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Patient Management in Neurology Intensive Care During COVID-19 Pandemic Period

COVID-19 Pandemi Sürecinde Nöroloji Yoğun Bakımda Hasta Yönetimi

Fergane Memmedova, Semra Arı Sevingil, Fatma Altuntaş Kaya, Fatma Ger Akarsu, Zaur Mehdiyev, Ulviyyat Jafarova, Özlem Aykaç, Atilla Özcan Özdemir

Eskisehir Osmangazi University Faculty of Medicine, Department of Neurology, Eskisehir, Turkey

Abstract

Objective: This study aims to evaluate data from coronavirus disease-2019 (COVID-19) patients with neurological manifestations hospitalized in the intensive care unit (ICU).

Materials and Methods: The study included data from COVID-19 patients with neurological manifestations hospitalized in ICU. Patients' demographic characteristics, risk factors, laboratory results, treatment methods, mechanical ventilation methods, use of non-invasive techniques to meet O_2 requirements, clinical outcome at discharge and after three months, and mortality rates were evaluated.

Results: The study included 25 patients. Mean age of the patients was 66.76±12.93. Fifty two percent of the patients were male. Of the patients 96% had a positive polymerase chain reaction test, and 92% had lung involvement. The comorbidities of the patients were hypertension (48%), diabetes mellitus (28%), coronary artery disease (28%), cerebrovascular disease (20%), cancer (20%), and chronic obstructive pulmonary disease (12%). Seventy two percent of the patients presented with stroke. Of the patients %12 presented with encephalopathy, whereas patients with epilepsy and myasthenia gravis accounted for 8%. Patients' average length of stay in ICU was 13.16±12.44 days. Pressure-synchronized intermittent mandatory ventilation mode was used in 56% of patients. Number of intubation days was 9.5±12.26. All patients were treated with favipiravir and antiaggregant, 92% with steroids and antibacterial therapy, 52% with antiaggregant, 20% with plasma therapy, 8% with cytokine filter and immunoglobulin therapy, and 4% with monoclonal antibody therapy. During hospitalization, mortality rate was 48%, good clinical outcome rate was 36%.

Conclusion: The rates of poor clinical outcomes are seen to be high during in-hospital treatment and follow-up of COVID-19 patients presenting with neurological symptoms, as well as at discharge.

Keywords: COVID-19, neurointensive care, stroke, seizure, encephalopathy, myasthenia gravis

Öz

Amaç: Bu çalışmada yoğun bakım ünitesine (YBÜ) yatan nörolojik manifestasyonları olan koronavirüs hastalığı-2019 (COVID-19) hastalarının verilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya nöroloji YBÜ'de nörolojik manifestasyonlar ile yatan COVID-19 hastalarının verileri dahil edildi. Hastaların demografik özellikleri, risk faktörleri, laboratuvar sonuçları, tedavi yöntemleri, mekanik ventilasyon süreçleri, O_2 ihtiyacını karşılayan non-invazif yöntemlerin kullanımı, taburculuk ve 3. ayda klinik sonlanım oranları, ölüm oranları değerlendirildi.

Bulgular: Çalışmaya nörolojik prezentasyonu olan toplam 25 COVID-19 hastası dahil edildi. Hastaların yaş ortalaması 66,76±12,93 (36-83) idi. Yüzde 52 oranını erkek cinsiyet oluşturuyordu. Hastaların %96'sında polimeraz zincir reaksiyonu testi pozitif, %92 oranında akciğer tutulumu vardı. Hastaların komorbitesini %48 hipertansiyon, %28 diabetes mellitus ve koroner arter hastalığı, %20 serebrovasküler hastalık, %20 kanser, %12 kronik obstriktif akciğer hastalığı oluşturdu. Hastaların %72'si inme ile prezente olan COVID-19 grubundan oluşuyordu. Yüzde 12 ensefalopati tablosunda gelen COVID-19 hastalarından, %8 epilepsi ve miyastenia gravis semptomları ile gelen hastalardan oluşuyordu. Hastaların ortalama YBÜ yatış süresi 13,16±12,44 gündü. Hastaların %56'sı yüksek mekanik ventilatör ayarlarında, senkronize intermittent mekanik ventilasyon modunda takip edildi. Entübasyon gün sayısı 9,5±12,26 idi. Hastaların tümüne favipravir ve antiagregan, %92'sine steroid ve antibakterial tedavi, %52'sine antiagregan, %20'sine plazma tedavisi, %8'ine sitokin filtiresi ve immünoglobulin tedavisi, %4'üne monoklonal antikor tedavisi uygulandı. Hastaların yatışı sürecinde ölümle sonuçlanma oranı %48, iyi klinik sonlanım oranı %36, saptandı.

Sonuç: Nörolojik belirtilerle gelen COVID-19 hastalarının hastane içi tedavi ve takip sürecinde, aynı zamanda taburculuklarında kötü klinik sonlanım oranları yüksek görülmektedir.

Anahtar Kelimeler: COVID-19, nöroyoğun bakım, inme, epilepsi, ensefalopati, miyastenia gravis

Address for Correspondence/Yazışma Adresi: Fergane Memmedova MD, Eskisehir Osmangazi University Faculty of Medicine, Department of Neurology, Eskisehir, Turkey Phone: +90 534 679 96 29 E-mail: drfergane@gmail.com ORCID: orcid.org/0000-0003-3021-1688
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Introduction

The severe acute respiratory syndrome-coronavirus-2 (2019-nCoV) has been in the spotlight of the scientific world since the pandemic has begun. Many scientists are researching the nature of the coronavirus family, its morphological characteristics, and the pathophysiological mechanisms in disease development (1). The 2019-nCoV is a non-segmented, pleomorphic, enveloped, single-stranded RNA virus with positive polarity that belongs to the coronavirus family. Since this virus has the largest positive-sense RNA genome, it is less dependent on the host cell for proliferation (2,3). The 2019-nCoV virus enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptor. These receptors are expressed in various body tissues, such as the heart, lungs, kidney, and intestines. ACE2 is also found in endothelial cells, including arterial and venous endothelial cells and arterial smooth muscle cells. Proliferation of the virus takes place in these cells (4,5). The causes of multi-organ dysfunction in patients with coronavirus disease-2019 (COVID-19) are hidden in the pathophysiological mechanisms of the virus (4,5). A cytokine storm is involved in the pathogenesis of COVID-19, including inflammatory cytokines [interleukins (IL) (IL-1, IL6, IL-8, IL-12), tumor necrosis factor (TNF-α) and interferon (INF)] and chemokines. Patients in intensive care units (ICU) had higher plasma levels of IL-6, IL-2, IL-7, IL-10, INF-inducible protein (IP10), monocyte chemoattractant protein, macrophage inflammatory protein, and TNF-α plasma levels. Cytokine storm with high circulating cytokine levels, lymphopenia, thrombosis, and mononuclear cell infiltration is considered a major cause of mortality in severe patients (3,6,7). After the virus enters the body, it invades the central nervous system and all systems through viremia, causing neurological disease (2,8). Neurological symptoms have been reported in approximately 80% of patients hospitalized for COVID-19. The most commonly reported symptoms are headache, anosmia and ageusia. Encephalopathy and stroke are the most common neurological complications in patients requiring ICU (9). In this study, we examined the data of patients with COVID-19 who were followed up in the neurology ICU (NICU) and who had neurological presentations like stroke, encephalopathy/encephalitis, seizures, or myasthenia gravis (MG).

Materials and Methods

During the pandemic, data were retrospectively reviewed from patients who developed neurological complications due to COVID-19 and who were treated and followed up in the NICU of the Neurology Department at Eskisehir Osmangazi University, Faculty of Medicine. The patients' demographic characteristics, risk factors, blood parameters, treatment methods (plasma therapy, steroid use, cytokine filter), non-invasive O_2 treatments [nasal mask, mask with reservoir, high-flow nasal cannula (HFNC)], intubation, and mechanical ventilator settings were evaluated. The treatment of patients who were admitted to the NICU with COVID-19 pneumonia and neurological complications was performed according to the protocol of the Scientific Advisory Board of the Ministry of Health of the Republic of Turkey. Neurological disability was assessed with modified Rankin scale (mRS), in which 0-3 points were determined as a good clinical outcome and 4-6 points as a poor clinical outcome. We assessed the relationship between stroke and COVID-19, as well as treatment methods [intravenous thrombolytic therapy (IV tPA), mechanical thrombectomy, antiaggregants, and anticoagulants], mRS score at discharge and 3rd month, and mortality rates. We also investigated the relationship between COVID-19 and encephalitis, epileptic seizures and MG. The patients with suspected COVID-19 who had a negative realtime reverse transcriptase-polymerase chain reaction (PCR) and the patients with COVID-19 who had a positive PCR test but no neurological complications were excluded.

Approval was received from the Ethics Committee of the Faculty of Medicine at Eskisehir Osmangazi University (E-25403353-050.99-182185. 2021-98).

Statistical Analysis

The IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) package software was used for the analysis. Categorical data are given as frequency distribution and percentage.

Results

The study included 25 patients with COVID-19-related neurological complications. The mean age of the patients was 66.76±12.93 (38-83). Fifty-two percent of the patients were male (Table 1). The PCR test was positive in 96% of patients and there was lung involvement in 92%. A patient with COVID-19 with a neurological complication, whose PCR test became negative was transferred to the general ICU. Considering concomitant diseases, 12 patients (48%) had hypertension (HT), 7 (28%) had diabetes mellitus (DM), 7 (28%) had coronary artery disease (CAD), 5 (20%) had cerebrovascular disease (CVD), 5 (20%) had cancer,

Table 1. Characteristic of COVID-19 patients

Demographic data	**n (%)**
Total	25
Age (age range, average)	66.76±12.93 (36-83)
Gender	
Male	13 (52%)
Female	12 (48%)
Comorbidity	
Hypertension	12 (48%)
Diabetes mellitus	7 (28%)
Coronary artery disease	7 (28%)
Cerebrovascular disease	5 (20%)
Cancer	5 (20%)
Chronic obstructive pulmonary disease	3 (12%)
Obesity	1 (4%)
Chronic kidney disease	1 (4%)
Atrial fibrillation	2 (8%)
Behcet's disease	1 (4%)
Myasthenia gravis	2 (8%)
Dementia	2 (8%)
Epilepsy	2 (8%)

COVID-19: Coronavirus disease-2019

3 (12%) had chronic obstructive pulmonary disease (COPD), 2 (8%) had MG, 2 (8%) had dementia, 2 (8%) had epilepsy (one of these patients had both dementia and epilepsy), 2 (8%) patients had atrial fibrillation (AF), 1 (4%) patient had chronic kidney disease (CKD), 1 (4%) patient had obesity, and 1 (4%) patient had newly diagnosed Behcet's disease (Table 1). Eighteen patients (72%) developed ischemic stroke as a result of the COVID-19. The number of patients presenting with COVID-19 encephalitis/encephalopathy was 3 (12%). During the examination phase, 2 (8%) patients with MG were admitted due to worsening disease symptoms and their COVID-19 PCR tests were found to be positive. Two (8%) of the patients were hospitalized due to recurrent epileptic seizures. One of these patients was a PCR-positive patient who had been previously diagnosed as having epilepsy and treated for it. This patient had COVID-19 and presented with seizures. The other patients did not have a diagnosis of epilepsy. Table 2 gives the lowest values for lymphocyte and platelet counts, and fibrinogen level, and the highest values for ferritin, D-dimer, CRP, procalcitonin, creatinine, alanine aminotransferase, and aspartate aminotransferase levels. The patients who were admitted to the NICU with COVID-19 pneumonia and neurological complications were treated according to the protocol of the Scientific Advisory Board of the Ministry of Health of the Republic of Turkey (Table 3). The mean length of stay in the NICU was 13.16±12.44 (2-43) days. Fourteen (56%) patients were intubated in pressure-synchronized intermittent mandatory ventilation (P-SIMV) mode at high mechanical ventilator settings. The mean number of intubation days was 9.5±12.26 (1-39). No tracheostomy was required in any of the patients. Eleven (44%) patients were not intubated during the treatment period. Non-invasive methods like high-flow, masks with reservoir, and nasal masks were used to meet the O_2 needs of these patients. Of the patients 72% had stroke. Among all patients who were hospitalized due to stroke, COVID-19 was detected in 4 (22.2%) by PCR test. The onset of stroke in these patients occurred on a mean of 4.39±5.5 days (0-16) after COVID-19 symptoms. Five patients with ischemic stroke who presented within the first 4.5 hours after the onset of stroke symptoms were administered IV tPA. Mechanical thrombectomy was performed in 3 patients due to large vessel occlusion. At discharge, 36% of the patients had a good clinical outcome and 64% had a poor clinical outcome. Twelve (48%) patients died during hospitalization. The causes of mortality were cardiac arrest, multiple organ failure, sepsis, brain death due to (re)occlusion of large vessels, acute renal failure, and liver failure. At the 3rd month after discharge, the rate of good clinical outcomes was 68% and the rate of poor clinical outcomes was 32% (Table 4).

Discussion

The COVID-19 is a viral infection, and when the virus comes into contact with endothelial cells, the body's well-known immunological response to viral infections, "the cytokine storm" occurs. Activation of the inflammatory cascade triggers thrombotic complications, endothelial dysfunction, thrombin production, and platelet activation. As in many organs and systems, this leads to the destruction of parenchymatous, leptomeningeal, and vascular structures in the central and peripheral nervous systems (2,10). According to the findings of multicenter studies, neurological symptoms and syndromes are common in patients with COVID-19 (9). In our study, all patients were hospitalized with a diagnosis of COVID-19 and had neurological symptoms. In our study, the rate

Table 3. Treatments administered to patients with COVID-19 in the intensive care unit

Treatments	n (%)
Steroid	23 (92%)
Anticoagulants	25 (100%)
Antiaggregants	13 (52%)
Favipravir	25 (100%)
Convalescent plasma therapy	5 (20%)
Cytokine filtration	2 (8%)
Monoclonal antibodies	1 (4%)
Antibacterial treatments	23 (92%)
IVIG	2 (8%)

COVID-19: Coronavirus disease-2019, IVIG: Intravenous immunoglobulin

Table 2. Laboratory findings of patients with COVID-19 and central nervous system symptoms

	n=Number of patients	Mean	Standard deviation	(Min-max values)
Lymphocyte %	25	20.61	±17.41	(1-88)
Platelet 10^3/ul	25	184.4	±94.57	(83-413)
Fibrinogen; mg/dl	23	434.1	±201.2	(83-900)
Prothrombin time; sec	25	19.76	±16	(11-82)
Creatinine; mg/dl	25	2.05	±2.1	(1-11)
Ferritin; mg/l	23	2352.7	±1925.6	(2-43247)
C-reactive- protein; mg/l	24	165.1	±119	(18-466)
Procalcitonin; ng/ml	12	13.57	±18	(1-54)
Aspartate aminotransferase; U/l	24	57	±36.97	(16-142)
Alanine aminotransferase; U/l	24	39.67	±22.53	(12-82)
D-dimer; mg/l	22	10.71	±16.65	(1-80)

COVID-19: Coronavirus disease-2019, min: Minimum, max: Maximum

Table 4. Modified Rankin scale score at discharge and at 3rd month follow-up visit

	mRS at discharge (good clinical outcome)	mRS on 3rd month (poor clinical outcome)
	n (%)	n (%)
mRS 0	4 (16%)	5 (20%)
mRS 1	2 (8%)	3 (12%)
mRS 2	1 (4%)	2 (8%)
mRS 3	2 (8%)	0 (0%)
mRS 4	2 (8%)	1 (4%)
mRS 5	2 (8%)	2 (8%)
mRS 6	12 (48%)	12 (48%)

mRS: Modified Rankin scale

of male gender was 52%. This is similar to some studies in the literature (9,10,11,12). The mean age of our patients was 66.76±12.93 years (36-83 years). The age range was quite wide, considering the multiplex study data (2,11). According to a comprehensive study based on data from dozens of countries around the world, 82% of all hospitalized patients reported symptoms ranging from mild neurological symptoms to severe neurological manifestations. This study reported the rate of stroke among patients with COVID-19 as 6% (9). Our study only included patients hospitalized in the NICU. Stroke accounted for 72% of all patients admitted to our department with severe neurological manifestations. Our patients with COVID-19 who suffered from a stroke had risk factors such as HT, DM, CAD, CVD, AF, cancer, COPD, and smoking. Although one young patient was found to have no risk factor on admission to the hospital, Behcet's disease was present on examination. Based on these data, we can say that COVID-19 promotes stroke development by triggering the coagulation cascade in patients with underlying risk factors. It should also be emphasized that occurred between days 0-16 of the first signs of COVID-19 in our patients. After admission to the hospital for stroke, 22.2% of the patients were diagnosed with COVID-19 by routine PCR test screening. Of the stroke patients 44.4% were treated within the first hours of the stroke. IV tPA was performed in 5 of these patients and mechanical thrombectomy was performed in 3 because a large vessel occlusion was detected. Thrombectomy resulted in modified thrombolysis in cerebral infarction (mTICI2b) recanalization in 2 patients and in mTICI2a (recanalization could not be achieved) in 1. In one of these patients, large vessel re-occlusion resulted in exitus during the early hours of intensive care follow-up. According to the literature, data from various centers have produced similar results (13). Given all these, there is a need to study the histopathological characteristics of the thrombus fragment in patients with large vessel occlusion and to perform studies with larger samples. Seizure was noted in 2 (8%) of the patients included in this study. One of these patients was a known epileptic patient. This patient survived the COVID-19 treatment process with O_2 support without intubation and he was discharged home. The other patient did not have previous diagnosis of epilepsy and arrived at the emergency department with repeated seizures. COVID-19 was identified when PCR positivity was established. The intensive care follow-up of this patient resulted in exitus. In the literature, many comprehensive studies have been conducted on the coexistence of epilepsy and COVID-19 since the onset of the pandemic (9,14,15,16,17,18,19,20). A retrospective review of hospitalized patient data showed that seizures in patients with epilepsy were triggered by COVID-19. Other than patients with epilepsy, recurrent seizures and epileptic states can occur in patients with COVID-19. It is known that the COVID-19 triggers seizures and these patients become resistant to antiepileptic treatment because of secondary problems such as fever, shortness of breath, hypoxia, and metabolic disturbances. Besides, medications used in the course of the disease may lower the seizure threshold and even result in the development of new seizures. Chou et al. (9) found that 49% of patients with neurological complaints hospitalized for COVID-19 had a clinical presentation of acute encephalopathy. This rate was 12% in our study. In-hospital mortality rates were five times higher in patients with acute encephalopathy (21). One patient in our cohort showed good clinical outcome at discharge, although the treatment and follow-up period of the second patient resulted in death. One patient was referred to the palliative center with the mRS score of 5. MG, another neurological condition, is a group in which COVID-19 is more severe. As a result of a viral infection precipitating a myasthenic crisis, symptoms worsen, especially in patients with bulbar weakness, who require intensive care (22). Camelo-Filho et al. (23) examined patients with MG hospitalized for COVID-19 and showed that 87% were followed up in the ICU, 73% were on a mechanical ventilator, and a total of 30% of these patients died during the follow-up period. We know that hypoxemic respiratory failure due to COVID-19 is common. Furthermore, neuromuscular respiratory failure, which occurs as a result of myasthenic exacerbation, complicates the situation. It is believed that high-dose steroids positively affect the treatment process in these patients (24). Patients with COVID-19 and MG made up 8% of our patients. One of these patients had bulbar involvement and was admitted to the ICU with an exacerbation of MG. During the follow-up period, difficulties were encountered in the administration of the treatments due to acute renal failure and sepsis, and the patient died. The other patient was admitted to the ICU with mild respiratory distress. In the following days, mechanical ventilation was started as the clinical status progressed rapidly. After many treatments, including high-dose steroids, intravenous immunoglobulin (IVIG), plasmapheresis, and cytokine filters, the patient was successfully extubated and discharged home without any disability. Mao et al. (25) compared the laboratory results of patients hospitalized with and without neurological manifestations for COVID-19 and showed that the group with neurological symptoms had lower lymphocyte counts and higher D-dimer levels. The lowest lymphocyte count was 300/mm^3, the highest D-dimer level was 80 mg/l, the highest ferritin level was 43247 mg/l, and the lowest fibrinogen level was 83.22 mg/dl in our study. Steroids, favipiravir, low molecular weight heparin, antiaggregants (in stroke patients), antibacterial therapy, plasma therapy, cytokine filters, monoclonal antibodies, antiepileptic therapy (in patients with seizures), IVIG, and plasmapheresis (in patients with MG and encephalopathy) were used to treat patients who were followed up in the NICU and in whom these laboratory results suggested a cytokine storm (4,26,27,28,29,30). Fourteen (56%) of the patients were intubated during the ICU follow-up period. The mean number of intubation days was 9.5±12.26 (1-39). All these patients were followed up in high-value P-SIMV mode. Tracheostomy was not performed in any patient in our study. Intermittent prone positioning was

performed in 8% of our patients. It has been reported in the literature that prone positioning for at least 16 hours per day in intubated patients with severe pneumonia improves oxygenation and reduces mortality (31,32,33,34). Non-invasive mechanical ventilation methods (mask with reservoir, continuous positive airway pressure, high-flow nasal cannula) are beneficial in place of intubation in patients with mild to moderate respiratory distress (31,35,36,37). During the early follow-up period in the ICU, almost all our patients were treated with a mask with a reservoir and HFNC treatment was performed only in 3 (12%) patients. In 4 (16%) patients intubation could be avoided after using non-invasive methods.

The causes of in-hospital mortality in patients with COVID-19 were investigated in many retrospective studies. In a retrospective study examining the data of 290 patients with lung damage followed up in the ICU with the diagnosis of COVID-19 pneumonia, it was shown that 50% of the patients resulted with an in-hospital mortality. It has been found that these patients with a mortal course have more comorbidities such as advanced age and CKD compared to patients discharged from the hospital (38). In an autopsy study conducted in Germany, the data of patients hospitalized due to COVID-19 were evaluated retrospectively. In almost all of these patients, the cause of in-hospital mortality was defined to be lung damage due to COVID-19 (39).

In our study, the in-hospital mortality rate was 48%. Almost all of the patients who died had severe pulmonary involvement. In addition, other pathologies such as sepsis and acute kidney injury contributed to this outcome.

It has been shown that in-hospital mortality is higher in patients with COVID-19 and neurological symptoms than in patients without neurological symptoms (9). In our study, all patients had neurological manifestations.

In a multicenter study by Ghoreishi et al. (40), the patients had an increase in mRS score at hospital discharge. At discharge, the rate of good clinical outcome (mRS 0, 1, 2 or 3) was 36% and the rate of poor clinical outcome (mRS 4, 5 or 6) was 64%. At the third month, in mRS assessment, the rate of good clinical outcome increased to 68%, while the rate of poor clinical outcome decreased to 32%.

Study Limitations

The small number of patients with MG, epilepsy, and other neurological manifestations and the absence of patients with neurological manifestations such as multiple sclerosis or Guillain-Barré syndrome.

Conclusion

COVID-19 causes multi-organ dysfunction with hypercoagulability, either by activating the inflammatory system or by activating the coagulation cascade. We frequently encounter central nervous system involvement. As noted in many studies, based on the results of our research, we can emphasize that patients with neurological manifestations have a higher mortality rate during hospitalization and a poorer clinical outcome at discharge.

Ethics

Ethics Committee Approval: Approval was received from the Ethics Committee of the Faculty of Medicine at Eskisehir Osmangazi University. E-25403353-050.99-182185. 2021-98.

Informed Consent: This study did not require informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.M., S.A.S., F.A.K., F.G.A., Z.M., U.J., Ö.A., A.Ö.Ö., Concept: F.M., Ö.A., A.Ö.Ö., Design: F.M., Ö.A., A.Ö.Ö., Data Collection or Processing: F.M., S.A.S., F.A.K., F.G.A., Z.M., U.J., Analysis or Interpretation: F.M., A.Ö.Ö., Literature Search: F.M., Writing: F.M.

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