

Manifestation of neurological sequels after COVID-19: literature review

Denise Gonçalves Moura Pinheiro ^{1,*}, Ana Paula Marques da Silva Benevides ¹, Ihoranna Freitas de Lima ¹, Joelma Nascimento Bacelar ¹, Milena Pinheiro Machado ¹, Tayane de Brito Araújo ¹, José Evaldo Gonçalves Lopes Júnior ¹, Eduardo de Almeida e Neves ¹, Edfranck de Sousa Oliveira Vanderlei ¹

¹ Curso de Fisioterapia. Centro Universitário Uniateneu, Fortaleza, Ceará, Brazil.

* Correspondence: denise.pinheiro@professor.uniateneu.edu.br.

Abstract: COVID-19 had its first case in the city of Wuhan, China, in December 2019, with a few isolated cases that soon became a pandemic within a short period of time. Studies report widely varying prevalences of neurological manifestations, ranging from 3% to 35%, with a higher incidence in severe or critical cases. Neurological manifestations generally occur between the first and 14th day after the onset of respiratory symptoms. To determine the prevalence and types of neurological sequelae in post-COVID-19 patients through a literature review. A literature search was conducted in the electronic databases BVS, PubMed, and SciELO. Inclusion criteria were studies with full text availability, on patients who contracted COVID-19, published from 2019 to 2022. After applying the inclusion and exclusion criteria, 17 articles were selected, with nine eligible articles. The main results showed that COVID-19 affects the central nervous system (CNS) and can also cause exacerbated activation of the immune system, leading to stroke, depression, anxiety, encephalopathies, headaches, among others. Patient follow-up is necessary since this is a disease still under study and relatively new. This review should be updated as new sequelae or consequences may arise in the long term after the virus.

Keywords: COVID-19; Neurological sequelae; SARS-CoV-2.

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1. Introduction

The SARS-CoV-2, also known as COVID-19, had its first case registered in the city of Wuhan, China, in December 2019. In a short period of time, isolated cases became a pandemic. Transmission occurs through saliva droplets or sneezing, but there are other forms of contagion, such as through the eyes, nose, mouth, and contaminated surfaces. The virus can be in an incubation state between the second and 14th day before the first symptoms, becoming highly contagious [1]. In Brazil, the first confirmed case was on February 25, 2020. After this date, there was an absolute growth and, in the following month, it culminated in the decree of lockdown in several regions of the country, becoming a global threat [2].

The virus can cause major complications, some immediate and others long-term, which can generate persistent sequelae in various areas. The most affected are: the pulmonary region, causing dyspnea, decreased exercise capacity, and hypoxia; the cardiovascular system, causing chest pain, arrhythmia, tachycardia, increased cardiometabolic (chances of having diabetes, heart disease, or stroke) and myocardial fibrosis; the hematological region, which can cause thromboembolic events; the neuropsychiatric region, causing headache, dysautonomia, cognitive impairment, anxiety, depression, and sleep

disorders; the dermatological area, which can cause hair loss; and the renal system, which can lead to renal failure [3].

Studies report very disparate prevalence of neurological manifestations, between 3% and 35%, being more frequent in severe or critical patients. Neurological manifestations usually begin between the first and 14th day after the onset of respiratory symptoms. In most cases, it is not possible to isolate the virus in cerebrospinal fluid, and it is believed that dissemination to the central nervous system is transient and that the viral load is lower than the detection capacity of available tests [4]. The recent onset of the pandemic has revived attention on the possible neurovirulence of this virus and the possible involvement of the CNS and the peripheral nervous system. Neuroinvasion usually occurs via hematogenous route or retrograde axonal transport, through a cranial nerve, such as the olfactory, trigeminal, glossopharyngeal, or vagus nerves, or through peripheral nerves [5].

Studies report that headache is the most frequent and early neurological manifestation, and that patients over 65 years of age or with pre-existing conditions, such as diabetes, obesity, hypertension, and heart disease, are more exposed, and may present post-COVID-19 neurological complications, such as anosmia, ageusia, Guillain-Barré syndrome, delirium, and impaired consciousness. Later, they may also present stroke, encephalitis, meningitis, encephalomyelitis, and acute myelitis. Physiotherapy had an individualized approach to conduct during the pandemic scenario, performing numerous procedures in ICUs or emergencies, interventions to assist intubation, patient positioning in bed, mechanical ventilation, weaning, and post-COVID rehabilitation. This scenario highlighted the importance of physiotherapists in intensive therapy, to promote their recognition by society. Here, this study is timely and of paramount importance, as it is justified based on the current pandemic scenario, in which COVID-19 cases are still increasing at a high rate.

2. Material and methods

The literature search was conducted on electronic databases: BVS (8), PUBMED (4,039), and SciELO (3), from April to June 5th, 2022. The keywords used in various combinations were "neurological sequelae," "COVID-19," and "SARS-CoV-2," along with the Boolean operator "AND." A total of 4,050 articles were captured, and the search was limited to studies conducted in humans and published in Portuguese, Spanish, or English. Inclusion criteria were studies with full-text availability, in patients who contracted COVID-19, and publications from 2019 to 2022. Exclusion criteria were studies without practical applicability (handbooks). Titles and abstracts were analyzed to obtain articles potentially relevant to the review. After applying the inclusion and exclusion criteria, 17 articles were selected, but only nine were readable.

2. Results

Table 1 shows the nine selected articles for the development of the results. Demographic risk factors, such as age and comorbidities, have been found to increase the risk of suffering a stroke as a complication of COVID-19. Firstly, patients who suffer a stroke as a complication of COVID-19 are generally individuals with an average age of 65.5 years. Regarding COVID-19 patients with pre-existing medical conditions, it is still unclear, but one theory is that the lower level of physiological reserves results in insufficient reserves to compensate for the physiological disturbances caused by COVID-19 [14].

To date, there are no definitive reports of detecting SARS-CoV-2 in the cerebrospinal fluid (CSF). The only available report of CSF findings does not describe abnormalities in a patient with encephalopathy during COVID-19 illness [6]. In the study by Hajikhani et al. [7], the estimated prevalence rates of olfaction were found to be 61%, and taste disorder was found to be 49% in confirmed COVID-19 patients. Subgroup analysis defined the degree of impairment of olfactory and gustatory symptoms. Hyposmia was more com-

mon than complete loss of smell. Hypogeusia and dysgeusia were more frequent than complete loss of taste.

Table 1. Demographic and clinical characteristics in the total population and according to presence of CAD.

Reference	Main findings
[6]	It is observed that headache and memory loss were the manifestations reported by the largest number of patients and primary studies. Cognitive deficits had a prevalence of 78%; concentration difficulties had a prevalence of 28% to 80%; facial diplegia followed by ataxia and paresthesia had a prevalence of 20%.
[7]	The estimated rate of gustatory disturbance in COVID-19 patients was 49.1%. The estimated prevalence rate of olfactory disturbance in COVID-19 patients was 61.3%.
[8]	The reported incidence of stroke in hospitalized patients with COVID-19 is 0.9% to 2%, with a higher incidence of 2.3% in young patients. Neurological manifestations caused by SARS-CoV-2 range from mild symptoms such as anosmia to severe symptoms such as ischemic or intracerebral stroke.
[9]	The study showed that among hospitalized and non-hospitalized patients, headache was reported by patients in all studies. The temporal evolution of post-COVID headache appears to be stable during the first 180 days, but longitudinal studies are needed to confirm this.
[10]	Among COVID-19 patients who suffered ischemic stroke, 30 out of 544 patients (5.51%; 95% CI 3.59%–7.43%) presented respiratory symptoms before neurological symptoms, while 29 out of 544 patients (5.33%; 95% CI 3.44%–7.21%) complained of neurological symptoms before respiratory symptoms. No clear onset of neurological or respiratory symptoms in COVID-19 patients was reported in 11 studies (485/544, 89.15%).
[11]	The prevalence of anosmia was 10.2 times higher, and that of dysgeusia was 8.6 times higher. The cumulative prevalence rate of anosmia and dysgeusia was calculated for COVID-19 cases by dividing the number of COVID-19 cases with anosmia by the total number of COVID-19 cases with and without anosmia,
[12]	The combined prevalence of anxiety was evaluated in 25 studies, with a combined prevalence of 47%.
[13]	Eleven studies reported the incidence of stroke as a complication of COVID-19, including two studies that reported the incidence of stroke as a complication in severe COVID-19 patients. Combining results, the combined incidence of stroke as a complication of COVID-19 was 1.74%.
[14]	The main sequels found were stroke, venous thrombosis, delirium, stroke, encephalopathy, seizure, myalgia, dizziness, and anosmia.

To date, there are no definitive reports of detecting SARS-CoV-2 in the cerebrospinal fluid (CSF). The only available report of CSF findings does not describe abnormalities in a patient with encephalopathy during COVID-19 illness [6]. In the study by Hajikhani et al. [7], the estimated prevalence rates of olfaction were found to be 61%, and taste disorder was found to be 49% in confirmed COVID-19 patients. Subgroup analysis defined the degree of impairment of olfactory and gustatory symptoms. Hyposmia was more common than complete loss of smell. Hypogeusia and dysgeusia were more frequent than complete loss of taste.

According to the information collected in the articles, patients affected by COVID-19 in a more severe way and who had to be hospitalized in the ICU, presented more sequelae and complications, unlike the affected population who managed to recover without hospitalization. In this literature review, nine articles published between 2019 and 2022 were found, indicating that the main post-COVID-19 neurological manifestations are

encephalopathies, headache, acute cerebrovascular disease, Acute Necrotizing Encephalopathy (ANE), immune-mediated disorders, neuropathy, myopathy, delirium, anosmia, cognition.

5. Conclusion

Several neurological changes triggered by the exacerbated activation of the immune system in response to the virus have been observed. Most patients who recover from COVID-19 take time to fully recover and may experience lifelong sequelae. Given the information obtained and the evolution of the coronavirus epidemic, it is necessary to conduct studies focused on short and long-term sequelae and symptoms in post-COVID-19 patients.

It is urgent to closely monitor patients, as the studied pathology is still relatively new. Thus, this review should be updated, as it is believed that new sequelae or consequences after virus infection may arise in the long term.

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