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Neurological manifestations in hospitalized COVID-19 patients: a cross-sectional study

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Abstract

Background Accumulating evidence on the neurological sequelae of COVID-19 is a serious concern, with patients possibly being at risk of permanent debilitation if not managed appropriately. We aimed to determine the prevalence and pattern of neurological manifestations and diagnostic and therapeutic findings among hospitalized COVID-19 patients consulted with the neurology service for neurological disorders. We conducted a retrospective, observational study at the Golestan Hospital of Ahvaz, Iran, between March 20, 2020, and March 19, 2021. Patients' demographic, clinical, paraclinical, and therapeutic characteristics were extracted from medical records and then subjected to statistical analysis.

Results Overall, 6.7% (157/2340) of COVID-19 patients at Golestan Hospital had a neurological disorder. Most of the patients (90/157) were men, and the mean age of patients was 62.91 ± 91 years. A total of 56.68% of patients (89/157) were SARS-CoV-2 RT-PCR positive. The mean chest CT severity score was 8.26 ± 4.4, ranging from 1 to 19. The most common neurologic disorders were cerebrovascular disease (72.6%), encephalopathy (8.9%), and Guillain–Barre syndrome (6.4%). The CSF SARS-CoV-2 PCR test was positive in one patient with Guillain–Barre syndrome. The in-hospital mortality rate was 43.9%. Definite COVID-19, ICU admission, history of stroke and dementia, and comorbidities were associated with an increased mortality risk in these patients.

Conclusions Patients with COVID-19 can present with serious neurological disorders such as cerebrovascular disease and impaired consciousness, even without typical COVID-19 symptoms. Close monitoring for neurological symptoms may help improve prognosis in hospitalized COVID-19 patients.

Keywords COVID-19, Neurological presentation, Hospitalized patients, Mortality, Global pandemic

Introduction

Almost seven million people have succumbed to coronavirus disease 2019 (COVID-19), representing the largest infectious disease crisis since the 1918 influenza pandemic [1, 2]. In Iran, there have been 7,597,982 documented cases and 145,571 documented deaths from COVID-19 to date [3]. Although the virus primarily targets the respiratory tract, there is widespread evidence of neurological manifestations [4]. Up to a third of people with COVID-19 show at least one neurological manifestation. Headache and dizziness are the most common; more serious manifestations include encephalopathy, meningoencephalitis, stroke, peripheral nervous system disorders, and myopathy. Neurotropism, direct central nervous system (CNS) invasion, and postinfectious neurological complications have been suggested as causes of these manifestations [5].

Accumulating evidence on the neurological sequelae of COVID-19 is a serious concern, with patients possibly being at risk of permanent debilitation if not managed appropriately [6]. Conversely, patients with a previous diagnosis of chronic neurological diseases may be at increased risk of serious COVID-19 [7]. Also, the probability of COVID-19 continuation is high due to the

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emergence of new viral mutations [8, 9]. In light of these factors, there is an urgent need to study the neurological effects of COVID-19. Hence, this study aims to identify the prevalence and the patterns of neurological manifestations among patients with COVID-19 and determine the predictors of mortality and debilitating neurological complications.

Methods

Study design

We conducted a retrospective, cross-sectional study of all patients hospitalized between 20 March 2020 and 19 March 2021 at the Department of Neurology of Golestan Hospital (Ahvaz, Iran) diagnosed with COVID-19 and neurological symptoms.

Definitions

Patients were classified as suspected, probable, or definite COVID-19 patients. Suspected cases met the related clinical and epidemiological criteria. Probable cases included suspected patients with a history of contact with a probable or definite patient, a cluster of patients with at least one definite case reported among them, suspected patients with imaging findings in favor of COVID-19, such as multi-lobular or bilateral infiltration, especially peripheral infiltration on chest CT scan or chest radiographic or/and ground glass on CT scan of the lung, patients with acute loss of sense of smell and taste, and death in a patient suspected of COVID-19 that is not justified by other reasons. Definite cases had a positive PCR result for SARS-CoV-2 infection, regardless of symptoms and signs [10, 11].

The neurological syndromes were categorized as cerebrovascular diseases, encephalopathy (impairment of consciousness without localized signs, presenting as confusion, lethargic status, delirium, or coma), meningitis, and meningoencephalitis (encephalopathy with inflammatory CSF), epilepsy, demyelinating disease, and peripheral nervous system syndromes (involving muscles, neuromuscular junction, nerves or roots).

The chest computed tomography (CT) severity score was calculated to describe the extent of pulmonary involvement; this method was based on the degree of involvement of the lung lobes as 0% (0 points), 1–25% (1 point), 26–50% (2 points), 51–75% (3 points), and 76–100% (4 points). The CT severity score was quantified by summing the five lobe indices (range 0–20) [2].

Treatment

Patients for COVID-19 were treated based on national COVID-19 treatment guidelines with medications like corticosteroids, hydroxychloroquine, atazanavir/ritonavir, remdesivir, and ReciGen® [12].

Data collection

All patients' information including demographic characteristics (age, sex), neurological presentations, clinical signs of respiratory infection, the interval between onset of neurological manifestations and clinical signs of respiratory infection, paraclinical and experimental findings, history of previous neurological disease, history of comorbidities, history of immunosuppression and corticosteroids (> 20 mg of prednisolone for > 2 weeks or cumulative dose of > 600 mg of prednisolone), therapeutic measures, and in-hospital outcomes (in-hospital mortality, discharge, and length of stay) were extracted from the medical records. Finally, the outcome of COVID-19 was also expressed as mortality or discharge from the hospital.

Statistical analysis

Statistical analysis was performed using SPSS version 21 software. The Shapiro–Wilk test was used to determine the normality of the distributions. Simple descriptive analysis of data was summarized as frequencies (%) and means ± standard deviations (SD) for normally distributed variables or medians with interquartile ranges (IQR) for non-normally distributed parameters. Normally distributed parameters were compared by the student t-test and others by the Mann–Whitney U test. Categorical variables were compared by chi-squared or Fisher's exact tests, where appropriate. A P-value of < 0.05 was considered significant.

Results

General findings

A total of 2,340 adult patients were admitted to different wards of Golestan Hospital with an initial diagnosis of COVID-19 during the study period; 157 (6.7%) presented with a serious neurological disorder and were consulted with or admitted by the neurology service. Of these, 90 (57.3%) were men. The mean age was 62.91 ± 91 years (median: 64; range: 19–99 years). Most of the patients (65%) were older than 60. The mean duration of hospitalization was 10.44 ± 8.43 days. Dyspnea (37.6%) and cough (24.2%) were the most respiratory symptoms. Hypertension and diabetes mellitus were the most common comorbidities (71.3% and 36.9%, respectively). Most patients (68.8%) had no preexisting neurological diseases; nevertheless, ischemic stroke and myasthenia gravis were seen in 20.4% and 3.8% of patients, respectively. Forty-nine percent of patients (77/157) had a neurologic manifestation several days after COVID-19 symptoms. Most patients

presented with a focal neurological deficit (48.4%) or loss of consciousness (26.8%). Table 1 presents a summary of the characteristics of the study participants.

Figure 1 depicts the frequency of different neurological disorders in our patients. The most common were cerebrovascular disease (114/157, 72.6%), peripheral nervous system disorder (10.8%), and encephalopathy (8.9%). No patient had myelitis or myelopathy related to SARS-CoV-2 infection (Fig. 1).

Table 2 summarizes the patients' neuroimaging, lung imaging, electromyography/nerve conduction velocity, cerebrospinal fluid analysis, and medications. Evidence of encephalitis (n = 1) and leptomeningeal enhancement (n = 1) were occasionally seen on brain MRI, and two patients had cerebral venous sinus thrombosis (CVST) in the superior sagittal sinus and transverse sinus (Table 2).

The in-hospital mortality rate was 43.9% (69 patients), compared with 31.2% (730/2340) of all hospitalized COVID-19 patients. A definite COVID-19 diagnosis, hospitalization in the COVID-19 ICU or internal medicine wards, previous history of stroke and dementia, and co-morbidities were significantly more common in those who died than in those who survived ($P < 0.05$). Moreover, leukocytosis, thrombocytopenia, anemia, uremia, positive troponin, and high titer of creatine phosphokinase (CPK) and D-dimer were associated with an increased risk of mortality in these patients ($P < 0.05$).

Ischemic stroke

Among 114 patients with cerebrovascular disease, an ischemic stroke was most common (74.5%; n = 85) and was seen in patients with a median age of 61 years, ranging from 28–99 years. Most (39%) were males. The mortality rate was 42.5% in these patients. Seventeen patients (20%) had COVID-19 symptoms simultaneously with stroke, while 13 patients (15.3%) developed COVID-19 symptoms during hospitalization after a stroke was diagnosed. The mean chest CT severity score was 8.51 ± 4.49. A focal neurological deficit was the most neurologic presentation (75%), while hypertension (75%) was the predominant risk factor. Most ischemic infarcts (56.5%) were in the middle cerebral artery territory. All patients with ischemic stroke received prophylactic anticoagulants for deep vein thrombosis subcutaneously, though 11 developed hemorrhagic changes during their hospital course. A total of 12 patients out of 85 (14%) with ischemic stroke received a brief course of low-dose corticosteroids, out of whom 5 died (41%). This mortality proportion was similar to that among ischemic stroke patients who did not receive corticosteroids (42%; 31 out of 73 patients; P = 0.5) (Table 3).

Intracranial hemorrhage

Intracranial hemorrhage (ICH) was the less prevalent type (25.5%; n = 29) of cerebrovascular disease. Most cases featured intraparenchymal or intraventricular hemorrhage (55.17%), predominantly in the basal ganglia. Like ischemic stroke, most patients (51.7%) were males, and the median age was 61 years (range 36–83). Most (58.5%) had COVID-19 symptoms several days before hospitalization. Mortality occurred in 15 out of 29 patients with an intracranial hemorrhage (51.5%). In two patients diagnosed with CVST, treatment with intravenous anticoagulants was prescribed. Patients diagnosed with ICH received deep vein thrombosis (DVT) prophylaxis in the form of subcutaneous anticoagulants. Considering the lower mortality proportion in patients with ischemic stroke, the prognosis was better in ischemic stroke patients than in hemorrhagic ones (Table 4).

Encephalopathy

Among fourteen patients with encephalopathy, six had a definite COVID-19 diagnosis. The median chest CT severity score was 9, and 85.5% received invasive mechanical ventilation. Brain CT showed generalized brain edema in two patients. The blood culture was positive for *Klebsiella* in one patient and for *Pseudomonas* in another. No leukocytosis was seen in the CSF analysis. The mortality rate in these patients was 78.5%.

Seizure

A total of 9 patients were admitted with the initial manifestation of seizure, among which four were diagnosed first with COVID-19. None had a prior history of seizures or epilepsy. Among them, two patients had encephalitis (both died), three had an ICH, one had a CVST (died), and three were diagnosed with an epileptic syndrome (one died). Excluding status epilepticus, all other patients with seizures responded well to a single appropriate antiepileptic drug. Two patients with status epilepticus, unresponsive to adequate doses of two or three antiepileptic drugs, were treated with intravenous midazolam, resulting in a satisfactory response. It seems that in 5 patients, the seizures were related to COVID-19, and in 4 patients, they were related to a cerebrovascular accident. A total of 4 patients died (44.4%) despite proper treatment.

Guillain–Barré syndrome (GBS)

Ten patients (6.4%) with a mean age of 49.10 ± 15.22 years (range 25 to 69) were diagnosed with GBS. Most were women (60%). Eight had a definite COVID-19 diagnosis. Two patients were in poor condition and required intubation. All of them had COVID-19

Table 1 Demographic, clinical, and laboratory findings among hospitalized COVID-19 patients with neurologic disorders according to hospital outcome

	Total (n = 157)	In-hospital death (n = 69)	Discharged or transferred (n = 88)	P-value
Age (years) (mean ± SD)	62.91 ± 91 (19–99)	64.8 ± 17.3 (28–99)	61.43 ± 16.35 (19–93)	0.2
Age group (years), n (%)				
< 20	1 (0.6%)	0	1 (1.1%)	
20–40	13 (8.3%)	7 (10.1%)	6 (6.8%)	
40–60	40 (25.5%)	16 (23.2%)	24 (27.3%)	0.8
> 60	103 (65%)	44 (66.7%)	57 (64.8%)	
Gender N (%)				
Male	90 (57.3%)	39 (56.5%/)	51 (58.7%)	0.85
Female	67 (42.7%)	30 (43.5%)	17 (19.3%)	
COVID-19 diagnosis				
Definite	89 (56.7%)	41 (59.5%)	48 (54.5%)	0.008
Probable	45 (28.7%)	28 (40.5%)	17 (23%)	
Possible	23 (14.6%)	0	23 (26.5%)	
Duration of hospitalization (days) (mean ± SD)	10.44 ± 8.43	10.04 ± 8.42 (1–40)	10.75 ± 8.47 (1–43)	0.6
Onset time of neurologic presentation, n (%)				
At the onset of COVID-19 symptoms	47 (29.9%)	21 (30.4%)	26 (29.5%)	
Several days after COVID-19 symptoms	77 (49%)	36 (52.2%)	41 (46.6%)	
Several weeks after COVID-19 symptoms	11 (7%)	2 (2.9%)	9 (10.2%)	0.73
Before clinical signs and symptoms of COVID-19	22 (12%)	10 (14.5%)	12 (13.6%)	
Department of admission, n (%)				
Neurology	26 (16.6%)	0	26 (29.5%)	
COVID-19 intensive care unit	47 (29.9%)	41 (59.4%)	6 (6.8%)	
Internal medicine	41 (26.1%)	8 (11.6%)	33 (37.5%)	< 0.001
Neurosurgery	4 (2.5%)	2 (2.9%)	2 (2.3%)	
Emergency	20 (12.7%)	10 (14.5%)	10 (11.4%)	
Stroke care unit	19 (12.1%)	8 (11.6%)	11 (12.5%)	
Comorbidities, n (%)				
Hypertension	112 (71.3%)	52 (75.4%)	60 (68.2%)	
Diabetes mellitus	58 (36.9%)	29 (42%)	29 (33%)	
Atrial fibrillation	7 (4.5%)	2 (2.9%)	5 (5.7%)	
Heart disease	20 (12.7%)	8 (11.6)	12 (136.6%)	
Chronic obstructive pulmonary disease	1 (0.6%)	0	1 (1.1%)	
End-stage renal disease	2 (1.3%)	2 (2.9%)	0	
Rheumatologic disorder	3 (1.9%)	2 (2.9%)	1 (1.1%)	> 0.05
Malignancy	3 (1.9%)	1 (1.4%)	2 (2.3%)	
Tobacco smoking	16 (10.2%)	4 (5.8%)	12 (13.6%)	
Opium addiction	4 (2.5%)	0	4 (4.5%)	
Respiratory symptom presentation, n (%)				
Cough	38 (24.2%)	11 (15.9%)	27 (30.7%)	
Fever	37 (23.6%)	14 (20.3%)	23 (26.1%)	
Dyspnea	59 (37.6%)	38 (55.1%)	21 (23.9%)	
Myalgia	4 (2.5%)	1 (1.4%)	3 (3.4%)	0.18

Table 1 (continued)

	Total (n = 157)	In-hospital death (n = 69)	Discharged or transferred (n = 88)	P-value
Headache	5 (3.2%)	0	5 (5.7%)	
None	14 (8.9%)	5 (7.2%)	9 (10.2%)	
Neurological symptom presentation, n (%)				
Loss of consciousness	42 (26.8%)	32 (46.6%)	10 (11.4%)	
Focal neurological deficit	76 (48.4%)	29 (42%)	46 (52.3%)	
Ataxia	2 (1.3%)	0	3 (3.4%)	
Headache	3 (1.9%)	1 (1.4%)	2 (2.3%)	
Seizure	7 (4.5%)	3 (4.3%)	4 (4.5%)	0.16
Status epilepticus	2 (1.3%)	1 (1.4%)	1 (1.1%)	
Abnormal movement (myoclonus and tremor)	1 (0.6%)	0	1 (1.1%)	
Muscle weakness	16 (10.19%)	2 (2.9%)	14 (15.9%)	
Visual loss	3 (1.9%)	0	3 (3.4%)	
Vertigo	2 (1.3%)	0	2 (2.3%)	
Cognitive disorder	4 (2.5%)	1 (1.4%)	3 (3.4%)	
Neurologic disorders, n (%)				
Encephalopathy (any type)	14 (8.9%)	11 (15.9%)	3 (3.4%)	
Cerebrovascular disorder (any type)				
Ischemic/transient ischemic attack	85 (54.1%)	36 (52.2%)	44 (57.7%)	0.99
Intracerebral/intraventricular hemorrhage	24 (15.3%)	12 (7.4%)	12 (13.6%)	
Spontaneous subarachnoid hemorrhage	2 (1.3%)	1 (1.4%)	1 (1.1)	
Subdural hematoma	1 (0.6%)	1 (1.4%)	0	
Sinuous vein thrombosis	2 (1.3%)	1 (1.4%)	1 (1.1)	
Seizure (clinical or electrographic)	4 (2.5%)	2 (2.9%)	2 (2.3%)	
Movement disorder	1 (0.6%)	0	1 (1.1)	
Neuroleptic malignant syndrome	1 (0.6%)	0	1 (1.1)	
Peripheral nerve system				
Guillain–Barre syndrome	10 (6.4%)	2 (2.9%)	8 (9.1%)	
Myopathy	1 (0.6%)	0	1 (1.1%)	
Exacerbation of myasthenia gravis	6 (3.8%)	1 (1.4%)	5 (5.7%)	
Encephalitis/meningitis	4 (2.5%)	1 (1.4%)	3 (3.4%)	
Demyelinating disease	2 (1.3%)	1 (1.4%)	1 (1.1%)	
Past neurologic history, n (%)				
None	108 (68.8%)	43 (62.3%)	65 (73.9%)	
Ischemic stroke	32 (20.4%)	18 (26.1%)	14 (15.9%)	
Intracerebral or intraventricular hemorrhage	2 (1.2%)	1 (1.4%)	1 (1.1)	
Dementia	6 (3.8%)	5 (7.2%)	1 (1.1%)	
Demyelinating disease/multiple sclerosis	2 (1.2%)	1 (1.4%)	1 (1.1%)	
Myasthenia gravis	6 (3.8%)	1 (1.4%)	5 (5.7%)	
Parkinson's and Parkinson-plus syndromes	1 (0.6%)	0	1 (1.1%)	

Table 1 (continued)

	Total (n = 157)	In-hospital death (n = 69)	Discharged or transferred (n = 88)	P-value
Chest CT severity score (0–20) (mean ± SD)	8.26 ± 4.4 (1–19)	9.98 ± 4.52 (1–19)	6.9 ± 3.8 (1–19)	< 0.001
History of immunosuppression use, n (%)	13 (8.3%)	5 (7.2%)	8 (9.1%)	0.68
History of corticosteroid use, n (%)	12 (7.6%)	5 (7.2%)	7 (8%)	0.86
Morbidity				
Acute renal failure	12 (7.6%)	8 (11.6%)	4 (4.5%)	
Sepsis	10 (6.4%)	10 (14.5)	0	
Electrolyte disorders	5 (3.2%)	4 (5.8%)	1 (1.1)	
Anemia	7 (4.5%)	3 (4.3%)	4 (4.5)	
Thrombocytopenia	6 (3.8%)	5 (7.2%)	1 (1.1)	< 0.001
Deep vein thrombosis	2 (1.3%)	2 (2.9%)	0	
Pulmonary embolism	12 (7.6%)	11 (15.9%)	1 (1.1)	
Urinary tract infections	1 (0.6%)	1 (1.4%)	0	
Heparin-induced thrombocytopenia	1 (0.6%)	1 (1.4%)	0	
Gastrointestinal bleeding	1 (0.6%)	0	1 (1.1)	
Invasive mechanical ventilation, n (%)	81 (51.6%)	65 (94.2%)	16 (18.2%)	< 0.001
Laboratory findings upon admission				
White blood cells (cells/μL)	10,988.78 ± 3892.49 (1100–25,000)	12,023.19 ± 4588.22 (1100–25,000)	10,168.39 ± 3020.42 (4000–18,000)	0.003
Platelets (cells/^{1}L)	190,175.64 ± 85,545.86 (10,500–440,000)	164,752.17 ± 82,826.7 (27,000–368,000)	210,339.08 ± 82,675.94 (10,500–440,000)	0.001
Hemoglobin (g/dl)	10.88 ± 2.08 (4.3–16.6)	10.28 ± 2.1 (4.3–15)	11.37 ± 1.9 (6.5–16.6)	
Erythrocyte sedimentation rate (mm/h)	34.88 ± 21.74	37.19 ± 21 (5–95)	32.82 ± 22.26 (5–91)	0.001
C-reactive protein				
(–)	49 (31.2%)	20 (29%)	29 (33%)	0.7
(+)	48 (30.6%)	24 (34.8%)	24 (27.3%)	
(++)	16 (10.2%)	12 (17.4%)	4 (4.5%)	0.2
(+++)	17 (10.8%)	5 (7.2%)	12 (13.6%)	
Creatine phosphokinase (U/L)	289.13 ± 379.17 (24–2884)	370.06 ± 235 (0–2884)	225.75 ± 232.39 (24–1296)	0.04
Aspartate aminotransferase (U/L)	54.92 ± 44.78 (15–367)	64.2 ± 58.19 (15.367)	47 ± 26.7(16–145)	0.02
Alanine transaminase (U/L)	42.63 ± 36.92 (7–290)	45.34 ± 45 (8–290)	40.32 ± 28.32(7–133)	0.42
Alkaline phosphatase (U/L)	212.94 ± 99.69 (35–640)	233.17 ± 118.63 (50–640)	195.67 ± 76.79(35–550)	0.02
Prothrombin time (s)	13.80 ± 3.01(12–31)	13.84 ± 3.03 (12–30)	13.7 ± 3.01(12–31)	0.89
Activated partial thromboplastin time (s)	36.35 ± 10.97 (12–100)	36.51 ± 7.9 (13–62)	36.2 ± 12.9 (12–100)	0.87
International normalized ratio	1.26 ± 0.32 (1–3.7)	1.26 ± 0.3 (1–2.4)	1.26 ± 0.34 (1–3.7)	0.9
Sodium (mEq/L)	140.97 ± 7.24 (126–179)	141.9 ± 8.1 (126–173)	140.23 ± 6.25 (130–179)	0.15
Potassium (mmol/L)	4.1 ± 0.6 (2.7–6.6)	4.1 ± 0.88 (2.7–6.6)	4.05 ± 0.43 (3–5.5)	0.3
Calcium (mmol/L)	8.45 ± 0.85 (6–11.8)	8.3 ± 0.86 (6–10.6)	8.45 ± 0.85 (6.7–11.8)	0.17
Lactate dehydrogenase (U/L)	982.60 ± 1142.99 (303–9871)	1158.91 ± 1441.54 (321–9871)	832.91 ± 793 (303–5931)	0.16
Blood urea nitrogen (mg/dL)	32.42 ± 31.21(6–213)	42.56 ± 40.5 (6–213)	24.41 ± 17.6 (6–103)	0.00
Creatinine (mg/dL)	1.57 ± 1.4 (0.5–9.3)	1.92 ± 1.9 (0.6–9.3)	1.29 ± 0.67 (0.5–4.5)	0.005
Blood sugar (mmol/L)	183.40 ± 91.15 (41–650)	203.04 ± 103.45 (75–650)	167.3 ± 76.6 (41–395)	0.017
Troponin				

Table 1 (continued)

	Total (n = 157)	In-hospital death (n = 69)	Discharged or transferred (n = 88)	P-value
Negative	134 (85.4%)	51 (73.9%)	83 (94.3%)	
Weakly positive	18 (11.5%)	14 (20.3%)	4 (4.5%)	0.03
Positive	4 (2.5%)	3 (4.3%)	1 (1.1%)	
D-dimer				
High	46 (29.3%)	27 (39.1%)	19 (21.6%)	0.03
Blood culture				
Pseudomonas aeruginosa	4 (2.5%)	4 (5.8%)	0	
Staph-coagulase negative	2 (1.3%)	2 (2.9%)	0	0.4
Klebsiella	8 (5.1%)	7 (10.1%)	1 (1.1%)	

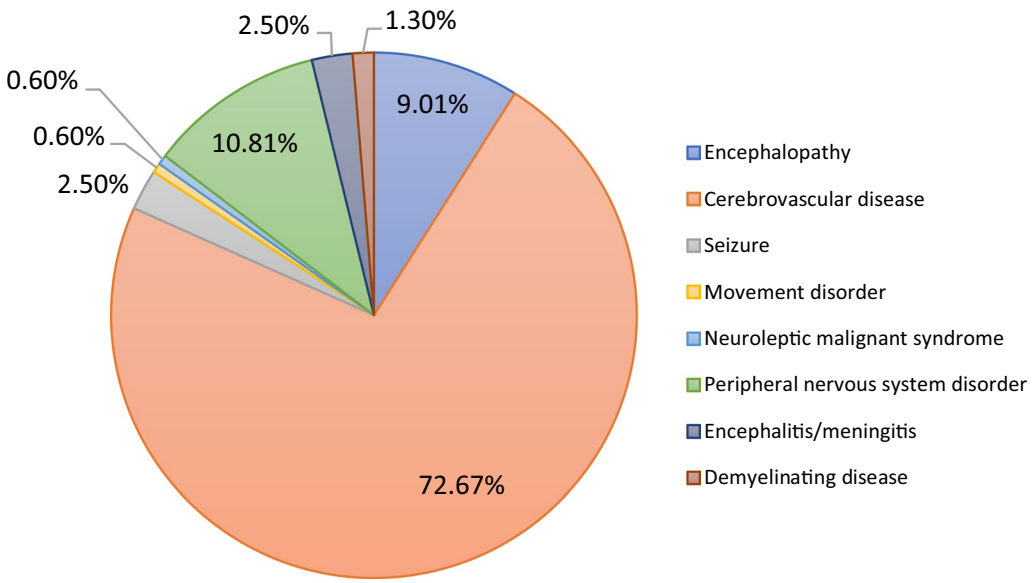

Fig. 1 Frequency of neurological disorders among hospitalized COVID-19 patients with neurological disorders

symptoms several days before neurological presentation. The protein concentration in CSF was high, with a median of 119 mg/dl, and there was no evidence of CSF leukocytosis. The CSF analysis was positive for SARS-CoV-2 (PCR) with elevated protein and no leukocytosis in one GBS patient—a 69-year-old woman with severe COVID-19 (chest CT score = 18). This patient eventually died. Six patients received plasma exchange therapy, three had contraindications (e.g., instability) and received IVIG instead, and one had only mild symptoms and was monitored without immunotherapy. Four patients received low-dose corticosteroids and antiviral drugs simultaneously for COVID-19. Among the four patients who received low-dose corticosteroids, one patient died. The overall mortality proportion among patients with GBS was 20%.

Myasthenia gravis (MG)/myopathy

Seven patients developed an exacerbation of MG (n = 6) or myopathy (n = 1). Three had a definite COVID-19 diagnosis; they had respiratory symptoms preceding muscle weakness, and only one patient developed severe respiratory involvement and died. All patients with MG exacerbation had a positive history of MG, but the patient with irritative myopathy had no history of myopathies or rheumatologic disorders. Regarding MG, two patients had a severe clinical course and required immunotherapy—one received plasma exchange, and the other received IVIG as plasma exchange was contraindicated. One patient received only rituximab. Three patients had a relatively mild clinical course and improved with treatment for COVID-19 (including antiretrovirals). One patient (1/7; 14%) died.

Table 2 Summary of patients' neuroimaging, lung imaging, electromyography/nerve conduction velocity, cerebrospinal fluid analysis, and medications

Variable	n (%)
Neuroimaging (computed tomography scan or magnetic resonance imaging) abnormalities	
Ischemic evidence in findings	85 (54.1%)
Hemorrhagic evidence in brain	24 (15.3%)
Leptomeningeal enhancement	1 (0.6%)
Encephalitis evidence in brain	1 (0.6%)
Cerebral venous thrombosis	2 (1.3%)
Demyelination (white matter involvement)	2 (1.3%)
Lung computed tomography scan	
Ground-glass opacities alone	111 (70.7%)
Ground-glass opacities with consolidation	36 (22.9%)
Consolidation alone	3 (1.9%)
Atelectasis	1 (0.6%)
Pleural effusion	6 (3.8%)
Electromyography and nerve conduction velocity	
Irritative myopathy	1 (0.6%)
Neuromuscular junction disorder (no evidence of myopathy + fibrillation)	1 (0.6%)
Subacute sensory & motor axonal polyradiculoneuropathy (fibrillation +)	1 (0.6%)
Acute mainly demyelinating motor > sensory polyradiculopathy with some axonal features	1 (0.6%)
Cerebrospinal fluid analysis	
White blood cells/mm^3 (normal range < 5/mm^3)	33 ± 94 (0–300)
Red blood cells /mm^3	2101.50 ± 6295.87 (0–20,000)
Glucose (normal range 40–70 mg/dL or ≥ 2/3 of plasma glucose)	103.5 ± 47.5 (39–211)
Protein (normal range 15–40 mg/dL)	97.8 ± 55.45 (32–186)
Oligoclonal bands – negative	5 (3.2%)
SARS-CoV-2 PCR negative	13 (8.3%)
SARS-CoV-2 PCR positive	1 (0.6%)
Medications, n (%)	
Corticosteroids	34 (21.7%)
Hydroxychloroquine	5 (3.2%)
Atazanavir/ritonavir	45 (28.6%)
Remdesivir	9 (5.7%)
ReciGen®	19 (21.34%)
Therapeutic anticoagulation	14 (8.9%)
Antibiotic therapy	105 (66.9%)
Anti-epileptic therapy	32 (20.4%)
Deep vein thrombosis prophylaxis	153 (97.5%)
Pack cell transfusion	20 (12.7%)
Hemodialysis	10 (6.4%)
Plasma exchange	8 (5.12%)
Intravenous immunoglobulin	10 (6.36%)
Rituximab	1(0.6%)

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, *PCR* polymerase chain reaction

Encephalitis

Four patients were diagnosed with encephalitis, out of which two were definitively diagnosed with COVID-19. The patients exhibited cognitive impairment and fever, requiring hospitalization. Only one patient required mechanical ventilation, and all patients with encephalitis received a triple-drug regimen for encephalitis along with simultaneous antiviral treatment for COVID-19. Unfortunately, one patient died.

Table 3 Characteristics of COVID-19 patients with acute ischemic stroke (n = 85)

Characteristic	n (%)
Age, years (mean ± SD)	65.31 ± 15.7 (28–99)
Age group (years)	
< 20	0
20–40	2 (2.4%)
40–60	22 (25.9%)
> 60	61 (71.8%)
Gender (female)	33 (38.8%)
Mechanical ventilation	42 (49.4%)
Chest computed tomography severity score (0–20) (mean ± SD)	8.51 ± 4.49 (1–18)
Timing of acute ischemic stroke, n (%)	
At the onset of COVID-19 symptoms	17 (20%)
Several days after COVID-19 symptoms	16 (18.8%)
Several weeks after COVID-19 symptoms	39 (45.9%)
Before clinical signs & symptoms of COVID-19	13 (15.3%)
Neurologic presentation, n (%)	
Focal neurological deficit	64 (75.3%)
Loss of consciousness	12 (14.1%)
Headache	0
Seizure	0
Vertigo	1 (1.2%)
Ataxia	2 (2.4%)
Visual loss	3 (3.5%)
Cognitive disorder	3 (3.5%)
Risk factor, n (%)	
Hypertension	64 (75.3%)
Diabetes mellitus	36 (42.4%)
Prior intracranial hemorrhage	21 (24.7%)
Heart disease	14 (16.5%)
Current smoker	12 (14.1%)
Rheumatologic disorder	2 (2.4%)
More than one risk factor	31 (36.47%)
Diagnosis of COVID-19, n (%)	
Definite	48 (56.8%)
Probable	24 (28.2%)
Possible	13 (15.3%)
Hemorrhagic infarct, n (%)	11 (12.9%)
Location of infarct evidence on CT or MRI, n (%)	
Superior middle cerebral artery (MCA)	14 (16.5%)
Inferior MCA	11 (12.8%)
Proximal stem middle cerebral artery	23 (27.1%)
Anterior cerebral artery (ACA)	1 (1.2%)
Posterior cerebral artery	5 (5.9%)
Posterior inferior cerebellar artery	1 (1.2%)
Basilar artery	11 (12.9%)
Lenticulostriate artery	14 (16.5%)
More than one territory in both hemispheres	2 (2.4%)
Cortical border zone (between ACA & MCA)	3 (3.5%)
Ejection fraction on echocardiography (mean ± SD)	43.97 ± 11.51 (10–60)
Laboratory findings upon admission (mean ± SD)	
Erythrocyte sedimentation rate (mm/hr)	36.39 ± 22.7
C-reactive protein (mg/L)	
(-)	30 (35.3%)
(+)	23 (27.1%)
(++)	6 (7.1%)
(+++)	8 (9.4%)
Prothrombin time (s)	14.08 ± 3.5
Activated partial thromboplastin time (s)	34.96 ± 9.15
International normalized ratio	1.28 ± 0
Blood sugar (mmol/L)	186.27 ± 82.37
Troponin, n (%)	
Negative	72 (84.7%)
Weakly positive	9 (10.6%)
Positive	3 (3.5%)
D-dimer – high, n (%)	21 (24.7%)
Medications, n (%)	
Antiplatelet therapy (dual or single therapy)	81 (95%)
Anticoagulation	10 (11.8%)
Intravenous tissue plasminogen activator	2 (2.4%)
Hemicraniectomy	1 (1.2%)
Osmotic therapy	2 (3.5%)
Outcomes, n (%)	
Discharged home	40 (47.1%)
Referred to another center	9 (10.6%)
Died in hospital	36 (42.4%)

Discussion

The COVID-19 pandemic has affected people from all walks of life, burdening patients, healthcare professionals, and governments in many countries [13]. Despite numerous reports of neurological deficits in patients with COVID-19 worldwide, the exact occurrence of these manifestations remains unknown. Patients with severe COVID-19 tend to have more severe neurological manifestations, possibly from cerebral hypoxia due to respiratory failure [7, 13]. We found that 6.7% of hospitalized COVID-19 patients had a serious neurologic disorder; the most common ones were ischemic stroke (54.1%), intracranial hemorrhage (18.5%), encephalopathy (8.9%), Guillain–Barre syndrome (6.4%) and MG exacerbation (3.8%).

The prevalence of neurologic manifestations in hospitalized COVID-19 patients was estimated at 36.4% in China and 57.4% in Europe [5, 7, 13, 14]. In a previous study from Iran, 4.8% (211/4372) of hospitalized COVID-19 patients had a neurological disorder; the most

Table 4 Characteristics of COVID-19 patients with intracranial hemorrhage (n = 29)

Characteristic	n (%)
Age, years (mean ± SD)	58.72 ± 12.58 (36–83)
Age group (years)	
< 20	0
20–40	4 (13.8%)
40–60	9 (31%)
> 60	16 (55.2%)
Gender (female)	15 (51.7%)
Mechanical ventilation	18 (62.1%)
Chest computed tomography severity score (0–20) (mean ± SD)	7.13 ± 3.55 (1–14)
Timing of intracranial hemorrhage, n (%)	
At the onset of COVID-19 symptoms	7 (24.1%)
Several days after COVID-19 symptoms	4 (13.8%)
Several weeks after COVID-19 symptoms	17 (58.62%)
Before clinical signs and symptoms of COVID-19	1 (3.4%)
Neurologic presentation, n (%)	
Focal neurological deficit	8 (27.6%)
Loss of consciousness	14 (48.3%)
Headache	2 (6.9%)
Seizure	4 (13.8%)
Vertigo	1 (3.4%)
Ataxia	0
Visual loss	0
Cognitive disorder	0
Risk factor, n (%)	
Hypertension	24 (82.8%)
Diabetes mellitus	8 (27.6%)
Prior intracranial hemorrhage	1 (4.2%)
Heart disease	2 (6.9%)
Current smoker	4 (13.8%)
Rheumatologic disorder	1 (4.2%)
More than one risk factor	6 (20.6%)
Diagnosis of COVID-19, N (%)	
Definite	18 (62.1%)
Probable	7 (24.1%)
Possible	4 (13.8%)
Type of hemorrhage (%)	
Intraparenchymal hemorrhage	8 (27.58%)
Intraparenchymal with Intraventricular hemorrhage	16 (55.17%)
Subarachnoid hemorrhage	2 (6.9%)
Subdural hemorrhage	1 (3.4?5)
Cerebral venous sinus thrombosis	2 (6.9%)
Primary location of hemorrhage evidence on imaging	
Frontal lobe	1 (3.4%)
Temporal lobe	3 (10.3%)
Occipital lobe	1 (3.4%)
Basal ganglia	15 (51.7%)
Pons	1 (3.4%)
Brain stem and cerebellum	5 (17.2%)
Laboratory findings upon admission (mean ± SD)	
Platelets (cells/μL)	173,675.86 ± 81,124.79 (33,000–35,2000)
Prothrombin time (s)	13.98 ± 2.92 (12–23)
Activated partial thromboplastin time (s)	37.28 ± 13.59 (30–100)
International normalized ratio	1.27 ± 0.33 (1–2.4)
Treatment, n (%)	
External ventricular drainage	1 (3.4%)
Osmotic therapy	15 (51.72%)
Anticoagulants	2 (6.9%)

frequent CNS manifestations were headache (40.3%), reduced consciousness (36%), and focal neurologic symptoms (18%) [2]. In New York City, a slightly higher prevalence of 13.5% (606/4491) was reported [15]. The reported prevalence rates are heterogeneous depending on the methods and definitions for detecting neurological manifestations. For instance, the prevalence recorded in the present study (6.7%) is lower than most of the mentioned studies, probably due to our selection of serious neurological disorders requiring consultation with or admission by the neurology service.

Neurologic symptoms are sometimes the initial presentation of COVID-19 [8]; this was seen in 30% (47/157) of cases in the present study. However, most patients developed neurological manifestations after several days of onset of clinical COVID-19 symptoms. Liotta et al. reported neurologic manifestations at COVID-19 onset in 42.2%, at hospitalization in 62.7%, and at any time during the disease course in 82.3%. The most frequent neurologic manifestations were myalgias (44.8%), headaches (37.7%), and encephalopathy (31.8%); strokes, movement disorders, motor and sensory deficits, ataxia, and seizures were uncommon [16]. Thirty-one percent of patients in our study had a previous history of neurological disease—mainly stroke, dementia, or myasthenia gravis. In the Herman et al. study, the rate of previous neurological illnesses varied from 0 to 40%, with a pooled percentage of 8%; cerebrovascular disease was the main comorbidity (16%), similar to our study [17]. Patients with a preceding neurological disease may be at increased risk of serious COVID-19, so special attention must be directed toward preventing COVID-19 in this population [7].

According to the current study, CNS manifestations were the most prevalent serious neurological manifestation in hospitalized COVID-19 patients, with ischemic

stroke being the most common (54.1%), followed by intracranial hemorrhage (18.4%) and encephalopathy (8.9%). Overall, 72.6% of patients had cerebrovascular disease, representing the most common group of neurological disorders. Stroke was reported at 1.7% in Spain [14], 3.5% to 5.7% in China [5], and 62% in a report from the UK [18]. Studart-Neto and colleagues reported a prevalence of encephalopathy (44.4%) and stroke (16.7%) in Brazil in hospitalized COVID-19 patients requiring neurology consultations [19]. A similar study by Brucki et al. in Latin America reported stroke as the most common neurologic disorder (47.6%), followed by encephalopathy (27%) [20]. In New York City, the main neurologic disorder was toxic/metabolic encephalopathy (51%), followed by stroke (14%), seizure (12%), and hypoxic/ischemic brain injury (11%) [15]. Although our findings are generally compatible with the literature, cerebrovascular disease might have been more prevalent in our study because our center is the referral center for stroke in Ahwaz, and because the internal medicine team sometimes manages encephalopathies without a neurological consultation. Other potential factors for the difference in the prevalence and frequency of neurological manifestations include SARS-CoV-2 strain variations and genetic factors, particularly polymorphisms in the angiotensin-converting enzyme 2 (ACE 2) gene [21, 22].

Possible mechanisms behind impaired consciousness and encephalopathy include infections, parenchymal lesions, electrolyte imbalance, hypoxia, toxic and metabolic encephalopathies, and non-convulsive epilepsy [13]. One suggested explanation for the increased ischemic and vascular events in COVID-19 patients is the reduction of ACE2 by the SARS-CoV-2 virus, which may cause an imbalance of the renin-angiotensin system (RAS), eventuating in endothelial cell dysfunction and ischemic accidents. ACE2 dysregulation by SARS-CoV-2 may also lead to vasoconstriction and dysfunction of the brain, resulting in increased blood pressure, which can trigger bleeding via the rupture of arterial walls [23]. SARS-CoV-2 also ruptures existing atherosclerotic plaques via the inflammatory response involving CRP, interleukin (IL-7), interleukin 6 (IL-6), and other inflammatory markers [24]. Cardiac manifestations and arrhythmic complications of COVID-19 can also contribute to ischemic events [24], as can coagulation disorders, which have been seen in patients with severe COVID-19 [25].

The overall prevalence of peripheral nervous system manifestations was less than about 10.8% in our study. GBS was diagnosed in 6.4% of patients, with a median age of 44 (25 to 69) years. Most developed neurological symptoms several days after COVID-19. Frontera et al. reported three patients with GBS within 2–4 weeks of documented SARS-CoV-2 infection; all three had a negative RT-PCR SARS-CoV-2 in the CSF [15]. While GBS is thought to occur via postinfectious or parainfectious mechanisms, we found a rare case of GBS with a positive CSF SARS-CoV-2 PCR test in a 69-year-old woman with severe COVID-19. This rare finding, coupled with evidence of ischemia on imaging, suggests the possibility of direct CNS invasion by SARS-CoV-2, which should be explored further in future studies.

In the current study, 50 (32%) patients were in poor condition upon hospitalization, and 81 (52%) patients received invasive mechanical ventilation during hospitalization. Our in-hospital mortality rate was 44%. A definite COVID-19 diagnosis, ICU admission, previous history of stroke and dementia and associated morbidity, uremia, anemia, thrombocytopenia, leukocytosis, positive troponin, and high titers of CPK and D-dimer were associated with increased risk of mortality. In a similar study, Frontera et al. found higher in-hospital mortality rates and lower discharge rates among patients with COVID-19 with a neurologic disorder than those without a neurologic disorder. History of medical and neurologic diseases, the severity of illness (invasive mechanical ventilation and SOFA scores), and acute renal failure differences in COVID-19-specific medication administration (therapeutic anticoagulation, hydroxychloroquine, corticosteroid, lopinavir/ritonavir use) were significantly associated with in-hospital death in those with a neurologic disorder (35%) than in those without a neurologic disorder (19%) [15]. Moreover, Yaghi et al. found that patients with laboratory-confirmed COVID-19 and ischemic stroke had higher mortality rates than contemporary and historical patients with ischemic stroke who did not have COVID-19 [26]. Hence, our findings align well with the literature.

There are limitations to this study that should be highlighted. First, although our sample size was large, the study's retrospective nature resulted in many patients being lost due to a lack of requesting a neurology consultation. Second, the current study included all patients diagnosed with COVID-19 based on clinical suspicion (with and without laboratory confirmation), meaning that undocumented diagnoses or unconfirmed SARS-CoV-2 infection may lead to inaccurate estimates of the prevalence rate. Third, some patients may not have provided an accurate history of neurological symptoms due to the severity of pulmonary symptoms, which can underestimate the prevalence. Finally, in most cases, it was impossible to determine whether COVID-19 caused new neurological symptoms or worsened pre-existing ones due to insufficient information in the medical records. Well-designed prospective studies can overcome these limitations.

Conclusion

In our study, over 5% of hospitalized COVID-19 patients developed life-threatening neurological complications. A definite COVID-19 diagnosis, a previous history of neurological disease, and comorbidities predicted mortality in these patients. Without proper care and treatment, COVID-19 patients with neurological disorders may become permanently disabled, burdening individuals, families, societies, and healthcare systems. As a result, we urgently need to understand and respond to the latent yet potentially debilitating neurological consequences of COVID-19 in the acute and chronic stages of the disease.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
CNS	Central nervous system
ICU	Intensive care unit
CSF	Cerebrospinal fluid
DVT	Deep vein thrombosis
ACE2	Angiotensin-converting enzyme 2
NMS	Neuroleptic malignant syndrome
TIA	Transient ischemic attack
GGO	Ground-glass opacity
MG	Myasthenia gravis
GBS	Guillain–Barré syndrome
OCB	Oligoclonal bands

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Author contributions

DK, DS, GS, and NFP contributed to the study's design, data collection, data analysis, data interpretation, manuscript drafting, and manuscript revision. All authors approve the final manuscript and accept accountability for all aspects of this work.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (1399.908).

Consent for publication

Not applicable.

Competing interests

The authors report no competing interests.

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