



Factors Associated With Neurological Manifestations in Patients With COVID-19

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Abstract

Background: The coronavirus disease 2019 (COVID-19) is the most terrible pandemic of a respiratory disease that we had in the past century. Most existing studies explore different manifestations in COVID-19. Few recent studies have described neurological manifestations of patients with COVID-19 but their associations with age, laboratory findings, and mortality rates have not been explored well.

Methods: This case-control study includes 263 patients with COVID-19 without neurological symptoms (control group) and all patients with COVID-19 with the central nervous system symptoms (n=460, case group) hospitalized between February 2020 and April 2020. Data on demographic factors, medical history, symptoms, and laboratory tests, all are extracted from medical records.

Results: Out of 723 patients with confirmed SARS-CoV-2 infection, 460 (63.6%) were identified to have at least one neurological manifestation. The mean ages of patients with and without neurological manifestation were 60.6 ± 18.0 and 60.8 ± 15.7 years, respectively. The most common symptoms were myalgia (41%), headache (20.3%), and loss of consciousness (LOC) (16.5%). Women were more likely to develop a neurological manifestation ($P = 0.001$). Moreover, smoking history was significantly more in patients with neurological manifestations ($P = 0.03$). Also, we compared two groups in terms of tracheal intubation. The need for tracheal intubation was 19% and 12% in patients with and without neurological manifestations, respectively. Furthermore, the prevalence of intensive care unit (ICU) admission was 28% and 24% in patients with COVID-19, with and without neurological manifestations, respectively. Some of the neurological manifestations such as LOC, limbs weakness, and seizure might need more ICU admission and tracheal intubation. The frequency of comorbidities and the laboratory test results were almost similar between the two groups.

Conclusion: Myalgia, headache, and LOC were the most common neurological manifestations and their distributions varied depending on age. Only a few neurological manifestations were related to mortality and morbidity rates, while some of them occurred in mild cases.

Keywords: Neurology; COVID-19; SARS-CoV-2; Neurological manifestation.

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Introduction

Currently, the coronavirus disease 2019 (COVID-19) pandemic continues to be a serious public health challenge facing the world.¹ Although coronavirus infections mainly invade the respiratory tract, available evidence suggests that they may also target several non-respiratory organs, including the nervous system.² This neuro invasive potential is supposed to be a feature of

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) such as headache and disturbed consciousness.^{3,4} A few studies have described multiple neurological symptoms in patients with SARS-CoV-2 infection, including headache, dizziness, encephalitis, and loss of consciousness (LOC).⁵ One of these studies also revealed the potential role of the central nervous system (CNS) symptoms as a prognostic factor for the poor outcomes

of COVID-19.⁶ However, not only the knowledge about the frequency of different neurological manifestations is still scant, but also their association with age, laboratory findings, prognosis, and mortality rates are not well explored. Here, we aim to first report the frequency of neurological manifestations of COVID-19, as then investigate the factors associated with neurological manifestations.

Methods

Study Design and Participants

This retrospective observational study was done at two referral centers of designated COVID-19 Hospitals in Iran, i.e., Rajaei Hospital of Alborz University of Medical Sciences (ABZUMS) and Firoozgar Hospital of Iran University of Medical Sciences (IUMS). We collected data from February to April 2020 and only focused on the confirmed cases of COVID-19. During this study, we considered a confirmed COVID-19 case if any of the following conditions existed: (1) a positive result on polymerase chain reaction (PCR) test of nasal and throat swab specimens; (2) recognize the chest computed tomography (CT) scan appearance of COVID-19 based on two radiology specialists reporting. Based on these two conditions, 723 admitted patients were enrolled in the analysis.

Data Collection

We explored both paper and electronic medical records, laboratory results, and radiological reports for all patients. The collected data included demographic characteristics, past medical history, clinical factors including neurological signs and symptoms, COVID-19 related symptoms, patients vital sign at first examination in triage emergency ward, the laboratory findings on the first day of the admission, reverse-transcription PCR (RT-PCR) test, and chest CT scan findings reported by two expert radiologists. Two assistant professors of neurology reviewed neurological manifestations. It should be noted that only hospitalized patients were included in the study. Therefore, it might not fully describe the condition of patients with mild to moderate COVID-19 that were not admitted. Patients with unreliable neurological manifestations, history of neurological diseases and those with LOS were excluded from the study. We divided patients into two major groups: 1) patients with at least one neurological manifestation; 2) patients without any neurological manifestation.

Laboratory Testing

The following blood parameters were extracted from the blood tests performed on the first day of admission: white blood cells (WBCs), lymphocyte count (LYM), absolute lymphocyte count, (ALC), serum hemoglobin level (Hb), platelet count (PLT), lactate dehydrogenase

(LDH), creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), aspartate transaminase (AST), alanine transaminase (ALT), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), blood sugar (BS), potassium (K), and concentrations and serum level of vitamin D.

Medical History and Comorbidities

On admission, we have checked the patients' medical history, including seizure, cerebrovascular accident (CVA), diabetes mellitus (DM), hypertension (HTN), multiple sclerosis (MS), coronary artery disease (CAD), brain mass, cardiovascular disease (CVD), cancer, chronic renal failure (CRF), chronic liver diseases, psychological disorder, chronic respiratory disease, asthma, hypothyroidism, hyperthyroidism, immunodeficiency, autoimmune disease, hematological disease, and any other notable disorder.

Neurological Symptoms

Two neurologists extracted neurological symptoms from the medical records. More specifically, myalgia, headache, dizziness/vertigo, disturbed consciousness, encephalopathy, agitation, seizure, sleep disorder, disturbed taste, disturbed smell, blurred vision, diplopia, dysphagia, speech disorders, weakness of limbs (mono or hemiparesis and para or quadriparesis), urine incontinency, ataxia, and movement disorders are assessed.

Statistical Analysis

Continuous variables are described as means and standard deviations and compared by using Fisher's exact test. All statistical analyses were performed using R (version 3.3.0) software. The significant threshold was set at a $P < 0.05$.

Results

Of the 723 hospitalized patients with confirmed SARS-CoV-2 infection, 460 (63.6%) were identified to have at least one neurological manifestation. The most common symptoms were myalgia (41%), followed by headache (20.3%) and LOC (16.5%). The frequency of the various types of neurological symptoms observed in patients with COVID-19 is mentioned in Table 1.

The mean $\pm$ SD ages of patients with and without neurological manifestations were 60.6 ± 18.0 and 60.8 ± 15.7 years, respectively. Table 2 shows the demographic factors and the early vital signs of the included patients by the study groups.

We divided patients into three different groups based on their ages and compared different age groups based on the prevalence of each neurological manifestation. More precisely, we assumed three groups G1, G2, and G3 as younger than 40, 40-60, and higher than 60 years old, respectively. The prevalence of myalgia in G1, G2,

Table 1. The Frequencies of Neurological Symptoms Observed in COVID-19 Patients

Symptoms	No. (%)
Myalgia	41.03
Headache	20.35
LOC	16.57
Dizziness Vertigo	9.20
Encephalopathy	2.76
Meningeal	0.14
Agitation	2.22
Seizure	3.10
sleep disorder	4.28
Taste disturbance	6.99
Smell disturbance	7.14
Visual disturbance	0.45
Diplopia	0.60
Dysphagia	1.73
Speech disorder	3.35
Hemiparesis	3.04
Quadriparesis	3.46
Hypoesthesia paresthesia	4.74
Sphincteric disturbance	0.58
Lumbar pain	6.01

Abbreviation: LOC, loss of consciousness.

Table 2. Demographic Findings and Early Vital Signs of the Patients With and Without Neurological Manifestations

	Total	With	Without
No. of Patient	723	460	263
Age (year), Mean $\pm$ SD	60.7 $\pm$ 17.2	60.6 $\pm$ 18.0	60.8 $\pm$ 15.7
Gender (male/female)	412/311	250/210	162/101
Admission (ward/ICU)	527/196	327/133	200/63
SBP (mm Hg)	123.9	125	122.1
DBP (mm Hg)	78.5	78.4	78.8
HR (beat/min)	85.1	85.7	84.2
RR (breaths/min)	19.5	19.1	20.1
T ($^{\circ}$ C)	37.2	37.4	36.8
SPO ₂ (%)	91	91.1	91

Abbreviations: ICU, intensive care unit; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; T, temperature; SPO₂, blood oxygen saturation.

and G3 was 54%, 45%, and 34%, respectively. While the prevalence of headache was about 32% in G1, and less than 18% in the other two groups. The prevalence of decreased consciousness was less than 9% in G1 and G2, and around 25% in G3. Finally, the prevalence of seizure was around 9% in patients in G1 and less than 2% in the other two groups. 54% of patients with at least one neurological manifestation were men, while 62% of patients in the other groups were women ($P=0.001$). Also, smoking was prevalent in 7.44% of the patients with

neurological manifestations, compared with only 1.09% in the other group ($P=0.03$). We might need further studies with larger sample sizes to confirm the last two observations.

We also compared the two groups in terms of tracheal intubation. While 19% of patients with neurological manifestations required tracheal intubation, only 12% required intubation in the other group. More precisely, more than 56% of the patients with a decreased level of consciousness, 57.89% of patients with encephalopathy, and 59.09% of patients with seizures were intubated. The prevalence of intensive care unit (ICU) admission was 28% and 24% in patients with COVID-19 with and without neurological manifestations, respectively. The prevalence of ICU admission was 73.19% in patients with disturbed consciousness, 63.15% in patients with encephalopathy, and 54.5% in patients with weakness of limbs. As a result, we can conclude that patients with COVID-19 with some neurological manifestations such as decreased level or impaired consciousness, weakness of limbs, and seizure might need ICU admission and tracheal intubation. They might also be considered to predict poor prognosis.

Mortality rate was 25% and 21% in patients with and without neurological manifestations, respectively. The high mortality rate of the patients in our study is mostly attributed to the way we enrolled the patients. As mentioned, we did not investigate patients that were not admitted to the hospitals. Moreover, the vital signs of the patients in both groups (with vs without neurological manifestations), including respiratory rate (19 vs 20), body temperature (37.36 vs 37.35), and O₂ saturation (91.17 vs 91.02) were very close. Table 3 shows that the frequency of comorbidities between two groups is almost the same.

In addition, the laboratory test results were almost similar between patients in the two groups, as all P values were greater than 0.05, except for ALT and CPK (Table 4).

Discussion

Shortly after the declaration of the COVID-19 pandemic,

Table 3. Comparison of the Frequency of Comorbidities Between Two Groups With and Without Neurological Symptoms

Comorbidities (%)	With Symptoms	Without Symptoms	P Value < 0.1
Seizure	2.85	1.96	NO
CVA	8.85	7.48	NO
DM	39.66	32.03	NO
HTN	48.58	39.45	NO
Brain mass	0	0.39	NO
MS	0.28	0.78	NO
CAD	23.93	27.34	0.03
Other	43.88	39.16	NO

Abbreviations: CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; MS, multiple sclerosis; CAD, coronary artery disease; NO, not observed.

Table 4. Comparison of the Laboratory Test Results Between Two Groups, With and Without Neurological Manifestations

Lab Findings	Total	With	Without	P Value
WBC ($\times 10^3/\mu\text{L}$)	8139.6	8103.1	8203.8	0.839
LYM ($\times 10^3/\mu\text{L}$), (%)	1672.7	1645, (20.3)	1714, (20.9)	0.55
ALC	1432.8	1462.4	1378.7	0.57
Hb (g/dL)	13.13	13.29	12.85	0.55
PLT ($\times 10^3/\mu\text{L}$)	205324	199919	214823	0.67
PTT (s)	34.5	34.4	34.5	0.76
PT (s)	15.1	14.9	15.39	0.37
INR	1.15	1.16	1.12	0.25
BS (mg/dL)	155.4	157.5	151.7	0.08
K (mEq/L)	4.1	4.06	4.2	0.62
ESR (mm/h)	41.3	41.02	41.7	0.2
AST (U/L)	70.5	63.8	81.6	0.08
ALT (U/L)	59.3	48.9	76.6	0.016
LDH (U/L)	659.9	652.4	672.5	0.25
CPK (U/L)	329.7	358.8	280.2	0.05
Vit D (ng/mL)	22.9	22.8	23.07	0.28

Abbreviations: WBC, white blood cell; LYM, lymphocyte; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelets; PTT, partial Thromboplastin Time; PT, prothrombin time; INR, international randomized ratio; BS, blood sugar; K, potassium; ESR, estimated sedimentation rate; AST, aspartate Aminotransferase; ALT, alanine Aminotransferase; LDH, lactate Dehydrogenase; CPK, creatine phosphokinase.

studies demonstrated numerous non-respiratory features of COVID-19. Among them, neurological symptoms were the most important ones. In this regard, dozens of neurological signs and symptoms in were reported in patients with COVID-19 by clinicians from different countries.^{7,8} There were some mechanisms in the development of neurological symptoms among these patients. The most important theory is the direct invasion of SARS-CoV-2 through neurons by the ACE2 receptor.⁹ In this study, we evaluated the frequency and characteristics of patients with COVID-19 with neurological manifestations. Among 21 neurological manifestations in this study, myalgia, headache, and disturbed consciousness were the most prevalent ones, followed by dizziness/vertigo, smell disturbance, and taste disturbance. The findings from recent studies showed similar results. In this regard, Bhola and colleagues, in a comprehensive review, demonstrated that headache and chemosensory impairment were the most prevalent neurological manifestations in patients with COVID-19.¹⁰ Moreover, some studies evaluated the post-COVID-19 neurological manifestations. A meta-analysis consisting of 18 studies (10530 cases) revealed some neurological symptoms such as fatigue, headache, brain fog, attention disorder, and myalgia as the post-COVID-19 complications three-month after disease onset.¹¹

Our study indicated a 63.6% prevalence of at least one neurological involvement among the patients with

COVID-19 who were assessed for the neurological symptoms. Previous studies have also presented a prevalence of 45.5 to 84% for neurological symptoms in patients with COVID-19.¹² Review studies about the neurological manifestations of COVID-19 usually divided these symptoms into CNS and PNS symptoms. In that regard, headache and loss of smell/taste are considered to be the most common symptoms in the CNS and PNS, respectively.^{12,13} We noticed that in our study, smell and taste disturbances were less prevalent compared to other reports.⁴ Based on a recent systematic review consisting of 83 studies ($n=27492$) about the olfactory dysfunction in patients with COVID-19, the pooled prevalence of overall smell disturbance was assessed to be 47.85%.¹⁴ This might be due to the collected data in which we excluded patients with mild to moderate COVID-19. Our results also showed that the neurological symptoms were not distributed uniformly for patients with different age ranges. While headache, myalgia, and seizure were the most prevalent symptoms in young patients, disturbed consciousness was mostly presented in older patients. In our study, some neurological manifestations including blurred vision, diplopia, ataxia, movement disorders, obvious autonomic symptoms, and urine incontinency are not seen in any patients. Based on this study, there are certain neurological manifestations including disturbed consciousness, encephalopathy and seizure that will predict poor prognosis. In addition, some neurological symptoms including myalgia, headache, taste and smell disturbances are more common in young patients and mild cases infected with SARS-CoV-2. The absence of a significant difference in admitting vital signs, including respiration rate per minute, body temperature and oxygen saturation, intubation rate, ICU admission, and mortality rate indicates that neurological manifestations, in general, cannot predict the prognosis. We also noticed that only disturbed consciousness, encephalopathy, weakness of limbs and seizure can be considered as the neurological sign or symptoms with a meaningful relationship to increased tracheal intubation, ICU admission, and mortality rate. Smoking rate was significantly higher in patients with COVID-19 with neurological manifestations. However, the number of smokers in our study was 48 requiring further investigation with higher sample sizes to get a more concrete conclusion. In this study, the underlying diseases and comorbidities were not associated with a higher incidence of neurological manifestations. No laboratory findings showed a significant difference between the two groups. However, Ashrafi and colleagues found a higher neutrophil to lymphocyte ratio and C-reactive protein in patients with COVID-19 with neurological manifestations compared to those without any neurological signs.¹⁵

In conclusion, a substantial proportion of the admitted patients with COVID-19 had at least one neurological manifestation which was seen more frequently among

smokers. Based on our findings, myalgia, headache and alteration in mental status were the most common symptoms that can be seen in patients with moderate to severe involvement. With respect to the large meta-analyses, it can be understood that patients with moderate to severe involvement had less manifestations in taste and smell disturbances compared to those with mild involvement. The prevalence of neurological symptoms among mild to moderate COVID-19 patients were a limitation in this research that must be considered in further studies.

Authors' Contribution

All authors have read and approved the manuscript. MRG involved in patient management, and revised the manuscript. ZM reviewed results and revised the manuscript. MZ, TK, MR, HD and PSS collected the data. MZ, MMN drafted and collected the data. EH drafted, analyzed the data, reviewed results and revised the manuscript. MY involved in patient management, and reviewed the results. MA did the background research, reviewed results and revised the manuscript.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to ethic consideration and policy of our center but are available from the corresponding author on reasonable request.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

This study was performed in accordance with the Declaration of Helsinki. The Research and Ethics Committees of both ABZUMS and IUMS approved the study protocols (IR.ABZUMS.REC.1399.025.). A unique identification number was assigned to each patient to protect the confidentiality of the participants.

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