BMC Infectious Diseases

RESEARCH

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Neurological syndromes associated with COVID-19: a multicenter study in Brazil

Aline de Moura Brasil Matos[1], Andre Borges Ferreira Gomes[2,3], Fernanda Martins Maia Carvalho[2,3], Francisco Tomaz Meneses de Oliveira[4], Lohana Santana Almeida da Silva[4], Flavia Esper Dahy[5], Joao Victor Luisi de Moura[5], Marcela Vieira Freire[5], Jose Ernesto Vidal[5], Rosa Maria Nascimento Marcusso[5], Jerusa Smid[5], Victor Rebelo Procaci[6], Rodrigo Meireles Massaud[6], Felipe Von Glehn[7], Jorge Casseb[1], Camila Malta Romano[1,8*†], Augusto Cesar Penalva de Oliveira[5†] and on behalf of NeurocovBR study group

Abstract

Background Neurological manifestations associated with COVID-19 remain partially described, mainly in low- and middle-income countries where diagnostic tools are limited. To address this, we assembled medical centers in Brazil with the goal of describing neurological syndromes associated with COVID-19 during the first wave of the pandemic.

Methods From June 1st, 2020 to June 1st, 2021, non-consecutive adult patients with new onset of six neurological syndromes up to 60 days after confirmed COVID-19 were included. Data were compiled from four tertiary centers and compared with general local COVID-19 data, as well as with a previous cohort focused on vascular syndrome.

Results 197 patients were included, presenting with vascular syndromes (81), encephalopathy (68), encephalitis (19), Guillain-Barré syndrome (13), other neuropathies (12), and myelitis (4). The incidence curve of neurocovid mirrored that of COVID-19. Neurological syndromes were present regardless of COVID-19 severity. The median time from COVID-19 to onset of neurological symptoms was 14 days, suggesting a post-infectious immune-mediated mechanism. Patients were 10 times more likely to die (χ^2 (1) = 356.55, $p < 0.01$, OR = 10.89) and 38 times more likely to be hospitalized than other COVID-19 patients (χ^2 (1) = 1167.9, $p < 0.01$, OR = 38.22). Those developing vascular syndromes patients were 3 times more likely to require ICU (χ^2 (1) = 37.12, $p < 0.01$, OR = 3.78) and 4 times more likely to die (χ^2 (1) = 58.808, $p < 0.01$, OR = 4.73) than patients with vascular syndromes due to different etiologies.

Conclusions Our study corroborates the association of neurological syndromes with COVID-19. The incidence correlated with local waves of COVID-19, and patients with neurocovid exhibited a higher susceptibility to adverse outcomes compared to other COVID-19 patients. Among all neurological syndromes, vascular syndromes were the most common, and their severity surpassed that of vascular syndromes not attributed to COVID-19.

Keywords COVID-19, Viral infections, Infection, Post-Infectious Disorders

†Camila Malta Romano and Augusto Cesar Penalva de Oliveira share senior authorship.

*Correspondence:
Camila Malta Romano
cmromano@usp.br
Full list of author information is available at the end of the article

Background

Throughout history, viral emergencies have consistently exhibited an intriguing association with concurrent neurological manifestations [1]. It is noteworthy that these neurological sequelae, although not typically the primary syndrome characterizing an epidemic, frequently emerge as a striking and critical facet, demanding specialized medical attention [2].

The COVID-19 pandemic serves as a pertinent contemporary example of this phenomenon. From the earliest reported cases in Wuhan, a significant proportion of infected individuals, estimated to be around 30%, exhibited neurological symptoms [3]. As our understanding of the novel coronavirus, SARS-CoV-2, progressed and global infection rates rose, these neurological presentations transitioned from sporadic symptoms to worrisome syndromes that have yet to be fully characterized [4].

Shifting our attention to the South American epicenter of the SARS-CoV-2 outbreak, Brazil bears a concerning burden with over 37 million confirmed COVID-19 cases and a tragic toll of more than 700,000 fatalities [5]. And while these numbers have been publicized and been the focus of a combination of political and social challenges [6, 7], the potential long-term health issues associated with COVID-19, such as neurological, cardiovascular, and musculoskeletal problems were consistently overlooked.

Recognizing the crucial gap in comprehending and addressing the broader implications of the pandemic, we proactively initiated collaboration with neurology reference centers experienced in neurovirology. This collaboration aimed to rapidly navigate the challenges posed by lockdown situations, with the overarching goal of characterizing and accounting for neurological manifestations associated with COVID-19 during a period of different variants insurgence [8, 9] and lack of vaccination.

In this report, we share our experience with the study of COVID-19-related neurological syndromes from the cohort assembled by the NeurocovBR study group during the early pandemics in Brazil.

Methods

NeurocovBR

In March 2020, following confirmation of the first case of COVID-19 in Brazil [6], the NeurocovBR study group was established. This group was comprised of national neurology reference centers (in public or private practice) with prior experience in neurovirology and was coordinated by the Tropical Medicine Institute of Sao Paulo (IMT USP). IMT USP also conducts bench research in virology and had the additional shared responsibility of developing and validating new assays related to SARS-CoV-2 in Brazil during the pandemic.

NeurocovBR was organized into two distinct layers: a comprehensive clinical-demographic layer and a laboratory layer. Each clinical participating center had the option to contribute solely to the clinical-demographic layer or to engage in both layers, depending on whether their internal protocols and contamination control measures allowed for full participation.

Study design and patient selection

For the clinical-demographic layer, a total of four sites situated in hotspot regions for COVID-19 participated in the study in addition to IMT USP. Three of these sites were located in Sao Paulo State (*Instituto de Infectologia Emilio Ribas, Irmandade Santa Casa de Misericordia de Sao Paulo and Hospital Israelita Albert Einstein*), southeast Brazil, while the fourth site was in Ceara State (*Hospital Geral de Fortaleza*), in the northeastern region of the country. Enrollment started on June 1, 2020, and continued until June 1, 2021. If the patient had the first COVID-19 and neurological symptoms starting before June 1, 2020, enrollment was acceptable if he remained with neurological signs or symptoms (it could be a sequelae) by the study start.

Inclusion criteria required patients to be 18 years of age or older, fulfill WHO criteria for COVID-19 [10], meet the provisional Ellul criteria for SARS-CoV-2 neurologic-associated syndromes [4], and exhibit novel neurological symptoms within 60 days of COVID-19 infection (Table s1).

It was admissible for patients to be referred to the designated study sites by general practitioners, and individuals also had the option to personally request an evaluation. Every patient, whether as an inpatient or an outpatient, underwent an evaluation conducted by a neurologist affiliated with the study group, to ensure the precise classification of the neurological syndrome.

Patients presenting with isolated neurological symptoms, such as anosmia, myalgia, or headache, were excluded from the study if no further neurologic syndrome developed in 60 days. This timeframe was adopted to ensure that syndromes, including those that may develop after mild symptoms, such as Guillain-Barré Syndrome, and persist for up to an additional four weeks, were not overlooked [11]. COVID-19 vaccination was not an exclusion criterion; however, during the study period, it was not available to participants for various reasons, and no patients received the vaccine.

Evaluation

Demographic data were collected from medical records, patient interviews, or interviews with a designated proxy when the patient was unable to provide the information directly. A structured interview was designed specifically

for this study (supplementary material). It included information such as age, gender, comorbidities, the date of onset of the first COVID-19 symptom, the date of the first neurological sign or symptom, COVID-19 signs and symptoms, and parameters for assessing the severity of COVID-19 [12].

For patients with vascular syndrome, the severity of COVID-19 was classified based on symptoms and signs observed the day before the onset of the first neurological symptom. This was necessary because otherwise, a stroke would automatically classify patients as having critical COVID-19, preventing us from demonstrating that individuals with mild, moderate, and severe COVID-19 could also develop COVID-19-associated stroke.

To assess the severity of neurological syndromes, we employed the Modified Rankin Scale (mRS) and the Glasgow Coma Scale (GCS) for all syndromes. For vascular syndrome patients, mRS was scored 24h after acute phase treatment. Furthermore, the Liverpool Outcome Score (LOS) was used for encephalopathy and encephalitis, the NIH Stroke Scale (NIHSS) for vascular syndrome, and the Overall Neuropathy Limitations Scale (ONLS) for conditions such as Guillain-Barré syndrome and other neuropathies.

To account for overall patient outcomes, we collected in-hospital data, which included the need for admission to the intensive care unit (ICU) and/or mechanical ventilation (MV) assistance, as well as the presence of complications such as acute kidney injury (AKI) or coinfections. We also documented the length of in-hospital stay, recorded cases of mortality, and tracked time-to-death.

All patients underwent SARS-CoV-2 testing through one or both of the ELISA IgA (Euroimmun, Lubeck, Germany) in serum samples and/or RT-PCR methods (RealStar RT-PCR kit, Altona Diagnostics, Hamburg, Germany) from oropharyngeal swab (samples during the COVID-19 acute phase). It is worth noting that additional cerebrospinal fluid (CSF) and serum measurements are not covered within the scope of this report.

Data storage

Data were stored in an electronic data capture system specifically designed for this study. Only the local site coordinator and the principal researcher designated by them were granted access to input the data. Subsequently, this data was centrally reviewed by the study coordinators to mitigate any potential inconsistencies.

Syndromic reclassification

After the latest data inclusion, all entries underwent review for a second confirmation of diagnosis. In our study design, we adopted the provisional Ellul criteria [4] to define neurocovid syndromes, which determines meningitis, encephalitis, acute disseminated encephalitis, myelitis, Guillain-Barré syndrome and cerebrovascular disease as primary syndromes. However, distinct and consistent clusters emerged within our sample. To highlight these differences and provide greater clarity to the reader, we reclassified the encountered syndromes into six distinct categories: (i) Vascular syndromes, encompassing confirmed cases of ischemic stroke, hemorrhagic stroke, or cerebral venous thrombosis; (ii) Encephalopathy, characterized as level 3 and 4 of SARS-CoV-2 encephalitis [4]; (iii) Encephalitis, identified as level 1 and 2 of SARS-CoV-2 encephalitis [4]; (iv) Guillain-Barré syndrome, specifically associated with SARS-CoV-2 [4]; (v) Other neuropathies, referring to acute neuropathies related to SARS-CoV-2 [4], (vi) Myelitis, defined as SARS-CoV-2-induced myelitis [4] (supplementary material, Table s1). It is noteworthy to mention that no instances of other syndromes were encountered within our sample.

Comparison data

To compare the NeurocovBR data with general COVID-19 data from the states of Ceara and Sao Paulo, we accessed publicly available information from the Brazilian governmental health authority (Coronavírus Brasil, OpenDATASUS) [5]. For comparing the NeurocovBR vascular syndrome data with data on vascular syndromes predating the COVID-19 pandemic, we relied on detailed local stroke data from a previously published article [13].

Statistical analysis

Continuous data were summarized as the mean and standard deviation or median plus interquartile range (IQR). Categorical data were presented as counts and percentages. Group comparisons were conducted using the chi-square test for categorical data, with Yates' correction applied in cases where expected cell frequencies were less than 5. Non-parametric rank tests were used for continuous data, except when comparing with general vascular data, where we employed a one-sided t-test. In this parametric test, no difference in results was observed when using bootstrapping with 2,000 repetitions on NeurocovBR vascular data to achieve normality assumptions; therefore, we worked with the original sample, assuming the central limit theorem.

We used Cohen's d to determine the size effect when a one-sided t-test was used and odds ratios for chi-square tests. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed, and graphs were created, using the R programming language version 3.3.0+.

Standard Protocol Approvals, Registrations and Patient Consents

This study obtained approval from the ethics committee at the Universidade de São Paulo (CAAE: 31,378,820.1.1001.0068) and the ethics committees of the study sites. Written informed consent was obtained from all patients or their next of kin, and their personal information is protected by ethical procedures. The study adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as relevant Brazilian regulations.

Results

Patient selection

From an initial cohort of 233 patients, 36 individuals (15.5%) were excluded, resulting in a final analysis cohort of 197 patients (Fig. 1). Among the ten syndromes that were not associated with COVID-19, eight were linked to various causative agents, while two were classified as psychogenic. Within the subset of six patients exhibiting isolated neurological symptoms, four presented with isolated headaches, one experienced a temporary loss of consciousness, and another reported vertigo. Furthermore, among the patients with vascular syndrome, encephalopathy, and encephalitis, three, five, and two patients, respectively exhibited concurrent neuropathy, which was categorized as critical illness polyneuropathy. This comorbidity was attributed to their prolonged in-hospital stay and their clinical conditions, rather than being directly linked to SARS-CoV-2. Additionally, one patient diagnosed with encephalitis also manifested myelitis with minimal clinical manifestations, ultimately receiving a final classification of encephalitis.

NeurocovBR

Among the six primary neurological syndromes, two—vascular syndrome and encephalopathy—accounted for over 75% of the cases, while the remaining four – encephalitis, GBS, other neuropathies, and myelitis – collectively accounted for less than 25%. It is noteworthy that obesity, which is recognized as risk factors for severe COVID-19, was not prevalent in this context [14]. Symptoms such as fever, cough, and dyspnea were commonly reported, with anosmia/hyposmia exceeding 30% only in cases of encephalitis (Table 1, Table s2).

Notably, in cases of GBS (4, 30.4%), vascular syndrome (11, 13.6%), encephalitis (1, 5.3%), and encephalopathy (1, 1.5%), some patients were asymptomatic for COVID-19 infection and were diagnosed through mandatory SARS-CoV-2 in-hospital screening (Table 1). The manifestation of neurological syndromes appeared irrespective of the severity of the associated COVID-19 infection and typically developed approximately two weeks following the initial infection (median 14 days, IQR 7–24). The timeline for the onset of neurological syndromes varied, with vascular syndromes and encephalitis presenting in a shorter period and neuropathies emerging over a longer duration (Table 1).

In-depth assessments of patients' clinical conditions revealed a significant proportion of individuals with moderate or severe scores on outcome scales such as GCS to all syndromes, LOS to encephalopathy and

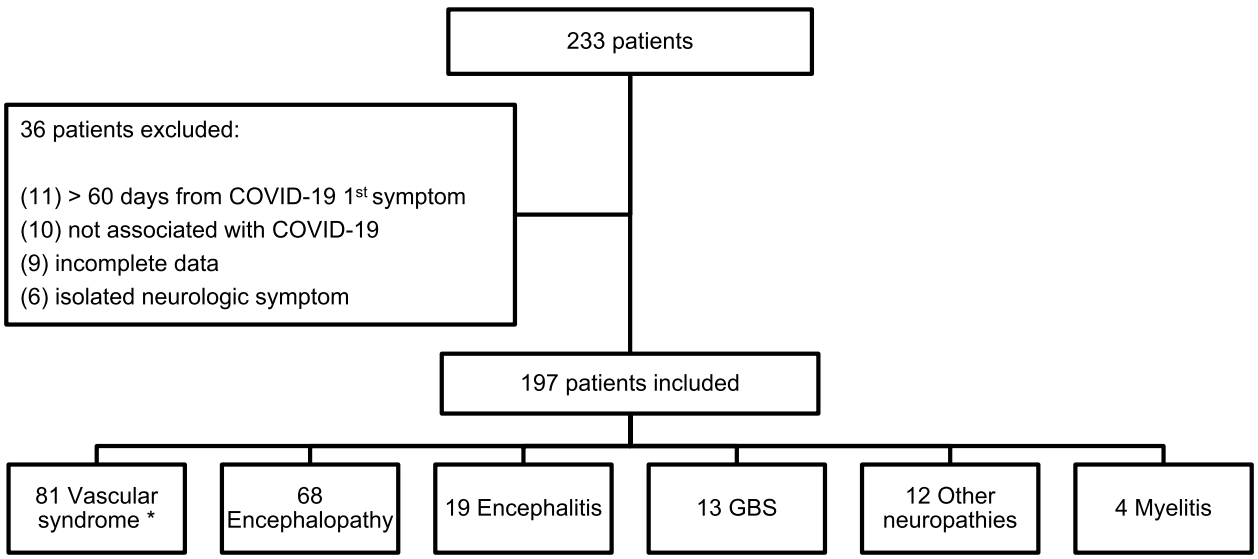

Fig. 1 NeurocovBR patient's flowchart. Legends: * The vascular syndrome includes 52 cases of ischemic stroke, 21 cases of hemorrhagic stroke, and 8 cases of cerebral venous thrombosis. GBS = Guillain-Barré Syndrome

Table 1 Demography of NeurocovBR patients

	All patients	Vascular	Encephalopathy	Encephalitis	GBS	Neuropathies	Myelitis
n, (%)	197 (100)	81 (41.1)	68 (34.5)	19 (9.6)	13 (6.6)	12 (6.1)	4 (2.1)
Age, median, (IQR)	57 (43–67)	62 (50–71)	57 (43.5–65)	55 (41.5–60.5)	45 (43–54)	40 (34.25–53)	40 (26–56.25)
Female, n, (%)	109 (55.3)	46 (56.8)	41 (60.3)	8 (42.1)	8 (61.5)	4 (33.3)	2 (50)
Comorbidities, n, (%)							
HBP	84 (42.6)	45 (51.1)	29 (42.6)	5 (26.3)	3 (23.1)	2 (16.7)	0 (0)
DM	57 (28.9)	28 (31.8)	16 (23.5)	5 (26.3)	2 (15.4)	5 (41.7)	1 (25)
Obesity	30 (15.2)	14 (15.9)	9 (13.2)	0 (0)	2 (15.4)	5 (41.7)	0 (0)
Smoker	27 (13.7)	15 (17)	9 (13.2)	1 (5.3)	2 (15.4)	0 (0)	0 (0)
Autoimmune disease	3 (1.5)	2 (2.3)	1 (5.3)	0 (0)	0 (0)	0 (0)	0 (0)
No comorbidities	47 (23.9)	18 (20.5)	17 (25)	4 (21.1)	5 (38.5)	1 (8.3)	2 (50)
COVID-19 signs and symptoms, n, (%)							
Fever	135 (68.5)	53 (60.2)	50 (73.5)	13 (68.4)	7 (53.8)	9 (75)	3 (75)
Cough	126 (64)	55 (62.5)	48 (70.6)	9 (47.4)	5 (38.5)	8 (66.7)	1 (25)
Sore throat	22 (11.2)	3 (3.4)	15 (22.1)	2 (10.5)	0 (0)	1 (8.3)	1 (25)
Runny nose	26 (13.2)	2 (2.3)	16 (23.5)	4 (21.1)	3 (23.1)	0 (0)	1 (25)
Myalgia	47 (23.9)	12 (13.6)	26 (38.2)	4 (21.1)	3 (23.1)	2 (16.7)	0 (0)
Headache	45 (22.8)	18 (20.5)	20 (29.4)	5 (26.3)	1 (7.7)	1 (8.3)	0 (0)
Asthenia	53 (26.9)	18 (20.5)	20 (19.4)	5 (26.3)	4 (30.8)	5 (41.7)	1 (25)
Dyspnea	85 (43.1)	45 (51.1)	32 (47.1)	1 (5.3)	1 (7.7)	6 (50)	0 (0)
StO2 < 95%	53 (26.9)	33 (37.5)	14 (20.6)	2 (10.5)	1 (7.7)	3 (25)	0 (0)
Anosmia/hyposmia	32 (16.3)	2 (2.3)	21 (3.8)	6 (31.6)	1 (7.7)	2 (16.7)	0 (0)
No COVID symptoms	14 (7.1)	7 (8)	1 (1.5)	1 (5.3)	4 (30.8)	0 (0)	1 (25)
COVID-19 severity, n, (%)*							
Asymptomatic	17 (8.6)	11 (13.6)	1 (1.5)	1 (5.3)	4 (30.8)	0 (0)	0 (0)
Mild	58 (29.4)	15 (18.5)	21 (30.9)	10 (52.6)	6 (46.2)	3 (25)	3 (75)
Moderate	32 (16.2)	12 (14.8)	14 (20.6)	2 (10.5)	2 (15.4)	1 (8.3)	1 (25)
Severe	21 (10.7)	9 (11.1)	9 (13.2)	3 (15.8)	0 (0)	0 (0)	0 (0)
Critical	69 (35)	34 (42)	23 (33.8)	3 (15.8)	1 (7.7)	8 (66.7)	0 (0)
Δt COVID-Neuro, d, median, (IQR)	14 (7–24)	10 (6–14)	18 (12–31)	8 (3–24)	23 (15–24)	24 (16.75–39.5)	18 (11.25–14)

Legends: *GBS* Guillain-Barré Syndrome, *HBP* high blood pressure, *DM* diabetes mellitus. * COVID-19 severity was attributed before the vascular syndrome ictus

encephalitis, NIHSS to vascular syndromes, and ONLS to GBS and other neuropathies upon admission (Table 2, Table s3). Additionally, patients from all syndromes presented with co-infections (vascular syndromes, 67.8%; encephalopathy, 38.2%; encephalitis, 52.6%; GBS, 30.8%; other neuropathies, 66.7%; myelitis, 25%), while acute kidney injury was present in only four syndromes (vascular syndromes, 59.3%; encephalopathy, 32.4%; encephalitis, 31.5%; other neuropathies, 33.3%). The mortality was higher among patients with vascular syndromes (55.6%), followed by encephalitis (15.8%), encephalopathy (11.8%) and other neuropathies (8.3%), while absent for GBS and myelitis (Table 2).

NeurocovBR – vascular syndromes vs. encephalopathy

In a separate analysis comparing detailed data from vascular and encephalopathy syndromes, which were significantly more prevalent (χ^2 (5) = 164.68, p < 0.01), we found that vascular patients were older (U = 2139.5, p = 0.019), with a nearly equal gender distribution (χ^2 (1) = 0.07, p = 0.79) in comparison with encephalopathy, and COVID-19 severity was not a determining factor for these syndromes (χ^2 (4) = 7.24, p = 0.12). Details are provided in Table 3.

The period between the onset of initial COVID-19 symptoms and the first neurological symptoms was found to be shortest in vascular patients versus encephalopathy patients (U = 3476.5, p < 0.01). Additionally, vascular patients exhibited more severe clinical symptoms when compared with encephalopathy patients, as indicated by a significantly higher probability of presenting with mRS ≥ 3 (χ^2 (1) = 29.605, p < 0.01, OR = 8.21) and a GCS < 9 (χ^2 (1) = 16.51, p < 0.01, OR = 7.41).

Six vascular patients (7.4%) and four encephalopathy patients (5.9%) (supplementary material, Table s2) had a previous ischemic stroke. Only two patients from the

Table 2 Clinical characteristics and outcomes of NeurocovBR patients

	All patients	Vascular	Encephalopathy	Encephalitis	GBS	Neuropathies	Myelitis
n, (%)	197 (100)	81 (41.1)	68 (34.5)	19 (9.6)	13 (6.6)	12 (6.1)	4 (2.1)
mRS at admission, n, (%)							
< 3	63 (32)	11 (13.6)	39 (57.4)	5 (26.3)	1 (7.7)	6 (50)	1 (25)
≥ 3	132 (67)	69 (85.2)	28 (41.1)	14 (73.7)	12 (92.3)	6 (50)	3 (75)
unknown	2 (1)	1 (1.2)	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)
Specific scales at admission, n, (%)							
GCS 9—12	_	24 (29.6)	4 (6.5)	3(15.8)	_	_	_
GCS < 9	_	30 (37)	5 (7.4)	3(15.8)	_	_	_
LOS 3	_	_	17 (25)	7 (36.8)	_	_	_
LOS < 3	_	_	32 (47)	2 (10.5)	_	_	_
NIHSS 6—15	_	21 (26)	_	_	_	_	_
NIHSS > 15	_	42 (51.9)	_	_	_	_	_
ONLS 5—9	_	_	_	_	5 (38.5)	1 (8.3)	_
ONLS > 9	_	_	_	_	4 (30.8)	3 (25)	_
Hospitalization, n, (%)							
Yes	156 (79.2)	72 (88.9)	46 (67.6)	14 (73.7)	12 (92.3)	10 (83.3)	2 (50)
Needed ICU	137 (60.5)	65 (80.2)	45 (66.2)	11 (57.9)	6 (46.2)	9 (75)	1 (25)
Needed MV	103 (52.3)	55 (67.9)	28 (41.2)	8 (42.1)	4 (30.8)	8 (66.7)	0 (0)
Neurocovid identified during hospitalization	82 (41.6)	42 (51.9)	27 (39.7)	5 (26.3)	1 (7.7)	7 (58.3)	0 (0)
Neurocovid identified after extubating	37 (18.8)	6 (7.4)	20 (29.4)	2 (10.5)	1 (7.7)	8 (66.7)	0 (0)
Δt hospitalization, d, median, (IQR)	22 (11–44)	13 (6.5–22)	24 (11–42)	17.5 (9.25–51)	15 (13–21)	36 (17–48)	11 (10–17)
In-hospital complications, n, (%)							
Co-infections	104 (52.8)	55 (67.9)	26 (38.2)	10 (52.6)	4 (30.8)	8 (66.7)	1 (25)
AKI with dialysis	41 (20.8)	26 (32.1)	12 (17.6)	1 (5.3)	0 (0)	2 (16.7)	0 (0)
AKI without	39 (19.8)	22 (27.2)	10 (14.7)	5 (26.3)	0 (0)	2 (16.7)	0 (0)
Specialist decision treatments, n, (%)							
HCQ	9 (4.6)	2 (2.5)	5 (7.4)	1 (5.3)	0 (0)	1 (8.3)	0 (0)
Anticoagulants	131 (66.5)	62 (81.5)	34 (50)	12 (63.2)	8 (61.5)	7 (58.3)	0 (0)
Corticosteroid therapy	125 (63.5)	53 (65.4)	42 (61.8)	16 (84.2)	3 (23.1)	8 (66.7)	3 (75)
Tocilizumab	2 (1)	0 (0)	1 (1.5)	0 (0)	1 (7.7)	0 (0)	0 (0)
Outcomes							
Death, n, (%)	57 (28.9)	45 (55.6)	8 (11.8)	3 (15.8)	0 (0)	1 (8.3)	0 (0)
Δt COVID-death, d, median (IQR)	24 (17–34)	22 (16.5–29.5)	30 (24.5–64)	92 (72.2–106)	-	43	-_
Δt Neurocovid-death, d, median, (IQR)	15 (7–24)	11.5 (6–21.5)	18.5 (15–40.8)	72.5 (62.8–85.8)	-	18	-

Legends: *GBS* Guillain-Barré Syndrome, *mRS* modified Rankin scale, *GCS* Glasgow coma scale, *LOS* Liverpool outcome score, *NIHSS* NIH stroke scale, *ONLS* overall neuropathy limitations scale, *ICU* intensive care unit, *MV* mechanical ventilation, *AKI* acute kidney injury, *HCQ* hydroxychloroquine

vascular syndrome group had a previous mRS score of 3, while all others had a score 1 or 2, thus not significantly affecting the mRS comparison between groups. In the encephalopathy group, two patients (2.9%) had mild dementia, with a prior mRS score of 2. All patients with a previously altered mRS showed and increment of at least 1 point in the study evaluation.

Vascular patients were also 3.83 times more likely to require hospitalization (χ^2 (1) = 8.8751, $p < 0.01$, OR = 3.83) and 9.38 times more likely to die (χ^2 (1) = 29.05, $p < 0.01$, OR = 9.38) when compared to encephalopathy patients.

Table 3 Characteristics of patients with Vascular Syndromes versus Encephalopathy

	Vascular	Encephalopathy	*p*	*OR*
n	81	68	< 0.01	_
Age, median, (IQR); mean (± SD)	62 (50–71)	57 (43.5–65)	< 0.05	_
Female, n, (%)	46 (56.8)	41 (60.3)	0.79	_
COVID-19 severity, n, (%)				
Asymptomatic	11 (13.6)	1 (1.5)	0.12	_
Mild	15 (18.5)	21 (30.9)		
Moderate	12 (14.8)	14 (20.6)		
Severe	9 (11.1)	9 (13.2)		
Critical	34 (42)	23 (33.8)		
Δt COVID-Neuro, d, median, (IQR)	10 (6–14)	18 (12–31)	< 0.01	_
mRS at admission, n, (%)				
≥ 3	69 (85.2)	28 (41.1)	< 0.01	8.21
Specific scales at admission, n, (%)				
GCS < 9	30 (37)	5 (7.4)	< 0.01	7.41
Hospitalization due to COVID-19, n, (%)				
Yes	72 (88.9)	46 (67.6)	< 0.01	3.83
Needed ICU	65 (80.2)	45 (66.2)	0.07	2.07
Needed MV	55 (67.9)	28 (41.2)	< 0.01	3.02
Neurocovid identified during hospitalization	42 (51.9)	27 (39.7)	0.18	_
Neurocovid identified after extubating	6 (7.4)	20 (29.4)	< 0.01	0.19
Δt hospitalization, d, median, (IQR)	13 (6.5–22)	24 (11–42)	< 0.05	
In-hospital complications, n, (%)				
Co-infections	55 (67.9)	26 (38.2)	< 0.01	2.46
AKI with dialysis	26 (32.1)	12 (17.6)	0.06	2.20
AKI without	22 (27.2)	10 (14.7)	0.10	_
Outcomes				
Death, n, (%)	45 (55.6)	8 (11.8)	< 0.01	9.38
Δt COVID-death, d, (IQR); mean (± SD)	22 (16.5—29.5)	30 (24.5—64)	< 0.05	_
Δt Neurocovid-death, d, median, (IQR)	11.5 (6—21.5)	18.5 (15—40.8)	0.07	_

Legends: *mRS* modified Rankin scale, *GCS* Glasgow coma scale, *ICU* intensive care unit, *MV* mechanical ventilation, *AKI* acute kidney injury

Comparative analysis

NeurocovBR vs COVID-19

The incidence histogram of neurologic syndromes mirrored the incidence histogram of confirmed COVID-19 cases (Fig. 2). NeurocovBR patients were generally older compared to the general Brazilian COVID-19 population (54.7 ± 15.9 vs. 43.2 ± 15.9 years, $p < 0.01$). Furthermore, NeurocovBR patients were 38 times more likely to require hospitalization (χ^2 (1) = 1167.9, $p < 0.01$, OR = 38.22), and the presence of a neurological syndrome was associated with an increased likelihood of mortality (χ^2 (1) = 356.55, $p < 0.01$, OR = 10.89). Refer to Table 4 for details.

Hospitalized NeurocovBR vs Hospitalized COVID-19

When focusing solely on hospitalized patients (Table 4), we observed that the mean age was similar between the two groups, with a slightly increased chance of being female (χ^2 (1) = 8.75, $p < 0.01$, OR 1.62) in NeurocovBR. The odds of death were also slightly higher for NeurocovBR patients (χ^2 (1) = 12.55, $p < 0.01$, OR 1.83).

Vascular NeurocovBR vs Vascular predating COVID-19

In a separate analysis comparing NeurocovBR vascular data with Brazilian vascular data from before the COVID-19 pandemic (Table 5), we observed that NeurocovBR patients were younger (t(80) = −4.70, $p < 0.01$, Cohen's d = 0.52). Notably, hypertension (HBP), diabetes mellitus (DM), and smoking were not identified as risk factors among our patients. Despite the absence of these well-established risk factors, NeurocovBR vascular patients were 3.78 times more likely to require ICU care (χ^2 (1) = 37.12, $p < 0.01$, OR = 3.78), 6.14 times more likely to acquire co-infections during hospitalization (χ^2 (1) = 75.95, $p < 0.01$, OR = 6.14), and 4.73 times more likely to die (χ^2 (1) = 58.808, $p < 0.01$, OR = 4.73) (Table 5)

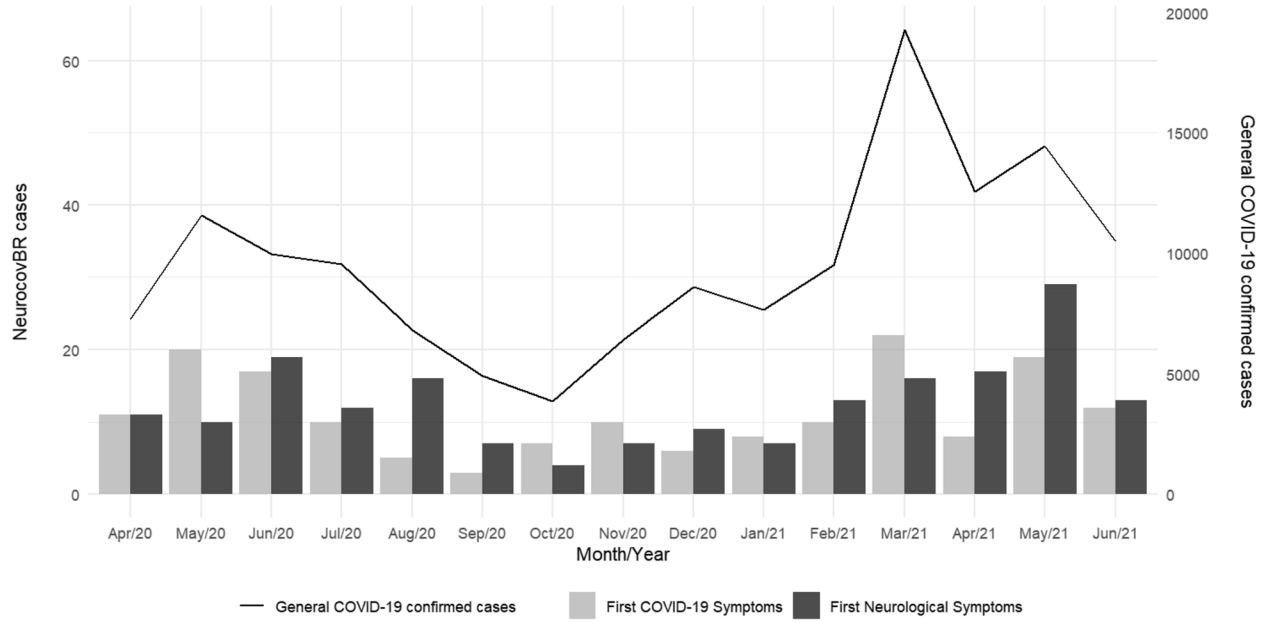

Fig. 2 Incidence of general COVID-19 confirmed cases* and incidence of COVID-19 and neurological symptoms in NeurocovBR. Legends: *Data from hospitalized COVID-19 patients

Table 4 Demography and outcomes comparisons between COVID-19 and NeurocovBR patients

	COVID-19	NeurocovBR	*p*	*OR*	COVID-19	NeurocovBR	*p*	*OR*
	all cases				**hospitalized patients**			
n	4,428,129	197			400,901	156		
Age, y, mean (± SD)	43.2 (± 15.9)	54.7 (± 15.9)	< 0.01		58 (± 16.6)	56 (± 15.6)	0.26	
Female, n, (%)	2,368,087 (53.4)	109 (55.3)	0.84	0.96	175,171 (43.7)	87 (55.8)	< 0.01	1.62
Hospitalizations, n, (%)	400,901 (9)	156 (79.2)	< 0.01	38.22	400,901 (100)	156 (100)		
Death, n, (%)	159,552 (3.6)	57 (28.9)	< 0.01	10.89	109,021 (30.3)	52 (33.3)	< 0.01	1.83

Legends: *OR* odds ratio, *SD* standard deviation

when compared with vascular patients negative for COVID-19.

Discussion

Our study corroborates the association of neurologic syndromes with COVID-19 in the early pandemics. Their incidence correlated with local waves of COVID-19 infection. Although their occurrence remained lower than that of respiratory tract infections, patients with neurocovid exhibited a higher susceptibility to adverse outcomes, as did hospitalized COVID-19 patients. Among all neurological syndromes, vascular syndromes were particularly prominent, and they were more severe than comparable vascular syndromes attributed to other well-known risk factors.

As in previous viral epidemics, like HIV, ZIKV, and CHIKV, the initial associated neurologic syndromes tended to manifest in a small subset of patients and mirror fluctuations in the incidence of the primary syndrome [15–21]. We observed here, similar to previous epidemics, an average two-week interval between the onset of infection and the emergence of neurologic symptoms. This is consistent with a disease mechanism likely associated with an inflammatory process [22]. The precise mechanism(s) for viral neuropathogenesis remains to be determined. In vivo viruses may circumvent anti-viral defense barriers, enter the bloodstream and by axonal transport reach the CNS and activate innate immune responses [23].

Considering that SARS-CoV-2 is transmitted primarily through respiratory droplets [24], a CNS invasion through the olfactory sensory nerves was the first hypothesis. This was influenced by the high incidence of anosmia and MRI studies demonstrating olfactory bulb and adjacent cortical alterations [25–27]. A deeper investigation into the olfactory bulb parenchyma, however,

Table 5 General stroke versus NeurocovBR stroke

	General Stroke [11]	NeurocovBR Stroke	*p*	*OR*
n, (%)	2407 (100)	81 (100)		
Age, mean (± SD)	67.6 (± 14.4)	59.5 (± 15.5)	< 0.01	_
Female, n (%)	1248 (51.8)	46 (56.8)	0.46	_
Comorbidities, n (%)				
HBP	2118 (88)	45 (51.1)	< 0.01	0.17
DM	1126 (46.8)	28 (31.8)	< 0.05	0.60
Smoker	736 (30.6)	15 (17)	< 0.05	0.51
Hospitalization, n, (%)				
Needed ICU	597 (24.8)	46 (56.8)	< 0.01	3.78
Δt hospitalization, d, mean (± SD)	15.4 (± 20.1)	18.7 (± 23)	0.20	_
In-hospital complications, n, (%)				
Co-infections	424 (17.6)	55 (67.9)	< 0.01	6.14
Outcomes				
Death, n, (%)	503 (20.9)	45 (55.6)	< 0.01	4.73

Legends: *OR* odds ratio, *HBP* high blood pressure, *DM* diabetes mellitus, *ICU* intensive care unit, *d* days

failed to identify SARS-CoV-2 RNA vestiges [28]. Surprisingly, analysis of the adjacent leptomeninges suggested not a classic neurotropism for the olfactory bulb, but possibly the CSF as a carrier for viruses present in the bloodstream or from a scaping of sustentacular cells of the olfactory mucosa, SARS-CoV-2 target cells [28].

In our population, encephalitis patients presented with the highest frequency of anosmia/hyposmia (31.6%). This led us to suggest an association between a high viral load near the olfactory bulb and viral encephalitis. This might also be a pathway for the initiation of other associated neurological syndromes, but it is not likely to be the predominant mechanism in all cases [22].

Evaluating the vascular cases, we observed a higher proportion of patients with recognized risk factors for stroke, such as HBP (51%), DM (31.8%), obesity (15.9%) and smoking (17%) [29, 30]. However, comparing those with non-COVID stroke patients and evaluating the majority of patients with NIHSS > 15 (therefore with large vessel stroke), we realized that SARS-CoV-2 probably exerted a substantial influence on the pathogenesis of these cases.

The median timeframe of 10 days between COVID-19 and vascular syndromes also suggests an underlying state of increasing immune system activation, initially associated with vascular wall inflammation. This hypothesis gains support from a previous study [31] that compared human autopsy specimens to rhesus macaques infected with SARS-CoV-2. Their study revealed a likely evolutionary cascade of inflammatory activation during a 14-day period, where the infection triggered the up-regulation of the inflammatory and complement pathways. This resulted in the initial intense recruitment of innate immune system components, leading to significant endotelitis [31].

This phenomenon would certainly justify the occurrence of small vessel vasculitis. But, it remains unclear, however, if it is enough to address the high proportion of large vessel strokes [32–34]. In thrombectomy reports, large vessels appeared normal, while pulmonary emboli and deep venous thrombosis were prevalent in many patients [32]. This underscores the consideration of paradoxical embolism as a significant possibility [32] and indicates that vasculitis is present and contributes to COVID-19 stroke, but probably through an indirect pathway.

Our general epidemiological findings on vascular syndromes align with those of large cohorts from the Americas, Europe, and Asia [35–40]. Similar to our study, these cohorts reported younger patients, a higher proportion of ischemic strokes (predominantly large-vessel strokes), and increased mortality rates with more co-infections when compared to stroke cases predating COVID-19. Unlike our study, which focuses on all neurological syndromes, those studies were specifically designed to examine vascular syndromes. As a result, they had the statistical power and appropriate methodology to investigate both traditional stroke risk factors and those associated with neuro-COVID. However, apart from atrial fibrillation, these factors do not appear to be the sole determinants of vascular syndromes in neurocovid, reinforcing the hypothesis that an underlying mechanism related to SARS-CoV-2, possibly inflammatory, is also involved.

Another consideration in favour of indirect inflammatory COVID-19 damage to the CNS is the large proportion of patients with encephalopathy. Patients referred to different studies as having brain fog, curiously, rarely present MRI alteration or CSF pleocytosis. However, their subacute cognitive impairment is evident [41]. In a previous report [42], we discussed the occurrence of such symptoms in several infectious and autoimmune diseases. Specifically, there is a possible influence of microglial monitoring [43], with aberrant synaptic pruning in inflammatory states such as in COVID-19, accompanied by massive complement recruitment. [43–45].

Surprisingly, neurologic syndromes occurred in our cohort regardless of COVID-19 severity. Nevertheless, it became evident in our study that neurocovid places a considerable burden on the healthcare system, increasing the demand for hospital beds and medical support. This is manifested by the considerably higher odds ratios for hospitalizations and death. Patients were

often hospitalized for more than 20 days, potentially in ICU settings. Furthermore, it is worth noting that surviving patients with high specific severity scores (mRS, GCS, LOS, NIHSS, ONLS) required an extended period of rehabilitation and faced a heightened risk of post-discharge mortality due to secondary complications [46–50].

A recurring challenge in large neurovirology cohorts, and thus a limitation, is the difficulty in gathering a sufficient number of subjects that meet appropriate criteria for statistical comparisons. Our cohort was no exception and faced the additional issue of non-consecutive inclusions due to asynchronous lockdown periods, shortage of personal protective equipment limiting neurologist assessments, and other pandemic restrictions. These conditions limited, for instance, our capability to perform subgroup analysis to statistically distinguish primary neurological effects of SARS-CoV-2 from complications secondary to systemic conditions, such as AKI, present in 40.6% of our sample.

To mitigate these limitations, however, we implemented rigorous inclusion criteria based on an experienced neurological evaluation, classified patients into strict syndromic categories, and included neurology centers from different states with different economic backgrounds, yet all allocated in the country's COVID-19 epicenters. We believe these measures approximate our findings from the actual numbers of neurological manifestations of COVID-19 in Brazil.

Conclusion

In conclusion, our findings illustrate the seriousness of COVID-19-associated neurologic syndromes, shedding light on how they intensify the burden on the healthcare system and may result in potential chronic, long-term consequences. The resemblance of certain data to that of previous viral epidemics underscores the need for establishing ongoing neurovigilance centers with the capacity for rapid national deployment. This will substantially aid in the formulation of timely recommendations to reduce mortality and disability.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10504-6.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

The NeurocovBR study group is composed by: MarianaSaconato, PhD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil, Coinvestigador. Jose Angelo L Lindoso,MD, PhD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Rosa PSFFerrarese,MD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Graziela ULDomingues,MSc,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. JaquesSztanjbok,MD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Michel EJHaziot,MD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Rene LMRivero,MD, PhD,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Lucio NABatista,Instituto de Infectologia Emilio Ribas,São Paulo, SP, Brazil,Coinvestigador. Cleonisio LRodrigues,MD, PhD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Isaac HMMaia, MD,Hospital Geral de FortalezaFortaleza, CE, Brazil,Coinvestigador. Norberto AFFrota,MD, PhD,Hospital Geral de FortalezaFortaleza, CE, Brazil,Coinvestigador. Daniele MLima,PhD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador, Fabricio OLima,MD, PhD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Felipe ARocha,MD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Tiago PFeijo,MD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Daniel GFTavora,MD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Karoline FMororo,MD,Hospital Geral de Fortaleza,Fortaleza, CE, Brazil,Coinvestigador. Francisco Silvanei SGonçalves,Hospital Geral de FortalezaFortaleza, CE, Brazil,Coinvestigador. Anderson VPaula,MSc,Universidade de Sao Paulo,São Paulo, SP, Brazil,Coinvestigador. Alvina ClaraFélix,MSc,Universidade de Sao Paulo,São Paulo, SP, Brazil,Coinvestigador. Caio SSouza,MSc,Universidade de Sao Paulo,São Paulo, SP, Brazil,Coinvestigador. Thais MRomano,MSc,Universidade Federal de Sao Paulo,São Paulo, SP, Brazil,Coinvestigador. Lorena SViana,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. GustavoBruniera,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. Marcel KUehara,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. Marcos VTFujino,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. Thiago DCorrea,MD, PhD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. Alcino ABarbosa, MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. FabianaHirata,MD, PhD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. IronDangoni ,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador. Natalia MAthayde,MD,Hospital Israelita Albert Einstein,São Paulo, SP, Brazil,Coinvestigador.

Authors' contributions

A.M.B.M., C.M.R. and A.C.P.O. contributed with study concept and design; A.M.B.M., A.B.F.G., F.M.M.C., F.T.M.O., L.S.A.S., F.E.D., J.V.L.M., M.V.F., J.E.V. R.M.N.M., J.S., V.R.P., R.M.M., C.M.R. and A.C.P.O. contributed to data acquisition; analysis and interpretation of data; all authors contributed with critical revision of the manuscript from important intellectual content.

Funding

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under the grant number 402794/2020–6 and Fundaçao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP) under the grant number 2020/05984–2.

Availability of data and materials

All data available regarding the patients reported in this study will be available to any qualified researcher upon pertinent request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study obtained approval from the ethics committee at the Universidade de São Paulo (CAAE: 31378820.1.1001.0068) and the ethics committees of the study sites. Written informed consent was obtained from all patients or their next of kin, and their personal information is protected by ethical procedures. The study adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as relevant Brazilian regulations.

Consent for publication

Not applicable.

Competing interests

Jorge Casseb is funded by Fundaçao de Amparo à Pesquisa do Estado de Sao Paulo (FAPESP) under grant number 2020/05984–2. Camila Malta Romano is

funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under grant number 402794/2020–6. There are no other conflicts of interest or other disclosures to report from the additional contributors involved in this study.

Author details
[1]Faculdade de Medicina, Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, SP, Brazil. [2]Hospital Geral de Fortaleza, Serviço de Neurologia, Fortaleza, CE, Brazil. [3]Graduate Program in Medical Sciences, Universidade de Fortaleza, Fortaleza, CE, Brazil. [4]Irmandade Santa Casa de Misericórdia, São Paulo, SP, Brazil. [5]Instituto de Infectologia Emilio Ribas, São Paulo, SP, Brazil. [6]Hospital Israelita Albert Einstein, São Paulo, SP, Brazil. [7]Faculdade de Medicina, Universidade de Brasília, Brasília, DF, Brazil. [8]Faculdade de Medicina, Hospital das Clinicas FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil.

Received: 21 October 2024 Accepted: 15 January 2025
Published online: 27 January 2025

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