Neurological complications in patients after COVID-19

Complicações neurológicas em pacientes pós-COVID-19

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Abstract

Introduction: COVID-19 is caused by the SARS-CoV-2 virus, which has an affinity mainly for alveolar epithelial cells and can affect other cells in the body, which justifies the impairment of the digestive, cardiovascular, and nervous systems. Neurons and glial cells are potentially affected by the virus, thus the nervous system becomes a target of the pathogen, causing damage or neurological changes. **Objective:** To verify the neurological complications in patients after COVID-19 and their association with clinical complications, length of hospitalization, origin, and comorbidities. **Methods:** This is a descriptive observational study, carried out in the COVID-19 infirmaries of the University Hospital of the Federal University of Maranhão, based on the analysis of data from 162 medical records of patients diagnosed with COVID-19, from March 2020 to March 2022. The IBM Statistical Package for the Social Sciences version 20.0 was used for statistical analysis. **Results:** The sample consisted of 162 medical records, whose patients had a higher prevalence of age between 30 and 39 years and brown ethnicity (61.1%). Cerebrovascular accident was the most frequent (45%) and tetraparesis (50%) was the most prevalent motor sequelae. These complications were significantly associated with increased hospital stay and clinical complications. **Conclusion:** Cerebrovascular accident and polyneuropathy were the most prevalent neurological complications in patients with COVID-19, and clinical complications and the total hospital and infirmary stay were significantly associated with such neurological complications.

Keywords: Covid-19. Neurological disorders. Physical disabilities.

Resumo

Introdução: *A COVID-19 é causada pelo vírus SARS-CoV-2, o qual tem afinidade principalmente pelas células epiteliais alveolares, podendo acometer outras células do corpo, o que justifica o comprometimento dos sistemas digestivo, cardiovascular e nervoso. Os neurônios e células da glia são potencialmente afetados pelo vírus; logo, o sistema nervoso torna-se alvo do patógeno, causando-lhe danos ou alterações neurológicas.* **Objetivo:** *Verificar quais as complicações neurológicas em pacientes pós-COVID-19 e a associação das mesmas com as complicações clínicas, período de internação, proveniência e comorbidades.* **Métodos:** *Trata-se de um estudo observacional descritivo, realizado nas enfermarias COVID-19 do Hospital Universitário da Universidade Federal do Maranhão, a partir da análise de 162 prontuários de pacientes com diagnóstico de COVID-19 no período de março de 2020 a março de 2022. Utilizou-se o programa IBM Statistical Package for the Social Sciences versão 20.0 para a análise estatística.* **Resultados:** *A amostra foi composta de 162 prontuários, cujos pacientes apresentaram maior prevalência de idade entre 30 e 39 anos e etnia parda (61,1%). O acidente vascular encefálico foi o mais incidente (45%) e a tetraparesia (50%) foi a sequela motora mais prevalente. Essas complicações apresentaram associação significatica com o aumento do período de internação e complicações clínicas.* **Conclusão:** *O acidente vascular encefálico e a polineuroparia foram as complicações neurológicas mais prevalentes em pacientes com COVID-19, sendo que complicações clínicas e o período de internação total hospitalar e nas enfermarias apresentaram associação significativa com tais complicações neurológicas.*

Palavras-chave: *COVID-19. Transtornos neurológicos. Deficiências fisicas.*

Introduction

In 2002, there was an outbreak of the virus in the world, more precisely in China, called SARS-COV (severe acute respiratory syndrome coronavirus), with many deaths due to respiratory complications. In 2012, a new outbreak occurred of a virus from the same family as SARS-COV, but more lethal, known as MERS-CoV (Middle East respiratory syndrome coronavirus).[1,2] And more recently, in 2020, a global pandemic has been established, whose protagonist was the virus belonging to the phylogeny of beta-coronavirus, known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), initially detected in Wuhan, in China, in December 2019. Its circulation occurred in January 2020 and in March of the same year, the World Health Organization (WHO) decreed the pandemic for this virus with high morbidity and mortality, causing coronavirus disease 2019 (COVID-19).[3,4]

According to data from the Ministry of Health, by the end of Epidemiological Week 39, held from 09/26 to 10/2 of 2021,234,627,330 cases were confirmed worldwide and Brazil was in third place. In relation to the number of deaths, until October 2, 2021, 4,797,562 deaths were confirmed worldwide, with Brazil occupying the second place. In Maranhão, there were more than 358,644 cases of the disease, with more than 10,211 deaths, and in the capital, São Luís, the cases reached more than 46,968 and deaths, more than 2,574. These data reflect the pandemic period when vaccines were still in development and effective treatment protocols were not yet established.[5]

The main transmission routes of the new coronavirus are through direct or indirect contact, through fluids and saliva expelled by coughing, sneezing and oral particles and transmission through contact with the oral, nasal and eye mucosa. Clinical symptoms of COVID-19 can range from asymptomatic infection to multisystemic impairment. In most cases, the symptoms described are fever, cough, myalgia, fatigue, headache and diarrhea. Severe cases are treated with intense respiratory discomfort associated with low levels of oxygen in the blood, requiring hospital and intensive care.[6,7]

The contamination by SARS-CoV-2 virus is triggered by the binding of its Spike protein to angiotensin-2 converting enzyme (ECA 2), which has affinity mainly for alveolar (pulmonary) epithelial cells, being able to affect other cells of the body, which justifies the impairment in the digestive, cardiovascular and nervous systems.[8]

The neurons and glial cells are potentially affected by SARS-CoV-2 virus, so the nervous system becomes a target for the pathogen, causing damage or neurological changes such as neuralgia, encephalopathy, meningitis, encephalitis, acute cerebrovascular diseases, in addition to signs and symptoms such as headache, dizziness, reduction of the level of consciousness, alteration of smell (anosmia, hyposmia) and taste (hypogeusia). The pathophysiology of COVID-19 in the nervous system is complex, as there is also the involvement of multifactorial

autoimmune factors, causing neuroinflammation, followed by large release of inflammatory cytokines, with major systemic alterations.[9,10]

Understanding the neurological complications of COVID-19 is important to contribute to scientific productions in the area, as well as to discussions on treatment strategies and the provision of patients in health systems, especially for the population surviving the disease that has acquired neurosequelae and that has ceased to be economically active in society as a result of temporary or permanent motor sequelae. The objective of this research, therefore, is to verify the neurological complications in post-COVID-19 patients and their association with clinical complications, hospitalization period, origin and comorbidities.

Methods

This is a descriptive observational study, conducted in the COVID-19 infirmaries of the University Hospital of the Federal University of Maranhão - President Dutra Unit (HUUFMA-UPD), in the city of São Luís, state of Maranhão, and approved by the Ethics Committee of UFMA, under the number 5.558.765. The exemption of informed consent was requested, since data collection was carried out through the investigation of medical records.

The inclusion criteria for this study were: patients over 18 years of age, of both sexes, hospitalized in HUUFMA-UPD, in the sectors of COVID-19 infirmaries,

with a confirmed diagnosis of COVID-19 in the period from March 2020 to March 2022 (Figure 1). The non-inclusion criteria were: medical records with insufficient information to answer the questions of the survey questionnaire.

Data were collected from the patients' medical records regarding identification, socioeconomic and demographic situation, diagnosis, comorbidities, length of stay, neurological complications, motor sequelae, complementary examinations and clinical complications. The sociodemographic variables were age, ethnicity, sex, level of education, marital status, family income and occupation. For this, a process was formulated via the Electronic Information System (SEI) destined to the Health Care Management (GAS) of HUUFMA, to access the list of patients with their respective medical records. Then, in the Management Application for University Hospitals (AGHU) platform, data were collected using a questionnaire developed by the researchers.

The patients selected for the research had a COVID-19 diagnosis confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) tests and/or positive serology, based on the signs and symptoms detected in the medical evaluation. Regarding the neurological complications of the acute or subacute phase of COVID-19, these were confirmed by means of neuroimaging and/or other complementary gold standard tests, computed tomography, magnetic resonance imaging, cerebrospinal electroneuromiography and electroencephalogram.[11-13]
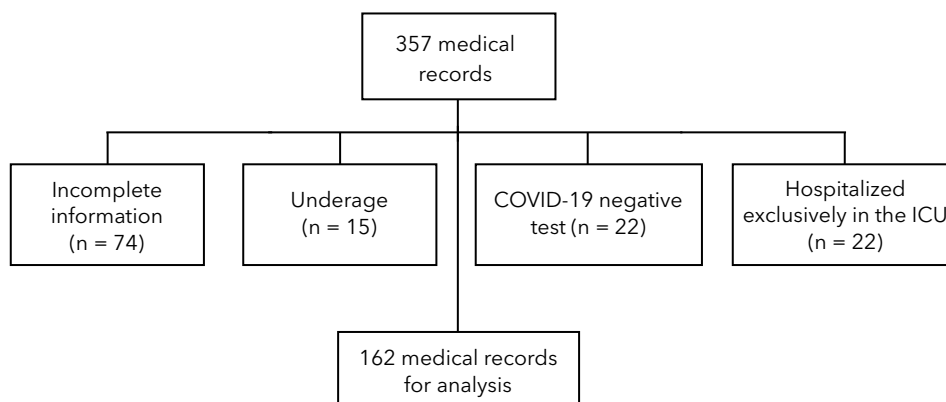

Figure 1 - Flowchart of the analysis of medical records of patients with suspected COVID-19 from March 2020 to March 2022.

Note: ICU = Intensive Care Uunit.

For data analysis, the usual procedures of descriptive statistics were used, such as absolute (n) and relative (%) frequency distribution. To test the association between sociodemographic and clinical variables with neurological complications of patients, bivariate analysis was performed using the chi-square Pearson and Fisher's exact tests. Data were exported from Google Forms to the Microsoft Excel Office spreadsheet and analyzed in IBM Statistical Package for the Social Sciences version 20.0. The significance level adopted was 5% ($p < 0.05$).

Results

The sample consisted of 162 medical records, 63% men and 37% women, aged between 18 and 90 years, with higher prevalence in the age between 30 and 39 years (21%) and brown ethnicity (61.1%). Among the participants, 44.4% were from São Luís and most had completed high school and higher education, with 38.3% and 22.2%, respectively. In relation to occupation, 30.9% were employed, with family income between 1 and 3 minimum wages (80.9%) being the most frequent (Table 1).

Most of the patients came from the Intensive Care Unit (ICU), corresponding to 61.1%, with a period of hospitalization in the infirmary of 1 to 7 days (40.7%) and total hospital admission of 8 to 15 days (40.1%). Among the comorbidities, hypertension had the highest prevalence (60.3%). The prevalence of neurological complications was 12.3%, with cerebrovascular accident being the most frequent (45%). In relation to motor sequelae, tetraparesis (50%) was the most prevalent, followed by hemiparesis (35%). In relation to clinical complications, tracheostomy and nasoenteral sonography were the most prevalent, with 88.2% and 76.5%, respectively (Table 2). Among the variables analyzed, the total time of hospitalization and in the infirmary and the clinical complications showed a significant relationship with neurological complications, not having relation only with origin and comorbidities (Table 3).

Discussion

In this study, with 162 patients infected with COVID-19, most were male and the most affected age group was between 30 and 39 years (21.0%).

Table 1 - Sociodemographic profile of patients diagnosed with COVID-19 admitted to the HUUFMA-UPD from March/2020 to March/2022

Variables		n (%)
Sex	Male	102 (63.0)
	Female	60 (37.0)
Age (years)	18 - 29	15 (9.3)
	30 - 39	34 (21.0)
	40 - 49	32 (19.8)
	50 - 59	33 (20.4)
	60 - 69	33 (20.4)
	70 or more	15 (9.3)
Ethnicity	White	52 (32.1)
	Yellow	3 (1.9)
	Brown	99 (61.1)
	Black	8 (4.9)
Origin	São Luís	72 (44.4)
	Inner state	58 (35.8)
	Other state	32 (19.8)
Education	Illiterate	6 (3.7)
	CES	12 (7.4)
	IES	31 (19.1)
	CHS	62 (38.3)
	IHS	8 (4.9)
	CHE	36 (22.2)
	IHE	7 (4.3)
Family income (minimum wage)	< 1	19 (11.7)
	1 - 3	131 (80.9)
	4 - 6	7 (4.3)
	7 - 9	3 (1.9)
	No income	2 (1.2)
Occupation	Employed	50 (30.9)
	Unemployed	6 (3.7)
	Retired	39 (24.1)
	Recipient	16 (9.9)
	Own-account employee	49 (30.2)
	Student	2 (1.2)
Marital status	Single	84 (51.9)
	Married	65 (40.1)
	Divorced	6 (3.7)
	Widowed	7 (4.3)

Note: HUUFMA-UPD = University Hospital of the Federal University of Maranhão - Presidente Dutra Unit; CES/IES = complete/incomplete elementary school; CHS/IHS = complete/incomplete high school; CHE/IHE = complete/incomplete higher education.

Table 2 - Clinical profile of patients diagnosed with COVID-19 admitted to the HUUFMA-UPD from March/2020 to March/2022

Variables		n (%)
Origin	Intensive Care Unit	99 (61.1)
	Kidney transplant	26 (16.0)
	Other hospital unit	35 (21.6)
	Hemodialysis	2 (1.2)
Time hospitalized in the infirmary (days)	1 - 7	66 (40.7)
	8 - 15	54 (33.3)
	16 - 30	23 (14.2)
	31 - 60	19 (11.7)
Total time hospitalized (days)	1 - 7	23 (14.2)
	8 - 15	65 (40.1)
	16 - 30	29 (17.9)
	31 - 60	22 (13.6)
	61 - 90	13 (8.0)
	Over 90	10 (6.2)
Comorbidities*	High blood pressure	73 (60.3)
	Lung disease	14 (11.6)
	Diabetes	39 (32.2)
	Heart failure	16 (13.2)
	Chronic kidney disease	41 (33.9)
	Cancer	4 (3.3)
	HIV	2 (1.7)
	Cerebrovascular disease	10 (8.3)
	Morbid obesity	18 (14.9)
Neurological complications	Yes	20 (12.3)
	No	142 (87.7)
	Cerebrovascular accident	9 (45.0)
	Encephalitis	4 (20.0)
	Polyneuropathy	6 (30.0)
	Others	1 (5.0)
Motor sequelae	Hemiparesis	7 (35.0)
	Tetraparesis	10 (50.0)
	Tetraplegia	1 (5.0)
	Paraplegia	2 (10.0)
Clinical complications*	Tracheostomy	30 (88.2)
	Nasoenteral probe	26 (76.5)
	Gastrostomy	4 (11.8)
	Pressure injury	17 (50.0)
	Others	2 (5.9)

Note: HUUFMA-UPD = University Hospital of the Federal University of Maranhão - Presidente Dutra Unit; HIV = vhuman immunodeficiency virus. *Multiple variable (the sum of the percentages exceeds 100%). Chi-square; Fisher's exact.

Table 3 - Association of the clinical profile of COVID-19 with neurological complications of patients admitted to the HUUFMA-UPD from March/2020 to March/2022

Variables	Neurological complications - n (%)		p-value
	Yes (n = 20)	No (n = 142)	
Origin			
ICU	19 (19.2)	80 (80.8)	
KT	-	26 (100)	0.008
OHU	1 (2.9)	34 (97.1)	
Hemodialysis	-	2 (100)	
Time hospitalized in the infirmary (days)			
1 - 7	3 (4.5)	63 (95.5)	
8 - 15	5 (9.3)	49 (90.7)	0.001
16 - 30	5 (21.7)	18 (78.3)	
31 - 60	7 (36.8)	12 (63.2)	
Total time hospitalized (days)			
1 - 7	1 (4.3)	22 (95.7)	
8 - 15	2 (3.1)	63 (96.9)	
16 - 30	3 (10.3)	26 (89.7)	<0.001
31 - 60	4 (18.2)	18 (81.8)	
61 - 90	4 (30.8)	9 (69.2)	
Over 90	6 (60.0)	4 (40.0)	
Comorbidities*			
HBP	10 (13.7)	63 (86.3)	
Lung disease	1 (7.1)	13 (92.9)	
Diabetes	5 (12.8)	34 (87.2)	
Heart failure	4 (25.0)	12 (75.0)	
CKD	2 (4.9)	39 (95.1)	0.259
Cancer	-	4 (100)	
IMS	1 (50.0)	1 (50.0)	
CRD	2 (20.0)	8 (80.0)	
MO	1 (5.6)	17 (94.4)	
Clinical complications*			
Tracheostomy	12 (40.0)	18 (60.0)	
NP	12 (46.2)	14 (53.8)	
Gastrostomy	3 (75.0)	1 (25.0)	<0.001
Pressure injury	8 (47.1)	9 (52.9)	
Others	-	2 (100)	

Note: HUUFMA-UPD = University Hospital of the Federal University of Maranhão - Presidente Dutra Unit; ICU = Intensive Care Unit; KT = kidney transplant; OHU = other hospital unit; HBP = high blood pres-sure; CKD = chronic kidney disease; IMS = immunosuppression; CRD = cerebrovascular disease; MO = morbid obesity; NP = nasoenteral probe. *Multiple variable (the sum of the percentages exceeds 100%). Chi-square; Fisher's exact.

These data corroborate the studies by Flores-Silva et al.[14] and Romero-Sánchez et al.,[15] which found male individuals of economically active age affected by COVID-19. The predominant self-declared ethnicity was the Brown (61.1%) and most were from the city of São Luís (44.4%). It is worth mentioning that among the 19.8% patients admitted to HUUFMA-UPD from other states, most were from Amazonas, due to lack of oxygen and collapse in their health network.

Regarding the educational level, complete high school had the highest frequency, corresponding to 38.3%. Concerning the professional occupation, most of the sample was formed by an economically active population (30.9% employed and 30.2% own-account-workers) that, with the onset of the pandemic, submitted to the risk of COVID-19 contamination in search of sustenance for their family. In relation to income, the highest prevalence was 1 to 3 minimum wages, with 80.9%, which corresponded to patients who had mainly completed high school education, since this educational level does not allow a greater variation in income.

Of the patients admitted to COVID-19 infirmaries, 61.1% came from the ICU, given that this may justify the clinical complications found, such as tracheostomy, present in patients who required invasive mechanical ventilation for a prolonged period in the ICU, use of nasoenteral or gastrostomy probe to ensure adequate nutritional support, and presence of pressure injury, skin injury due to the patient's immobility time in bed, mainly due to the need for mechanical ventilation and the use of sedatives. These clinical complications show a significant association with patients who presented neurological complications (p = 0.001), as well as there was an association of neurological complications with the total hospital stay time (p = 0.001) and time of hospitalization in the infirmary (p = 0.001), data corroborating the study by Frontera et al.[16]

Patients with COVID-19 who presented neurological complications had a longer hospital stay, with an average length of 60 days or more, which reflects the association with clinical and motor complications acquired during hospitalization. Regarding the length of hospitalization in the infirmaries, 40.7% of patients with COVID-19 were hospitalized from 1 to 7 days; this group included those without neurological and clinical complications, who were discharged from the ICU with a stable clinical condition. Patients who had a total hospitalization period of 8 to 15 days (40.1%) reflect those who did not require mechanical ventilation support, coming from the ICU.

Among the comorbidities most present in hospitalized patients, hypertension and diabetes were the most frequent, data resembling the study by Frontera et al.[16] Another common comorbidity was chronic kidney disease, which is justified by the fact that HUUFMA-UPD is a reference center in renal health, to which many of the patients were admitted directly from hemodialysis or kidney transplantation unit. In addition, it is noteworthy that most patients with chronic kidney disease presented one or more comorbidities, but did not present a significant association with neurological complications.

The frequency of neurological complications in hospitalized patients after COVID-19 in the HUUFMA-UPD (12.3%) was similar to that found in the study by Heneka et al.[17] (13,5%). Such complications found, as cerebrovascular accident, encephalitis and polyneuropathy, associated with pressure injury, use of a probe, nasoenteral, gastrostomy and tracheostomy, which often occurred simultaneously, They favor the increase of hospital stay, generating more costs, more risk of new infections to patients in vulnerable situation and, consequently, delay in dehospitalization and bed turnover. Moreover, hospitalization contributes greatly to the patient's immobility, reducing the stimuli necessary for recovery of possible motor sequelae of patients affected by neurological complications.

Cerebrovascular accident was the most frequent neurological complication, with 45%, which can be explained by the fact that COVID-19 causes changes in coagulation and, in particular, disseminated intravascular coagulation (DIC) induced by inflammation. In addition to endothelial dysfunction, DIC can cause cerebrovascular ischemia even in young patients, and consequent ischemic cerebrovascular accident of large vessels. There are several hypotheses of how SARS-CoV-2 affects the nervous system, how these neurological complications arise through secondary immunological mechanisms and the severe inflammatory state in response to infection and severe hypoxemia promoted by critical disease and comorbidities.[17]

Among the patients affected by neurological complications, all presented motor sequelae. Tetraparesis, which is characterized by partial paralysis of the upper and lower limbs movements as a consequence of polyneuropathy, was the most frequent (50%), causing great physical limitation to the patient and with a reserved prognosis for his/her return to daily life activities and the labor market, as well as hemiparesis (35%), present in patients affected by cerebrovascular accident.

This scenario reflects the deleterious impact of COVID-19 on the life of the patient, in the routine of his/her family and in the socioeconomic aspects, since the continuity of his/her treatment in a rehabilitation center, besides being necessary as a citizen's right, generates more expenses to the government and family until this patient has his/her autonomy again, whether total or partial.

Conclusion

This study showed that cerebrovascular accident and polyneuropathy were the most prevalent neurological complications in patients with COVID-19, complications that generate a great physical impairment, affecting the personal and social sphere. The clinical complications and total hospital and hospitalization in infirmaries were significantly associated with these neurological complications. Therefore, care strategies should be developed to reduce the time of hospitalization, such as multiprofessional meetings, with the aim of defining goals and behaviors to be carried out for problem solving, promoting safe hospital discharge protocols, ensuring referral and counter-referral care and optimizing public policies that prioritize and ensure human dignity, especially for patients with neurosequalae.

Authors' contributions

GHMS and RSBM contributed equally and approved the final version of the article.

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