NEUROLOGICAL MANIFESTATIONS OF SARS-COV-2 INFECTION AMONG HOSPITALIZED PATIENTS

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ABSTRACT

Introduction*: Neurological symptoms in SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infected patients and the course of COVID-19 in patients with neurological findings are determined.*

Material and methods*: Inpatient cases aged ≥18 years, followed-up in clinical services for COVID-19 diagnosis are studied. Patients were visited on 04.20.2020 and examined for central nervous system (CNS), peripheral nervous system (PNS) manifestations and muscular injury, from onset of symptoms to hospitalization. Risk factors associated with the severity of COVID-19 and the comparison of variables in terms of existence of neurological findings including CNS and PNS findings were performed.*

Results*: Overall, 133 (54%) of the 242 patients of the study were male, mean age was 56.82±16.35 (18–91) years. Of these, 128 (52%) cases were defined as severe COVID-19. Outstanding symptoms at the onset were cough (62.8%), fever (46.7%), dyspnea (45.9%), and tiredness (31%). Further, 82 (33.9%) cases showed neurological findings at the first admission. Of those with neurological symptoms, 25.6% had CNS, 16.1% had PNS, 1.7% had muscular symptoms. In patients with CNS manifestations, the most common symptoms were headache (20.6%) and dizziness (7.4%). Impaired taste was the most common manifestation of PNS (11.2%). Neurological symptoms showed no significant difference between severe and non-severe COVID-19 groups except impaired taste (significantly higher in non-severe group). During follow-up, 17 (7%) patients needed intensive care unit. Nine (3.6%) patients died.*

Conclusion*: Frequency and variety of neurological findings in COVID-19 cases is too high to underestimate. Early diagnosis of these findings may prevent spread of COVID-19.*

Keywords*: COVID-19, SARS-CoV-2, neurological manifestations.*

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Introduction

Coronaviruses are important pathogens that often cause respiratory and enteric diseases in humans and animals. In early December 2019, reviews on a number of unexplained severe cases of atypical pneumonia in Wuhan City, Hubei, China, indicated that this causative agent of pneumonia is a new type of corona virus, and it was named as severe acute respiratory syndrome CoV-2 (SARS-CoV-2).

The clinical picture caused by this new agent was defined as Coronavirus disease 2019 (COVID-19), and COVID-19 cases have been reported in many regions around the world. On March 12, 2020, the World Health Organization (WHO) declared it a pandemic. Presently, nearly 12 million COVID-19 cases have been identified in the world[1,2].

SARS-CoV-2 invades human respiratory epithelial cells via its S-proteins and angiotensin-converting enzyme 2 (ACE2) receptors on alveolar

epithelium[3]. ACE2 receptors are primarily present in lung epithelium but are also present on the surface of neurons, which is responsible for potential neurotropism [4]. SARS-CoV-2 enters the central nervous system (CNS) via the hematogenous or neuronal retrograde route. In the hematogenous route, the virus will either infect endothelial cells of the blood-brain-barrier or epithelial cells of the blood-cerebrospinal fluid barrier in the choroid plexus located in the ventricles of the brain or leukocytes. The other route for CNS invasion is via neuronal dissemination. Initially, the virus infects the neurons in the periphery and uses the active transport present in these cells, and then enters the CNS [5,6]. Coronaviruses first invade peripheral nerve terminals and then enter to the CNS via a synapse connected route. The trans synaptic transmission has been well documented for hemagglutinating encephalomyelitis virus 67 (HEV67). HEV67 is single stranded RNA virus belongs to betacoronaviruses like SARS-CoV 2. HEV virions initially budded from endoplasmic reticulum-Golgi intermediate compartments in the neurons and collect in coated vesicles through Golgi complexes then they exocytosed from the host neuronal cells and entered into the next-order neurons by endocytosis. Intraneuronal dissemination rate for SARS-CoV2 and other human coronaviruses has not been well documented. In a study, virus antigens were detected in the olfactory bulb during 60-66 h postinfection. SARS-CoV may enter the brain via the olfactory bulb, leading to rapid transneuronal dissemination in transgenic mice. They also detected viral invasion in regions of the cortex (pyriform, infralimbic cortices, basal ganglia, and midbrain) connected with the olfactory bulb[7, 8]. SARS-CoV-2 was identified in the cerebrospinal fluid by PCR in a case of encephalitis associated with SARS-CoV-2[9,10].

Although the most common symptoms in those infected with SARS-CoV-2 belong to the lower respiratory tract, COVID-19 may also present neurological symptoms[11-12]. Underestimating some neurological symptoms that are usually considered in most viral diseases that are not life-threatening might lead to the late diagnosis of COVID-19, especially when such symptoms are not questioned.

In the present study, we therefore questioned the neurological symptoms that are present at the time of first admission to the hospital in cases administered inpatient treatment for COVID-19 to determine which neurological symptoms COVID-19 may present and how the course of COVID-19 progresses in patients with neurological findings.

Material and methods

This prevalence study included inpatient cases aged ≥18 years who were followed-up in clinical services, excluding those followed-up in the intensive care unit (ICU), for COVID-19 diagnoses made with the ICD code U07.3 on 04.20.2020. Those who did not have pneumonia or mild pneumonia were not included in the study because they were followed-up as outpatient cases as per the national guidelines on COVID-19[14]. Our hospital is a tertiary training and research hospital serving in Istanbul, which is the most populous city with more than 17 million inhabitants in Turkey. SARS-CoV-2 infection was confirmed by PCR performed by taking nasopharyngeal samples from those suspected of COVID-19 based on the clinical and radiological findings in Turkey. In our country, the diagnosis of COVID-19 is based on the guidelines published by the WHO. According to the guidelines, among those diagnosed with COVID-19, we followed-up and treated the following as inpatients: those with confusion, tachycardia (>125/min), respiratory distress, tachypnea (>22/min), or hypotension; those who had comorbid disease; those aged >50 years; those with bilateral diffuse pneumonia on thoracic CT or pulmonary radiography; those with blood lymphocyte count of <800/mm^3, serum C-reactive protein (CRP) level of 40 mg/L, or ferritin level of >500 ng/mL, or D-dimer of >1000 ng/mL. Patients were individually visited on 04.20.2020 and examined for CNS manifestations (headache, dizziness, change in consciousness, ataxia, seizures, or acute cerebrovascular disease), peripheral nervous system disorders (taste/smell impairment, vision/acoustic impairment, hyper-hypoesthesia, or peripheral nervous disorders), and muscular injury (myalgia and CK > 200 U/L), which are defined as neurological manifestations in the consensus for the prevention and management of COVID-19, during the period from the onset of symptoms to hospitalization, and their findings were recorded accordingly. After examining the records, the data concerning age, gender, underlying diseases, complaints of hospitalization, examination findings, SpO2 values, laboratory findings during initial admissions (complete blood count, coagulation testing, CRP level, and blood chemical analysis), and imaging findings (chest radiography, thorax CT, cranial CT, cranial MRI, and MRI diffusion) were added to the existing records.

The neurological data obtained from the patients were interpreted by two neurologists and a

neurosurgeon. The diagnosis of acute cerebrovascular disease was made based on the physical examination and imaging findings. Patients with neuropsychiatric disorders are excluded from the study.

According to the report by the Chinese Center for Disease Control and Prevention COVID-19, cases with at least one of the following findings were defined as severe COVID-19 cases: saturation of ≤93% in room air, tachypnea (respiratory rate of >30 breaths/min), or respiratory distress; and >50% involvement of lung parenchyma on chest imaging; whereas the following were defined as critical COVID-19 cases: those with respiratory failure, shock, or multiorgan dysfunction.

In accordance with the COVID-19 diagnosis and treatment guidelines of Turkey, all nonsevere COVID-19 patients were treated with hydroxychloroquine ± azithromycin for 5 days and severe COVID-19 patients were administered 5-7-day treatment of favipiravir alone or in addition to the hydroxychloroquine ± azithromycin treatment. Those who were pregnant were treated with hydroxychloroquine or lopinavir/ritonavir and were not administered favipiravir. ECG was performed to assess QT lengthening before and during the treatment period. All patients were administered low-molecular weight heparin (unless there were contraindications) by calculating individual doses for each patient based on their weight.

The patients were followed-up on a daily basis using the hospital registration system data on their discharge, transport to ICU, and survival, and the results were recorded in the database.

Statistics

Data were analyzed using SPSS 22.0 software (Chicago, IL, USA). Continuous variables were described as mean ± standard deviation and range. Percentage values were described using two decimals. Risk factors associated with the severity of COVID-19 and the comparison of variables in terms of the existence of neurological findings including CNS and peripheral nervous system (PNS) findings were performed using Pearson's test, Fisher's exact test for categorical variables, and unpaired Student's t-test for continuous variables.

Bivariate logistic regression analysis was conducted to obtain adjusted odd's ratio (OR; 95% confidence interval; P value) in the comparison of the severe and nonsevere groups, group with neurological findings including CNS and PNS, and group without neurological findings. All tests were based on two-tailed tests and p-values of <0.05 were considered significant.

Results

Of the 262 patients who were followed-up at the time of the study, 20 were excluded due to underlying neuropsychiatric conditions (dementia in eight, Parkinson's disease in five, schizophrenia in four, severe depression in three, previous cerebrovascular attack in three, and bipolar disorder in one) because these conditions hindered clear assessment of COVID-19-specific clinical findings.

Overall, 133 (54%) of the 242 patients included in the study were male, and the mean age was 56.82 ± 16.35 (18-91) years. Of these, 11 were pregnant, and 128 (52%) cases were defined as severe COVID-19. Severe course of COVID-19 was observed in three (27%) of the 11 pregnant cases.

Of all patients, 152 (62.8%) had at least one of the following underlying diseases: hypertension in 103 (42.5%), diabetes mellitus (DM) in 74 (30.5%), coronary heart disease in 50 (20.6%), chronic obstructive lung disease in 32 (13.2%), cancer in 17 (7%) and chronic renal disease in 15 (6.2%). Seven of 15 patients with chronic renal failure were patients who regularly underwent dialysis thrice a week, and three of these seven who underwent dialysis had severe COVID-19.

The most common symptoms at the onset of the disease were cough in 152 (62.8%), fever in 113 (46.7%), dyspnea in 111 (45.9%), and tiredness in 75 (31%). Further, 82 (33.9%) cases showed neurological findings at the time of the first admission at our hospital. Of those with neurological symptoms, 62 (25.6%) had CNS, 39 (16.1%) had PNS, and four (1.7%) had muscular symptoms. In patients with CNS manifestations, the most common symptoms were headache in 50 (20.6%) and dizziness in 18 (7.4%). Impaired taste was the most common manifestation of PNS in 27 (11.2%) patients.

During the follow-up of 17 (7%) of the 242 patients, the need for treatment in ICU emerged on the mean day of admission [7.41 ± 6.85 (range: 1–27) days] upon being defined as critical case. Nine (3.6%) patients died during the follow-up.

Demographic characteristics, comorbidities, neurological complaints, and relationship with COVID-19 severity are presented in Table 1.

As shown in the table 1, COVID-19 was significantly nonsevere in patients who complaint of impaired taste.

Table 2 presents the assessment of cases with and without neurological symptoms in terms of age, gender, presence of comorbidity, COVID-19-specific symptoms, laboratory findings, elapsed time from the onset of complaints until hospitalization, duration of hospital stay, progression of the disease

	Total (n = 242) n (%)	Nonsevere COVID-19 (n = 114) n (%)	Severe COVID-19 (n = 128) n (%)	P value
Age				
years, mean	56.82 ± 16.35	54.43 ± 17.15	58.95 ± 15.37	0.032
<50	82	44 (38.5)	38 (29.6)	0.752
³50	160	70 (61.4)	90 (70.3)	
Sex				
Female	109 (45)	53 (46.5)	56 (43.7)	0.669
Male	133 (55)	61 (53.5)	72 (56.3)	
Comorbidities				
Any	152 (62.8)	65 (57)	87 (67.9)	0.896
Diabetes	74 (30.5)	36 (31.5)	38 (29.6)	0.781
Hypertension	103 (42.5)	48 (42.1)	55 (42.9)	0.941
Coronary heart disease	50 (20.6)	20 (17.5)	30 (23.4)	0.354
COPD*	32 (13.2)	13 (11.4)	19 (14.8)	0.575
Chronic renal failure	15 (6.2)	8 (7)	7 (5.4)	0.605
Malignancy	17 (7)	9 (7.9)	8 (6.2)	0.623
Neurologic symptoms				
Any	82 (33.8)	40 (35)	42 (32.8)	0.198
Headache	50 (20.6)	24 (21)	26 (20.3)	0.876
Dizziness	18 (7.4)	7 (6.1)	11 (8.5)	0.543
Change of consciousness	8	3 (2.6)	5 (3.9)	0.867
Ataxia	3	1 (0.8)	2 (1.5)	0.984
Seizure	2	2 (1.7)	-	0.462
Acute cerebrovascular attack	4 (1.7)	1 (0.8)	3 (2.3)	0.102
Impaired taste	27 (11.2)	21 (18.4)	6 (4.6)	0.001
Impaired smell	16	8 (7)	8 (6.2)	0.783
Peripheral pain	16	11 (9.6)	5 (3.9)	0.118
Myalgia + CK > 200 U/L	4 (1.7)	2 (1.7)	2 (1.5)	0.203

Table 1: Demographic characteristics, comorbidities and neurological complaints of patients affecting severity of COVID-19.
**Chronic obstructive pulmonary disease*

(discharge, hospitalization to the ICU, and death). Among those who had neurological symptoms, women were significantly more. Of the symptoms specific to COVID-19, fatigue was significantly more in those with neurological symptoms.

Age, gender, presence of comorbidity, laboratory characteristics, and progression of COVID-19 in patients with CNS and PNS symptoms are presented in Tables 3 and 4, respectively.

Discussion

Overall, 1/3 (33.9%) of our patients infected with SARS-CoV-2 had neurological complaints in their first admission. Further, 62 (25.6%) of those with neurological symptoms had CNS, 39 (16.1%)

	Total (n = 242) n (%)	Those with neurological signs (n = 82) n (%)	Those who do not have neurological signs (n = 160) n (%)	P value
Age, years				
Mean	56.82 ± 16.35	56.74 ± 18.09	56.86 ± 15.45	0.690
<50	82 (33.9)	31(37.8)	51 (31.8)	
³50	160 (66.1)	51 (62.2)	109 (68.1)	
Sex				
Female	109 (45)	45(54.8)	64 (40)	0.028
Male	133 (55)	37 (45.2)	96 (60)	
Comorbidities				
Any	152 (62.8)	49 (59.7)	103 (64.3)	
Diabetes	74(30.6)	23 (28)	51 (31.8)	0.539
Hypertension	103 (42.6)	34 (41.5)	69 (43.1)	0.804
Coronary heart disease	50 (20.6)	17 (20.7)	33(20.6)	0.985
COPD*	32 (13.2)	7 (8.5)	25(15.6)	0.161
Chronic renal failure	15 (6.2)	4 (4.9)	11(6.8)	0.779
Malignancy	17 (7)	6 (7.3)	11 (6.8)	0.899
General symptoms and signs				
Fever	113 (46.7)	40 (48.8)	73 (45.6)	0.642
Cough	152 (62.8)	54 (65.9)	98 (61.3)	0.482
Dyspnea	111 (45.9)	33 (40.2)	78 (48.8)	0.223
Sore throat	9 (3.7)	6 (7.3)	3 (1.9)	0.065
Chilling	7 (2.9)	3 (3.7)	4 (2.5)	0.692
Vomiting	25 (10.3)	10 (12.2)	15 (9.4)	0.509
Diarrhea	15 (6.2)	4 (4.9)	11 (6.9)	0.779
Back pain	20 (8.3)	8 (9.8)	12 (7.5)	0.623
Fatigue	75 (31)	35 (42.7)	40 (25)	0.005
Laboratory findings				
WBC mean ± SD (/mm³)	6915.12 ± 3466.88	7200.60 ± 3654.19	6768.81 ± 3369.24	0.360
Lymphocyte mean ± SD (/mm³)	1419.5 ± 671.98	1508.17 ± 649.96	1374.06 ± 680.52	0.142
PLT mean ± SD (/mm³)	209015.96 ± 83920.92	216890.24 ± 81900.57	204980.4 ± 84907.71	0.297
CRP mean ± SD (mg/L)	67.85 ± 66.62	65.82 ± 67.06	68.86 ± 66.59	0.741
AST mean ± SD (U/L)	30.35 ± 29.26	36.21 ± 20.24	42.48 ± 32.82	0.116
ALT mean ± SD (U/L)	33.37 ± 29.36	30.58 ± 21.31	34.81 ± 32.72	0.291
LDH mean ± SD (U/L)	319.58 ± 119.22	302.90 ± 102.96	328.18 ± 126.23	0.119
Ferritin mean ± SD (mg/L)	310.73 ± 419.8	260.71 ± 346.06	336.05 ± 451.48	0.189
D-dimer mean ± SD (mg/mL)	8.62 ± 15.76	8.84 ± 15.64	8.5 ± 15.87	0.875
CK mean ± SD (U/L)	204.86 ± 366.53	175.14 ± 237.91	220.09 ± 417.28	0.371
GFR mean ± SD (mL/min/1.73 m²)	87.87 ± 30.29	88.4 ± 31.13	87.61 ± 29.94	0.848
Elapsed time from the onset of complaints until hospitalization (e.g.) mean ± SD (days)	5.95 ± 3.66	6.16 ± 3.83	6.84 ± 3.57	0.529
Duration of hospital stay (days)	11.29 ± 6.41	11.29 ± 7.55	11.30 ± 5.77	0.992
Those who needed ICU in their follow-up (days)	17 (7)	9 (11)	8 (5)	0.094
Those who died (days)	9 (3.7)	3 (3.7)	6 (3.8)	0.978

Table 2: Characteristics of COVID-19 patients with and without neurological symptoms.
**Chronic obstructive pulmonary disease*

had PNS, and four (1.7%) had muscular symptoms. Human coronaviruses affect the respiratory tract and CNS. Neuroinvasion and neurotropism are common features of human coronaviruses[15]. Some of the SARS-CoV-1-infected 8000 individuals in 2003 had neurological symptoms such as encephalitis, seizure, generalized polyneuropathy, and primary myopathy[15]. MERS-CoV also caused neurological disorders including seizures, stroke, polyneuropathy, ataxia, focal motor deficits, and altered mental status ranging from confusion to coma[17]. SARS-CoV-2 is genetically similar to SARS-CoV-1, and according to a recent study in 214 patients infected with SARS-CoV-2, neurological symptoms were reported in 78 (36%) cases, which involved CNS,

PNS, and skeletal muscles. Mild CNS involvement entailed dizziness (16.8%), headache (13.1%), ataxia (0.5%), hypogeusia (5.6%), and hyposmia (5.1%), and peripheral symptoms such as neuralgia (2.3%). Severe neuromuscular and CNS manifestations included skeletal muscle injury (10.7%), acute cerebrovascular disease (2.8%), and epilepsy (0.5%)[13].

	With CNS symptoms (N = 62) N%	Without CNS symptoms (N = 180) N%	P value
Age (years)			
<50	26 (41.9)	56 (31.1)	0.124
³50	36 (58.1)	124 (68.9)	
Sex			
Female	35 (56.5)	74 (41.1)	**0.039**
Male	27 (43.5)	106 (58.9)	
Comorbidities			
Any	39 (62.9)	113 (62.7)	0.149
Diabetes mellitus	20 (32.3)	54 (30)	0.63
Hypertension	27 (43.5)	76 (42.2)	0.216
Coronary heart disease	13 (21)	37 (20.5)	0.406
COPD	7 (11.3)	25 (13.9)	**0.015**
Chronic renal failure	4 (6.5)	11 (6.1)	0.670
Malignancy	5 (8)	12 (6.7)	0.774
Laboratory findings			
WBC (mean) (/mm³)	7472.74 ± 3752.92	6723.05 ± 3352.29	0.142
PNL (/mm³)	5205.16 ± 3359.8	4770.38 ± 2991.2	0.340
Lymphocyte mean ± SD (/mm³)	1571.12 ± 695.07	1367.27 ± 657.74	**0.039**
PLT mean ± SD (/mm³)	224467.74 ± 82243.28	203693.68 ± 84058.8	0.093
CRP mean ± SD (mg/L)	64.16 ± 64.29	69.10 ± 67.52	0.621
AST mean ± SD (U/L)	36.5 ± 21.43	41.68 ± 31.47	0.230
ALT mean ± SD (U/L)	30.54 ± 22.89	34.35 ± 31.29	0.381
GGT mean ± SD (U/L)	46.49 ± 44.65	49.44 ± 43.96	0.665
LDH mean ± SD (U/L)	289.37 ± 95.15	330.05 ± 125.03	**0.020**
Ferritin mean ± SD (mg/L)	271.03 ± 372.14	324.18 ± 434.91	0.358
D-dimer mean ± SD (mg/mL)	1.18 ± 0.08	1.11 ± 0.57	0.477
CK mean ± SD (U/L)	167.57 ± 241.46	217.54 ± 400.3	0.388
GFR mean ± SD (mL/min/1.73 m²)	88.16 ± 33.26	87.78 ± 29.29	0.933
Elapsed time from the onset of complaints until hospitalization (e.g.) (days)	5.85 ± 3.99	5.98 ± 3,55	0,802
Mean duration of hospital stay (days)	11.8 ± 8.02	11.12 ± 5.77	0.539
Those who needed ICU in their follow-up (days)	8 (12.9)	9 (5)	0.090
Those who died (days)	2 (3.2)	7 (3.9)	0.738

Table 3: Characteristics of COVID-19 cases with and without central nervous system (CNS) symptoms.

An observational study showed that 84% patients had neurologic signs: confusion (65%), agitation (69%), corticospinal tract signs (67%), and dysexecutive syndrome (36%). Eight of 13 (62%) patients who underwent brain MRI showed leptomeningeal enhancement[10]. In our study, in patients with CNS symptoms, the most common symptoms were headache in 50 (20.6%) and dizziness in 18 (7.4%). The most common PNS symptom of our patients was hypogeusia, which was detected in 27 (11.2%).

The primary symptoms of patients with COVID-19 infection are fever, dry cough, and fatigue. However, some patients diagnosed with COVID-19 do not show typical respiratory symptoms at the time of diagnosis. They only present neurological symptoms such as headache, difficulty in walking

	With PNS symptoms (N = 39) N%	Without PNS symptoms (N = 203) N%	P value
Age (years)			
<50	13 (33.3)	69 (33.9)	0.937
³50	26 (66.7)	134 (66.1)	
Sex			
Female	23 (58.9)	86 (42.4)	0.078
Male	16 (41.1)	117 (57.6)	
Comorbidities			
Any	21 (53.8)	131 (64.5)	0.211
Diabetes	10 (25.6)	64 (31.5)	0.570
Hypertension	17 (43.6)	86 (42.4)	0.195
Coronary heart disease	8 (20.5)	42 (20.7)	0.980
COPD	1 (2.6)	31 (15.3)	**0.036**
Chronic renal failure	1 (2.6)	14 (6.9)	0.477
Malignancy	3 (7.7)	14 (6.9)	0.742
Laboratory findings			
WBC mean ± SD (/mm³)	7320.76 ± 4019.32	6837.19 ± 3356.02	0.426
PNL mean ± SD (/mm³)	5146.15 ± 3560.44	4830.98 ± 2996.61	0.581
Lymphocyte mean ± SD (/mm³)	1493.07 ± 559.15	1405.36 ± 691.87	0.158
PLT mean ± SD (/mm³)	206333.33 ± 68380.25	209531.34 ± 86724.75	0.492
CRP mean ± SD (mg/L)	77.02 ± 71.65	66.11 ± 65.67	0.356
AST mean ± SD (U/L)	35.23 ± 21.44	41.34 ± 30.49	0.267
ALT mean ± SD (U/L)	30.25 ± 20.63	33.97 ± 30.76	0.075
GGT mean ± SD (U/L)	41.00 ± 25.01	50.22 ± 46.87	0.369
LDH mean ± SD (U/L)	308.51 ± 118.52	321.72 ± 119.53	0.528
Ferritin mean ± SD (mg/L)	273.12 ± 344.95	317.99 ± 433.13	0.574
D-dimer mean ± SD (mg/mL)	8.66 ± 16.79	8.61 ± 15.60	0.379
CK mean ± SD (U/L)	180.79 ± 250.72	209.55 ± 385.40	0.655
GFR mean ± SD (mL/min/1.73 m²)	88.94 ± 31.35	87.67 ± 30.16	0.690
Elapsed time from the onset of complaints until hospitalization mean ± SD (days)	6.07 ± 3.05	5.92 ± 3.77	0.817
Mean duration of hospital stay mean ± SD (days)	11.5128 ± 7.71	11.25 ± 6.16	0.821
Those who needed ICU in their follow-up (days)	7 (17.9)	10 (4.9)	**0.009**
Those who died (days)	2 (12.8)	7 (3.4)	0.641

Table 4: Characteristics of COVID-19 cases with and without peripheral nervous system (PNS) symptoms.

and malaise, cerebrovascular diseases, and other neurological diseases[18,19].

In their study, Mao et al. defined 41% cases as severe and 59% as non-severe based on the respiratory findings of the patients followed-up for COVID-19 and reported that severe patients had more neurological manifestations[13]. In our study, severe COVID-19 cases were more (52%). Neurological symptoms showed no significant difference between the severe and non-severe groups except that impaired taste was significantly higher in the nonsevere group. Moreover, 17 (7%) of all the cases needed treatment in the ICU during the follow-up on the mean day (7.41 ± 6.85 day) after admission (range:

1-27 days) upon being defined as critical case, whereas nine (3.6%) died during this period. The need for intensive care of patients with PNS symptoms was significantly higher. The rate of patients with intensive care needs (7%) was lower than the rate (32%) reported previously[18]. This difference might be due to early diagnosis, filiation study used in Turkey, early treatment of all patients diagnosed with COVID-19, or due to the exclusion of patients in ICU in our study.

In a retrospective study by Mao et al., severe COVID-19 cases were older and often had comorbid conditions such as hypertension (36%) and DM (17%)[12]. Huang et al. reported that the first 41 hospitalized patients with confirmed COVID-19 had pre-existing DM type 2 (20%), hypertension (15%), and cardiovascular disease (15%)[18]. In our study, 152 (62.8%) patients had at least one comorbid disease. Hypertension (42.5%) and DM (30.5%) were the most common comorbid diseases in COVID-19 in the present study, as reported in the literature[20-25]. Despite the severe course of COVID-19 in elderly patients with hypertension, there was no difference between the severe and non-severe patients in our study in terms of age and comorbid diseases. Comorbidities were higher in patients with no PNS symptoms, but COPD was significantly lower in patients with CNS and PNS symptoms. This may be due to the deterioration of PNS signs such as impaired smell and taste due to frequent recurrent runny nose and rhinitis in COPD cases.

Inflammation that develops with SARS-CoV-2 infection causes coagulation disorders and develops signs such as stroke in CNS. In a study conducted in Wuhan, acute ischemic stroke developed in 5% patients with COVID-19[26,27]. In our study, acute ischemic stroke was detected in four (1.7%) patients. COVID-19 was detected in two of these patients after acute stroke, and two of them developed stroke during follow-up due to COVID-19. Three of these four cases were severe COVID-19, one had DM and hypertension, one had breast cancer and deep vein thrombosis, and one did not have any underlying condition. Right MCA infarction was reported in three cases, right MCA and PCA infraction in one, whereas two were followed-up in ICU, and all patients were discharged.

Among the laboratory parameters, low count of blood lymphocytes and LDH elevation are values indicative of severity and poor prognosis in COVID-19 cases. Previously, patients with CNS involvement have shown significantly lower lymphocyte levels, platelet counts, and higher blood urea nitrogen than patients without CNS involvement[12,27].In our study, lymphocyte count was significantly lower and LDH level was high. This may be due to similar proportions or low number of cases among our severe and nonsevere COVID-19 patients with CNS findings.

Conclusion

To conclude, the frequency and variety of neurological findings in COVID-19 cases is too high to underestimate. However, ignoring some neurological symptoms such as headache and muscle pain that are usually considered in many viral diseases might cause delay in COVID-19 diagnosis and increase in its spread, particularly when such symptoms are not questioned. SARS-CoV-2 should be considered in the etiology of patients presenting with neurological findings, especially during the pandemic period we live in. During the follow-up of COVID-19 cases, it should be borne in mind that serious neurological conditions may develop due to systemic inflammatory responses in severe cases as well as in nonsevere ones.

References

1) Zhu N, Zhang D, Wang W, Xingwang. L, Yang B, Song J. A Novel Coronavirus From Patients With Pneumonia in China, 2019. N Engl J Med 2020; 382(8): 727-33.
2) World Health Organization. Coronavirus disease (COVID-19) pandemic. Accessed May 30, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
3) Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 92(6): 552-5.
4) Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem. 2008; 107(6): 1482-94.
5) Koyuncu, O.O.; Hogue, I.B.; Enquist, L.W. Virus infections in the nervous system. Cell Host Microbe 2013; 13: 379-93.
6) Berth, S.H, Leopold, P.L. Morfini, G.N. Virus-induced neuronal dysfunction and degeneration. Front. Biosci 2009; 14: 5239-59.
7) Li YC, Bai WZ, Hirano N, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. J Comp Neurol. 2013;521(1):203-212. doi:10.1002/cne.23171
8) Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008; 82(15): 7264-75.

9) Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J. A first Case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020; 94: 55-8.
10) Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, Reznikov LR, Gibson-Corley KN, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human Dipeptidyl peptidase 4. J Infect Dis 2016; 213(5): 712-22.
11) Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020; 382: 2268-70.
12) Baig AM. Updates on What ACS Reported: Emerging Evidences of COVID-19 With Nervous System Involvement. ACS Chem Neurosci 2020; 11(9): 1204-5.
13) Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6): 1-9.
14) Turkish Ministry of Health, General Directorate of Public Health. COVID-19 (SARS-CoV-2 infection) Treatment Guideline for Adults. https://covid19bilgi.saglik.gov.tr/depo/rehberler/covid-19-rehberi/covid-19_rehberi_eriskin_hasta_tedavisi.pdf. Accessed May 30, 2020 (In Turkish)
15) Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dube M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses. 2019 Dec; 12(1): 14.
16) Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005; 14: 113-9.
17) Arabi YM, Harthi A, Hussein J, Bouchama. A, Johani S, Hajeer. AH, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015; 43(4): 495-501.
18) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506.
19) Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020; 63(3): 457-60.
20) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061-9.
21) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
22) Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma. CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606. doi: 10.1136/bmj.m606.
23) Zhang JJ, Dong X, Cao YY, Yuan YD, Ynag YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730-41.
24) Liu W, Tao ZW, Lei W, Yuan ML, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020; 133(9): 1032-8.
25) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229): 1054-62.
26) Li Y, Li M, Wang, M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational stıdy. Stroke Vasc Neurol 2020; svn-2020-000431.
27) Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020; 87: 115-9.
28) Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med 2020 May 27.

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