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Neurologic symptoms and signs observed in critical COVID-19 patients may be precursors of existing cerebrovascular disease

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ABSTRACT

Introduction: Although COVID-19 disease often includes respiratory system findings, that affects the gastrointestinal system, circulatory system, coagulation system and neurological system. In this study, we identified the neurological signs and symptoms observed in critical COVID-19 patients.

Material and Method: This retrospective study reviewed 595 COVID-19 patients admitted to our intensive care unit (ICU) between January to June 2020. Patients with neurologic symptoms that were divided into two groups were diagnosed neurological disease (group ND) and non-neurological disease (group non-ND). Clinical signs and symptoms, radiological findings, demographic data (age, gender, presence of comorbidities), white blood cell (WBC), lymphocyte, platelet, lactic acid, glucose, and D-dimer levels, length of hospitalization, requirement of mechanical ventilation, and mortality were recorded for each patient.

Results: Neurologic symptoms were observed in 148 (24.8%) patients. Of these, 44 patients were diagnosed neurological disease and 104 patients were non- neurological disease. The prevalence of neurologic symptoms was significantly higher in group ND. The rate of acute ischemic cerebrovascular disease in 595 critical COVID-19 patients was 6.2%.

Conclusion: Presence of cerebrovascular diseases should be suspected in COVID-19patients with paresis, altered consciousness, numbness, taste/smell disorders, and plegia. The rate of ischemic cerebrovascular disease was approximately seven times higher than the rate of hemorrhagic cerebrovascular disease in critically COVID-19 patients.

Keywords: Intensive care unit, neurology, COVID-19, acute ischemic stroke

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) has spread all over the world and has become a pandemic, creating a 'new normal' for almost all nations (1). Although the disease initially showed itself with respiratory tract disease findings, it was observed that it had an effect on the gastrointestinal system, circulatory system, coagulation system and similar systems. Among these conditions, the most common cardiovascular complications, persistent hyperlipidemia, glucose hemostasis irregularities, acute renal failure, acute gastrointestinal effects, acute viral hepatitis, and acute diabetes mellitus have been reported due to its effects on pancreatic islet cells (2). Acute and post-acute neurologic symptoms, signs, and diagnoses of COVID-19 disease have been documented in an increasing number of patients (3). SARS-CoV-2 can invade and damage angiotensin-converting enzyme-2 (ACE2) receptors, and the condition can have neurologic consequences (4). There are studies reporting that systemic hyperinflammation, cerebrovascular events, seizures, and toxic-metabolic encephalopathy caused by a potential SARS-CoV-2 central nervous system infection may cause mental changes in COVID-19 (5).

Neurological symptoms/signs or diagnoses were evaluated in a retrospective cohort study of COVID-19 positive patients. In this study, neurological symptoms were grouped as major and minor symptoms. Encephalopathy, ischemic or hemorrhagic stroke, and seizures were defined as major manifestations, while minor neurological manifestations included headache,

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anosmia, dysgeusia, dizziness or vertigo, and myalgia. The study found that the development of major neurological signs during the course of the disease was an independent predictor of mortality (6).

In this study, we aimed to determine the neurologic signs and symptoms observed in critical COVID-19 patients.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Researchs Ethics Committee (Date:11/02/2021, Decision No: 2020-KAEK-143-39). All procedures were carried out in accordance with the ethical rulesand the principles of the Declaration of Helsinki.

This retrospective study reviewed 595 COVID-19 patients admitted to XXX hospital intensive care unit (ICU) between January to June 2020. All the patients were classified as critical COVID-19 patients according to the COVID-19 Adult Patient Management Guidelines published by the Ministry of Health (7). Of these, 148 (24.9%) patients were suspected to have neurologic diseases. Data on the signs and symptoms of the patients were retrieved from the clinical notes taken by the physicians that examined the state of consciousness, and the patient anamnesis obtained from the patient or the relatives.

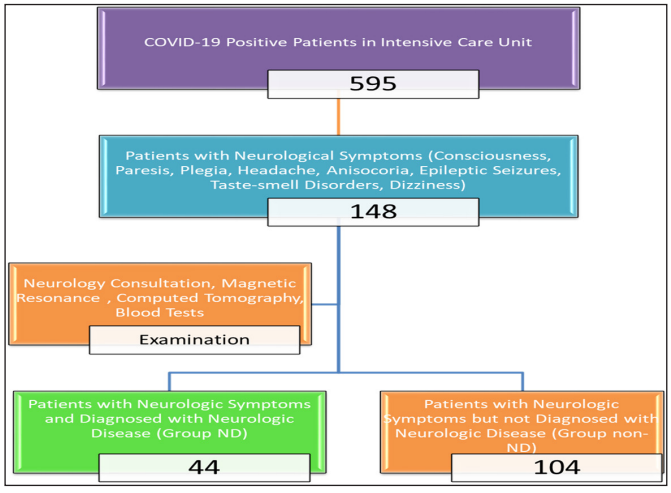

Figure 1: Patient's flow chart

Only patients that were consulted by an experienced neurologist for the assessment of the state of consciousness, paresis, plegia, headache, anisocoria, epileptic seizures, taste-smell disorders, and dizziness were included in the study. Some symptoms of patients were learned from relatives or physicians. When the neurologist consulted, she could not detect the symptoms stated in some of the patients and radiological imaging was not deemed appropriate. Based on the neurologic examination and laboratory and radiological findings, 44 out of 148 patients were diagnosed neurologic disease and these patients were assigned to Group neurological disease (ND). The remaining 104 patients who were not diagnosed with neurologic disease but had neurologic symptoms were assigned to Group non- neurologic disease (non-ND). All the patients had a positive polymerase chain reaction (PCR) test result. Clinical signs and symptoms, radiological findings, demographic data (age, gender, presence of comorbidities), white blood cell (WBC), lymphocyte, platelet, lactic acid, glucose, and D-dimer levels, length of hospitalization, requirement of mechanical ventilation, and mortality were recorded for each patient.

Statistical Analysis

Data were analysed using SPSS for Windows version 22 (Armonk, NY: IBM Corp.). Normal distribution of continuous variables was assessed using One-Sample Kolmogorov-Smirnov test. Variables with normal distribution were compared using Independent-Samples t-test and variables with non-normal distribution were compared using Mann-Whitney U test. Categorical variables were compared using Pearson Chi-square and Fisher Exact tests. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequencies (n) and percentages (%). A p value of <0.05 was considered significant. Data were defined as median (1st quartile-3rd quartile) for non-normal continuous variables and frequency (percent) for categorical variables.

RESULTS

Neurologic symptoms were detected in 148 of 595 critical COVID-19 patients. Of these 148 patients, 44 patients were diagnosed with neurological disease as ischemic cerebrovascular disease, hemorrhagic cerebrovascular disease and Guillain-Barre Syndrome (GBS) (Group ND) and 104 were non-neurological disease (Group non-ND). 90 of 148 patients had radiological imaging. Diagnostic imaging could not be performed on other patients because their clinical conditions were not suitable for transfer. In group ND, only cranial computed tomography (CT) was performed in 1, only magnetic resonance imaging (MRI) was performed in 26, and both CT and MRI were performed in 17 patients. In group non- ND, CT was performed in 15, MRI was performed in 18, and both CT and MRI were performed in 13 patients.

Group ND consisted of 26/44 (59.1%) male and 18/44 (40.9%) female and group non-ND consisted of 76/104 (73.1%) male and 28/104 (26.9%) female. Mean age was significantly higher in Group ND than in Group non-ND (71.1±13.6 vs. 65.64±13.4 years) (p=0.002).

No significant difference was observed between the two groups with regard to the presence of comorbidities, requirement of mechanical ventilation, and length of ICU stay. Mortality occurred in 19 (43.2%) patients in Group ND and in 63 (60.6%) patients in Group non-ND (p=0.052) (**Table 1**).

Table 1: Demographic data of the patients

Demographic data	Group ND (n: 44)	Group non-ND (n: 104)	P
Female	18 (40.9%)	28 (26.9%)	0.093[a]
Male	26 (59.1%)	76 (73.1%)	0.093[a]
Age (Mean + SD)	71.1 (+ 13.6)	65.64(+13.4)	*0,002[b]
Additional disease presence			
Diabetes mellitus	10 (22.7%)	22 (21.2%)	0.832
Hypertension	17 (38.6%)	38(36.5%)	0.809[a]
Cardiovascular disease	15 (34.1%)	31 (29.8%)	0.607[a]
Other (malignant, hematological patient etc.)	31 (70.5%)	62(59.6%)	0,212[a]
Need for mechanical ventilator	29 (65.9%)	77 (74.0%)	0,316[a]
Number of ICU treatment days (Mean + SD)	11.55 (+7.3)	14,03 (+12.8)	0,231[b]
Mortality	19 (43.2%)	63 (60.6%)	0.052[a]

All data are expressed as mean ± standard deviation (SD), as percent (%) or as numbers. [a]Chi-Square Test. [b]Independent Samples T-Test.*p<0.05

Both WBC and lymphocyte values were significantly higher in group ND. In contrast, C-reactive protein (CRP) and ferritin levels were found to be significantly higher in group non – ND. Although glucose levels were higher in group non- ND, no significant difference was observed (**Table 2**).

Table 2: Laboratory data of the patients

	Group ND (n: 44) (Mean+SD)	Group non- ND (n:104) (Mean+SD	p
White blood cell	9.42+3.89	7.79+4.39	*0.012[a]
Lenfosit	1.17+0.58	0.98+0.60	*0.035[a]
Platelet count	203.64+92.63	198.56+95.87	0.76[b]
D dimer	2.41+2.65	2.78+3.20	0.33[a]
C-reactive protein	79.41+64.17	131,31+79.12 (1-412)	*<0.001[a]
Lactate	2.96+1.86	2.66+1.45	0.46[a]
Glucose	175.16+73.68	271.27+72.17	0.78[a]
Ferritin	330.01+302.62	636.43+457.41 (5-1500)	*<0.001[a]

All data are expressed as mean ± standard deviation (SD) or as numbers.a İndependent Samples T-Test.b Mann-Whitney U Test *p<0.05

Numbness was the most common neurologic symptom (70/595, 13.4%), followed by altered consciousness (39/595, 6.5%), dizziness (39/595, 6.5%), paresis (35/595, 5.8%), headache (34/595, 5.6%), taste disorder (35/595, 5.8%), smell disorder (35/595, 5.8%), plegia (26/595, 4.3%), epileptic seizure (22/595, 3.6%), and anisocoria (13/595, 2.1%). The prevalence of neurologic symptoms was significantly higher in Group ND. While the anisocoria observed in Group non- ND patients are accepted as physiological or error evaluation by the neurologist, the anisocoria observed in Group ND are the patients with hemorrhagic cerebrovascular disease or stroke (**Table 3**).

Table 3: Distribution of neurologic symptoms and signs in critical COVID-19 patients

Neurologic Symptoms And Signs	Group ND 44 (%)	Group non – ND 104 (%)	All COVID-19 Patients in ICU 595 (%)
Change of Consciousness	29 (65.9%)	10 (9.6%)	39 (6.5%)
Headache	19 (43.1%)	15 (14.4%)	34 (5.6%)
Dizziness	18 (40.9%)	21 (20.1%)	39 (6.5%)
Plegia	25 (56.8%)	1 (0,96%)	26 (4.3%)
Paresis	32 (72.7%)	3 (2.8%)	35 (5.8%)
Anisocoria	9 (20.4%)	4 (3.8%)	13 (2.1%)
Taste Disorder	27 (61.3%)	8 (7.6%)	35 (5.8%)
Smell Disorder	25 (58.8%)	10 (9.6%)	35 (5.8%)
Epileptic Seizure	20 (45.4%)	2 (1.9%)	22 (3.6%)
Numbness	28 (63.6%)	42 (40.3%)	70 (13.4%)

All data are expressed as numbers and as percent (%)

Of the 595 critically ill patients, 44 were diagnosed with neurologic disease. 37/595 (6.2%) had ischemic cerebrovascular disease, 5/595 (0.8%) had hemorrhagic cerebrovascular disease, 2/595 (0.3%) had Guillain-Barre Syndrome (GBS).

DISCUSSION

In this study, neurological symptoms were observed in 148 of 595 admitted to our COVID-19 intensive care unit. Forty-four of 148 patients were diagnosed with neurological disease. While both lymphocyte and WBC levels were higher in patients diagnosed with neurological disease, CRP and ferritin levels were significantly higher in patients with neurological symptoms but not diagnosed with neurological disease. On the other hand, the prevalence of neurological symptoms was higher in patients diagnosed with neurological disease. In addition, although mortality was higher in patients without a diagnosis of neurological disease than in patients with a diagnosis of neurological disease, no significant difference was observed between them.

The mean age of patients diagnosed with neurological disease was found to be significantly higher than patients without a diagnosis of neurological disease, and in accordance with the literature, the number of male patients was higher than females in both groups (8,9,10).

Admission of patients to the intensive care unit is decided by evaluating severe respiratory distress, hemodynamic instability, changes in consciousness and serious changes in laboratory evaluation. In the case of all patients with

COVID-19, the high lymphocyte and neutrophil values of the patients in the ND group led us to think that these patients needed intensive care not because of the severity of the COVID-19 disease, but because of the severity of their underlying neurological condition. Among the prognostic factors of COVID-19 disease are low lymphocyte, high ferritin and high CRP. In this context, the low lymphocyte high CRP and ferritin values in patients in the non-ND group can also be explained for the same reason. A meta-analysis evaluating 83 studies reports that inflammatory markers such as ferritin and neutrophil-lymphocyte ratio have a significant relationship with mortality in COVID-19 patients (11). Another study reported that lymphocyte and platelet levels were lower in COVID-19 patients with central nervous system (CNS) involvement compared to those without (12). However this study was not conducted in intensive care patients.

In our study, paresis, altered consciousness, and numbness were associated with a higher prevalence of cerebrovascular diseases. Although the effect of COVID-19 on CNS remains unclear, there are several theories to explain it. The first theory is that the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) causes endotheliitis in COVID-19 disease, thereby invading CNS through a hematogenous route. The second is that SARS-CoV-2 initially causes peripheral neuritis and then invades CNS via retrograde axonal transport from peripheral nerves (13). The third theory is that SARS-CoV-2 accesses CNS through the olfactory bulb, thereby causing neurodegeneration (14). The fourth theory is that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) in brain endothelial and smooth muscle cells, followed by depletion of ACE2 by SARS-CoV-2, resulting in an elevation in Angiotensin II that increases the risk of proinflammatory, vasoconstrictive, and organ damage. In addition, it has also been hypothesized that clinical conditions causing tissue damage (e.g. stroke) occur due to an increase in Angiotensin II. Based on the fourth theory, Hess et al. (15) found a relationship between COVID-19 and stroke.

Mao et al. (16) detected neurologic symptoms in 78 (36.4%) out of 214 COVID-19 patients . Similarly, Helms et al. (17). observed neurologic symptoms in 84% of patients with severe SARS-CoV-2 infection requiring intensive care, with the most common symptoms including encephalopathy, agitation, and confusion. In our study, neurologic symptoms were detected in 148 (24.8%) out of 595 COVID-19 patients.

Literature indicates a wide range of prevalence for neurologic symptoms in COVID-19 patients. In our study, the rate of altered consciousness in COVID-19 patients was 9% (18). In a study conducted with COVID-19 patients in Wuhan, headache was observed in 8% and confusion/confusion was detected in 9% of the patients (19). Amanat et al. (20) evaluated neurologic symptoms accompanying COVID-19 in 873 patients and reported that the most common neurologic symptoms included myalgia (24.8%), headache (12.6%), and dizziness (11.9%). There are some studies suggesting that symptoms such as smell and taste disorders may be among the early signs of COVID-19 (21). In a systematic meta-analysis, Whittaker et al. (22) evaluated 31 studies investigating neurologic symptoms of COVID-19 patients and reported that the most common symptoms included headache (6-45%), dizziness (7-17%), altered consciousness (8%), taste disorders (6-89%), smell disorders (5-86%), and epileptic seizures (0.5%) (21).

In a large cohort study, Yaghi et al. (23) diagnosed ischemic stroke in 32 (0.9%) out of 3556 patients hospitalized with a diagnosis of COVID-19 infection. However, unlike our study, the study included non-critical COVID-19 patients. Toscano et al. (24) reported on five patients with GBS from three hospitals in northern Italy during the COVID-19 outbreak. In the study by Amanat et al. (25) 10 out of 873 COVID-19 patients had cerebrovascular diseases, one patient had status epilepticus, one patient had demyelinating disease, and one patient was diagnosed with Guillain-Barre Syndrome (GBS).

An epileptic seizure is a transient event with signs or symptoms due to abnormal excessive and synchronous neuronal activity in the brain. If it is thought to be a seizure, it should be examined whether it was provoked or unprovoked. In order to distinguish whether there is a seizure triggered by the COVID-19 disease, blood tests and lumbar puncture are applied to the patient. SARS-CoV2 features neurotropism (26). The prognosis of patients with seizures mostly depends on any underlying cause. Patients with seizures due to curative medical or toxicological causes should manage these problems well. One epilepsy patient in our non-ND group did not have any seizures afterward, and lumbar puncture could not be performed due to the use of antiaggregant and anticoagulation. The plegic patient in the non-ND group unfortunately died before the necessary examinations were completed.

Neural invasion by the virus, difficulty in blood pressure regulation, a systemic hyperinflammatory state characterized by hypercytokinemia, and thrombocytopenia are theories that can explain intracranial hemorrhages in COVID -19 patients. COVID-19 associated coagulopathy (CAC) may be a good explanation for ischemic cerebrovascular diseases. Mechanisms such as inflammation, endothelith, hyperviscosity and hypercoagulation lead to a high thrombotic risk in patients with COVID-19. If we look at

the studies of Hernández–Fernández (27) and Meppiel (28), considering the published cases of intracranial hemorrhage in COVID-19 patients, the majority of them are multi-lobular in nature and mortality is reported at a rate of 47%. Cerebral hemorrhages observed in COVID-19 patients are thought to be possibly related to COVID-19 coagulopathy (29). In our study, ICH was only noticed in patients with severe COVID-19 disease.

Among postmortem studies, a study by Li et al.(25) evaluated viral neuroinvasion of SARS-CoV-2 via cerebrospinal fluid testing and brain autopsies and found that the detection rate of SARS-CoV-2 was higher in the olfactory system and brain stem, both of which had severe microgliosis and lymphocytic infiltrations, unlike in the cerebrum and cerebellum. Accordingly, it can be asserted that there are some other neurologic diseases that have not yet been defined in COVID-19. In their study, Eray et al. (30) showed that various neuropsychiatric complications may be an important part of the long-term effects of COVID-19. These diseases can be in the form of inflammatory encephalitis or peripheral neuritis. However, the criticality of the patients' condition, presence of bleeding and coagulation problems, and the requirement of follow-up with neuromuscular blockers may prevent the implementation of cerebrospinal fluid testing or electromyography procedures. Although symptomatic patients do not have a neurologic diagnosis, the higher inflammatory markers in non-ND group indicate the presence of viral sepsis.

Due to the simultaneous admission of multiple COVID-19 patients to hospitals during the pandemic period, the use of diagnostic techniques including MRI, cerebrospinal fluid testing, and electromyography was avoided due to increased risk of cross-infection and bleeding. Therefore, only subjective symptoms of our patients were evaluated in the study. Another limitation of this study was the evaluation of patients at first admission to ICU. The initial acceptance of most of the patients was the COVID-19 reporting and data system values of 2-3, and the thoracic tomography evaluations of the worsening periods were not evaluated.

CONCLUSION

Presence of neurologic diseases should be suspected in COVID-19 patients with paresis, altered consciousness, numbness, taste/smell disorders, and plegia. COVID-19 is a disease with bleeding coagulation disorder and the rate of ischemic cerebrovascular disease is approximately seven times higher than the rate of haemorrhagic cerebrovascular disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researchs Ethics Committee (Date:11/02/2021, Decision No: 2020-KAEK-143-39).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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