Epilepsi 2021;27(4):221-225 DOI: 10.14744/epilepsi.2021.87609

ORIGINAL ARTICLE

Epileptic Seizures Observed in Hospitalized COVID-19 Patients

Nuray CAN USTA

Department of Neurology, University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey

Abstract

Objectives: Pneumonia cases that first started in Wuhan were defined as Severe Acute Respiratory Syndrome Coronavirus-2 by The World Health Organization in January 2020. Neurological complications such as epileptic seizures may occur during COVID-19 infection. These seizures may occur for the first time or in the form of acute seizures that can be observed in epilepsy patients during the course of the disease.

Methods: Demographic data of the patients, presence of the diagnosis of epilepsy disease, accompanying diseases, number of seizures during hospitalization, follow-up to the intensive care unit, COVID-19 clinical day during seizures, presence of disease that can be detected in the etiology of epilepsy, and discharge status were examined in this retrospectively planned study.

Results: Seizure rate was determined to be 0.57% in these patients. 18 (58.1%) patients did not have a history of epilepsy, whereas 13 (41.9%) patients had a history of epilepsy. It was found that mortality was higher in the first seizures; there was no difference between age, gender, COVID-19 clinical day, presence of hospitalization in the intensive care unit, and Modified Charlson Comorbidity Index when the data of patients with and without epilepsy were compared.

Conclusion: COVID-19 infection can increase the likelihood of seizures like other viral infections, but we do not have strong data that it can trigger seizures in different ways compared to other viral agents with all the data.

Keywords: COVID-19; epilepsy; modified charlson comorbidity index score.

Cite this article as: Can Usta N. Epileptic Seizures Observed in Hospitalized COVID-19 Patients. Epilepsi 2021;27:221-225.

Introduction

Pneumonia cases that first started in Wuhan were defined as Severe Acute Respiratory Syndrome Coronavirus-2 by The World Health Organization in January 2020.[1] It was found in a study evaluating more than 200 patients hospitalized for COVID-19 infection in Wuhan that more than one-third of the patients developed different neurological signs and these patients had more severe respiratory diseases.[2]

Angiotensin-converting enzyme-2 (ACE-2) receptor, which is responsible for the regulation of cardiovascular and respiratory functions and is mostly located in the brain stem, plays an important role in the initiation of Coronavirus infection.[3] In addition, the virus can pass through the olfactory tract and reach the brain directly without needing the ACE-2 receptor.[4] Central Nervous System (CNS) signs that may occur in COVID-19 patients after reaching the brain include headache, dizziness, altered consciousness, acute cerebrovascular events, ataxia, acute disseminated encephalitis, and seizures.[5]

Seizures may occur for the first time during COVID-19 infection and infection-induced seizures in epilepsy patients may be observed.[6] Cases of generalized tonic-clonic seizures occurring for the 1st time during the course of COVID-19 disease have also been presented in patients diagnosed with epilepsy.[7] Hypoxia, trauma, electrolyte imbalance, and infections are among the blamed causes even though the mechanism underlying the seizure has yet to be fully explained.[8]

The relationship between COVID-19 and epilepsy has still not been fully established in the literature. The data of patients who had seizures for the 1st time during COVID-19 infection and patients with previous epilepsy and seizures were evaluated in this study and this study aims to contribute to the effort to clarify the relationship between COVID-19 disease and epilepsy.

Nuray CAN USTA, M.D.

Corresponding author
Nuray CAN USTA, M.D.
e-mail dr.nuraycan@hotmail.com

Received 08.06.2021
Accepted 29.09.2021
Online date 09.11.2021

Hospitalize Edilen COVID-19 Hastalarında Gözlenen Epileptik Nöbetler

Öz

Amaç: The World Health Organization (WHO) tarafından ilk kez Wuhan'da başlayan pnomöni olguları Ocak 2020 de Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) olarak tanımlanmıştır. COVID-19 enfeksiyonu sırasında epileptik nöbet gibi nörolojik komplikasyonlar ortaya çıkabilir. Bu nöbetler hastalık seyri sırasında ilk kez olabileceği gibi epilepsi hastalarında gözlenebilen akut nöbetler şeklinde de olabilir.

Gereç ve Yöntem: 15 Mart 2020 ve 15 Mayıs 2021 tarihleri arasında COVID-19 enfeksiyonu nedeniyle hospitalize edilen 5430 hasta içinde epileptik nöbet geçiren hastalar incelenmiştir. Retrospektif olarak planlanan bu çalışmada hastalara ait demografik veriler, epilepsi hastalık tanısının varlığı, ek hastalıkları, hastanede yatış döneminde geçirdiği nöbet sayısı, yoğun bakım ünitesine takip edilme durumu, nöbet geçirdiği sırada COVID-19 klinik günü, epilepsi etiyolojisinde saptanabilen hastalık varlığı, taburculuk durumu (live-death) gibi parametreler incelenmiştir.

Bulgular: Hastaların nöbet geçirme oranı %0.57 olarak saptandı. 13 (%41.9) hastanın epilepsi özgeçmişi mevcut iken 18 (%58.1) hastanın epilepsi öyküsü yoktu. Epilepsi öyküsü olan ve olmayan hastaların verileri karşılaştırıldığında ilk nöbet geçirenlerde mortalitenin daha yüksek olduğu; yaş, cinsiyet, COVID-19 klinik günü, yoğun bakım ünitesinde yatış varlığı ve Modifiye Charlson Komorbidite İndeksi arasında fark olmadığı saptanmıştır.

Sonuç: Toplam 5430 COVID-19 nedeniyle hospitalize edilen hastadan 16 erkek (%51.6), 15 kadın (%48.4) toplam 31 hasta çalışmaya dahil edildi. Bu hastalarda nöbet geçirme oranı %0.57 olarak saptandı. On üç (%41.9) hastanın epilepsi özgeçmişi mevcut iken 18 (%58.1) hastanın epilepsi öyküsü yoktu. Epilepsi öyküsü olan ve olmayan hastaların verileri karşılaştırıldığında ilk nöbet geçirenlerde mortalitenin daha yüksek olduğu; yaş, cinsiyet, COVID-19 klinik günü, yoğun bakım ünitesinde yatış varlığı ve Modifiye Charlson Komorbidite İndeksi arasında fark olmadığı saptanmıştır.

Anahtar sözcükler: COVID-19; Epilepsi; MCCI skoru.

Materials and Methods

The files of patients hospitalized for COVID-19 infection between March 15, 2020, and May 15, 2021, at Trabzon Kanuni Training and Research Hospital of the University of Health Sciences serving as a reference hospital for the pandemic in the region were retrospectively reviewed. Hospital management and Local Non-Drug Clinical Research Ethics Committee approval was obtained (2021/104) and the study was conducted in accordance with the Helsinki Declaration.

Of the 5430 patients hospitalized for COVID-19 between the specified dates, patients who had seizures regardless of their history of epilepsy were included in the study. Patients whose file data could not be reached under optimum conditions, neuroradiological imaging examinations were missing, or the quality of imagining results was not appropriate were excluded from the study.

Demographic data of the patients, presence of the diagnosis of epilepsy disease, accompanying diseases, number of seizures during hospitalization, follow-up to the intensive care unit, COVID-19 clinical day during seizures, presence of disease that can be detected in the etiology of epilepsy, and discharge status (live-death) were examined. The severity of the disease due to COVID-19 pneumonia was scored as mild, moderate, severe in 3 groups.[9] Modified Charlson Comorbidity Index (MCCI) was used to calculate the comorbidity status of the patients.[10]

Statistical analysis– The statistical analysis was performed through SPSS for Windows (version 22.0). Descriptive analyses were presented by mean ± standard deviation, minimum and maximum. The Kolmogorov-Smirnov test was used to reveal whether the data were normally distributed. Parametric tests were used to analyze normally distributed data, and non-parametric tests were used to analyze non-normally distributed data. Student t-test was used for quantitatively comparing two independent groups. Non-normally distributed continuous variables were compared using the Mann-Whitney U-test. Chi-square test was used to compare qualitative data. Any $p<0.05$ was considered as statistically significant.

Results

A total of 31 patients (0.57%), 16 males (51.6%), and 15 females (48.4%) out of a total of 5430 patients hospitalized for COVID-19 were included in the study. The mean age was 67.4±16.3 (28–92) years. 18 (58.1%) patients did not have a history of epilepsy whereas 13 (41.9%) patients had a history of epilepsy. Demographic data of patients with and without a history of epilepsy are summarized in Table 1. There was no statistically significant relationship between the presence of epilepsy history and COVID-19 disease severity of the patients (p=0.07). Table 2 shows in detail the severity of COVID-19 disease and the patients who had seizures. In patients with epilepsy, skipping the dose of antiepileptic drugs or difficulty in accessing the drug was not detected. While 10 of the epilepsy patients used antiepileptic drugs

as monotherapy, three of them used polytherapy. A second antiepileptic drug was added as recurrent seizures occurred in five of the patients who received monotherapy.

Cerebral atrophy was detected in 14 patients, acute ischemic cerebrovascular event was diagnosed in 4 patients, brain metastasis was diagnosed in two patients, demyelinating lesion in two patients (chronic MS plaques due to Multiple Sclerosis were detected in one patient, systemic lupus erythematosus with CNS involvement triggered by COVID-19 infection was diagnosed in the other patient), hemorrhagic cerebrovascular event was diagnosed in two patients (bleeding for ventricle, subdural hematoma in one patient), hydrocephalus in one patient, fracture in frontal bone (post-trauma) in one patient, and anomaly was not detected in the examinations of five patients in the imaging examination results of the patients.

Accompanying diseases were detected in patients with hypertension (n=22), coronary arterial disease-heart failure (n=11), diabetes mellitus (n=9), renal failure (n=9), dementia (n=6), chronic obstructive pulmonary disease-asthma (n=5), previous cerebrovascular disease (n=5), Parkinson's disease (n=3), and patients with no accompanying diseases were detected (n=4).

A single seizure was observed in 13 patients during their clinical follow-up whereas more than one epileptic seizure was detected in 18 patients. One patient was classified as focal aware seizure in the form of tonic contraction in the right arm, and three patients were classified as focal to bilateral tonic-clonic seizure while intubated three patients were classified as generalized seizure.

Status epilepticus was observed in the follow-up of 2 of 31 patients. The first patient was a 76-year-old male patient who was followed up with a diagnosis of normal pressure hydrocephalus without a history of epilepsy and applied to the hospital with status epilepticus on the 1st day of COVID-19 infection. Magnetic resonance imaging (MRI) of the brain revealed images consistent with diffuse cerebral atrophy and hydrocephalus. The patient had a history of hypertension, dementia, renal failure, and severe COVID-19 disease. The intubated patient died on the fourth day of hospitalization while being followed up in the intensive care unit. The patient, who was diagnosed with other status epilepticus, was 41 years old female, diagnosed with epilepsy for 10 years, had fever and weakness complaints, fell down after dizziness at home the day she was diagnosed with COVID-19 and was followed up in the intensive care unit with the diagnosis of status epilepticus after three generalized tonic-clonic seizures following head trauma and admitted to the hospital without regaining consciousness. No pathological signs were detected on brain MRI. She did not have a seizure again during her follow-ups in the hospital and he was discharged with the good general condition.

Discussion

Epileptic seizures, which is one of the neurological complications observed in patients during COVID-19 infection, are seen with a frequency of 0.5%, which is a similar fre-

Table 1. General demographic charactersistics of patients

	Patients without epilepsy (n=18)	Patients with epilepsy (n=13)	p-value
Age (year)	69.6±17.3	64.3±14.9	0.27*
Male/Female	9/9	7/6	0.83†
Clinical day of COVID-19 disease	6.9±8.9	5.5±4.9	0.79*
Alive/Death	9/9	11/2	0.04†
İntesive care unit +/-	12/6	7/6	0.25†
Modified charlson comorbidity index	18	13	0.43*

*Man–Whitney U test; †Chi-square test.

Table 2. Relationship between seizure and severity of COVID-19 disease

	Severity of COVID-19 disease			p-value†
	Mild COVID-19	Moderate COVID-19	Severe COVID-19	
Patient without epilepsy (n=18)	7	0	11	0.07
Patient with epilepsy (n=13)	9	1	3	

†P-values indicate p>0.05 and are considered statistically significant. †Chi-square test.

quency in the literature, in our study.[7] It was found that more than 50% of the patients had epileptic seizures for the 1st time without the diagnosis of epilepsy when the patients hospitalized for COVID-19 infection were evaluated with 1st-time epileptic seizures and with diagnosed epileptic diseases and seizures. It was also seen that epileptic seizures detected in patients with severe COVID-19 mostly occurred in patients who had seizures for the 1st time. There was no significant difference in terms of age, gender, follow-up in the intensive care unit, clinical day of COVID-19 disease, and MCCI score of the patients; however, the mortality rate was found to be higher in those who had seizures for the 1st time compared to those diagnosed with epilepsy.

Epileptic seizures may be observed due to brain dysfunction and neuronal damage during viral infections.[11] The first seizure during COVID-19 infection was reported in Japan and the second in Iran, and both patients were previously reported to have generalized tonic-clonic seizures without a history of epileptic seizures.[12] It is thought that proinflammatory cytokines (TNF-α, IL-6, IL-1B), nitric oxide, prostaglandin E2, and free radicals may cause hyperexcitability, decrease in seizure threshold and seizures by initiating the inflammatory process after the virus reaches CNS during COVID-19 infection.[13] In addition, the hypothesis that increased glutamate and decreased GABA levels in the hippocampus and cerebral cortex also may cause seizures has been suggested. An increase in the tendency to experience seizures due to deterioration of the blood brain barrier due to fever, sepsis or hypoxia is more thought to be the suggested cause in older patients due to COVID-19 disease which primarily targets the respiratory system.[6]

Status epilepticus occurring during the course of COVID-19 has been reported mostly as case reports in the literature.[14,15] Status epilepticus was detected in two patients in our study. One patient was found not to have a mortality course thanks to being young, having no radiological anomaly, and mild course of COVID-19 infection whereas the other patient had a mortality course due to the presence of accompanying diseases, accompanied by radiological anomalies, and severe COVID-19 infection. This difference may be due to the underlying accompanying diseases and the severity of the infection.

The most common radiological anomaly due to the advanced age of COVID-19 patients who have epileptic seizures is cerebral atrophy. This suggests that the disease triggers seizures as a result of systemic effects rather than cerebral effects. The most common acute neuroradiological anomaly detected in COVID-19 patients with epileptic seizures is ischemic acute cerebrovascular events in parallel with the literature.[2] Approximately 10% of all epilepsy patients have a stroke and about 55% of seizures that occur at an advanced age.[16] This may be related to the increased susceptibility of COVID-19 to thromboembolism.[17] Stroke is a risk factor for epileptic seizures and the risk of developing acute symptomatic seizures after stroke varies between 3.1% and 33%.[18] Seizures may occur during stroke due to various factors such as acute hypoxia, metabolic diseases, as well as increased and decreased blood brain perfusion. Situations identified as risk factors for the development of neurological complications during COVID-19 infection may be higher in this group because they are also risk factors for acute cerebrovascular events. It is thought that hemorrhagic stroke may occur in COVID-19 patients and the accumulation of hemosiderin may trigger seizure by leading to neuronal hyperexcitability in addition to ischemic stroke.[19,20]

Epileptic seizures were detected earlier in the COVID-19 clinical day, suggesting that epileptic seizures occurring during COVID-19 may be mostly due to mechanisms suggested in the acute period in our study. The limited data on late-stage seizures may be due to the lack of seizure data of patients after COVID-19 recovery in our study.

It was observed that those who had epileptic seizures during the course of COVID-19 disease had advanced age and accompanying multiple comorbidities. The number of patients was not sufficient to show a significant difference when the patients were analyzed even though the mortality rate of patients with a history of epilepsy and seizures was found to be less compared to those who had seizures for the first time. COVID-19 infection can increase the likelihood of seizures like other viral infections, but we do not have strong data that it can trigger seizures in different ways compared to other viral agents with all the data.

Limitations– The retrospective nature of our study prevented us from having sufficient information about late-stage neurological complications that may occur during the follow-up of the patients. Ancillary diagnostic methods used in epilepsy such as electroencephalography recording were not utilized sufficiently. Failure to detect disease groups in which epileptic seizures such as encephalitis can be observed in the study may be the result of failure to perform further examination in patients due to severe COVID-19 clinic. Studies in larger study groups are necessary.

Acknowledgment– I thank Betul Onal Gunay for her support.

Informed Consent– Due to the retrospective design of the study, informed consent was not taken.

Ethics Committee Approval– This study approved by the University of Health Sciences, Trabzon Kanuni Training and Research Hospital Ethics Committee (Date: 10.06.2021, Number: 2021/104).

Peer-review– Externally peer-reviewed.

Conflict of interest– The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91(1):157–60.
2. Josephson SA, Kamel H. Neurology and COVID-19. JAMA 2020;324(12):1139–40. [CrossRef]
3. Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord 2020;46:102535. [CrossRef]
4. Steardo L, Steardo L Jr., Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol (Oxf) 2020;229(3):e13473. [CrossRef]
5. 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):683–90. [CrossRef]
6. Vohora D, Jain S, Tripathi M, Potschka H. COVID-19 and seizures: Is there a link? Epilepsia 2020;61(9):1840–53. [CrossRef]
7. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: A systematic review and current update. Acta Neurol Scand 2020;142(1):14–22. [CrossRef]
8. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55–8. [CrossRef]
9. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7(1):4. [CrossRef]
10. Brusselaers N, Lagergren J. The charlson comorbidity index in registry-based research. Methods Inf Med 2017;56(5):401–6.
11. van den Pol AN. Viral infections in the developing and mature brain. Trends Neurosci 2006;29(7):398–406. [CrossRef]
12. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia 2020;61(6):e49–53. [CrossRef]
13. Roy D, Ghosh R, Dubey S, Dubey MJ, Benito-León J, Ray BK. Neurological and neuropsychiatric impacts of COVID-19 pandemic. Can J Neurol Sci 2021;48(1):9–24. [CrossRef]
14. Chen W, Toprani S, Werbaneth K, Falco-Walter J. Status epilepticus and other EEG findings in patients with COVID-19: A case series. Seizure 2020;81:198–200. [CrossRef]
15. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: A case report. Seizure 2020;78:109–12. [CrossRef]
16. Feyissa AM, Hasan TF, Meschia JF. Stroke-related epilepsy. Eur J Neurol 2019;26(1):18–e3. [CrossRef]
17. Trejo-Gabriel-Galán JM. Stroke as a complication and prognostic factor of COVID-19. Neurologia 2020;35(5):318–22. [CrossRef]
18. Leung T, Leung H, Soo YO, Mok VC, Wong KS. The prognosis of acute symptomatic seizures after ischaemic stroke. J Neurol Neurosurg Psychiatry 2017;88(1):86–94. [CrossRef]
19. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis 2020;29(8):104984. [CrossRef]
20. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): Encephalopathy. Cureus 2020;12(3):e7352. [CrossRef]