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Alterations in Seizure Frequency in Patients with Epilepsy Following Coronavirus Disease 2019

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Background and Purpose: During the coronavirus disease 19 (COVID-19) pandemic, a considerable number of studies have focused on the difficulties for accessing the medical services and telemedicine-related issues. However, it is not clear whether COVID-19 affects the clinical course of epilepsy. Therefore, in the current study we aimed to assess the effects of COVID-19 infection on seizure frequency in patients with epilepsy (PWE).

Methods: We evaluated PWE who consecutively referred to the neurology clinics of 22 Bahman and Qaem hospitals, who had experienced a recent polymerase chain reaction-confirmed-COVID-19 infection. Data were collected through a pre-defined electronic questionnaire.

Results: A total of 104 patients were included. Females represented 52% of the population. The mean age of the patients was 36.73±17.87. Thirty-six patients (34%) reported increased seizure frequency. The mean age of the patients who had exacerbated seizure frequency was significantly lower than the non-exacerbated group (27.50±9.8 vs. 40.14±18.39; p=0.005). The number of the male patients were significantly higher in the exacerbated group (52% vs. 25%; p=0.014). The majority of exacerbated group had a history of drug resistance (44.4% vs. 8.5%; p=0.022). The number of epileptic seizures before COVID-19 infection was higher in the exacerbated (p=0.04).

Conclusions: About 34% of PWE experienced exacerbated epileptic seizures after COVID-19 infection. Male patients, young patients, patients with the history of drug resistance, and the patients who had higher seizure frequency were at increased risk for seizure exacerbation. Our results highlight the importance of screening, early diagnosis, and treatment in PWE. **(2023;13:7-12)**

Key words: Coronavirus disease 2019, Seizure, Epilepsy, Infection

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Introduction

Although pneumonia is known as the most frequent manifestation of coronavirus disease 2019 (COVID-19), many other extrapulmonary symptoms including neurologic manifestations have also been reported.[1] A growing body of data shows that neurotropism is a common feature of Coronaviridae family.[2] Regarding to published case series, other corona respiratory viruses such as Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome-related coronavirus (SARS-CoV) have caused many neurologic complications including ischemic stroke, intracranial hemorrhage, encephalitis, polyneuropathy, and Guillain-Barre syndrome.[3-5] In a prospective study examining neurologic manifestations in patients with COVID-19, headache, dizziness, anosmia, and dysgeusia were the most common symptoms which tended to occur in early stages. Alterations in consciousness level occurred commonly in hospitalized patients, particularly in older ages and advanced cases. Other symptoms such as myopathy, dysautonomia, cerebrovascular diseases, seizures, movement disorders, encephalitis, Guillain-Barré syndrome, and optic neuritis also occurred with less frequency.[6]

Patients with epilepsy (PWE) have faced some important issues during COVID-19 pandemic that need to be managed and clarified. So far, problems such as disruptions in clinical services in accessing medical centers, telemedicine issues, and psychological distresses have been widely explored. However, only few numbers of studies focused on alterations in the number seizures in PWE who were infected with COVID-19.[7,8] Therefore, it is still unclarified whether COVID-19 infection affects the clinical course of epilepsy. Hence, we

aimed to clarify the possible effects of COVID-19 infection on seizure frequency in PWE and the factors, which may contribute to deterioration of seizures.

Methods

The current study was a cross-sectional study that was performed on the PWE who referred to 22 Bahman and Qaem hospitals in 2021. One hundred four PWE were entered to the study. The inclusion criteria included having the confirmed diagnosis of epilepsy based on a neurologist's opinion for at least 1 year, age 18 and older, and having a history of COVID-19 based on a positive polymerase chain reaction test for at least 1 month ago. We also excluded the patients who were not able to fill in the questionnaire, did not have an access to the internet, and were re-infected with COVID-19 during the study or with severe forms of COVID-19 infection, for example, mechanical ventilation. An online survey was created through using the free open-access GoogleTM Forms (Google, Mountain View, CA, USA; https://www.google.com/forms/about/) application. The survey also included an informed consent verification that made it possible for the patients who did not agree with the terms of use of the survey to end the survey without any further question. No personal identification was collected. Before distribution of the survey among the patients, the study protocol was confirmed by the ethical committee of Mashhad Islamic Azad Medical University.

The persian form of questionnaire included the following sections: 1) introduction and a brief description of the study; 2) informed consent (mandatory); 3) socio-demographic characteristics (age, gender, marital status, and economic status); 4) epilepsy-related information (the frequency of seizures per month after and before infection with COVID-19, type of seizure, and epilepsy duration); and 5) anti-epileptic drug (AED) data (drug resistance, the number of AEDs, and adherence to anti-seizure medication).

It worth mentioning that seizure exacerbation was defined as having one more seizure per month compared with previous usual seizure frequency per month. In order to make sure about exacerbation of epileptic seizures, a telephone call was made by the researcher for those patients who reported worsening of their seizure frequencies and all of the seizure-related information was asked. These information sources included a description of the seizure, any changes during seizure occurrence, duration of seizure, and type of seizure. Data were analyzed by using SPSS software version 23 (IBM, Armonk, NY, USA) and we report means, standard deviations and percentage ratio. Independent *t*-test was used to compare the differences among groups and analysis of variances was recruited in more than two groups. The significance level of 0.05 was considered.

Results

A total of 115 patients received the online survey. However, four patients and seven patients were excluded from the study, due to not signing the consent form and incomplete filling of the questionnaires, respectively. Finally, we collected the answers of 104 PWE and the responsiveness level of the patients was 90%.

Demographic and patient characteristics

Demographic and clinical characteristics of included patients are listed in Table 1. The mean age of the patients was 38.73±17.87 years old and females represented 52% of the entire sample. More than half of the patients were married and the rest of them were single and the majority of the patients (76%) had moderate economic

Table 1. Demographic and clinical characteristics

Variable	Value
Age	36.73±17.87 (15-77)
Gender (male/female)	49/55
Marital status (single/married)	40/64
Economic level (middle income*)	80
Number of AEDs	
One drug	82
Two drugs	15
Three drugs	7
Type of seizure	
Focal	56
Generalized	48
Drug resistance	
Yes	20
No	84
Duration of disease	
<10 years	76 (1-47)
≥10 years	28
Number of seizures before COVID-19 infection	0.64±1.25 (0-8)

Values are presented as mean±standard deviation (minimum-maximum or number (minimum-maximum).
AED, anti-epileptic drug; COVID-19, coronavirus disease 2019; US, United States.
*Middle income=200 to 400 million Rials. 1 million Rials=24 US dollars of 6 August 2022.

levels. About 53% of the patients had generalized epilepsy and in 73% of the patients, disease duration was less than 10 years. Eighty-two patients (78%) were taking only one AED and drug resistance existed in 20 patients (19%).

Seizure frequency following COVID-19 infection

Our results demonstrated that 36 PWE (34%) experienced exacerbated epileptic seizures, while 68 patients (65%) did not report any changes in the number of their seizures. None of the patients stated decreased frequency of their seizures after COVID-19 infection (Table 2).

Table 2. Seizure frequency after COVID-19 infection

	Value
Increased seizure frequency	36 (34.0)
Decreased seizure frequency	0 (0.0)
No difference in seizure frequency	68 (65.0)

Values are presented as number (%).
COVID-19, coronavirus disease 2019.

Differences in demographic and clinical characteristics between patients with or without seizure exacerbation

Table 3 compares demographic and clinical data among PWE with increased seizure frequency (exacerbated group) and those who did not have any change in their seizure frequency (non-exacerbated group). The mean age of the exacerbated group was significantly lower (p=0.005). The number of the male patients were significantly higher in the exacerbated group (p=0.014). The history of drug resistance was significantly higher in the exacerbated group (p=0.022). The exacerbated group had a significantly higher number of seizure frequency before COVID-19 infection (p=0.04).

Discussion

In the current study, we aimed to examine whether COVID-19 can induce any alterations in the frequency of seizures in PWE. We demonstrated that seizure exacerbation was experienced by PWE following COVID-19 infection. Furthermore, we identified demographic

Table 3. A comparison of demographic and clinical features of PWE who experienced increased (exacerbated group) and those who did not report changes in their seizure frequency (non-exacerbated group)

Variable	Exacerbated group (n=36)	Non-exacerbated group (n=68)	p-value
Age	27.50±9.8	40.14±18.39	0.005
Gender (male)	19 (52.0)	17 (25.0)	0.014
Marital status (single)	19 (52.7)	21 (30.8)	0.670
Economic level (moderate)	33 (91.6)	57 (83.8)	0.661
Type of epilepsy			
Focal	16 (44.0)	40 (58.0)	0.738
Generalized tonic-colonic	21 (58.3)	27 (39.7)	0.523
Drug resistance			0.022
Yes	16 (44.4)	4 (5.8)	
No	20 (55.5)	64 (94.1)	
Number of AEDs			0.977
1	26 (72.2)	56 (82.3)	
2	3 (8.3)	12 (17.6)	
3	1 (2.7)	6 (8.8)	
Disease duration			0.805
<10 years	13 (36.1)	63 (92.6)	
≥10 years	23 (63.8)	5 (7.3)	
Number of epileptic seizures before COVID-19			0.040
<3 seizures per month	2 (5.5)	39 (57.3)	
≥3 seizures per month	34 (94.4)	29 (42.6)	

Values are presented as mean±standard deviation or number (%).
PWE, patients with epilepsy; AED, anti-epileptic drugs; COVID-19, coronavirus disease 2019.

features and epilepsy-related data was different significantly between PWE who had exacerbation and those with no alteration in their seizure frequency. Analysis of socio-demographic features of our study population demonstrated a female preponderance (52.88%) with a mean age of 38.73±17.87 years. In a study that investigated socio-demographic characteristics of a large number of epileptic patients with COVID-19 infection, males constituted 67% of the patients but their mean age was similar with our results, which was 58 years.[9] The most common type of epilepsy was generalized epilepsy though in previous similar studies, focal epilepsy was reported as the most frequent type among the studied population.[9,10]

Our results demonstrated that after COVID-19 infection, 34% of PWE had an increase in seizure frequency. It is known that as similar as other coronaviruses, COVID-19 possesses neuro-invasive potency, and therefore causes neurologic symptoms. The virus can enter the brain through two routes: 1) binding with angiotensin converting enzyme 2 receptor, which is mainly presented on the surface of the neurons located in the brainstem controlling cardiovascular and respiratory function; and 2) via olfactory tract in case of COVID-19.[11-13] Following the invasion, COVID-19 triggers microglial activation and leads to an inflammatory cascade. The release of pro-inflammatory cytokines such as interleukin (IL)-1B, IL-6, and tumor necrosis factor-α (TNF-α) results in neural hyper-excitability with the clinical presentation of seizure.[14,15] It is worth mentioning that microglial cells are not the only source for the production of inflammatory cytokines and cytokines including IL-6 and TNF-α can enter the brain via active or passive transmission routes. Furthermore, COVID-19 infection breaks down the integrity of blood brain barrier (BBB), impairing brain homeostasis and causing neuronal death. On the other hand, BBB breakdown causes the migration of white blood cells and proteins like albumin, disrupting the osmotic balance in the central nervous system terminating in seizure.[16,17]

Another mechanism for seizure induction in COVID-19 patients is fever and hyperthermia. It is shown that hyperthermia leads to activation of neurons and glial cells and increases BBB permeability.[18] It is speculated that COVID-19 infection may act similarly with febrile seizure in children. For instance, fever in children not only increases the temperature of the brain but also causes inflammatory cytokine release, and high levels of inflammatory cytokines such as interleukin-1β has been detected in their cerebro-spinal fluid.[19-21] In addition, some drugs used for treatment of COVID-19, such as hydroxychloroquine/chloroquine, may change seizure threshold, change AEDs serum levels, or cause drug-drug interactions with AEDs.[22]

Regardless of the role of COVID-19 infection in exacerbating seizures, it is well-established that the wake of disasters such as outbreaks are strongly associated with high level of stress and anxiety. On the other hand, stress is one of the most common self-reported precipitating factors that are associated with seizures in PWE.[23] For example, a number of patients with focal epilepsy stated that their seizures began after their stressful life events.[24] Another study examining the risk of seizure recurrence in patients with single unprovoked seizure and in newly diagnosed epilepsy found that markers of stress had greater risk for seizure recurrence.[23] PWE who are infected with SARS-CoV-2 are more prone to experience the anxiety and fear of COVID-19 complication and mortality which may precipitate seizure exacerbation.

In our study we observed that among PWE who had an increase in their seizure frequency were mostly-males. In accordance with this, previous epidemiologic studies reported that the prevalence and incidence of seizure and epilepsy is relatively higher in males than in females.[25] Generally, it is known that beside the main role of sex hormones in reproductive organs, they are critical for maintaining normal brain functions because they regulate and affect neuronal excitability and survival. Not surprisingly, studies have implicated seizures reflect changes in sexual hormone levels. For instance, in some women with epilepsy, exacerbation in seizure frequency may be related to the hormonal fluctuations during ovarian cycles that is called catamenial epilepsy.[26] Although we found that the mean age of the exacerbated group was significantly lower than the non-exacerbated group, it is demonstrated that epilepsy is more common among the elderly. The cause of inconsistency is complicated and it can be explained as: 1) we only included patients who referred to two hospitals in the 6th and 7th waves of COVID-19 pandemic in Iran; 2) we did not aim to study patients with all ranges of age but only included patients who were older than 18 and met the inclusion criteria; and 3) the sample size of this study was small and therefore does not let these results be generalized to the PWE population. As well as the two demographic features, we found that two epilepsy-related features are associated with increased numbers of seizures: 1) number of epileptic seizures 1 month prior to COVID-19 infection and 2) drug resistance. It is well known that patients with poorly managed epilepsy experience worse long-term outcomes and have higher prevalence of recurrence.[27,28] Hence, appropriate pharmaceutical management to achieve seizure freedom is necessary for reducing the risk of seizure exacerbation in conditions with seizure provoking potency. This issue highlights the importance of optimizing AED therapy to de-

crease the number of attacks and obtain remission in epilepsy.

On the other hand, duration of disease, number of AEDs, and type of epilepsy were not found to be associated with disturbed seizure control. In a prospective study examined seizure control in PWE during the COVID-19 pandemic, none of 18 patients who had suspected COVID-19 infection had worsened seizure control while they were symptomatic.[7] In another study, seizure as a symptom of COVID-19 occurred more frequently in PWE than the healthy control group.[8] In accordance with our findings, DelÍL et al.[10] found that PWE with younger age and higher seizure frequency were more likely to experience increased seizure after COVID-19.

First, the present study was designed as a cross-sectional study that only allows the conclusions to be considered as correlations, not causations. Second, natural variations occur from month to month in PWE and may affect the number of seizures during the month of COVID-19 outbreak. Third, many factors including COVID-19-related stress can contribute to seizure exacerbation, and however no stress assessment scale was recruited in this study to assess its correlation with seizure exacerbation. Fourth, this study did not include laboratory data of the patients that may play a critical role in seizure frequency. Fifth, we only studied outpatients and hospitalized patients were ruled out.

Taken together, our results showed that almost one third of PWE who were infected with SARS-CoV-2 experienced seizure exacerbation, which may be caused by the effects of COVID-19 infection or the stress of its complications. We found that male patients, young patients, patients with the history of drug resistance, and the patients who had higher baseline seizure frequency were at increased risk for seizure exacerbation. Our results confirm the influence of COVID-19 infection on this group of patients, and highlights the importance of the screening, early diagnosis and treatment of this disease among PWE the population.

Conflicts of Interest

The anthors declare that they have no conflicts of interest.

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