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ORIGINAL ARTICLE

Neurological complications of COVID-19 in hospitalized patients: The registry of a neurology department in the first wave of the pandemic

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Abstract

Objective: To describe the spectrum of neurological complications observed in a hospital-based cohort of COVID-19 patients who required a neurological assessment.

Methods: We conducted an observational, monocentric, prospective study of patients with a COVID-19 diagnosis hospitalized during the 3-month period of the first wave of the COVID-19 pandemic in a tertiary hospital in Madrid (Spain). We describe the neurological diagnoses that arose after the onset of COVID-19 symptoms. These diagnoses could be divided into different groups.

Results: Only 71 (2.6%) of 2750 hospitalized patients suffered at least one neurological complication (77 different neurological diagnoses in total) during the timeframe of the study. The most common diagnoses were neuromuscular disorders (33.7%), cerebrovascular diseases (CVDs) (27.3%), acute encephalopathy (19.4%), seizures (7.8%), and miscellanea (11.6%) comprising hiccups, myoclonic tremor, Horner syndrome and transverse myelitis. CVDs and encephalopathy were common in the early phase of the COVID-19 pandemic compared to neuromuscular disorders, which usually appeared later on (p = 0.005). Cerebrospinal fluid severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction was negative in 15/15 samples. The mortality was higher in the CVD group (38.1% vs. 8.9%; p = 0.05).

Conclusions: The prevalence of neurological complications is low in patients hospitalized for COVID-19. Different mechanisms appear to be involved in these complications, and there was no evidence of direct invasion of the nervous system in our cohort. Some of the neurological complications can be classified into early and late neurological complications of COVID-19, as they occurred at different times following the onset of COVID-19 symptoms.

KEYWORDS
COVID-19, neurological complications, SARS-CoV-2

INTRODUCTION

Cases of pneumonia caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first reported in Wuhan (China) in December 2019.[1] These were followed by rapid spread of the related infectious disease known as coronavirus disease 2019 (COVID-19) around the world, and the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020.[2]

By 1 August 2020, a total of 17,396,943 cases of COVID-19 and 675,060 deaths had been reported worldwide.[3] In Spain, COVID-19 spread throughout the country after the first imported case was reported at the end of February 2020 in Madrid.

This new SARS-CoV-2 has been classified in the betacoronavirus genus along with severe acute respiratory syndrome coronavirus (SARS-CoV, 2002) and Middle East Respiratory Syndrome (MERS, 2012), among others. Neurological complications have been reported in association with SARS and MERS, including central nervous system (CNS) complications and neuromuscular disorders.[4–7] Similarly to its SARS-CoV and MERS infection predecessors, SARS-CoV-2 infection has been associated with possible pathogenic processes in the nervous system.[8]

The first reports of neurological manifestations associated with COVID-19 in hospitalized patients included non-specific symptoms such as myalgia, dizziness, and headache as the most common neurological features.[9,10] In other series of patients, severe SARS-CoV-2 infection has been shown to be associated with encephalopathy and corticospinal tract signs.[11] Cerebrovascular disease (CVD) has also been reported with severe COVID-19.[12] As the pandemic progressed, other neurological complications have been described such as acute necrotizing encephalopathy,[13] acute necrotizing myelitis,[14] Guillain-Barré syndrome (GBS),[15] and other para-/post-infectious complications such as encephalitis.[16] Anosmia and dysgeusia are common in the early phase of the disease.[17]

The pathogenesis of these neurological manifestations and complications has not yet been elucidated. Limited access to proper neurological assessments and diagnostic procedures could have led to the possible neurological complications being overlooked or misjudged during the peak of the COVID-19 pandemic.

In order to obtain a better understanding of the neurological symptoms associated with SARS-CoV-2 infection, we here describe the spectrum of neurological complications observed in a hospital-based cohort of COVID-19 patients who required a formal neurological assessment.

METHODS

To evaluate the possible neurological complications of SARS-CoV-2 infection we generated a prospective registry of patients admitted to the COVID-19 wards and the intensive care unit (ICU) at the Hospital General Universitario Gregorio Marañón (Madrid, Spain) and who had been referred to the neurology department. In this survey, we considered consecutive patients registered from 7 March to 7 June 2020. Patients were recruited at the time that they were referred to the neurology department. The inclusion criteria comprised being an adult; a confirmed or probable COVID-19 diagnosis, and new onset of neurological symptoms. Patients with a previous neurological disease or condition that could either in part or fully explain the new neurological symptoms were excluded.

We extracted the personal history, demographic data, COVID-19 non-neurological symptoms, and the first ancillary tests results of every patient from the electronic medical records.

The diagnoses of COVID-19 were confirmed by the presence of SARS-CoV-2 RNA in real-time reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or of bronchoalveolar lavage fluid. Probable diagnoses of COVID-19 were established based on radiological criteria and analytical parameters according to the WHO classification.[18]

The COVID-19 treatments were also documented for every patient.

The severity of the disease was established according to clinical (severe hypoxemia: partial pressure arterial oxygen and fraction of inspired oxygen [PaO2:FiO2] ratio < 300 mmHg), laboratory (D-dimer, C-reactive protein, ferritin, interleukin-6 levels), or radiological (bilateral pneumonia) prognostic factors on admission to the COVID-19 ward.

The time from the onset of COVID-19 symptoms to the manifestation of neurological symptoms was recorded.

We also evaluated the complementary test results after neurological assessments comprising cerebrospinal fluid (CSF) analysis, neurologic radiological examinations (brain computed tomography [CT], computed tomography angiography [CTA], and brain magnetic resonance imaging [MRI]), and neurophysiology testing (electromyography [EMG] and electroencephalography [EEG]).

The clinical outcome was evaluated after 1–4 months of follow-up.

The patients were managed according to the standards of care in our hospital during the ongoing COVID-19 pandemic. Our study received approval from the Ethics Committee for Research with Medicines of the Hospital General Universitario Gregorio Marañón.

Details of some of the patients have been submitted for publication as case reports by their treating physicians.

Statistical analysis

The statistical analysis was performed using the SPSS® (Statistical Package for the Social Sciences) software, version 26. The categorical variables are reported as the number of cases and percentages. The continuous variables are expressed as medians and ranges. The ratios were compared using Chi-squared or Fisher's exact tests. The quantitative variables were compared using non-parametric tests (Mann–Whitney *U*, Kruskal–Wallis, or Wilcoxon test).

A p value <0.05 was considered statistically significant. Multiple comparisons were applied in cases of more than two quantitative variables and a p value <0.05.

RESULTS

During the 3-month period of the first wave of the pandemic in Spain 2750 COVID-19 patients were admitted to the Hospital General Universitario Gregorio Marañón (Madrid, Spain).

Seventy-one patients (2.6%) met the study requirements and were included in the survey. Six of them received two different neurological diagnoses. Their demographic and clinical characteristics are shown in Table 1.

Thirteen of these patients (18.3%) were admitted to the ICU, and 12 patients (16.9%) died during the follow-up period.

Seventy-seven neurological complications were recorded. The time between when the COVID-19 symptoms started to the development of neurological symptoms ranged from 0 days (coincidence of the SARS-CoV-2 diagnosis and the manifestation of neurological symptoms) to 60 days, with a median of 13 (range 0, 60) days.

The presence of concomitant hyposmia or dysgeusia was investigated, and it was only documented in three patients (4.2%).

Based on the clinical, neurophysiological, neuroradiological, and laboratory features, the neurological complications associated with COVID-19 were classified into five categories: neuromuscular disorders, cerebrovascular diseases, encephalopathy, seizures, and miscellaneous issues. The main clinical features of the different categories are summarized in Table 2.

TABLE 1 Baseline characteristics of 71 patients with neurological complications

Characteristic	Patients (n = 71)
Age (yr), median (range)	69 (23, 91)
Sex male, *n* (%)	50 (70.4%)
Comorbidities, *n* (%)	
Hypertension	40 (56.3%)
Dyslipidaemia	27 (38%)
Diabetes mellitus	25 (35.2%)
Obesity	5 (7%)
Heart disease	12 (16.9%)
Previous treatment, *n* (%)	
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	26 (36.6%)
Immunosuppressant	3 (4.2%)
SARS-CoV-2 RT-PCR positive result, *n* (%)	58 (81.7%)
Chest radiography, *n* (%)	
Normal	9 (12.7%)
Unilateral pneumonia	6 (8.5%)
Bilateral pneumonia	56 (78.9%)
Blood test at admission, median (range)	
Lymphocyte count	0.9 (0.3, 4)
D-dimer (ng/ml)	567 (75, 23120)
Creatine kinase (CK) (U/L)	111 (18, 15478)
Lactate dehydrogenase (LDH) (U/L)	279.50 (167, 1273)
C-reactive protein (mg/dl)	6.9 (0.4, 32.2)
Ferritin (ng/ml)[a]	866 (21, 7851)
Interleukin-6(IL-6) (pg/ml)[b]	25.1 (2.1, 1037)
COVID-19 treatment, *n* (%)	65 (91.5%)
Lopinavir/ritonavir	54 (76.1%)
Hydroxychloroquine	63 (88.1%)
Azithromycin	25 (35.2%)
Corticosteroids	37 (52.1%)
Tocilizumab	18 (25.4%)

Abbreviations: RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Available in 46 patients.

[b]Available in 23 patients.

Neuromuscular disorders

Twenty-six patients (33.7%) experienced neuromuscular complications. This group of patients was younger than the rest of the cohort (60 vs. 69 years; p = 0.05), and the median time between the onset of COVID-19 symptoms and the manifestation of neurological symptoms was 23 (range 0, 60) days, which was longer (23 vs. 13 days; p = 0.002) than the time for the rest of the cohort. The main characteristics of the patients with neuromuscular complications are summarized in Table S1.

The most common diagnosis was *critical illness polyneuropathy (CIP) and critical illness myopathy (CIM)*, which were diagnosed in 12 patients (46.1%). All of them required mechanical ventilation and they remained in the ICU for a median of 38.5 (range 15, 83) days. The creatine kinase (CK) levels recorded at the time of admission were higher compared to the rest of the sample (185.5 vs. 111 U/L; p = 0.033). Neurophysiological studies revealed that a myopathic pattern was the most common. Eleven patients received neuromuscular blocking agents (NMBAs), and corticosteroids were used more in this group than in the rest of the cohort (11 [91.2%] vs. 31 [47.7%] patients; p = 0.005).

Six patients had *non-cranial mononeuropathies* (three peroneal nerve palsy, two cubital nerve palsy, and one femoral cutaneous meralgia paresthetica). No other issues were found after a complete neurological examination, suggesting possible pressure palsy in the context of immobilization due to the prolonged admission and weight loss.

Three patients were diagnosed with *acute inflammatory polyneuropathies*, including a case of classical GBS and two variants: isolated facial diplegia (FDi) and the pharyngeal-cervical-brachial variant (PCB). At the time of the onset of the neurological symptoms, three patients had experienced a partial or total recovery of

TABLE 2 Summary of main clinical characteristic of 77 neurological complications

Cases	Age (yr)Median (range) Male, *n* (%)	Time from onset to neurological symptoms in days Median (range)	Percentage bilateral pneumonia in chest X-ray *n* (%)	Nasopharyngeal or bronchoalveolar SARS-CoV-2 PCR+ *n* (%)	CSF SARS-CoV-2 PCR+ (x/number tested)	Poor prognostic factor at admission *n* (%)	Death *n* (%)
Neuromuscular disorders (*n* = 26)	60 (23, 91) 21, 80.8%	23 (0, 60)	22 (84.6%)	23 (88.5%)	0/5	20 (76.9%)	2 (2.7%)
Cerebrovascular disease (*n* = 21)	70 (30, 90) 14 (66.7%)	5 (0, 53)	15 (71.4%)	16 (76.2%)	0/1	13 (61.9%)	8 (38.1%)
Encephalopathy (*n* = 15)	74, (58, 87) 10 (66.7%)	10 (0, 57)	11 (73.3%)	13 (86.7%)	0/5	8 (53.3%)	1 (6.7%)
Seizures (*n* = 6)	77 [57, 89] 3 (50%)	5 [0, 43]	4 (66.7%)	5 (83.3%)	0/3	5 (83.3%)	1 (16.7%)
Hiccups (*n* = 6)	55.5 (26, 84) 6 (100%)	17 (10, 35)	6 (100%)	5 (83.3%)	NT	3 (50%)	0
Myoclonic tremor (*n* = 1)	69 1 (100%)	45	1 (100%)	1 (100%)	NT	1(100%)	0
Horner syndrome (*n* = 1)	52 0 (0%)	30	1 (100%)	0 (0%)	NT	0 (0%)	0
Transverse myelitis (*n* = 1)	56 0 (0%)	15	1 (100%)	1 (100%)	0/1	1 (100%)	1 (100%)

Abbreviations: CSF, cerebrospinal fluid; NT, not tested; PCR+, positive polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the respiratory symptoms and two patients were already positive for immunoglobulin G (IgG) antibodies against SARS-CoV-2. The patient with classical GBS had antiganglioside antibodies (GM-1 immunoglobulin M and GD-1 immunoglobulin G) in their serum. One week after therapy, the neurological symptoms had significantly improved, with nearly complete neurological recovery in the classical GBS case and the FDi variant.

Three patients were diagnosed with *brachial plexopathies*. In one patient, a diagnosis of traumatic brachial plexopathy was made at the time of admission, which was associated with trauma as a result of syncope on the same day that the respiratory symptoms started. The two remaining patients developed weakness after being placed in a prone position to reduce their respiratory distress.

Finally, two patients developed *cranial mononeuropathies* (trochlear nerve palsy and facial palsy) in the early stage of the disease. In both cases the respiratory symptoms were mild. The neuroimaging evaluations were normal. Corticosteroids were started in the patient with facial palsy. One week after the start of the neurological symptoms, total recovery was noted in the trochlear palsy case and partial recovery occurred in the patient with facial palsy.

Cerebrovascular disease

The second largest group in our study comprised the patients with CVD (21 cases, 27.3%): ischemic stroke (16 cases, 76.2%), intracranial hemorrhage (3 cases, 14.3%), and cerebral venous thrombosis (1 case, 4.8%). Stroke was suspected in another patient, but a brain CT was not carried out due to logistical limitations during the peak of the pandemic and due to the severe respiratory condition of the patient.

The D-dimer levels at admission, with a median of 576 mg/dl (range 152, 23,120 mg/dl), were similar between the CVD group and the rest of the sample. However, the D-dimer levels were higher the day before a stroke compared to the initial D-dimer levels in eight patients ($p = 0.015$).

CVD appeared earlier in the course of COVID-19 (median of 5 days [range 0, 53] from the onset of COVID-19 to stroke) than for the other neurological symptoms (5 vs. 13 days; $p = 0.01$). The mortality was higher in the CVD group (8 patients [38.1%] died vs. 5 patients [8.9%] in the rest of the sample; $p = 0.05$). The main characteristics of the patients with CVD are summarized in Table S2.

In one 61-year-old woman who exhibited a left middle cerebral artery (MCA) stroke 14 days after the onset of COVID-19, multiple vascular stenoses and a collateral pattern consistent with a Moyamoya angiopathy were documented in a CT angiogram and by brain MRI (Figure 1). She had been treated with tacrolimus for 4 years because of a liver transplant and she had no previous history of CVD. A comprehensive evaluation including normal autoimmunity and CSF analyses, and a peripheral blood smear, ruled out the most common etiologies associated with Moyamoya syndrome.

The patient with cerebral venous thrombosis was a healthy 30-year-old man who developed a headache and who lost consciousness while in the emergency department. A brain CT and contrast CT revealed a venous infarct with secondary hemorrhagic transformation in the right temporal lobe and a right internal jugular vein, right sigmoid, and transverse sinus thrombosis (Figure 2). The level of D-dimers was 2954 mg/dl, and no abnormalities were found in the hemostasis assessment, including negative results for antiphospholipid antibodies and genetic testing of the more common etiologies of coagulopathy. A decompressive craniectomy was

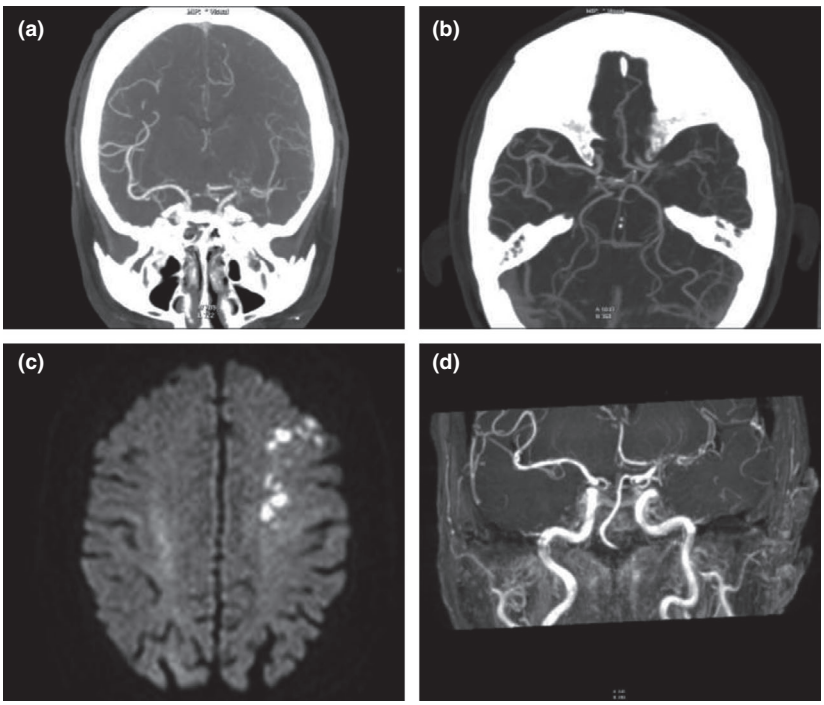


FIGURE 1 Neuroimaging study of a patient with an ischemic stroke and left Moyamoya angiopathy. Computed tomography angiography images showing subocclusive stenosis of terminal segment of left internal carotid artery and presence of deep collaterals with a Moyamoya pattern in a coronal (a) and transversal (b) section. (c) Image showing acute ischemic lesions in diffusion-weighted imaging localized in the border zone between middle cerebral artery (MCA) and anterior cerebral artery and MCA anterior branch. Left Moyamoya angiopathy observed in brain magnetic resonance angiography (d).

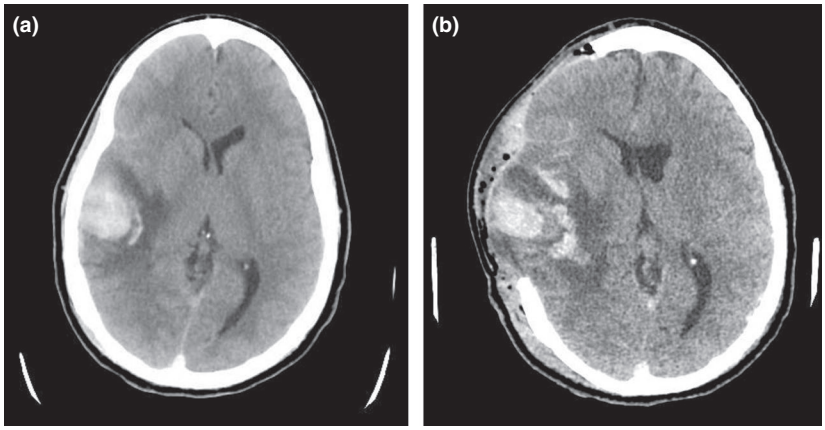


FIGURE 2 Brain computed tomography of a patient with a venous sinus thrombosis. Venous sinus thrombosis with associated hemorrhagic infarct in territory of right Labbe vein which is causing midline shift and local mass effect at the time of patient admission in the emergency department (a), and after a decompressive craniectomy 4 days later (b).

required to decrease intracranial pressure. Despite these measures, the patient died a few days after admission.

Encephalopathy

Fifteen patients (19.5%) were diagnosed with encephalopathy. This group was older (74 vs. 69 years; $p = 0.03$) compared to the rest of the sample. Only one patient died and three had to be admitted to the ICU due to COVID-19. The main characteristics of the patients with encephalopathy are summarized in Table S3.

The encephalopathy was caused by serotonin syndrome in two patients (13.3%), which was due to the use of lopinavir/ritonavir (LPV/r) while on lithium and duloxetine in one patient and risperidone and morphine in the other patient. These two patients developed impaired consciousness, hyperthermia, myoclonus, and hyperreflexia. Serotoninergic drugs were discontinued, and the outcome was favorable with progressive improvement of the neurological symptoms.

The remaining 13 patients (86.6%) were diagnosed with acute encephalopathy. The most frequent symptom in this group was disorientation – in nine patients (69.2%), followed by disturbance of awareness, confusion, agitation, and lastly memory loss. Previous cognitive impairment and metabolic imbalance were detected as risk factors for encephalopathy. However, four patients did not exhibit any metabolic imbalance at the onset of the neurological symptoms.

No other etiologies of encephalopathy were observed in this group after ancillary testing.

Seizures

Six patients (7.8%) suffered epileptic seizures. No status epilepticus occurred, EEG did not reveal signs of epileptiform discharges in any of the patients, and none of the patients had developed epilepsy by the end of the follow-up. The main characteristics of the patients with seizures are summarized in Table S4.

The epileptic seizures were generalized tonic–clonic in four patients. Only one first seizure was recorded in each patient, due to hypoxemia in two cases and severe hyponatremia in another. The other patient was a 71-year-old woman with a previous history of cognitive impairment.

Two patients suffered focal seizures with impaired awareness. No other symptoms were reported in any of the cases and the neurological examination did not reveal neurological focality. The neuroimaging was unremarkable. Analysis of the CSF revealed high protein levels (46–47 mg/dl), with normal white blood cell counts and negative RT-PCR SARS-CoV-2.

Miscellaneous

Six patients (7.8%) suffered persistent hiccups (lasting longer than 48 h). All of these patients were male, and they exhibited bilateral pneumonia. The median duration of the hiccups was 6 (range 2, 18) days. No alterations were noted upon neurological examination of this group of patients. A brain and cervical MRI scan was performed in one of the cases, revealing no abnormalities. These six cases were treated with at least one drug: chlorpromazine in five cases, metoclopramide in four cases, omeprazole in two cases, and gabapentin in one case. The outcomes were favorable, with complete resolution of the hiccups after symptomatic therapy in all cases. The main characteristics of the patients with hiccups are summarized in Table S5.

A single patient developed a generalized myoclonic tremor, without impairment of consciousness, during their stay in the ICU, 69 days after the onset of COVID-19 symptoms. The symptoms were more prominent in the thorax and the proximal upper limbs and they improved after treatment with clonazepam. At the time of symptoms onset, no metabolic imbalance was found, and the brain CT and an EEG were normal. Unfortunately, no other ancillary tests could be performed to clarify the etiology.

Horner syndrome occurred in a middle-aged woman admitted to the ICU for multifocal pneumonia that affected the apex of the left lung and the adjacent pleura. Carotid dissection was excluded by CTA and the syndrome progressively resolved.

One case of transverse dorsal myelopathy was reported in a patient with leukemia treated with intrathecal methotrexate and a bone marrow transplant. The patient developed lower limb weakness with

hyperreflexia, sensory impartment, and sphincter dysfunction 15 days after the onset of COVID-19 symptoms. A spine MRI and CSF analysis were unremarkable. Treatment with intravenous immunoglobulins was started but did not result in clinical improvement of the neurological symptoms. Unfortunately, the patient died 3 weeks after they developed neurological symptoms as a result of respiratory distress. Testing for anti-neuronal antibodies in the serum and CSF was negative.

DISCUSSION

Neurological complications have been reported in COVID-19 patients since the onset of the pandemic. We here report a prospective hospital-based cohort of patients with SARS-CoV-2 infection who required an assessment by a neurologist. In contrast to previous studies, the prevalence of neurological complications in our series was low (2.6%). This could be because most of the previous series included non-specific symptoms, were retrospective, did not include patients assessed by a neurologist, or included patients with previous neurological disease, thereby making the diagnosis of neurological complications less accurate.[9–11,19–21]

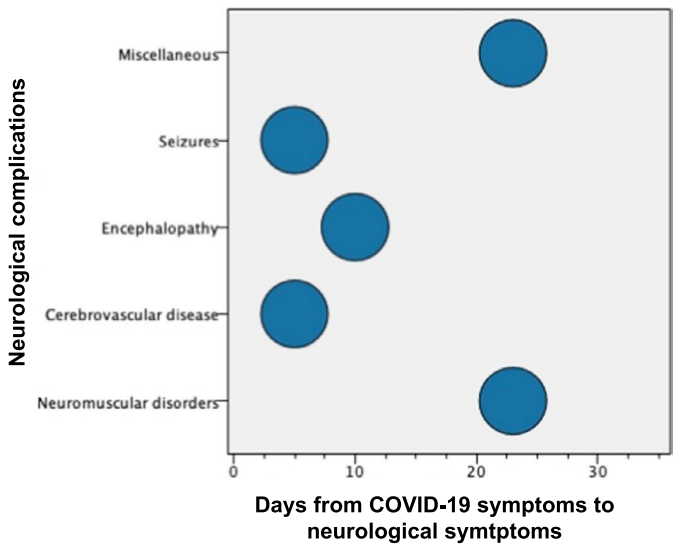
The prospective design of our series, comprising 3 months of follow-up during the first wave of the pandemic, allowed us to establish that the time in which different neurological complications occurred after the onset of COVID-19 symptoms varied (Figure 3): stroke and encephalopathy were common in the early phase of the disease, while neuromuscular disorders tended to appear later.

Moreover, these differences in the time at which the neurological complications appeared suggest that different mechanisms may be involved:

CVD, which arose in the early stage of the disease, could be related to a hypercoagulability syndrome and vascular endothelial dysfunction caused by the virus.[22] Even though some of these patients also had a previous history of vascular risk factors, the higher D-dimer levels the day before a stroke compared to the initial levels at the time of admission, and the previously healthy 30-year-old patient who developed a fatal cerebral sinus thrombosis, highlight the potential severity of the thrombotic state associated with SARS-CoV-2 infection.[23] Additionally, the case involving Moyamoya syndrome potentially related to tacrolimus in a patient who did not suffer any symptoms until 2 weeks after infection by COVID-19 suggests that COVID-19 could act as a final trigger of endotheliitis.[24]

Conversely, the hyperimmune response and cytokine storm, which are more prominent in the later stages of the disease, may play a major role in some of the neuromuscular complications.[25] Thus, in patients with acute inflammatory polyneuropathy, the onset of symptoms during the convalescent period of the disease, together with the detection of ganglioside antibodies in one of the cases, suggest a post-infectious mechanism mediated by molecular mimicry associated with COVID-19.[26]

Nevertheless, the broad range of the various complications described means that other factors need to be considered. First of all, the cases of CIM/CIP warrant particular mention. The fact that the CK levels at admission were higher in this group could indicate an individual susceptibility or this could be related to the severity of the systemic disease.[27] On the other hand, the combination of NMBAs and corticosteroids may be involved in muscle damage.[27,28] The use of prone positioning to improve the respiratory distress appears to have been a cause of brachial plexopathy due to compression or stretching of the brachial plexus in two patients.[29,30] Weight loss and prolonged hospitalization could be determinant in non-cranial mononeuropathies. Accordingly, CIM/CIP, brachial plexopathies, and non-cranial mononeuropathies appear to be complications of hospitalization and measures needed in the COVID-19 treatment. The case involving facial nerve palsy could be related to viral infection.[31]



Time (days) from COVID-19 symptoms to neurological symptoms was different in different neurological complications (Kruskal-Wallis test), p = 0.005

	Days (median, range)
Neuromuscular disorders	23 [0, 60]
Cerebrovascular disease	5 [0, 53]
Encephalopahty	10 [0, 47]
Seizures	5 [0, 43]
Miscellaneous	23 [10, 45]

Multiple comparisons between paired groups revealed statistically significant differences:

Neuromuscular disorders versus cerebrovascular disease	p = 0.0024
Neuromuscular disorders versus encephalopathy	p = 0.040

FIGURE 3 Differences between time from onset of COVID-19 symptoms to neurological complications. [Colour figure can be viewed at wileyonlinelibrary.com]

Encephalopathy was associated with previous cognitive impairment or a metabolic imbalance consequence of severe systemic disease. One important consideration that should alert physicians is the use of LPV/r, which was one of the most used drugs in our sample, as it can trigger serotonin syndrome if it is used in combination with other serotoninergic drugs.[32] In 4 of 15 patients, no toxic-metabolic etiology was found, although a clear relationship with COVID-19 could not be established.

Generalized tonic–clonic seizures were acute symptomatic due to a metabolic imbalance consequence of severe systemic illness in three patients.[33]

The peripheral nerve damage of the afferent or efferent motor fibers of the phrenic or accessory nerve caused by multiple pulmonary infiltrates is the most probable cause of persistent hiccups.[34] Similarly, Horner syndrome, which is a rare complication of pneumonia that affects the adjacent pleura, was noted in one patient due to focal pneumonia in the ipsilateral lung apex and pleura.[35]

An immune-mediated origin related to SARS-CoV-2 infection was suspected in a patient with a self-limited myoclonic tremor that had a late onset of symptoms after COVID-19.[36]

Finally, the etiologies of the other complications, such as four cases of unexplained acute encephalopathy, one case of generalized tonic–clonic seizure, two focal seizures with impaired awareness, a trochlear palsy, and a para-infectious dorsal myelitis remain unknown. Therefore, a clear relationship with COVID-19 cannot be established.

The presence of concomitant hyposmia or dysgeusia was low in our cohort (4.2%). This could be explained by a lower prevalence of these symptoms in hospitalized patients compared to non-hospitalized patients.[37] Moreover, the greater severity of patients with neurological complications could mask these symptoms.

The mortality in our cohort was low (16.9%). The death rate was higher in the CVD group, while the encephalopathy cases had a better outcome, probably due to the presence of a reversible etiology in most of them.

This study has limitations associated with the study design, while the pandemic context resulted in difficulties with performing a complete workup. Additionally, limiting the inclusion to patients who required a neurological assessment could have led to underestimation of some of the neurological complications.

Further studies with longer follow-ups will be invaluable for elucidation of the complete spectrum of neurological complications associated with SARS-CoV-2.

CONCLUSIONS

Our findings indicate that neurological complications associated with SARS-CoV-2 infection are uncommon in hospitalized patients and that they appear to be due to a variety of causes. However, no evidence of a potential direct invasion of the nervous system was observed in our cohort.

The various causal mechanisms could explain the broad clinical spectrum and the different times at which the neurological symptoms appeared during the infection. This allowed them to be classified into early and late neurological complications of COVID-19. We also report, for the first time, cases of persistent hiccups and Horner syndrome related to COVID-19.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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