

Publication status: Preprint has been published in a journal as an article DOI of the published article: Not informed

Neurological consultations and diagnoses in a large, dedicated COVID-19 university hospital

Adalberto Studart-Neto, Bruno Fukelmann Guedes, Raphael De Luca E Tuma, Antonio Edvan Camelo Filho, Gabriel Taricani Kubota, Bruno Diógenes Iepsen, Gabriela Pantaleão Moreira, Júlia Chartouni Rodrigues, Maíra Medeiros Honorato Ferrari, Rafael Bernhard Carra, Raphael Ribeiro Spera, Mariana Hiromi Manoel Oku, Sara Terrim, Cesar Castello Branco Lopes, Carlos Eduardo Borges Passos Neto, Matheus Dalben, Julia Carvalhinho Carlos De Souza, José Pedro Soares Baima, Tomás Fraga Ferreira Da Silva, Cristiane Araujo Martins Moreno, Andre Macedo Serafim Silva, Carlos Otto Heise, Rodrigo Holanda Mendonça, Ida Fortini, Jerusa Smid, Tarso Adoni, Marcia Rubia Rodrigues Gonçalves, Samira Luisa Apóstolos Pereira, Lecio Figueira Pinto, Helio Rodrigues Gomes, Edmar Zanotelli, Sonia Maria Dozzi Brucki, Adriana Bastos Conforto, Luiz Henrique Martins Castro, Ricardo Nitrini

https://doi.org/10.1590/0004-282X20200089

Submitted on: 2020-07-16

Posted on: 2020-07-16 (version 1)

(YYYY-MM-DD)

10.1590/0004-282X20200089

Original Article

Neurological consultations and diagnoses in a large, dedicated COVID-19 university hospital

Consultas neurológicas e diagnósticos em um grande hospital universitário dedicado a COVID-19

Adalberto STUDART-NETO^{1*} 0000-0003-2260-5986

Bruno Fukelmann GUEDES^{1*} 0000-0001-8391-21170

Raphael de LUCA E TUMA¹ 0000-0002-2100-5869

Antonio Edvan CAMELO FILHO¹ 0000-0002-1213-1687

Gabriel Taricani KUBOTA¹ 0000-0001-7790-8111

Bruno Diógenes IEPSEN¹ 0000-0002-6828-9600

Gabriela Pantaleão MOREIRA¹ 0000-0002-4482-5659

Júlia Chartouni RODRIGUES¹ 0000-0002-8121-7572

Maíra Medeiros Honorato FERRARI¹ 0000-0002-9504-4211

Rafael Bernhard CARRA¹ 0000-0001-6898-8455

Raphael Ribeiro SPERA¹ 0000-0003-3066-3457

Mariana Hiromi Manoel OKU¹ 0000-0003-3677-9100

Sara TERRIM¹ 0000-0001-8524-0705

Cesar Castello Branco LOPES¹ 0000-0002-5731-2553

Carlos Eduardo Borges PASSOS NETO¹ 0000-0001-6350-188X

Matheus DALBEN¹ 0000-0002-2996-9451

Julia Carvalhinho Carlos DE SOUZA¹ 0000-0002-2319-5037

José Pedro Soares BAIMA1 0000-0003-2708-1181

Tomás Fraga Ferreira DA SILVA¹ 0000-0003-3364-7540

Cristiane Araujo Martins MORENO¹ 0000-0002-5867-6359

Andre Macedo Serafim SILVA¹ 0000-0002-5792-5878

Carlos Otto HEISE¹ 0000-0003-3956-3073

Rodrigo Holanda MENDONÇA¹ 0000-0001-7520-3353

Ida FORTINI¹ 0000-0003-1084-340x

Jerusa SMID^{1,2} 0000-0001-9513-0964

Tarso ADONI^{1,3} 0000-0002-5008-2783

Marcia Rubia Rodrigues GONCALVES¹ 0000-0001-7819-4499

Samira Luisa Apóstolos PEREIRA¹ 0000-0003-3493-1199

Lecio Figueira PINTO¹ 0000-0002-2694-5120

Helio Rodrigues GOMES^{1,4} 0000-0003-4461-0305

Edmar ZANOTELLI¹ 0000-0002-4991-6760

Sonia Maria Dozzi BRUCKI¹ 0000-0002-8303-6732

Adriana Bastos CONFORTO¹ 0000-0001-7869-3490

Luiz Henrique Martins CASTRO¹ 0000-0003-1878-2012

Ricardo NITRINI¹ 0000-0002-5721-1525

¹Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Departamento de Neurologia, São Paulo SP, Brazil.

⁴Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Divisão de Laboratório Central, São Paulo SP, Brazil.

Correspondence: Ricardo Nitrini; E-mail: rnitrini@uol.com.br.

Conflicts of interest: There is no conflict of interests to declare.

Authors' contributions: Studart-Neto and Guedes: conceptualized the paper, collected data, participated in consensus meetings, analyzed data and wrote the initial draft. They contributed equally to the present work.

Tuma, Camelo Filho, Kubota, Iepsen, Moreira, Rodrigues, Ferrari, Carra, Spera, Oko, Lopes, Passos Neto, Dalben, de Souza, Baima, Ferreira da Silva, Moreno, Serafim Silva, Heise, Mendonça. Fortini, Smid, Adoni, Gonçalves, Pereira, Pinto, Gomes, Zanotelli, Brucki, Conforto, and Castro: collected data, participated in consensus meetings, reviewed the manuscript for important intellectual content.

²Instituto de Infectologia Emílio Ribas, São Paulo SP, Brazil.

³Hospital Sírio-Libanês, São Paulo SP, Brazil.

Nitrini: conceptualized the paper, participated in consensus meetings, wrote and reviewed the manuscript for intellectual content, supervised the study.

Received on June 18, 2020; Received in its final form on June 22, 2020; Accepted on June 22, 2020.

ABSTRACT

Background: More than one-third of COVID-19 patients present neurological symptoms ranging from anosmia to stroke and encephalopathy. Furthermore, pre-existing neurological conditions may require special treatment and may be associated with worse outcomes. Notwithstanding, the role of neurologists in COVID-19 is probably underrecognized. Objective: The aim of this study was to report the reasons for requesting neurological consultations by internists and intensivists in a COVID-19dedicated hospital. Methods: This retrospective study was carried out at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil, a 900-bed COVID-19 dedicated center (including 300 intensive care unit beds). COVID-19 diagnosis was confirmed by SARS-CoV-2-RT-PCR in nasal swabs. All inpatient neurology consultations between March 23rd and May 23rd, 2020 were analyzed. Neurologists performed the neurological exam, assessed all available data to diagnose the neurological condition, and requested additional tests deemed necessary. Difficult diagnoses were established in consensus meetings. After diagnosis, neurologists were involved in the treatment. Results: Neurological consultations were requested for 89 out of 1,208 (7.4%) inpatient COVID admissions during that period. Main neurological diagnoses included: encephalopathy (44.4%), stroke (16.7%), previous neurological diseases (9.0%), seizures (9.0%), neuromuscular disorders (5.6%), other acute brain lesions (3.4%), and other mild nonspecific symptoms (11.2%). Conclusions: Most neurological consultations in a COVID-19-dedicated hospital were requested for severe conditions that could have an impact on the outcome. First-line doctors should be able to recognize neurological symptoms; neurologists are important members of the medical team in COVID-19 hospital care.

Keywords: Coronavirus Infections; COVID-19; Neurology; Seizures; Stroke; Metabolic Encephalopathy; Neuromuscular Diseases.

RESUMO

Introdução: Mais de um terço dos pacientes com COVID-19 apresentam sintomas neurológicos que variam de anosmia a AVC e encefalopatia. Além disso, doenças neurológicas prévias podem exigir tratamento especial e estar associadas a piores desfechos. Não obstante, o papel dos neurologistas na COVID-19 é provavelmente pouco reconhecido. Objetivo: O objetivo deste estudo foi relatar os motivos para solicitar consultas neurológicas por clínicos e intensivistas em um hospital dedicado à COVID-19. Métodos: Estudo retrospectivo realizado no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil, um centro dedicado à COVID-19 com 900 leitos (incluindo 300 leitos para unidades de terapia intensiva). O diagnóstico de COVID-19 foi confirmado por SARS-CoV-2-RT-PCR em swabs nasais. Todas as interconsultas de neurologia hospitalar entre 23 de março e 23 de maio de 2020 foram analisadas. Os neurologistas realizaram o exame neurológico, avaliaram todos os dados disponíveis para diagnosticar a patologia neurológica e solicitaram exames adicionais conforme necessidade. Diagnósticos difíceis foram estabelecidos em reuniões de consenso. Após o diagnóstico, os neurologistas participaram da condução dos casos. Resultados: Foram solicitadas consultas neurológicas para 89 de 1.208 (7,4%) em pacientes internados por COVID-19 durante o período. Os principais diagnósticos neurológicos incluíram: encefalopatia (44,4%), acidente vascular cerebral (16,7%), doenças neurológicas prévias (9,0%), crises epilépticas (9,0%), transtornos neuromusculares (5,6%), outras lesões encefálicas agudas (3,4%) e outros sintomas leves inespecíficos (11,2%). Conclusões: A maioria das consultas neurológicas em um hospital dedicado à COVID-19 foi solicitada para condições graves que poderiam afetar o desfecho clínico. Os médicos na linha de frente devem ser capazes de reconhecer sintomas neurológicos. Os neurologistas são membros importantes da equipe médica no atendimento hospitalar à COVID-19.

Palavras-chave: Infecções por Coronavírus; COVID-19; Neurologia; Convulsões; Acidente Vascular Cerebral; Encefalopatias; Doenças Neuromusculares.

INTRODUCTION

In March 2020, the World Health Organization declared COVID-19 a pandemic disease with unknown consequences¹. As of mid-May 2020, there had been almost five million reported infections, and more than 300,000 deaths worldwide caused by SARS-CoV-2². Although COVID-19 was initially described as a mainly respiratory disease, accumulating evidence suggests neuropsychiatric complications play an important role in the disease^{3,4}. In a Chinese retrospective cohort, impaired consciousness was observed in 7.5% of COVID-19 patients, and in 14.8% of severe cases⁵. Neurological signs are almost ubiquitous in very severe COVID-19 patients, with agitation or positive CAM-ICU findings noted in over 65% of cases³. COVID-19 may also be complicated by encephalopathy, headache, and stroke.

Pre-existing neurological disease is associated with increased disease severity and poorer outcome in COVID-19⁶⁻⁸. Likewise, comorbid SARS-CoV-2 infection can lead to higher rates of disability in acute neurological patients⁹. There is also an emerging concern on the potential negative impact of COVID-19 in the management of chronic neurological diseases such as Parkinson's disease¹⁰ and epilepsy¹¹.

These issues underscore the importance of inpatient neurological evaluation and treatment during the pandemic. Neurology societies have highlighted the importance of reorganizing neurology consultation services for in- and outpatient clinics¹²⁻¹⁵. Although a few retrospective case series have described the occurrence of specific neurological symptoms and signs in COVID-19 patients³⁻⁵, we were not able to find systematic reports of the real-life experience of consulting neurologists, other than the anecdotal editorial by Bersano and Pantoni¹².

The objective of this study was to report the main reasons for requesting neurological consultations by internists and intensivists in a COVID-19 dedicated hospital and the frequency of individual neurological diagnoses in a real-life situation over a 60-day period.

METHODS

Study design and participants

In March 2020, the Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP) was designated a COVID-dedicated tertiary referral center, with 900 beds (including three hundred Intensive Care Units – ICU – beds). Since its reorganization, a team of seven neurologists and eight neurology residents was assigned to provide on-demand consultations exclusively for COVID-19 patients.

Patients with confirmed or suspected COVID-19 requiring hospitalization underwent SARS-CoV-2 RNA detection with throat swab real-time reverse transcription-polymerase chain reaction (RT-PCR). In high clinical suspicion PCR-negative cases, a repeat RT-PCR test was performed.

This retrospective study enrolled exclusively PCR-positive cases evaluated by the neurology inpatient consultation team between March 23rd and May 23rd, 2020. This is a real-life situation study: neurological consultations were requested at the discretion of each patient's attending physician.

Patient clinical evaluation included clinical examination, routine laboratory testing (blood cell count, biochemical analysis, liver and renal function tests, C-reactive protein, D-dimer, lactate dehydrogenase, creatine phosphokinase) and chest computed tomography (CT). Patients were divided into two groups based on the severity of the respiratory

symptoms (severe and non-severe). Severe respiratory symptoms were defined as respiratory insufficiency requiring mechanical ventilation.

For each case, the reason for requesting the neurological consultation and the final neurological diagnosis were recovered from the specialist consult electronic form. Neurological evaluation consisted of neurological examination and additional ancillary tests (brain CT, Magnetic Resonance Imaging – MRI, cerebrospinal fluid – CSF – analysis), requested at the neurologist's discretion.

Difficult diagnosis cases were presented in a consensus meeting with the Neurology Department staff at *Hospital das Clínicas*. In cases with two or more neurological diagnoses, the final diagnosis was that of the most severe condition, or of the more plausible cause for the condition (for example: in an encephalopathy due to a confirmed stroke, the final diagnosis was stroke). Neurological diagnoses were finally classified into four main groups: encephalopathy, cerebrovascular disease, epilepsy, and neuromuscular disease. A fifth group (named "others") included diagnoses not fitting in the four other groups (*i.e.*, headache, vertigo), including management or follow-up of pre-existing neurological conditions.

Statistical analysis

All analyses were performed with the Statistical Package for Social Sciences software, version 21.0 (SPSS, IBM Statistics, Chicago, IL, USA). Categorical variables were expressed as absolute and relative frequencies and compared using Pearson's χ^2 univariate analysis. All continuous variables were expressed as mean and standard deviations and compared with Student's *t*-test or Mann-Whitney test according to normality distribution. All tests were two-tailed. Statistical significance was accepted at p<0.05.

Standard protocol approvals

The institutional review board approved the investigation protocol, and waived the informed consent, since this was a retrospective study, and no patient had undergone an experimental intervention.

RESULTS

During the studied period, 1,208 patients with confirmed COVID-19 were admitted to the hospital and 89 neurological consultation requests were placed (7.4%). The number of neurological consultations rose from 0.3 consults/day in the first week, to 3.6/day in the last week, representing a twelve-fold increase (Figure 1).

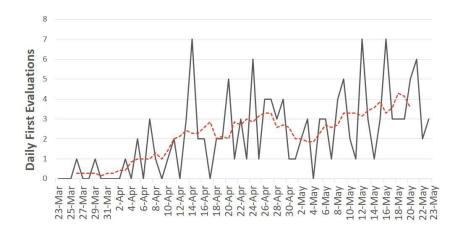


Figure 1. The solid line displays the number of patients who underwent initial neurological evaluation between March 23rd and May 23rd, 2020 at Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP). The dotted red line indicates the 7-day moving average. For any given day (D0), this number corresponds to the mean of all 7 values ranging from D-3 to D+3, and annotated on D0, and is therefore available from March 25th through May 21st.

Approximately half of the patients had severe respiratory conditions, requiring orotracheal intubation and mechanical ventilation (Table 1). Mean age of the 89 cases was 57.4+/-15.9 years, with no difference between groups; the majority of patients (61.8%) were men. Hypertension and *diabetes mellitus* were the most common comorbidities. The most prevalent typical symptoms of COVID-19 were fever, cough, and dyspnea. Anosmia and dysgeusia were rarely reported by patients. Thirty-nine patients (43.8%) had a previous neurological diagnosis (Table 1).

The main reasons for neurological consultation were: altered level of consciousness, muscle weakness, and psychomotor agitation. In eleven cases, the neurologist was called to assist in the management and follow-up of patients with pre-existing neurological diseases without acute neurological manifestations (Table 2). In some cases, two or more symptoms were reported by the clinician on neurological consultation requests. Main ancillary exams performed were brain CT (in 71 patients) and lumbar puncture (in 27 patients), while brain MRI was performed in only 15 patients (20.0%).

Table 1. Clinical features of patients with COVID-19 evaluated by the Neurology team between March 23rd and May 23rd, 2020 at Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP).

Characteristics	Nonsevere respiratory condition	Severe respiratory condition	Total	p-value	
Number of patients	44	45	89		
Age, mean (SD), y	57.7 (16.2)	56.9 (15.8)	57.4 (15.9)	0.811	
Gender					
Female	15 (34.1%)	19 (42.2%)	34 (38.2%)	0.515	
COVID-19 symptoms					
Fever	24 (60%)	33 (76.7%)	57 (68.7%)	0.155	
Cough	30 (75%)	29 (67.4%)	59 (71.1%)	0.478	
Dyspnea	22 (56.4%)	37 (84.1%)	59 (71.1%)	0.008	
Myalgia	5 (12.8%)	13 (29.5%)	18 (21.7%)	0.108	
Fatigue	15 (38.5%)	14(31.8%)	29 (34.9%)	0.645	
Diarrhea	5 (12.8%)	3 (6.8%)	8 (9.6%)	0.465	
Anosmia	3 (8.1%)	5 (11.4%)	8 (9.9%)	0.570	
Dysgeusia	0	3 (9.4%)	3 (4.8%)	0.135	
Comorbidities					
Hypertension	23 (59.0%)	28 (65.1%)	51 (62.2%)	0.651	
Diabetes	12 (30.8%)	19 (44.2%)	31 (37.8%)	0.257	

Table 2. Reason for Neurological Consultation in patients with COVID-19 between March 23rd and May 23rd, 2020 at Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP).

Symptom (reported by the internist)	Nonsevere respiratory condition	Severe respiratory condition	Total	p-value
Altered level of consciousness	17 (38.6%)	18 (40.0%)	35 (39.3%)	0.534
Psychomotor agitation	8 (18.2%)	4 (8.9%)	12 (13.5%)	0.166
Slow awakening from sedation	0	5 (11.1%)	5 (5.6%)	0.029
Focal neurological signs	2 (4.5%)	1 (2.2%)	3 (3.4%)	0.491
Muscle weakness	6 (13.6%)	10 (22.2%)	16 (18.0%)	0.219
Vertigo	1 (2.3%)	1 (2.2%)	2 (2.2%)	0.747
Headache	3 (6.8%)	0	3 (3.4%)	0.117
Seizure and transient changes in consciousness	3 (6.8%)	4 (8.9%)	7 (7.9%)	0.513
Seizure in epileptic patient	4 (9.1%)	1 (2.2%)	5 (5.6%)	0.173
Movement disorder*	2 (4.5%)	4 (8.9%)	6 (6.7%)	0.349
Management or follow-up of pre- existing neurological disease	6 (13.6%)	5 (11.1%)	11 (12.4%)	0.484

^{*}Myoclonus, nonspecific psychomotor agitation.

The most prevalent diagnoses were delirium/encephalopathy, stroke, previous neurological diseases, seizures, neuromuscular disorders, other acute brain lesions, as well as other mild nonspecific symptoms (Table 3 and Figure 2).

Associations between some reasons for neurological consultation requested by the internist and the final diagnoses established by the neurologist were found: altered level of consciousness correlated with encephalopathy, muscle weakness with cerebrovascular disease, seizure and transient changes in consciousness with epilepsy (Table 4).

Table 3. Final neurological diagnoses of COVID-19 patients evaluated by the Neurology team between March 23rd and May 23rd, 2020 at Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP).

Neurological diagnosis	Nonsevere respiratory condition	Severe respiratory condition	Total
Diffuse encephalopathy	20 (45.5%)	20 (44.4%)	40 (44.4%)
Stroke	5 (11.4%)	6 (13.3%)	11 (12.3%)
Cerebral venous thrombosis	1 (2.3%)	1 (2.2%)	2 (2.2%)
Intracranial hemorrhage	1 (2.3%)	1 (2.2%)	2 (2.2%)
Acute non-vascular structural encephalic lesions*	1 (2.3%)	2 (4.4%)	3 (3.4%)
Seizure in epileptic patient	2 (4.5%)	2 (4.4%)	4 (4.5%)
Acute symptomatic or provoked seizure	2 (4.5%)	2 (4.4%)	4 (4.5%)
Peripheral neuropathy	0	3 (6.7%)	3 (3.4%)
Rhabdomyolysis	2 (4.5%)	0	2 (2.2%)
Pre-existing neurological disease	4 (9.1%)	4 (8.9%)	8 (9.0%)
Others**	6 (13.6%)	4 (8.9%)	10 (11.2%)

^{*}Wernicke encephalopathy and central pontine myelinolysis (01 case), acute disseminated encephalomyelitis (01 case), and Posterior Reversible Encephalopathy Syndrome (01 case).

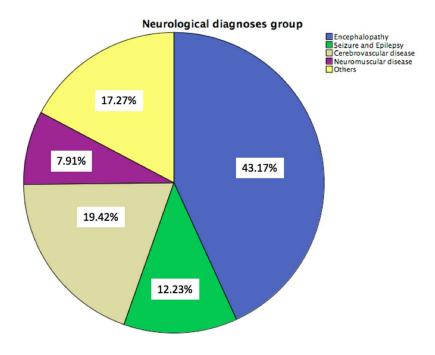


Figure 2. Graphic distribution of neurological diagnoses by disease group in the period between March 23rd and May 23rd, 2020 at Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil (ICHC-HCFMUSP). Group "Others" included "management or follow-up of previous neurological disease", headache, vertigo, syncope, somatoform disorder, and primary psychosis.

Table 4. Association between reason for neurological consultation and final diagnosis by disease group.

	Final diagnosis by disease group				p-value	
Reason for Neurological consultation	Encephalopathy	Seizure and Epilepsy	Cerebrovascular disease	Neuromuscular disorder	Others	
Altered level of consciousness	28 (80.0%)	1 (2.9%)	4 (11.4%)	1 (2.9%)	1 (2.9%)	<0.001
Psychomotor agitation	7 (58.3%)	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	0.925
Slow awakening from sedation	4 (80.0%)	0	1 (20.0%)	0	0	0.562
Focal neurological signal	1 (33.3%)	0	2 (13.3%)	0	0	0.215
Muscle weakness	3 (18.8%)	0	7 (43.8%)	5 (31.3%)	1 (6.3%)	<0.001
Vertigo	0	0	1 (50.0%)	0	1 (50.0%)	0.403
Headache	0	0	0	0	3 (100%)	0.004
Seizure and transient changes in consciousness	4 (57.1%)	3 (42.9%)	0	0	0	0.011
Seizure in epileptic patient	0	4 (80.0%)	0	0	1 (20.0%)	<0.001
Movement Disorder	4 (66.7%)	0	1 (16.7%)	0	1 (16.7%)	0.808
Management or follow-up of pre-existing neurological disease	3 (27.3%)	0	1 (9.1%)	2 (18.2%)	5 (45.5%)	0.001

DISCUSSION

In this study, 89 neurological consults were analyzed, requested among 1,208 COVID-19 patients admitted to a single University-based tertiary referral hospital dedicated to severe COVID-19 patient care (7.4% of total cases). In this setting, patients were evaluated by neurologists with the same training; more difficult cases were discussed in a weekly consensus meeting with the neurology department staff.

More than half of these complications (65.1%) were severe or potentially severe, consisting of encephalopathy, acute cerebrovascular disease, and non-vascular acute encephalic lesions, some of which can cause serious neurological sequelae. These

severe complications were seen both in patients who required mechanical ventilation and in those with less severe degrees of the disease.

In the early stage of the COVID-19 pandemic, Mao et al. reported the occurrence of neurological manifestations in 214 patients admitted to three COVID-19 dedicated hospitals in Wuhan, China⁵. In a retrospective analysis of medical records, the authors found that 78 (36.4%) of the patients had central or peripheral nervous system involvement. Manifestations ranged from mild, such as anosmia and headache, to stroke and encephalopathy. Although the reported frequency in the Wuhan study was high, severe central nervous system (CNS) diagnoses (acute cerebrovascular diseases and impaired consciousness) were reported in 28.2% of these 78 patients.

Another study applying a similar methodology to that used in Wuhan⁵ found neurological manifestations in 512 (57.4%) of 841 patients in two COVID-19 hospitals in Spain⁴. Severe manifestations of CNS involvement, using the same disease categorization used in the present study, were described in 36.5% of the cases⁴.

In an observational case series, Helms et al. recorded neurological manifestations in 58 consecutive patients admitted to the hospital due to COVID-19-related acute respiratory distress syndrome, in Strasbourg, France. All patients were treated in ICUs. Agitation was noted in 69% of the patients when neuromuscular blockade was discontinued. Diffuse corticospinal tract signs were observed in 67% of patients. The severity of the neurological manifestation in these cases with acute respiratory failure was even higher than in our sample³.

The lower frequency and the greater severity of neurological involvement that we found were most likely due to case ascertainment, similarly to the real-life situation, in which neurologists are called to evaluate patients who present signs or symptoms that concern internists or intensivists. Therefore, a bias toward potentially more serious and, therefore, less frequent manifestations was present in our study.

Our data also revealed that neurological manifestations are frequent both in cases that required mechanical ventilation, as well as in less severe ones. The fact that more serious neurological conditions, such as stroke and encephalopathy, were equally frequent in more and in less severe patient groups was unexpected.

Neurological manifestations in COVID-19 can be due to indirect nervous system involvement resulting from systemic diseases, such as hypoxia, uremia, coagulopathy, and critical care neuropathy, due to the invasion of the CNS by SARS-CoV-2, or caused by other mechanisms such as inflammatory and immune-mediated (including post-infectious) reactions.

Factors that support an indirect (systemic) mechanism for neurological complications of SARS-COV2 infection, such as encephalopathy, are the absence of SARS-CoV2 genetic material in the CSF, and the lack of signs of brain involvement on neuroimaging (CT and MRI) in the vast majority of cases in which these tests were obtained ¹⁶. More recently, postmortem pathological examination of brain specimens obtained from 18 patients who died from COVID-19 failed to demonstrate inflammatory changes indicative of encephalitis or changes related to a direct viral effect and disclosed only hypoxic changes ¹⁷.

On the other hand, case reports and small case series provided evidence of direct CNS involvement in COVID-19 infection. Moriguchi et al., in Japan, reported a meningoencephalitis case with medial temporal lobe lesions on MRI, in which SARS-CoV-2 was detected in the CSF by RT-PCR¹⁸. In the previously cited study by Helms et al., leptomeningeal enhancement was noted on MRI in 8/13 patients, and bilateral frontotemporal hypoperfusion was noted in all 11 patients who underwent perfusion MRI³. In another report, MRI showed a subtle hyperintensity in the olfactory bulbs and cortical hyperintensity in the right gyrus rectus, consistent with local invasion and direct brain parenchymal lesion by SARS-CoV-2 in a case with anosmia¹⁹. Most remarkable was the documented finding of the presence of SARS-CoV-2 in neurons and endothelial cells in the frontal lobe of a case of COVID-19 on electronic microscopy, which was confirmed by detection of SARS-CoV-2 genetic material in the brain with RT-PCR²⁰. In that case, PCR for SARS-CoV-2 was negative in the CSF.

SARS-CoV-2 encephalopathy may be also caused by acute necrotizing encephalopathy^{21,22} and encephalitis related to an exaggerated inflammatory reaction in the CNS, with high cytokine and other inflammatory mediators levels in the CSF^{23,24}, probably related to a hyperinflammatory systemic reaction against SARS-CoV-2, with a breakdown of the blood-brain barrier. Alternatively, encephalitis may be caused by a

CNS-specific inflammatory response^{23,24}. Acute disseminated encephalomyelitis (ADEM) has been reported in SARS-CoV-2 patients, indicating a probable virally triggered immune-mediated mechanism leading to CNS inflammatory lesions^{25,26}.

In our study, the occurrence of neurological manifestations in cases with less severe COVID-19 systemic disease, may indicate that neurological symptoms, at least in part of our cases, occurred regardless of systemic involvement, and that neurological symptoms are probably due to heterogeneous causes. Further studies are needed to elucidate the precise mechanism underlying the neurological manifestations of SARS-CoV-2²⁷, which will contribute to the development of more rational therapeutic interventions and, possibly, reduce the severity of the impact of SARS-CoV-2 in the nervous system.

The limitations of our study are those of a retrospective study. The history of COVID-19 pre-admission symptoms and neurological symptoms, for instance, was frequently obtained from relatives of critically ill or confused patients and could be prone to recall bias. Some potentially relevant clinical and demographical information, such as the prevalence of obesity or angiotensin-converting enzyme inhibitors, were not available. Our patient population originated from neurology consultation requested by internists, which corresponds to 7.4% of the total COVID-19 population in our hospital. This makes our study inadequate to evaluate the total prevalence of specific signs and diagnoses in the general COVID-19 population. Perception of the need for a neurological evaluation, especially in severely ill patients, may have varied among different medical teams. Of note, the daily number of requests for neurological consultations increased along the study period, probably reflecting an increased awareness of the frequency and severity of neurological manifestations of SARS-CoV-2 infection, as well as of the importance of neurology specialized care for this patient population. Like all studies carried out in COVID-19 dedicated hospitals, there were restrictions on the availability of MRI, CT, electroencephalography, CSF, electroneuromyography, and neuropathological examinations. Also, the purpose of this work was not to evaluate the details of each case to establish the pathophysiology of stroke, encephalopathy, seizures, and other neurological conditions, which we intend to do in forthcoming manuscripts. Along the same lines, neuroimaging and CSF findings are also being prepared for future communications.

The main conclusions of this study are:

- Severe neurological complications that require neurologist interventions are relatively common in COVID-19 patients.
- These complications are equally frequent in patients with severe respiratory failure, who require respiratory assistance, and less severely ill patients, without significant respiratory symptoms.
- Neurologists should be part of the medical team of COVID-19 in dedicated hospitals, and internists must be trained to recognize signs of neurological complications and to appropriately request neurology consultations in such cases.

Future studies are needed to further understand the pathophysiology of nervous system manifestations in SARS-CoV-2 patients, so that more effective therapeutic interventions can be implemented to prevent and minimize severe neurological complications.

References

- Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ. 2020 Mar;368:m1036. https://doi.org/10.1136/bmj.m1036
- 2. Johns Hopkins University & Medicine. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available from: coronavirus.jhu.edu/map.html.
- Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020 Jun;382(23):2268-70. https://doi.org/10.1056/NEJMc2008597
- Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology. 2020 Jun. https://doi.org/10.1212/WNL.0000000000009937
- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr;77(6):683-90. https://doi.org/10.1001/jamaneurol.2020.1127

- Aggarwal G, Lippi G, Henry BM. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19):
 A pooled analysis of published literature. Int J Stroke. 2020 Jun;15(4):385-9.
 https://doi.org/10.1177/1747493020921664
- 7. Yin R, Yang Z, Wei Y, Li Y, Chen H, Liu Z, et al. Clinical characteristics of 106 patients with neurological diseases and co-morbid coronavirus disease 2019: a retrospective study. medRxiv. 2020.04.29.20085415. https://doi.org/10.1101/2020.04.29.20085415
- Pranata R, Huang I, Lim MA, Wahjoepramono PEJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis.
 2020 May;29(8):104949. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104949
- Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology. 2020 May; 10.1212/WNL.0000000000009848. https://doi.org/10.1212/WNL.0000000000000009848
- 10. Bhidayasiri R, Virameteekul S, Kim J-M, Pal PK, Chung S-J. COVID-19: an early review of its global impact and considerations for Parkinson's disease patient care. J Mov Disord. 2020 Apr;13(2):105-14. https://doi.org/10.14802/jmd.20042
- 11. Kuroda N. Epilepsy and COVID-19: Associations and important considerations. Epilepsy Behav. 2020 Apr;108(2020):107122. https://doi.org/10.1016/j.yebeh.2020.107122
- 12. Bersano A, Pantoni L. On being a neurologist in Italy at the time of the COVID-19 outbreak. Neurology. Neurology. 2020 May;94(21):905-6. https://doi.org/10.1212/WNL.0000000000000508
- 13. Majersik JJ, Reddy VK. Acute neurology during the COVID-19 pandemic: Supporting the front line. Neurology. 2020 Jun;94(24):1055-7. https://doi.org/10.1212/WNL.00000000000009564

- 14. Sellner J, Taba P, Öztürk S, Helbok R. The need for neurologists in the care of COVID-19 patients. Eur J Neurol. 2020 Apr. https://doi.org/10.1111/ene.14257
- 15. Rubin MA, Bonnie RJ, Epstein L, Hemphill C, Kirschen M, Lewis A, et al. AAN position statement: The COVID-19 pandemic and the ethical duties of the neurologist. Neurology. 2020 May;10.1212/WNL.000000000009744. https://doi.org/10.1212/WNL.000000000000009744
- 16. Radmanesh A, Raz E, Zan E, Derman A, Kaminetzky M. Brain imaging use and findings in COVID-19: A single academic center experience in the epicenter of disease in the United States. AJNR Am J Neuroradiol. 2020 May. https://doi.org/10.3174/ajnr.A6610
- 17. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. N Engl J Med. 2020 Jun. https://doi.org/10.1056/NEJMc2019373
- 18. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020 Mar;94(2020):55-58. https://doi.org/10.1016/j.ijid.2020.03.062
- 19. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. JAMA Neurol. 2020 May. https://doi.org/10.1001/jamaneurol.2020.2125
- 20. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020 Jul;92(7):699-702. https://doi.org/10.1002/jmv.25915
- 21. Dixon L, Varley J, Gontsarova A, Mallon D, Tona F, Muir D, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. Neurol Neuroimmunol Neuroinflamm. 2020 May;7(5):e789. https://doi.org/10.1212/NXI.000000000000000789
- 22. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute hemorrhagic necrotizing encephalopathy: CT and MRI Features. Radiology. 2020 Mar:201187. https://doi.org/10.1148/radiol.2020201187

- 23. Bernard-Valnet R, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. Eur J Neurol. 2020 Mar. https://doi.org/10.1111/ene.14298
- 24. Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. Ann Neurol. 2020 May. https://doi.org/10.1002/ana.25783
- 25. Novi G, Rossi T, Pedemonte E, Saitta L, Rolla C, Roccatagliata L, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. Neurol Neuroimmunol Neuroinflamm. 2020 Jun;7(5):e797. https://doi.org/10.1212/NXI.0000000000000797
- 26. Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020 May. https://doi.org/10.1007/s00415-020-09951-9
- 27. Munhoz RP, Pedroso JL, Nascimento FA, Almeida SM, Barsottini OGP, Cardoso FEC, et al. Neurological complications in patients with SARS-CoV-2 infection: a systematic review. Arq Neuropsiquiatr. 2020 Mat;78(5):290-300. https://doi.org/10.1590/0004-282x20200051

This preprint was submitted under the following conditions:

- The authors declare that they are aware that they are solely responsible for the content of the preprint and that the deposit in SciELO Preprints does not mean any commitment on the part of SciELO, except its preservation and dissemination.
- The authors declare that the necessary Terms of Free and Informed Consent of participants or patients in the research were obtained and are described in the manuscript, when applicable.
- The authors declare that the preparation of the manuscript followed the ethical norms of scientific communication.
- The authors declare that the data, applications, and other content underlying the manuscript are referenced.
- The deposited manuscript is in PDF format.
- The authors declare that the research that originated the manuscript followed good ethical practices and that the necessary approvals from research ethics committees, when applicable, are described in the manuscript.
- The authors declare that once a manuscript is posted on the SciELO Preprints server, it can only be taken down on request to the SciELO Preprints server Editorial Secretariat, who will post a retraction notice in its place.
- The authors agree that the approved manuscript will be made available under a <u>Creative Commons CC-BY</u> license.
- The submitting author declares that the contributions of all authors and conflict of interest statement are included explicitly and in specific sections of the manuscript.
- The authors declare that the manuscript was not deposited and/or previously made available on another preprint server or published by a journal.
- If the manuscript is being reviewed or being prepared for publishing but not yet published by a journal, the authors declare that they have received authorization from the journal to make this deposit.
- The submitting author declares that all authors of the manuscript agree with the submission to SciELO Preprints.