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Neurological Involvements in COVID-19: A hospital-based study

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Abstract

Objectives

The SARS-CoV-2 pandemic is the most challenging crisis in the contemporary world. Besides severe pulmonary involvement, the disease also has several extrapulmonary manifestations, and new signs and symptoms are associated with it every dayThe present study aimed to inquire about the frequency of neurological manifestations and risk factors of COVID-19.

Materials & Methods

This retrospective, descriptive study included patients with neurological involvement admitted to the Alborz University of Medical Sciences academic hospitals from March 2020 to July 2020 with confirmed COVID-19 infection. The data included in the analysis were the patient's demographic information, underlying diseases, neurological manifestations, and laboratory findings.

Results

The study included ninety-five patients with a mean age of fifty-nine. Neurological symptoms and signs were observed in 91.6% and 10.5% of the patients, respectively. The most frequently associated neurological symptoms of COVID-19 were fatigue (49.5%), headache (47.4%), and dizziness (45.3%). Furthermore, the most common neurological involvements included gait disorders (6.3%), cerebellar dysfunction (4.2%), and cerebrovascular accidents (3.15%). Positive troponin was shown to be the strongest predictor of neurological signs (OR=21, P=0.017), followed by WBC≥15,000 (OR = 20.75, P=0.018) and a history of respiratory disease (OR=7.42, P=0.007).

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Conclusion

Neurological symptoms were observed in more than 91% of the patients, while neurological signs were present in 10.5% of the COVID-19 patients. Additionally, positive troponin, WBC≥15,000, and a history of respiratory disease were the strongest predictors of neurological signs.

Keywords: COVID-19; Neurological Manifestations; SARS-CoV-2
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Introduction

Human coronaviruses (HCoVs) characterize a major group of coronaviruses (CoVs) associated with multiple respiratory diseases of varying severity, including the common cold, pneumonia, and bronchiolitis (1). Four viruses of this group, including HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, are widely circulating in the human population globally, causing almost one-third of all common cold cases in humans (2). Although these four viruses often result in mild-to-moderate infections, they may lead to life-threatening bronchiolitis and pneumonia in severe cases. These are primarily seen in older patients, children, and immunocompromised patients. However, other HCoVs, including SARS-CoV, MERS-CoV, and SARS-CoV-2, are highly virulent and cause fatal infections and multiple extrapulmonary manifestations, which have been observed in the related epidemics/pandemics (2).

Thus far, there have been three outbreaks due to these viruses. SARS-CoV was first reported as unusual pneumonia in 2002 in Guangdong, China, with fever, headache, and respiratory manifestations such as cough and severe dyspnea. It was highly contagious, spreading rapidly in thirty-seven countries. SARS-CoV had a mortality rate of about 10%, responsible for 8,448 infection cases and 774 deaths (3). The MERS-CoV epidemic started in 2012 in Saudi Arabia with clinical symptoms similar to SARS-CoV; however, it had a much higher mortality rate of about 35%. Unlike SARS-CoV, which caused a pandemic, MERS-CoV had a more limited geographical spread. It ended with more than 1,000 infection cases and 400 deaths in the first epidemic, while just a few outbreaks of

this virus have been reported since then (2, 4). The SARS-CoV-2 (COVID-19) pandemic originated in Wuhan, China, and led to the discovery of the most recent HCoV. In Iran, the first confirmed cases of COVID-19 were reported on February 19, 2020, with the first mortalities reported on the same day (5). As of this writing, more than 248 million infected cases and more than five million deaths have been reported globally due to SARS-CoV-2 (6). Although the mortality rate is still lower than that of the SARS-CoV and MERS-CoV, infection cases and deaths are much higher. Among all the countries involved, Iran ranks 8th with 5,954,962 infected cases and 126,763 deaths (6).

It has been observed that all the coronavirus family viruses have extrapulmonary manifestations and their common pulmonary symptoms. These manifestations vary in type and prevalence between different HCoVs and can increase the mortality of the affected patients. For SARS-CoV, these extrapulmonary manifestations include hematologic manifestations, such as lymphopenia, thrombocytopenia, neutrophilia, and disseminated intravascular coagulation (DIC); diarrhea; hepatic impairments; headache(7); myopathy; neuropathy; and stroke (8). In MERS-CoV, these manifestations are more extensively studied and reported. They can be hematologic, such as lymphopenia, thrombocytopenia, and neutrophilia, or gastrointestinal, such as abdominal pain, diarrhea, and vomiting. Neurological involvement such as encephalitis, Guillain-Barré syndrome, seizures, confusion, polyneuropathy, stroke, ataxia, decreased level of consciousness, and motor disorders are also seen along with renal problems such as acute renal failure (4, 9, 10).

Regarding SARS-CoV-2, several pulmonary and extrapulmonary manifestations have been reported, with new manifestations being attributed to this infection every day. So far, renal, hepatic, hematologic, gastrointestinal, cardiovascular, and neurological involvements have been reported (11, 12). Since neurological involvement can rapidly lead to death or permanent sequelae, early detection of potential neurological complications and their predictors before the onset of the complication can help identify high-risk patients that may need special care. Therefore, the present study intended to investigate the frequency of neurological signs and symptoms of SARS-CoV-2 and their predictors.

Materials & Methods

The present retrospective, descriptive study was conducted at the academic hospitals of the Alborz University of Medical Sciences, Karaj, Iran, from March 2020 to July 2020. Based on the census method, all the patients who presented with neurological involvement to the mentioned hospitals in the study duration with COVID-19 infection confirmed by the polymerase chain reaction (PCR) or Computed tomography (CT) scan were included. The data was extracted from patients' records with the approval of the Ethics Committee of the Alborz University of Medical Sciences (Approval ID: IR.ABZUMS.REC.1399.083). The participants gave written or oral informed consent for face-to-face or telephone interviews or any clinical or paraclinical measures needed (in the case of telephone interviews). The data included age, gender, and underlying diseases (hypertension, diabetes, ischemic heart disease, ischemic and non-ischemic cerebral diseases, malignancy, renal impairments, and hepatic diseases). It also included clinical symptoms (fever, myalgia, cough, sore throat, diarrhea, vomiting, dyspnea, and abdominal pain), clinical

signs (body temperature, respiratory rate, evidence of respiratory distress, oxygen saturation, lung examination findings), laboratory findings (blood cell count, inflammatory markers, renal function tests, electrolytes, liver function tests, arterial blood gas analysis), and imaging findings (radiographs and chest CT images).

Neurological manifestations were divided into two groups of symptoms and signs. Neurological symptoms included olfactory, auditory, taste, or visual disturbances, seizures, balance disorders, mood swings, and involuntary movements, such as tremors, paresthesia, dizziness, weakness, fatigue, and decreased level of consciousness. Neurological signs included focal neurological findings, cerebellar function tests, musculoskeletal examination, and cranial nerve examination findings. To prevent the disease from spreading, this study minimized unnecessary visits for further examinations, and the data were collected mainly from patients' records. The disease severity was determined using the guidelines of the American Thoracic Society (13).

Data were analyzed using the SPSS software version 21. Qualitative data were reported in frequency percentage, while quantitative data were reported in mean±standard deviation. Moreover, qualitative data comparisons were performed using the Chi-square and Fisher's exact tests, while the inter-variable correlations were investigated using Spearman's correlation. Inter-group comparisons of the quantitative data were performed using the independent t-test and Mann-Whitney test. Cut-off points were determined for quantitative variables correlated to neurological symptoms through the receiver operating characteristic curve. Logistic regression was then used to identify neurological signs and symptoms predictors.

Results

The study included ninety-five patients with a mean age of fifty-nine years (min:16 - max:88) who were confirmed COVID-19 cases, of which fifty-three were female, and forty-two were male. 70.5% of the patients suffered from at least one primary underlying disease (see Table 1). The most common clinical symptoms observed in the participants were dyspnea (64.2%), dry cough (54.7%), myalgia (53.7%), and fever (50.5%).

Table 2 summarizes the frequency of neurological signs and symptoms. Neurological symptoms were observed in 91.6%, while neurological signs were observed in 10.5% of the patients. The most common neurological symptoms included fatigue (49.5%), headache (47.4%), and dizziness (45.3%). Furthermore, the most common neurological signs were gait disorders (6.3%) and impaired cerebellar tests (4.2%). Similarly, 3.15% of patients presented with cerebrovascular accidents (CVA). Using the Chi-square test (see Table 3), it was evident that gender and disease severity were not correlated with neurological manifestations. However, the presence of the underlying disease was significantly associated with neurological signs ($P<0.001$).

According to Spearman's correlation (see Table 4), it was shown that the presence of neurological signs had a significant positive correlation with WBC count ($r = 0.340$, $P=0.001$), serum sodium level ($r = 0.261$, $P=0.013$), and positive troponin ($r = 0.330$, $P=0.001$), and it had a significant negative correlation with the percentage of lymphocytes ($r = -0.272$, $P=0.009$) and serum LDH level ($r = -0.285$, $P=0.018$). Moreover, after adjusting for age, only respiratory diseases were significantly associated with neurological signs among all underlying diseases ($r = 0.316$, $P=0.003$). Age was also significantly correlated with neurological

signs after adjusting for the underlying diseases (r = 0.219, P=0.039). In other words, age and respiratory diseases were independently correlated with neurological signs. However, neurological symptoms were present in most patients, so no significant relationship was observed between these symptoms and other study variables.

Indicatively, positive troponin was the strongest predictor of neurological signs (OR=21, P=0.017), followed by WBC≥15,000 (OR = 20.75, P=0.018) and a history of respiratory disease (OR=7.42, P=0.007) using univariate logistic regression (see Table 5).

Table 1. Baseline characteristics of the patients

characteristics	Mean (SD) / %
Age (years)	59.37 (17.38)
Sex Male Female	 44.2% 55.8%
Comorbidity	70.5%
IHD	10.5%
HTN	33.7%
DM	27.4%
Neurologic disease	9.5%
Respiratory disease	6.3%
Hypothyroidism	10.5%
Etc.	21.1%

Table 2. Frequency distribution of signs and symptoms

Neurological symptom	90.1%
Fatigue/weakness	49.5%
Headache	47.4%
Dizziness	45.3%
Balance disorder	26.3%
Decreased LOC	17.9%
olfactory disorders	14.7%
taste disorders	12.6%
Paresthesia	7.4%
Seizure	3.2%
Etc.	4.3
Neurological sign	10.5%
cerebrovascular accident	3.15%
Impaired cerebellar tests	4.2%
Gait disorders	6.3%
Impaired deep tendon reflexes	2.1%
impaired muscular examination (tone, strength, volume)	1.1%
Impaired cranial nerve examination	1.1%

Table 3. Frequency distribution of qualitative variables by neurological signs and symptoms.

Clinical Finding Variable Yes (%) (n=10)		Neurological Sign			Neurological Symptom		
		No (%) (n=85)	P.Value	Yes (%) (n=87)	No (%) (n=8)	P.Value	
Gender	Male	30%	45.9%	0.322	43.7%	50%	0.733
	Female	70%	54.1%		56.3%	50%	
Underlying Disease	Absent	0%	32.9%	<0.001	28.7%	37.5%	0.626
	Present	100%	67.1%		71.3%	62.5%	
Disease Severity	Medium	66.7%	55.6%	0.729	58.3%	58.3%	1
	Severe	33.3%	44.4%		41.7%	41.7%	

Table 4. Frequency distribution of quantitative variables by neurological signs and symptoms.

Variable	Neurological Sign			Neurological Symptom			Total
	Present	Absent	P.Value	Present	Absent	P.Value	
Age (years)	73±10	58±17	0.007	59±18	65±13	0.424	59±17
Temperature (Ċ)	37.22±0.45	37.36±0.94	0.924	37.33±0.89	37.40±0.85	0.845	37.3±0.88
Respiratory Rate (per/min)	22±3	19±3	0.009	20±3	17±4	0.054	20±3
O2 Sat (%)	84±12	87±8	0.784	87±8	83±13	0.295	86±9
WBC (*109 cells/per lit)	11.203±4.460	6.674±3.192	0.001	7.226±3.599	6.398±3.824	0.326	7.156±3.604
Lymph (%)	12±5	20±10	0.009	19±10	16±7	0.481	19±10
ESR (mm/hr)	52±29	55±32	0.963	54±31	56±38	0.825	55±31
CRP (mg/L)	72±59	65±57	0.638	66±59	68±34	0.608	66±57
CPK (units/L)	142±93	362±954	0.889	347±950	357±460	0.788	347±922
BUN (mg/dL)	24±22	22±18	0.442	21±18	28±20	0.143	22±18
Creatinine (mg/dL)	1.57±1.12	2.5±10	0.63	1.46±1.32	2.35±2.82	0.124	1.53±1.50
Na (mEq/L)	140±9	134±14	0.013	134±14	138±7	0.239	135±14
K (mmol/L)	4.33±1.11	4.45±0.72	0.449	4.44±0.86	4.39±0.83	0.597	4.44±0.76
Ca (mg/dL)	8.62±0.56	8.33±0.57	0.216	8.39±0.57	8±0.53	0.068	8.35±0.6

Variable	Neurological Sign			Neurological Symptom			Total
	Present	Absent	P.Value	Present	Absent	P.Value	
Positive Troponin(%)	20%	1.2%	0.001	3.4%	0.0%	0.594	3.2%
LDH (U/L)	295±152	526±254	0.018	500±245	588±385	0.294	506±255
ALT (IU/L)	47±42	38±22	0.793	38±25	45±23	0.285	39±57
AST (IU/L)	72±109	42±24	0.547	45±45	48±16	0.187	46±44
PT (sec)	14±0.52	13±2.22	0.559	13±1	13±2	0.837	13±2
INR	1.13±0.06	1.09±0.30	0.059	1.09±0.28	1.09±0.12	0.662	1.09±0.3
PTT (sec)	34±8	34±6	0.85	34±6	30±6	0.476	34±6
BS (mg/dL)	160±168	140±89	0.511	143±15	84±30	0.183	145±98
P O2 (mmHg)	46±18	40±18	0.461	40±18	37±20	0.508	40±18
HCO3- (mEq/L)	23±2	23±6	0.721	24±6	20±3	0.063	23±6
P CO2 (mmHg)	44±7	39±9	0.233	40±9	34±3	0.204	39±9
pH	7.33±0.10	7.35±0.13	0.455	7.35±0.13	7.39±0.09	0.558	7.35±0.12

IU: International Units, WBC: White Blood Cell, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, CPK: Creatine Phosphokinase, BUN: Blood Urea Nitrogen, LDH: Lactate Dehydrogenase, ALT: Alanine Transaminase, AST: Aspartate Transaminase, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio, BS: Blood Sugar

Table 5. Univariate logistic regression for predictors of neurological sign

Predictors	OR	P.value
Age ≥ 65	7.42	0.015
Underlying Respiratory disease	11.71	0.007
Respiratory rate ≥ 20	5.68	0.021
WBC ≥ 15000	20.75	0.018
Na ≥ 138	6	0.020
Lymphocyte ≤ 10%	4.6	0.028
LDH ≤ 395	10.23	0.039
positive Troponin	21	0.017

Discussion

COVID-19 (SARS-COV2) has become a pandemic threatening healthcare systems worldwide (14). Transmission of the virus in humans occurs mainly through respiratory droplets. Like the previous coronavirus, it enters the cell through the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is also present in the brain (15).

In the present study, 70% of patients had at least one underlying disease, similar to the study

by Zhou et al. (16), in which the most common underlying diseases were hypertension (33.7%) and diabetes (27.4%). The most common symptoms of COVID-19 in the study of Wang et al. included fever, cough, and fatigue (17), which is relatively similar to this study's most frequent symptoms, including dyspnea (64.2%), dry cough (54.7%), and fever (50.5%), respectively. In addition, SARS-COV-2 causes several extrapulmonary symptoms. In the present study, about 90.1% of patients had neurological symptoms. Although the most common symptoms were fatigue (49.5%), headache (47.4%), and dizziness (45.3%), more severe manifestations such as balance disorder (26.3%), decreased level of consciousness (17.9%), and seizures (3.2%) were also significant. Moreover, the prevalence of neurological signs (10.5%) was significant in this study. Elevated troponin levels, WBC≥15,000, and a history of lung disease were the strongest predictors of neurological symptoms. Headache (16.8%) and dizziness (13.9%) were the most common manifestations in the systematic review of Correia et al. (18), which examined the neurological manifestations of coronaviruses. Although common neurological symptoms have been reported in various studies, their prevalence varies. For example, the first study which examined the neurological manifestations of SARS-COV-2 conducted by Mao et al. in Wuhan reported that 36.4% of patients had a neurological involvement. They mentioned that neurological manifestations were more common in people with the severe form of the disease, and headache (17%) and dizziness (13%) were the most common symptoms (19). In the meta-analysis of Favas et al. (20), the most common neurological manifestations were taste (38.5%) and olfactory disorders (35.8%). In the study of Kremer et al., consciousness alteration (73%), abnormal wakefulness (41%), confusion (32%), and agitation (19%) were the most common manifestations in severe COVID-19 patients with brain MRI findings (21). In comparison, headache (70.3%) and hyposmia (70.2%) were the most common manifestations in the study by Lechien et al. (22).

CVAs are one of the most severe neurological manifestations, which Mao et al. reported for the first time with a prevalence of 2.8% (19). Since then, several studies have reported CVA in hospitalized patients, most of whom have had ischemic strokes (23, 24). The prevalence of stroke varies from 0.7% in Annie et al.'s (25) study in patients under fifty years of age to 31% in Mahammedi et al. (26). In the current study, the prevalence of CVA was 3.15%. Although risk factors such as age and blood pressure may be involved in stroke in these patients, the prevalence of stroke is even higher in patients younger than fifty years with SARS-COV2 than in non-infected patients (25).

Following multiple viral infections, demyelinating encephalomyelitis and viral meningoencephalitis have been reported (27). Previously, Boucher et al. (28) obtained the human coronavirus OC43 (HcoV-OC43) from nasopharyngeal secretions and CSF in a fifteen-year-old boy diagnosed with acute disseminated encephalomyelitis (ADEM). Recently, SARS-CoV-2 has also been identified in the CSF of infected patients (21). The prevalence of encephalitis was reported to be 0.03% in Jain et al.'s study (29) and 0.1% in Romero-Sánchez et al.'s study (30).

The prevalence of seizures also varies in different studies. In the current study, seizures were present in 3.2% of patients. In the study of Mao et al. (19), seizures were reported in only one case out of 214 patients, while in Mahammedi et al.'s

study (26), the prevalence of seizures was 9%. A variety of focal and generalized seizures and even status epilepticus have been reported in studies (31). Numerous other neurological manifestations have been reported in studies. Altered levels of consciousness and delirium (32), ataxia, neuralgia (33), Guillain-Barré syndrome (34), and visual disturbances (19, 30) are some of them.

Although neurological manifestations are one of the most severe symptoms of SARS-COV2, few studies have directly examined the risk factors for neurological manifestations. Archie et al. (35) showed that smoking with increased ACE2 receptors is associated with an increased risk of SARS-COV2 infection neurological manifestations, including CVA. Also, in the study by Li et al. (36), elevated levels of d-dimer, CRP, inflammatory response, and older age were CVA risk factors. In the present study, leukocytosis was one of the strongest predictors of neurological signs (OR = 20.75, P = 0.018), indicating the inflammatory response's role in neurological signs. Besides, old age, a history of respiratory disease, tachypnea, and positive troponin were other predictors associated with secondary neurological disorders and other organ failures. Therefore, patients with these associated factors need more careful monitoring for the early detection of neurological symptoms, particularly vascular events.

The routes of virus entry into the CNS may be hematogenous, cranial nerves, or even the intestinal nervous system (37). Still, it is unclear whether the damage mechanism is directly related to the virus, the host's immune response against the virus, or both. Studies have shown that viral encephalopathy is mainly the result of cytokine inflammation, hypoxia, and metabolic dysfunction due to the failure of other organs. In contrast, stroke can be caused by hypercoagulability and endothelial damage induced by SARS-COV2 (38).

In Conclusion

the findings of this study showed that neurological symptoms are found in more than 91% of patients with SARS-COV2, the most common of which were fatigue, headache, and dizziness, respectively. Neurological signs were also observed in 10.5% of patients, and the most common of them were gait disturbance, cerebellar test dysfunction, and impaired deep tendon reflexes, respectively. Risk factors for neurological signs include age over sixty-five years, a history of respiratory disease, a respiratory rate greater than 20 bpm, WBC≥15,000, positive troponin, and LDH level less than 395.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available; however, the data can be shared for research and authentication purposes upon reasonable request.

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Author's contribution

HM, MN, FA, and AHMEK conceived the study and participated in the study design, data collection, and data analysis. HM, MN, and AHMEK wrote the manuscript. MQ, MAH, AN, and NBS participated in data collection and data analysis. AHMEK, FA,

MD, AN MA, KM, and MQ assisted with preparing the document and interpreting the results. All the authors have read and approved the final submitted manuscript.

Conflict of interest

The authors have declared no competing or potential conflicts of interest

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