Neurological Manifestations in Critically Ill COVID-19 Patients

Laya Amoozadeh[1], Mohammad Taghi Beigmohammadi[1,2]

[1] *Department of Anesthesiology and Intensive Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Research Center for War-Affected People, Tehran University of Medical Sciences, Tehran, Iran*

Received: 03 Oct. 2021; Accepted: 26 Mar. 2022

Abstract- Patients with COVID-19 frequently experience neurological symptoms. Headaches and dizziness are common but non-specific symptoms. Both peripheral and central nervous systems can be impacted in severe stages. We focused on the neurological manifestations of COVID-19 patients in critical care. A cohort study evaluated the acute neurological manifestations in 204 patients admitted to intensive care units (ICU) tertiary Imam Khomeini hospital complex, Tehran, Iran. Patients with positive COVID-19 tests and severe clinical symptoms in both sexes, older than 16 years, were included in the study. Two groups of patients with positive or negative neurologic complications were compared by chi-square or Fisher exact test for categorical variables. The differences in continuous variables between the two groups were investigated using an independent sample t-test. The Kolmogorov-Simonov test was used to verify the normality assumption. A *P* less than 0.05 was considered statistically significant. The study included 204 individuals (130 males and 74 females) out of 270 ICU patients. Ninety (44.1%) patients were discharged, while 114 (55.9%) died. Overall, 17 (8.3%) patients had neurological complications, while 187 (91%) did not (*P*=0.005). The two groups did not have significantly different mean age (*P*=0.325) and sex (*P*=.793). The ventilation support was significantly different in the two groups (*P*=0.002). The death group had a higher incidence of loss of consciousness (*P*=0.003). COVID-19 causes neurological symptoms, especially during the inflammatory phase, and clinicians should be alert for neurological issues.

Acta Med Iran 2022;60(4):210-214.

Keywords: Coronavirus disease 2019 (COVID-19); Neurology; Manifestations; Critical care

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first found in China in December 2019. After that, it spread over the world and caused the COVID-19 pandemic (1).

The mortality range in critically ill patients with COVID-19 is as wide as 11-61% (2). There are some predictors of disease severity such as older ages (3), comorbidities such as cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes mellitus (4), and laboratory tests and markers such as white blood count (WBC) count (5), D-dimer (6) and lactate dehydrogenase (LDH) (7).

Neurological symptoms are prevalent among COVID-19 patients. Some of them are minor and non-specific, like headache and dizziness (8). In the advanced stages of the disease, both the peripheral and central nervous systems (CNS) may be affected (8).

Possible CNS complications include meningitis, acute myelitis, stroke, and encephalopathy (9,10,11). Complications of the peripheral nervous system may include Guillain-Barré syndrome, anosmia, chemosensory dysfunction, and skeletal muscle damage (12,13). Through the enteric network or terminal nerves of the respiratory tract, the virus can invade the CNS (8). Invasion of the virus, besides the cytokine storm and inflammatory responses, may cause complications like acute myelitis, meningitis, encephalitis, and encephalopathies (11). Another neurologic complication

Corresponding Author: M.T. Beigmohammadi
Department of Anesthesiology and Intensive Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9121759016, Fax: +98 2166940033, E-mail address: mbage46@gmail.com

may be rupture of the vessels wall because of the interaction of the ACE2 receptor and damage of the arteries due to SARS-CoV-2 and coagulation disorders such as disseminated intravascular result hemorrhagic stroke (14,15). This COVID-19 related stroke can cause focal inflammation and secondary brain injury (16).

We conducted this study to evaluate the acute neurological manifestations in critically ill patients with COVID-19.

Materials and Methods

Study population and setting

After review and approval by the university ethics committee (IR.TUMS.VCR.REC. 1399. 192), a cohort study was conducted to evaluate the acute neurological manifestations in 204 patients admitted to intensive care units (ICU) tertiary Imam Khomeini hospital complex, Tehran university of medical sciences, Tehran, Iran. The participants included laboratory-confirmed positive tests and clinical manifestations for severe COVID-19 from both sexes, age>16 years old. Severe COVID-19 criteria are defined as: Shortness of breath, RR≥30 times/min, Oxygen saturation≤93%, Oxygenation index≤300 mmHg, Chest radiographic images showing more than 50% of affected tissue within 24-48 h.

Data collections and outcome

Demographic data, comorbidities, chronic medical conditions, vital signs, and laboratory values (as based value) were collected by physicians who visited patients in ICU immediately after admission. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scoring were performed and recorded in the first 24 hours and day to day for SOFA score. The primary outcome was neurological complications, and the secondary outcome was death or discharge from ICU. The patients were divided into two groups: 1) the patients with neurologic complications and 2) the patients without neurologic complications. We recorded neurologic complications during ICU admission, including loss of consciousness (LOC) with Glasgow Coma Scale (GCS)<10, seizure, lethargy, delirium, and paresis. Risk factors include hypertension, diabetes mellitus, obesity, respiratory diseases, and a history of cerebrovascular or cardiovascular events. Other data such as ICU and hospital length of stay and the need for additional ventilation support were considered factors that may affect patient outcomes.

Statistical analysis

Two groups of patients with positive or negative neurologic manifestations were compared by chi-square or Fisher exact test for categorical variables. An independent sample t-test was applied to study the differences between the two groups' continuous variables. Normality assumption was checked using the Kolmogorov-Simonov test. Values are shown as mean±SD or as number and percentage for continuous and categorical variables, respectively. In this study, *P* less than 0.05 was considered statistically significant. Statistical analyses were carried out by SPSS version 16.0 for Windows.

Results

Of 270 ICU patients, finally, 204 patients (130 male and 74 female) with severe confirmed COVID-19 have been enrolled in the study. Of all patients, 90 (44.1%) patients were discharged, and 114 (55.9%) expired. Overall, 17 (8.3%) patients were with neurological manifestations and 187 (91.7%) without neurological manifestations (*P*=0.005, RR=5.921). The two groups did not have significantly different mean age (59.5±17.1, 62.8±13.3, 95% CI: -10.258_3.413, *P*=0.325) and sex (*P*=0.793). The kind of ventilation support was significantly different in the two groups (*P*=.002) (Table 1).

The duration of mechanical ventilation in the group with neurologic complications was significantly less than in the other group (16 vs. 93 hours, *P*<0.001, 95% CI: 2.102-124.438). The rate of neurologic manifestations was significantly different in the two groups of discharged and dead patients (15 vs. 99, *P*=0.005). The most neurologic manifestation was LOC. The rate of LOC was significantly more in the death group (*P*=0.003, 95% CI: 1.036-1.160) (Table 2).

Table 1. Characteristics of patients in two groups with and without neurologic manifestations

Variable		Neurologic manifestations		*P*	RR	95% CI	
		Yes	NO			Lower	Upper
Age, yr, %	**≥ 60**	12 (10.3)	105 (89.7)	0.311	1.8	0.653	4.759
	< 60	5 (5.7)	82 (94.3)				
Sex, %	**Male**	10 (8.3)	120 (91.7)	0.793	.8	0.323	2.046
	Female	7 (9.9)	64 (90.1)				
BMI, %	**≥ 30**	6 (17.2)	29 (82.8)	0.083	2.7	1.017	6.995
	< 30	9 (6.5)	131 (93.5)				
Comorbidities, %	**Yes**	14 (8.5)	152 (91.5)	0.607	3.3	0.554	24.574
	No	3 (7.9)	35 (92.1)				
Kind of ventilation support, %	**Invasive**	5 (17.3)	24 (82.7)	0.002	--	--	--
	Non-invasive	1 (1.1)	93 (98.9)				
	Both	11 (13.6)	70 (86.4)				
APACHE-II, mean±SD		14.3±4.1	11.9±6.1	0.121	--	-.626	5.337
SOFA, Mean±SD	**First day,**	7.4±3.5	4.3±2.7	0.000	--	1.512	4.639
	Daily mean SOFA	8.2±3	5.3±3.1	0.001	--	1.145	4.653
Laboratories data	**WBC**	11×10^3 ±3×10^3	1×10^3 ±5×10^3	0.042	--	-1199.079	3974.445
	Neutrophil, %	85±6.7	82.7±8.5	0.196	--	-1.844	6.500
	Lymphocytes, %	9.9±6.1	12.26.8	0.688	--	-5.628	1.161
	Platelets	206×103 ±107×103	268×103 ±127×103	0.421	--	-1.258	358.364
	Hb	11.4±1.4	11.9±1.8	0.290	--	-1.441	.364
	ESR	61.1±27.5	79.1±26.6	0.701	--	-33.517	-2.648
	CRP	79.3±48.4	120.9±83	0.149	--	-89.689	6.384
Oxygenation	**PaO2**	87.2±29.4	72.6±22.3	0.422	--	-2.337	24.169
	SpO2%	91.6±4.5	91±5.1	0.947	--	-2.073	3.179

BMI: Body Mass Index, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, WBC: White Blood Cell, Hb: Hemoglobin, ESR: Erythrocyte Sedimentation Rate, CRP: C- Reactive Protein, PaO2: Partial Pressure of Oxygen, SpO2: Saturation of Peripheral Oxygen

Table 2. Comparison of neurologic manifestations in the discharged and dead patients

Variable		Manifestations		*P*	RR	95% CI	
		Death	Discharge			Lower	Upper
Neurologic manifestations, %	**Yes**	15 (13.2)	99 (86.8)	0.005	5.9	1.390	25.224
	No	2 (2.2)	88 (97.8)				
	LOC	12	0	0.003	1.9	1.637	2.126
	Delirium	5	2	0.468	1.3	0.795	2.097
	Lethargy	7	0	NA			
	Seizure	2	0	NA			
	Paresis	1	0	NA			

LOC: loss of consciousness, RR: Relative risk, CI: Confidence interval

Discussion

Of 204 patients, 114 (55.9%) patients had mild to severe neurological manifestations, and a total of 17 (14.9%) patients died. The total mortality rate was 8.3%. Klok *et al*., (17) reported a cumulative incidence of stroke of 3.7%. Ashrafi *et al*., (18) showed the patients had at least one neurologic symptom (55.4%). A prospective multicenter cohort study by Koh *et al*., (19) included a total of 47,572 patients. Thirty-nine patients had neurological manifestations; of these patients, 84.4% were asymptomatic or had mild symptoms, 2.2% had severe, and 13.3% had critical SARS-CoV-2 infection. (8). In the Nurtz study (20) rate of severe neurologic complications was 18.4%. This difference in the rate of neurologic complications comes back to the kind and severity of neurologic complications in various studies. It is not clear whether the neurological complications are because of the SARS-Cov2 infection or critical illness (20). In fact, data regarding the incidence of neurological complications in COVID-19 are scarce, and the precise pathophysiology of SARSCoV2 viral spread remains largely unknown (20).

COVID-19 is associated with a broad spectrum of neurological manifestations; the peripheral and central nervous systems may be affected by inflammation and

vascular events (8).

The underlying mechanisms of these syndromes may be multifactorial, resulting from combined or independent effects of sepsis, hypoxia, thrombosis, and cytokine storms (8).

The mechanism of neurologic complications of COVID-19 is not well understood. Several mechanisms have been explained for neurologic complications of COVID-19. Previously, neurological infections were reported in patients with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) caused by other forms of coronavirus (21).

A systematic review found that 6% of the patients who had a CSF analysis had a positive SARS-CoV-2 in their CSF (21). CSF cell count was increased in 43% of fatal cases, 25.7% of severe cases, and 29.4% of non-severe cases (21). The potential direct viral invasion of the nervous system is supported by many observations (21). Cytokine storms can cause damage to the blood-brain barrier, and their potential role in neurological complications has been documented, specifically in acute necrotizing encephalopathy cases (21). Another factor that plays a role in neurological complications associated with COVID-19 is the severity of the illness. Since the brain is susceptible to hypoxia, prolonged COVID-19-mediated hypoxia could cause serious complications (21). In our study, the WBC count was significantly different in the two groups (P=.04). Also, Mao *et al*., (10) showed that the lymphocyte and platelet count was significantly lower in the patients with neurological manifestations.

In the clinical approach, our study showed that above the age of 60 years and BMI>30 risk of neurologic complications increased 1.7 and 2.6 times, respectively. However, statistically, neurologic manifestations did not increase with age and BMI. Against this, some studies showed increased BMI with an increase in the age rate of neurologic manifestations (18). Against Sharifi's study (18), in our study, O2 saturation was the same in two groups with and without neurologic manifestations, and neurologic complications were higher in critically ill patients.

Moreover, identifying patients at risk for neurological complications and how to control these risks should be elucidated, together with the underlying pathophysiological mechanisms. Given the hyperinflammatory state, it would be interesting to study whether the incidence of neurological complications has changed with the standard use of dexamethasone in patients with COVID-19 during the second wave (8).

The acute ischemic stroke might occur due to a destabilized carotid plaque or as a result of atrial fibrillation. Viral replication in the cerebral blood vessels could be a possible reason for such complications (8).

This study may provide important clinical information on COVID-19 to help clinicians improve awareness of its involvement in neurologic manifestations. In case of a significant mortality rate associated with COVID-19, it is crucial to recognize that sudden clinical deterioration may be linked to a neurologic event such as stroke. Furthermore, during the epidemic period of COVID-19, clinicians should consider SARSCoV-2 infection as a possible diagnosis in patients with neurological manifestations.

Limitations

Some neurological features such as encephalitis, encephalopathy, and myelitis might not be diagnosed at the time of hospitalization as they manifest later. Furthermore, sepsis and other conditions in the intensive care unit are important risk factors for neurological complications such as encephalopathy and neuropathy that we cannot differentiate between them. Further investigations are needed to understand the pathophysiology and neurologic complications of COVID-19.

COVID-19, caused by SARS-CoV-2, is associated with neurological manifestations, particularly during the hyperinflammatory phase. Even though the underlying pathophysiology is still not fully known, clinicians in the ICU should be vigilant of neurological problems while treating critically ill patients with COVID-19. This will improve our knowledge and help investigate the pathophysiology of this novel disease, potentially leading to better therapies. The neurological manifestations are a frequent consequence of SARS-CoV-2 infection and COVID-19 infection that affects millions of people worldwide, with all stages of COVID-19 severity and with or without comorbidities.

Acknowledgments

We want to thank the ICUs and research center staff at Imam Khomeini Hospital Complex for supporting this study.

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