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Increased Seizure Risk Among the Patients During the COVID-19 Pandemic: Is a Single-Drug Regime Better?

COVID-19 Pandemisi Sırasında Hastalarda Artan Nöbet Riski: Tek İlaç Rejimi Daha İyi mi?

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ABSTRACT

Objectives: Increased stress, anxiety, depression, multi-anti-epileptic drug usage, and COVID-19 infection were all being related with an increased rate of seizures among subjects with epilepsy. Thus, in this study, we aimed to investigate whether social isolation increased the frequency of seizures among the cases with epilepsy during the COVID-19 pandemic and to define the possible underlying cause of it.

Methods: In this retrospective, cross-sectional study, 103 subjects with a diagnosis of epilepsy were included in the study. Hospital anxiety and depression scales were used to determine the underlying anxiety and depression.

Results: In this study, 58 out of 103 subjects were female and 51.4% of them had focal epilepsy. Subjects in focal and generalized epilepsy groups were similar based on age, gender, the presence of comorbid diseases, and anxiety and depression scores. However, the subjects presenting with increased rates of seizure had higher anxiety scores and more comorbid diseases, and in addition, the majority of them were on multi-anti-epileptic medications.

Conclusion: The risk of having an increased seizure rate was greater among the subjects with epilepsy who were on multi-anti-epileptic drugs and who had comorbid diseases and increased anxiety scores.

Keywords: Anxiety; COVID-19 infection; depression; epilepsy; polypharmacy; seizure rate; social isolation; stress.

ÖZET

Amaç: Artan stres, anksiyete, depresyon, çoklu antiepileptik ilaç kullanımı ve koronavirüs hastalığı (COVID-19), epilepsili denekler arasında artan nöbet oranı ile ilişkiliydi. Bu nedenle bu çalışmada, COVID-19 pandemisi sırasında epilepsili olgularda sosyal izolasyonun nöbet sıklığını artırıp artırmadığının araştırılması ve altta yatan olası nedenin tanımlanması amaçlandı.

Yöntem: Bu retrospektif, kesitsel çalışmaya epilepsi tanılı 103 olgu dahil edildi. Altta yatan anksiyete ve depresyonu belirlemek için hastane anksiyete ve depresyon ölçekleri kullanıldı.

Bulgular: Bu çalışmada 103 olgunun 58'i kadındı ve bunların %51,4'ü fokal epilepsi hastasıydı. Fokal ve jeneralize epilepsi gruplarındaki denekler yaş, cinsiyet, eşlik eden hastalık varlığı ile anksiyete ve depresyon puanları açısından benzerdi. Ancak nöbet oranlarında artış ile başvuran deneklerin anksiyete skorları daha yüksek ve yandaş hastalıkları daha fazlaydı. Ek olarak çoğunluğu çoklu antiepileptik ilaçlar kullanıyordu.

Sonuç: Çoklu antiepileptik ilaç kullanan epilepsili olgularda, eşlik eden hastalıkları ve anksiyete skorları yüksek olanlarda nöbet hızında artış riski daha fazlaydı.

Anahtar sözcükler: Anksiyete; COVID-19 koronavirüs hastalığı; depresyon; epilepsi; polifarmasi; nöbet oranı; sosyal izolasyon; stres.

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The number of people who contracted COVID-19 has continuously increased and reached to 70 million since it was first reported in Wuhan, China, in December 2019.[1] Even though the main cause of COVID-19-related death is acute respiratory distress syndrome, there are some concerns that it may cause death by worsening already present disorders.[2] COVID-19-induced neurocognitive disturbances such as headache, anosmia, confusion and/or encephalopathy, and anxiety-related problems are prominent findings.[3] Whether COVID-19 itself has an altering effect on seizures among subjects with epilepsy is controversial.[4] In critical illness, regardless of COVID-19 presence, increased seizure frequency has been reported among epileptic cases.[5,6]

The governments announced strict lockdowns to control the COVID-19 pandemic all over the world. Even though precautions for chronic cases to reach their ongoing medications have been taken, the stress burden of COVID-19 itself may a strong effect on the lives of patients. Social isolation was found to be related with increased seizure rates even in animal models.[7,8]

Thus, we aimed to investigate whether if there is an increased frequency of seizures among epileptic patients who are under treatment during the COVID-19 pandemic.

Methods

This study was a questionnaire-based cross-sectional study which included 103 subjects with an epilepsy diagnosis. Each of the participants was evaluated by a single neurologist at the outpatient Neurology Clinic of Balıkesir University Medical Faculty Hospital between September 1st, 2020, and November 1st, 2020. The government announced strict lockdown was effective from March 21st, 2020, to July 1st, 2020.[9]

The demographic characteristics of the participants were obtained from the hospital's digital archive. The subjects were questioned specifically for a recent COVID-19 infection, the number of the seizure seen during the lockdown period, and the compliance for the anti-epileptic medications. The participants with a history of COVID-19 infection or any hospitalization for any reason were excluded from the study.

The term, polypharmacy, was used to define the subjects using two or more anti-epileptic medications in the current study.[7] We used the hospital anxiety and depression scale to define the underlying anxiety.[10]

Ethical Considerations

The study has been approved by the Ethics Committee of Balıkesir University Faculty of Medicine at its meeting numbered 173 on October 14, 2020 and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We also state that all participants gave their informed consent before their inclusion in the study.

Statistical Analysis

Statistical analyses, including comparing of categorical or continuous variables for a possible difference between the groups, were performed using Chi-square, Kruskall–Wallis, and Mann–Whitney U test (SPSS 23.0, IBM Corp., US). The cutoff level for statistical significance was accepted as $p<0.05$. Multimodal logistic regression test was used to predict the impacts of the different variables on the outcome.

The local ethical committee for clinical trials of Balıkesir University approved the study and all of the participants signed the informed consent before being enrolled into the study.

Results

We included 103 subjects with the diagnosis of epilepsy, in which 58 out of them were female (56.3%). The subjects with the diagnosis of focal and generalized epilepsy were similar based on age, gender, and comorbid diseases; however, only half of the cases with focal epilepsy were on a single anti-epileptic medication, whereas 89.6% of the generalized epilepsy group on single-drug therapy (Table 1). Around one-third of the subjects in each group reported an increased rate of seizure in the last 6 months (p value, 0.220). Anxiety and depression scores in each group were similar (p values, 0.084 and 0.312, respectively).

As seen in Table 2, the groups were similar according to the gender, age of the subjects, the presence of comorbid diseases, and the type of underlying seizure (whether it is focal or generalized epilepsy). When compared for the anti-epileptic medication usage, 37.0% of the patients who were on multiple drug regimens had an increased rate of seizure in the last 6 months, whereas this rate was 30% in single-drug users (not shown in table).

In addition, both anxiety and depression scores were found to be higher among the subjects with increased seizure rates

Table 1. Characteristic features of the subjects included into the current questionnaire-based study

	Focal epilepsy (n=53)	Generalized epilepsy (n=50)	p
Sex, male, n (%)	24 (45.2)	21 (42.0)	0.843
Age, mean, years old (SD)	37.6 (+/- 17.5)	42.5 (±17.4)	0.387
Increase in seizure rates*, n (%)	16 (30.8)	15 (31.3)	0.220
Comorbid disease, n (%)	16 (30.8)	11 (22.9)	0.379
Medication, a single drug, n (%)	30 (57.7)	43 (89.6)	<0.001
Anxiety score, mean (SD)	9.7 (3.6)	8.6 (3.5)	0.084
Depression score, mean (SD)	8.0 (3.4)	7.3 (3.2)	0.312

SD: standard deviation; *: during the COVID-19 precautions were effective (strict social isolation).

Table 2. The differences between the groups based on the change in seizure rates in the last 6 months

	Subjects with no seizure for a long time (n=54)	Subjects with a decreased rate (n=9)	Subjects with a stable rate (n=7)	Subjects with an increased rate (n=33)	p
Sex, male, n (%)	33 (61.1)	5 (55.6)	2 (28.6)	18 (54.5)	0.434
Age, mean, years old (SD)	37.6 (+/- 17.5)	34.6 (±19.6)	33.7 (±13.9)	41.8 (±13.9)	0.542
Comorbid disease, n (%)	19 (35.2)	1 (11.1)	1 (14.3)	7 (21.2)	0.250
Medication, a single drug, n (%)	48 (88.9)	2 (22.2)	3 (42.9)	23 (69.7)	<0.001
Focal Epilepsy, n (%)	22 (41.5)	4 (44.4)	4 (57.1)	15 (48.4)	0.220
Anxiety score, mean (SD)	8.2 (3.6)	8.2 (1.9)	6.7 (1.9)	11.7 (3.0)	<0.001
Depression score, mean (SD)	6.7 (3.0)	7.7 (4.2)	6.1 (1.6)	9.7 (3.1)	<0.001

compared to the other groups (p values <0.001 and <0.001, respectively) (Table 2).

In multiple regression analyses, in which age, gender, the presence of comorbid disease, type of seizure, anxiety and depression scores, and single or multi-drug use were included into the model, multiple drug usage and the presence of comorbid disease were found to be have significant impacts on the increased rate of seizure rates (Table 3).

Almost half of the subjects who had increased seizure rate reported increased stress or fatigue while one-fourth had drug inadherence, and one-fourth had an infection other than COVID-19.

Discussion

Regardless of the type of epilepsy, either focal or generalized, the subjects using multiple anti-epileptic drugs have an increased risk for seizure rate.

Polypharmacy has been a growing problem, especially among older individuals. Almost half of the cases over 75 years old were reported to be prescribed more than five drugs and about one-fourth were more than ten medications.[7,8] Since polypharmacy is a well-known risk factor for adverse drug interactions, extended hospitalizations, and even mortality, the researchers have focused on to prepare some protocols to decrease it.[8] In this study, even though

Table 3. Multinominal logistic regression analyses for increased seizure rate

	B	SE of β	OR	p	%95 CI for OR
Type of seizure	0.56	0.590	0.943	0.331	0.178–1.791
Presence of comorbidities	5.91	0.724	6.0	0.014	1.431–24.450
Polipharmacy	0.192	0.700	5.54	0.019	0.049–0.759
Anxiety score	1.312	0.138	3.87	0.049	1.001–1.718
Depression score	1.141	0.141	0.862	0.353	0.865–1.502

we took into account the presence of comorbid diseases, we did not analyze if the drug interactions put the subjects on an additional risk of seizure.

Similar to the literature, our data revealed that about 60–80% of the epileptic patients were on single-drug regimens and the seizures were well controlled.[11,12] The subjects who did not respond to a single anti-epileptic medication are always prone to drug side effects, worse compliance rates, and high treatment failure.[13] In addition, it was reported that seizures which cannot be controlled with a single drug had almost at two-fold risk not to respond to the subsequent treatments.[14] In other words, subjects receiving more than one anti-epileptic drug are at a higher risk for treatment failure. In this cross-sectional study, we found that using more than one anti-epileptic medication increased the risk for having a seizure during the lockdown period. Among the subjects with an increase rate of seizure during COVID-19 lockdowns, one-fourth of the subjects reported inadherence to the therapy, including cessation of the therapy, or a rapid decrease of the drug dosage. Only 1 out of 100 patients reported that they could not reach anti-epileptic drugs during the strict lockdowns. This may imply that because of the high stress that the subjects facing, the non-compliance with the medications was higher than expected. Our study showed that an increased anxiety score elevates the risk of seizure 3.87 times (p value 0.049). Thus, to ease the anxiety, using new technology to stay in contact with patients who have chronic diseases is very important during the lockdown period.[15] This COVID-19 pandemic has proved the urge of telemedicine revolution all around the world.[16]

Conclusion

Even though the response rate to the anti-epileptic drug decreased after a failure of a single medication, the prominent stress level that subjects experiencing due to the COVID-19 pandemic and strict lockdowns might be an important risk factor for epileptic patients. This risk increased among the cases under multiple anti-epileptic drug regimens than a single drug.

Limitations

Since we did not use any validated stress measurement index in the current study, we can only speculate that COVID-19 pandemic-related stress might be a significant factor to increase the rate of seizure attacks among the subjects with epilepsy.

Disclosures

Ethics Committee Approval: The study has been approved by the Ethics Committee of Balıkesir University Faculty of Medicine at its meeting numbered 173 on October 14, 2020 and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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