during the acute period of COVID-19, and it is assumed that the main cause could be the depletion of sustentacular cells caused by the SARS-CoV-2 virus[16,17].

Therefore, the potential involvement of the nervous system due to SARS-CoV-2 has led to studies on neuroinvasion and neurotropism, seeking to understand the virus's ability to penetrate and replicate in nervous tissue cells. SARS-CoV-2 is a virus that uses various mechanisms to infect the human body. Its entry into the host cell is mediated by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, with the S protein of SARS-CoV-2 having a high affinity for ACE2[18].

Regarding headaches, this symptom can herald serious complications, such as encephalitis reported in studies. Such conditions may be challenging to recognize during COVID-19, especially if headache is initially the

only complaint[19].

However, the mechanisms altering brain function or structure in COVID-19 are not yet fully determined, as are the lesions in endothelial cells caused by the virus, which may lead to cerebrovascular syndromes. Analysis of reverse transcription-polymerase chain reaction (RT-PCR) has shown that the virus is commonly absent in cerebrospinal fluid (CSF) examinations. The absence of the virus in CSF tests, despite indicating inflammation, reinforces the possibility that encephalitis may occur without direct invasion by SARS-CoV-2[3]. Neurological symptoms or manifestations related to COVID-19 tend to be more frequent in individuals with associated comorbidities, such as renal and hepatic dysfunction[20].

It is important to emphasize that the pathophysiological mechanisms leading to olfactory and gustatory dysfunctions in diagnosed patients need to be better described. While studies report occurrences of ischemic stroke in older patients, with a higher presence of comorbidities such as diabetes, hypertension, among others, there are still cases of stroke in young individuals infected with SARS-CoV-2[20].

There is evidence of neuroinvasion and neurotropism resulting from SARS-CoV-2 infection; however, further studies are needed to investigate central and peripheral neurological manifestations associated with COVID-19.

Final considerations

The narrative literature review provides data on the repercussions and main sequelae related to SARS-CoV-2, with studies highlighting various neurological manifestations and potential sequelae: encephalitis, leukoencephalitis, meningitis, ischemic and hemorrhagic stroke. Regarding symptoms, headache was commonly mentioned, as well as impaired taste and smell, often recurring in the early stages of infection and possibly lasting for days or weeks after contact with the virus, thus indicating possible neurological manifestations observed in COVID-19 positive patients. Despite the studies presented, it is suggested that research should follow the evolution of these patients, furthering our understanding of the long-term neurological repercussions and sequelae resulting from COVID-19.

Conflict of interests

The authors declare that there is no potential conflict of interest.

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