Epilepsi 2021;27(3):144-149 DOI: 10.14744/epilepsi.2021.39259

ORIGINAL ARTICLE

The Effects of Coronavirus Disease-19 Infection On Seizure Recurrence in Patients with Epilepsy

Şakir DELİL, Bade GÜLEÇ, Esra KOÇHAN KIZILKILIÇ, Gülçin BENBİR ŞENEL, Seher Naz YENİ, Ciğdem ÖZKARA

Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Abstract

Objectives: We aimed to investigate the effects of coronavirus disease (COVID)-19 infection on seizure recurrence in patients with epilepsy and the factors which may possibly be related to a deterioration of the seizure control.

Methods: We evaluated the patients with epilepsy consecutively for 6 months. Data were collected in a pre-defined questionnaire from the patients and/or their parents, and past medical records.

Results: A total of 574 patients were investigated during the study period, and 104 patients (18.1%) with epilepsy had COVID-19 infection. The majority of the patients (59.6%) were males. Sixteen patients with epilepsy (15.4%) had an increase in seizure frequency during COVID-19 infection. The mean age of the patients and the age at disease onset were significantly lower in patients with seizure exacerbation. The seizure frequency and the frequency of having a seizure within 1 month before the COVID-19 infection were also higher in these patients. Myalgia was significantly more common in patients with an increase in seizure frequency. The duration of the loss of smell and/or taste has lasted much more longer in this group of patients (48.0+60.6 vs. 13.8+13.4 days; p=0.013). The need for hospitalization was also more common in patients with seizure exacerbation (25.0% vs. 6.8%, p=0.045).

Conclusion: This is the first study showing that one out of every six or seven patients with epilepsy will have seizure exacerbation during COVID-19 infection. Young patients, patients with early-onset epilepsy, and those with high seizure frequency were at higher risk for the seizure exacerbation.

Keywords: Coronavirus disease-19 infection; epilepsy; seizure recurrence.

Cite this article as: Delil S, Güleç B, Koçhan Kızılkılıç E, Benbir Şenel G, Yeni SN, Özkara C. The Effects of Coronavirus Disease-19 Infection On Seizure Recurrence in Patients with Epilepsy. Epilepsi 2021;27:144-149.

Introduction

Coronaviruses primarily affect the respiratory system and are associated with major problems, like outbreaks of severe acute respiratory syndrome (SARS) in 2002, and the Middle East respiratory syndrome in 2012.[1] Coronavirus disease (COVID-19) caused by SARS-CoV2 (coronavirus disease COVID-19 infection) has recently been a global threat and potentially fatal disease worldwide.[2] Although the most common symptoms of COVID-19 infection include fever, cough, or fatigue; pneumonia, acute respiratory distress syndrome, or cardiac failure may occur in severe cases. In one study investigating the neurological manifestations of COVID-19 infection, it was observed that one-fourth of the patients have experienced at least one neurological symptom or disease, including headache, dizziness, impaired consciousness, or stroke.[3,4] The epileptic seizures were reported to occur in about 0.5% of the patients with COVID-19 infection in the same study.

COVID-19 infection in patients with epilepsy has brought some important issues to be answered and clarified. The need for alteration in the management of the patients and anti-seizure medications, the problems in the access to medications, or the issues with telemedicine have been widely covered.[5] Nevertheless, it is still unclear whether COVID-19 infection affects disease course in patients with epilepsy. Here, we aimed to investigate the effects of COVID-19 infection on seizure recurrence in patients with

Şakir DELİL, M.D.

Corresponding author
Şakir DELİL, M.D.
e-mail sakirdelil@yahoo.com

Received 18.06.2021
Accepted 28.06.2021
Online date 30.07.2021

Epilepsi Hastalarında COVID-19 Enfeksiyonunun Nöbetler Üzerindeki Etkisi

Öz

Amaç: Bu çalışmada COVID-19 enfeksiyonunun epilepsi hastalarındaki nöbet kontrolü üzerindeki etkilerini ve alevlenmeye neden olan muhtemel faktörleri incelemeyi amaçladık.

Gereç ve Yöntem: Epilepsi hastaları altı ay boyunca ardışık olarak incelendi. Önceden hazırlanmış bir anket ile gerekli veriler hastalardan, yakınlarından ve geçmiş tıbbi dokümanlardan elde edildi.

Bulgular: Çalışma boyunca 574 hasta değerlendirildi, 104 epilepsi hastasında (%18.1) COVID-19 enfeksiyonu saptandı. Hastaların çoğunluğu (%59.6) erkekti. On altı hastada (%15.4) nöbet sıklığında artış izlendi. Hastaların ortalama yaşları ve hastalık başlangıç yaşları nöbet alevlenmesi olan grupta istatistiksel anlamlı olarak daha düşüktü. Nöbet sıklığı ve COVID-19 enfeksiyonu öncesindeki son bir ay içerisinde nöbet geçirme oranı da bu hasta grubunda daha yüksekti. COVID-19 enfeksiyonu bulgusu olarak miyalji, nöbet sıklığı artan grupta daha sık olarak bildirilmişti. Koku ve/veya tat kaybı süresi ise yine bu grupta yer alan hastalarda belirgin olarak daha fazlaydı (48.0+60.6 karşın 13.8+13.4 gün; p=0.013). COVID-19 enfeksiyonu nedeni ile hastane yatış oranı da nöbet alevlenmesi yaşayanlarda daha fazlaydı (%25.0 karşın %6.8, p=0.045).

Sonuç: Çalışmamızda ilk kez, COVID-19 enfeksiyonu olan her 6–7 epilepsi hastasından birinde nöbet sıklığında artış olduğu gösterilmiştir. Genç hastalar, erken nöbet başlangıç yaşı olanlar ve sık nöbet geçiren hastalar nöbetlerin alevlenmesi için artmış risk altındadır.

Anahtar sözcükler: Covid-19 enfeksiyonu; epilepsi; nöbetler.

epilepsy and the factors which may possibly be related to a deterioration of the seizure control.

Materials and Methods

Study design and the participants– In this study, we evaluated the patients with epilepsy, who were being followed-up in the epilepsy center in the department of neurology. All patients were consecutively evaluated for the 6 months between January and June 2021. Inclusion criteria were set as (1) having definitive epilepsy; (2) being followed up for at least 1 year; (3) being adolescent or adult (>13 years of age), and (4) being volunteer to participate. Patients with severe medical and/or neurological diseases with unstable condition were not included.

Data were collected systematically in a pre-defined questionnaire from the patients and/or their parents, and from the past medical records. The demographic and disease-related data were noted; including the sex, age of the patients, age at disease onset, disease duration, types of epilepsy (generalized, focal symptomatic, focal cryptogenic, or undetermined), seizure frequency (per month and per year) before COVID-19 infection, the date of the last seizure, the change in the frequency of seizures and the presence of status epilepticus during COVID-19 infection, and the use of anti-seizure medications. Regarding COVID-19 infection, the exact date at which the first symptom occurred, the symptoms of the disease (including fever, cough, dyspnea, myalgia, fatigue, diarrhea, headache, loss of taste and/or smell, and the loss of appetite), the onset and the duration of the loss of taste and/or smell, anti-COVID medications, and the need for hospitalization were questioned. COVID-19 infection was determined as the period starting from the 5 days before the appearance of first symptom (to include the incubation period) till the day at when all tests were resulted negative and the anti-COVID therapies were titrated and/or stopped.

Statistical analysis– All data were analyzed using Statistical Package for the Social Sciences (SPSS) software (version 21.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean + standard deviation, and the categorical variables were expressed as percentages. For the comparisons of data between the groups, the non-parametric Mann–Whitney U-test, Fisher's exact test, or Chi-square test were used accordingly. P<0.050 was accepted as statistically significant.

Ethical approval– The study was approved by the Local Ethics Committee (ID: 90300). Informed consent was obtained from all patients and/or their parents participating into the study.

Results

A total of 574 patients were investigated during the study period, and 104 patients (18.1%) with epilepsy had COVID-19 infection. The demographic and clinical features of the study population are given in Table 1. The majority of the patients (59.6%) were male. The most common type of epilepsy was observed as focal epilepsy (focal epilepsy with structural etiology) that was encountered in almost half of the study population (46.2%, Table 1).

The most common symptom of COVID-19 infection was reported as fever (48.1%), followed by the loss of taste and/or smell (45.2%), fatigue (42.3%), cough (41.3%), myalgia

Table 1. The demographic and clinical features of the study population

Parameters	Patients with epilepsy having COVID-19 infection (n=104)			
	n	%	Min.–Max.	Mean+SD
Sex (males/females)	62/42	59.6/40.4		
Age (years)			14–70	34.9+12.7
Age at onset (years)			1–54	18.0+11.4
Disease duration (years)			1–53	16.8+11.6
Seizure types				
Generalized	14	13.5		
Focal symptomatic	48	46.2		
Focal cryptogenic	33	31.7		
Undetermined	9	8.7		
Seizure frequency (per year)			1–360	22.3+56.7

COVID: Coronavirus disease; Min: Minimum; Max: Maximum; SD: Standard deviation.

(39.4%), dyspnea (30.8%), headache (23.1%), loss of appetite (10.6%), and diarrhea (6.7%). The mean time at which the loss of taste and/or smell was appeared was 3.1+1.7 days (varying between 1st and 10th days), and the mean duration was reported as 19.0+28.1 days (between 2 and 180 days). COVID-19 infection was resolved spontaneously in 17 patients (16.3%) without any need for the treatment, and only 10 patients (9.6%) were hospitalized for the treatment of COVID-19 infection. Favipravir was the choice of treatment in 80 patients (76.9%), and hydroxychloroquine was given in only 7 patients (6.7%).

Of 104 patients with epilepsy and COVID-19 infection, 16 patients (15.4%) had an increase in seizure frequency. The comparisons of the demographic and clinical data between patients with COVID-19 infection having an increase in seizure frequency (Group 1) and those who did not show a change in seizure frequency (Group 2) are given in Table 2. An increase in seizure frequency was observed in 21.4% of female patients and in 11.3% of males with epilepsy and COVID-19 infection. This difference, however, was not found to be statistically significant (Table 2). The mean age of the patients and the age at disease onset, however, were significantly lower in Group 1 than those in Group 2. The duration and the type of epilepsy were found similar between two groups. On the other hand, the seizure frequency and the frequency of having a seizure within 1 month before the COVID-19 infection were higher in Group 1, as well (Table 2).

Table 2. The demographic and clinical features of the patients with COVID-19 infection having an increase in seizure frequency (Group 1) and those who did not show a change in seizure frequency (Group 2)

Parameters	Group 1 (n=16)	Group 2 (n=88)	p-value
Sex (males, %)	43.8	62.5	0.130
Age (years)	28.3+10.5	36.2+12.8	0.023*
Age at onset (years)	11.8+6.1	19.2+11.7	0.013*
Disease duration (years)	16.5+9.0	16.9+12.0	0.871
Seizure types (%)			
Generalized	18.8	12.5	0.282
Focal symptomatic	62.5	43.2	
Focal cryptogenic	12.5	35.2	
Undetermined	6.3	9.1	
Seizure frequency (per year)	58.8+118.4	15.6+33.2	0.005*
Seizure within 1 month before COVID-19 infection (%)	75.0	36.4	0.005*

Data are given as mean + standard deviation, unless stated otherwise. *P-value is below 0.05 and significant. COVID: Coronavirus disease.

The comparison of the symptoms related to COVID-19 infection showed that, except for the headache, all symptoms of the COVID-19 infection questioned in our study were more common in patients with an increase in seizures during the infection; though the only significant difference was observed in myalgia (Table 3). Although the presence of the loss of smell and/or taste was more common in Group 1, not significantly, the duration of the loss of smell and/or taste has lasted much more longer in Group 1 (48.0+60.6 days) than Group 2 (13.8+13.4 days), which was statistically significant (p=0.013). The anti-COVID treatments and drug choices were also similar between Groups 1 and 2. The need for hospitalization due to COVID-19 infection, however, was present in 25.0% of the patients in Group 1 in contrast to 6.8% of the patients in Group 2 (p=0.045).

Regarding different types of epilepsies, myalgia was especially common in patients with generalized epilepsy (57.1%) during COVID-19 infection in compared to those with focal epilepsy (38.3%), but the difference in between failed to reach a statistically significant level (p=0.151). Neither the presence (p=0.249) nor the duration (p=0.385) of the loss of smell and/or taste was significantly different between patients with generalized and focal epilepsies. Other symptoms related to COVID-19 infection were also not found to be associated with the type of epilepsy. Three patients with epilepsy had status epilepticus during COVID-19 infection, all of whom had focal epilepsy (p=0.726), and all were the patients within Group 1, exhibiting an increase in the seizure frequency (p=0.003). Only one patient in the whole study population has missed his anti-seizure medication, who had a generalized epilepsy, and had no increase in the seizure frequency (Group 2, p=0.846).

Discussion

OHere, we demonstrated that 18.1% of the patients with epilepsy had COVID-19 infection in this study cohort. Although it was suggested that these patients were not more prone to COVID-19 infection than the individuals without epilepsy, and the disease severity was also similar,[6] a recent study demonstrated that the patients with epilepsy had a higher cumulative incidence to have COVID-19 infection.[7] On the other hand, the effects of COVID-19 infection on seizure recurrence have not been studied in detail, so far.

Sociodemographic characteristics of the study population showed a male preponderance (59.6%) in the patients with epilepsy having COVID-19 infection, with a mean age of 34.9+12.7 years. In one study investigating the characteristics of patients with epilepsy and COVID infection, males also constituted the majority of the population, while the mean age was reported to be higher (with a mean age of 58 years) than those observed in our study.[7] The most common epilepsy type was focal epilepsy in patients with epilepsy and COVID infection in our study, which was also the same in the above-mentioned study. Of 21 patients with epilepsy, the authors have note that only 2 patients (9.5%) had seizures during the infection.

In this study, we observed that among patients with epilepsy and COVID-19 infection, 15.4% had an increase in seizure frequency during the period of infection. The investigation of the demographic factors showed that the patients with an increase in seizure frequency were mostly of females, though not significantly. On the other hand, we observed that the patients with an increase in seizure frequency were significantly younger with an earlier disease onset. The duration of the epilepsy, however, was not found to

Table 3. The symptoms of the COVID-19 infection between patients with an increase in seizures during the infection (Group 1) and those who did not show a change in seizure frequency (Group 2)

Symptoms	Group 1 (n=16)	Group 2 (n=88)	p-value
Fever	62.5	45.5	0.163
Cough	62.5	37.5	0.057
Dyspnea	37.5	29.5	0.359
Myalgia	62.5	35.2	0.039*
Fatigue	56.3	39.8	0.170
Loss of smell and taste	50.0	44.3	0.439
Headache	12.5	25.0	0.227
Diarrhea	12.5	5.7	0.293
Loss of appetite	18.8	9.1	0.225

Data are given as percentages. *P-value is below 0.05 and significant. COVID: Coronavirus disease.

be associated with the disturbances in seizure control. As one may expect, patients having a higher seizure frequency per year and those having a seizure within 1 month before the COVID-19 infection were more likely to have seizure exacerbation during COVID-19 infection. There is only one study, in which a survey was conducted among the physicians with a response rate of 9%, and these physicians have reported that there was no change in seizure frequency in their patients with epilepsy.[8]

In the literature, new-onset seizures were reported during COVID-19 infection, and the underlying mechanisms were suggested as the effects of an acute systemic illness, involvement of the central nervous system, production of pro-inflammatory cytokines, or adverse effects of the medication used in the patients with COVID-19 infection.[3,4,9–11] Although the use of hydroxychloroquine/chloroquine was accused of lowering the seizure threshold and, therefore, triggering the seizures in prone individuals,[12] this was not the case in our study. On this basis, the possibility of seizure exacerbations was proposed in patients with epilepsy, drawing attention to the importance of a comprehensive approach in the management of these patients. This is the first study showing that one patient out of every six or seven patients with epilepsy will have an exacerbation in seizure control because of and/or during COVID-19 infection. It was also observed that young patients, patients with early-onset epilepsy, and those with high seizure frequency were at higher risk for the seizure exacerbation.

The symptoms related to COVID-19 infection were all more common in patients with an increase in seizures during the infection; while the only significant difference was obtained in higher frequency of myalgia. An intriguing finding was that of a very significantly higher duration of the loss of smell and/or taste in patients with seizure exacerbation. The hospitalization rate (25%) was also higher in this group of patients. These findings might indirectly indicate that the patients with epilepsy have a more severe COVID-19 infection. In a very recent paper, Asadi-Pooya et al.[13] studied 82 patients with epilepsy and reported that cough was less commonly present in these patients in compared to those without epilepsy, while the gastrointestinal symptoms such as vomiting and anorexia were more common. As for the need for intubation, on the other hand, internalization into intensive care unit and fatality, the authors reported that there was no difference between patients with and without epilepsy. Another recent paper, on the other hand, reported that the patients with epilepsy had a more severe COVID-19 infection, though only 10 patients were present in that study having pre-existing epilepsy.[14] It seems that the effects of COVID-19 infection and different presentations of the disease may have an influence in the course of epilepsy and seizure control, while larger studies with longitudinal study design are further needed to clarify this issue.

Among the most important limitations of this study, the design was cross-sectional, and data were collected retrospectively in some patients, who had COVID-19 infection before their admission to the epilepsy center. Nevertheless, all patients were reevaluated by the same physician (S.D.) in terms of the disease-related symptomatology during COVID-19 infection. The small sample size constitutes another limitation of this study, which may explain the lack of statistical significance in some of the analysis. A control group was not included in this study; the comparison of the detailed characteristics of patients with epilepsy who did not have COVID-19 infection or the individuals with COVID-19 infection without any pre-existing epilepsy would provide a more comprehensive data about the bidirectional interaction and the association between epilepsy and COVID-19 infection. Last but not least, this study lacks laboratory data of the patients, which may play an important role in seizure recurrence.

Conclusion– Our study is the first study showing that one out of every six to seven patients with epilepsy had seizure exacerbation during COVID-19 infection. We demonstrated that young patients, the patients with early-onset epilepsy, and the patients having high seizure frequency were at higher risk for the seizure exacerbation. Our results emphasize the influence of COVID-19 infection in this peculiar group of patients, and underlies the importance of the protection from the disease, early diagnosis and treatment. The safety and the possible beneficial effects of the vaccination deserve further attention in patients with epilepsy.

Informed Consent– Written informed consent was obtained from all patients and/or their parents who participated in this study.

Ethics Committee Approval– This study approved by the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 03.04.2021, Decision No: 90300).

Peer-review– Externally peer-reviewed.

Authorship Contributions– Concept: Ş.D., S.N.Y.; Design: Ş.D., S.N.Y.; Supervision: Ş.D., S.N.Y.; Data collection &/or processing: B.G., E.K.K.; Analysis and/or interpretation: G.B.Ş.; Literature search: G.B.Ş.; Writing: G.B.Ş., Ş.D.; Critical review: S.N.Y., C.Ö.

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. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433. [CrossRef]
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20. [CrossRef]
3. Mao L, Wang M, Hu Y, Chen S, He Q, Chang J, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: A retrospective case series study. JAMA Neurol 2020;77(6):e201127. [CrossRef]
4. Emami A, Fadakar N, Akbari A, Lotfi M, Farazdaghi M, Javanmardi F, et al. Seizure in patients with COVID-19. Neurol Sci 2020;41(11):3057–61. [CrossRef]
5. French JA, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, et al. Keeping people with epilepsy safe during the Covid-19 pandemic. Neurology 2020;94(23):1032–7. [CrossRef]
6. International League Against Epilepsy. FAQs about COVID-19 and epilepsy for clinicians in English. Available at: https://www.ilae.org/patient-care/covid-19-and-epilepsy/covid-19-information-for-clinicians/faqs-for-clinicians. Accessed on 2021 Jun 17.
7. Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, Pons-Pons G, Castro-Sánchez MV, Serrano-Castro PJ. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. Neurology 2020;95(10):e1417–25. [CrossRef]
8. Albert DV, Das RR, Acharya JN, Lee JW, Pollard JR, Punia V, et al. The impact of COVID-19 on epilepsy care: A survey of the American epilepsy society membership. Epilepsy Curr. 2020;20(5):316–24. [CrossRef]
9. Iroegbu JD, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: Implications for the novel SARSCoV-2. Neurol Sci 2020;41(6):1329–37. [CrossRef]
10. Asadi-Pooya AA, Simani L, Shahisavandi M, Barzegar Z. COVID-19, de novo seizures, and epilepsy: A systematic review. Neurol Sci 2021;42(2):415–31. [CrossRef]
11. 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.
12. Asadi-Pooya AA. Seizures associated with coronavirus infections. Seizure 2020;79:49–52. [CrossRef]
13. Asadi-Pooya AA, Emami A, Akbari A, Javanmardi F. COVID-19 presentations and outcome in patients with epilepsy. Acta Neurol Scand 2021;143(6):624–8. [CrossRef]
14. Sun M, Ruan X, Li Y, Wang P, Zheng S, Shui G, et al. Clinical characteristics of 30 COVID-19 patients with epilepsy: A retrospective study in Wuhan. Int J Infect Dis 2021;103:647–53. [CrossRef]