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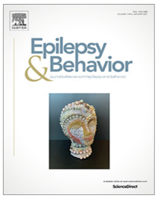

Clinical Research

Effect of the COVID-19 pandemic on drug compliance and stigmatization in patients with epilepsy

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ABSTRACT

Objective: Pandemics like coronavirus disease 2019 (COVID-19) bring along many individual and social problems. We aimed to investigate what changes the COVID-19 pandemic can cause in patients with epilepsy on drug compliance and stigmatization.

Material and method: Modified Morisky Scale (MMS) and stigmatization scales were used between October and November 2019 to assess drug compliance and stigmatization in epilepsy patients. These scales were renewed in June and July 2020 in the same patient group to assess the impact of the epidemic on drug compliance and stigmatization in patients with epilepsy. Statistical analysis was performed using the statistical software SPSS 17.0 for Windows (SPSS, Inc). Demographic and clinical characteristics of the patients were recorded in SPSS. The interviews were conducted during the interictal period. Paired-samples *t*-test was used to compare the stigma scale results of epilepsy patients before and during COVID-19. The Wilcoxon test was used to compare MMS groups before and during COVID-19.

Results: A total of 110 patients were included in the study. There was no significant difference between the pre-pandemic and pandemic period in epilepsy stigma scale used to evaluate stigmatization levels in patients. During the pandemic period, it was observed that patients had higher motivation and higher knowledge than before the pandemic ($p = 0.048$). There were seven patients (6.4%) whose seizure frequency increased during the pandemic period. There were two patients (1.8%) who had difficulty in accessing drugs during the pandemic period. In multivariate analysis, only parameter that predicted an increase in seizure frequency was the number of drugs used In the of COVID-19 period. In correlation analysis, a negative correlation was found between the stigma total score during COVID-19 period and education level.

Conclusion: A slight increase in the frequency of seizures was observed in our patients during the pandemic period, and no significant problem was experienced in accessing drugs. The COVID-19 pandemic made patients more motivated and informed in drug compliance in the patient group and had no effect on stigmatization.

1. Introduction

In December 2019, an atypical pneumonia outbreak known as coronavirus disease 2019 (COVID-19) was detected in Wuhan, China. The newly described zoonotic coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by rapid human-to-human transmission. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly and caused an epidemic in China and then became a global health emergency. In March 2020, the World Health Organization (WHO) made the assessment that COVID-19 can be characterized as a pandemic. Despite the implementation of control measures and isolations for prevention, infection increased, resulting in a pandemic [1,2].

Epilepsy is a chronic neurological disease that may require long-term or lifelong treatment and is caused by increased excitability of nerve cells in the brain. As in previous pandemics, epidemics such as COVID-19 have many negative effects on both society and individuals. Chronic diseases such as epilepsy are likely to be affected by these epidemics, and we have little knowledge on this subject [3].

Following the announcement of COVID-19 in China, an increase in negative emotions (anxiety, depression and anger) and sensitiv-

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ity to social risks, positive emotions and a decrease in life satisfaction were detected. Moreover, people were more interested in health and family but less in entertainment and friends. Among those suffering from the 2003 SARS epidemic, the stigma associated with the disease was pronounced strikingly even years after the illness, negatively affecting the lives of most people. Similarly, the COVID-19 pandemic, with all its social and economic consequences, can lead to stigmatizing factors such as fear of isolation, racism, discrimination, and marginalization. A stigmatized community tends to seek medical care late and hide important medical history, especially travel. This will increase the risk of transmission of the disease to society [4,5].

Especially in chronic diseases such as epilepsy, one of the most important factors determining the success of treatment is compliance to treatment, a factor that both reduces the cost of treatment and affects the course of the disease [6,7]. The Modified Morisky Scale (MMS) is a short, easily applicable, reliable test that can evaluate motivation and knowledge level separately. This scale is useful in evaluating compliance to long-term drug therapy in chronic diseases [8].

We aimed to investigate what changes the COVID-19 pandemic can cause in patients with epilepsy in drug compliance and stigmatization. Epilepsy patients who were evaluated with the stigma scale and MM scale before the COVID-19 pandemic were reevaluated to examine the effect of the pandemic on drug compliance and stigmatization.

2. Material and method

In October and November 2019, 110 patients were evaluated with a MMS and stigma scales to assess drug compliance and stigmatization in epilepsy patients. With the acceptance of COVID-19 as a pandemic by the World Health Organization in March 2020, these scales were renewed in June and July 2020 to evaluate the impact of the epidemic on drug compliance and stigmatization in epilepsy patients. We started to evaluate the effect of the pandemic on epilepsy patients on 1st of June, 2020, when the data in our country was declared as the total number of COVID-19 patients of 164.769, the total number of deaths of 4.563, the number of deaths per day of 23 and the number of cases per day of 827. The epidemic in our country peaked in late April 2020.

Demographic data of the patients such as age, gender, habits, marital status, and education level were obtained. In addition, information such as the age of onset of the epilepsy disease, the duration of the disease, the type of seizure, the frequency of seizures, the increase in the frequency of seizures during the COVID-19 period, and the number of drugs were recorded by the researchers in the SPSS format. The Epilepsy Stigma Scale and MMS tests were applied to all epilepsy patients included in the study.

Written consents from volunteer patients who met the working conditions were obtained. The interviews were conducted during the interictal period. The study consisted of patients aged 18–65 who had focal or generalized epileptic seizures for at least 1 year and were diagnosed with definite epilepsy. The study did not include any psychiatric medication use and family history of psychiatric drugs. However, patients whose seizures were due to causes such as metabolism disorder, tumoral mass, or acute infection were excluded from the study. Among the patients who participated in the pre-pandemic questionnaire, those who could not be reached or followed up during the pandemic period were not included in the study. Approval was obtained from the ethics committee of Bakirkoy Dr Sadi Konuk Training and Research Hospital and the Ministry of Health.

On the stigma scale, 32 questions were asked to the patients about their false beliefs of epilepsy, whether they were subject to exclusionary discrimination because of their illness, whether they see themselves inadequate at work and family life, whether they experienced social isolation due to resistance to stigma, and whether they had false beliefs about their illness. The version of the stigmatization scale, used in Turkey for epilepsy patients were developed and validated by Baybas et al. [9]. In the stigma scale, there are subtitles consisting of social isolation, discrimination, inadequacy, false beliefs, and stigma resistance. The total stigmatization score was calculated by adding the scores related to the answers to each question.

The final version of the Turkish MMS, which the researchers agreed on and its accuracy was demonstrated by back translation, has emerged. In our study, Turkish MMS was used. This questionnaire is a short, easy-to-apply, reliable test that can evaluate motivation and knowledge level separately and consists of 6 questions [8]. Questions in MMS were answered as yes/no. In questions 2 and 5, yes is equivalent to 1 point and no to 0 point. In other questions, yes is equivalent to 0 point and no to 1 point. If the patient's total score from questions 1, 2, and 6 is 0 or 1, it indicates low motivation level; if it is >1, it indicates a high level of motivation. If the total score for questions 3, 4, and 5 is 0 or 1, it indicates low level of knowledge; if it is >1, it indicates high level of knowledge.

2.1. Statistical analysis

Statistical analysis was performed using the statistical software SPSS 17.0 for Windows (SPSS, Inc). A P value <0.05 was considered significant. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as a percentage. Paired-samples t-test was used to compare the stigma scale results of epilepsy patients before and during COVID-19. The Wilcoxon test was used to compare MMS groups before and during COVID-19. For multivariate analysis, possible factors determined by univariate analysis ($p < 0.1$), further logistic regression analysis was performed to identify independent predictors of increased seizure frequency in COVID-19 period. Pearson correlation analysis was used for correlation analysis of parameters.

3. Results

A total of 110 patients who were evaluated with a diagnosis of epilepsy before COVID-19 were reevaluated during the COVID-19 pandemic period. The patients had a mean age of 32 years and consisted of 48 males and 62 females between the ages of 18–65. There were seven (6.4%) patients whose seizure frequency increased during the pandemic period. There were two patients (1.8%) who had difficulty in accessing drugs during the pandemic period. Of these patients, 34 were diagnosed with focal epilepsy and 76 with generalized epilepsy. Table 1 summarizes the baseline demographic and clinical characteristics of the study groups.

Table 2 presents the total stigma scale and subgroup values before and during the COVID-19 period. There was no significant difference between the pre-pandemic and pandemic period in epilepsy stigma scale used to evaluate stigmatization levels in patients ($p > 0.5$).

Table 3 presents the MMS values during and before the COVID-19 period. During the pandemic period, it was observed that patients had higher motivation and higher knowledge than before the pandemic. In our study, an increase in motivation and knowledge levels in drug compliance was observed statistically ($p = 0.048$).

In the univariate and multivariate logistic regression analysis, the independent parameters affecting the frequency of seizures

Table 1
Demographic characteristics of epilepsy patients.

Age, median (min–max)	32 (18–65)
Female, *n* (%)	62 (56.4)
Male, *n* (%)	48 (43.6)
Smoker, *n* (%)	20 (18.2)
Using alcohol, *n* (%)	6 (5.5)
Single drug, *n* (%)	64 (58.2)
Dual drug, *n* (%)	35 (31.8)
Multidrug, *n* (%)	11 (10)
Education level	
Primary school, *n* (%)	23 (20.9)
Middle School, *n* (%)	18 (16.4)
High school, *n* (%)	35 (31.8)
University, *n* (%)	34 (30.9)
Marital status	
Single, *n* (%)	49 (44.5)
Married, *n* (%)	57 (51.8)
Divorced, *n* (%)	4 (3.6)
Disease onset age, years, *n* (%)	16.9 ± 9.06
Duration of illness, years, *n* (%)	16.5±10.9
Seizure type	
Focal, *n* (%)	34 (30.9)
Generalized, *n* (%)	76 (69.1)
Seizure frequency	
More than 1 month, *n* (%)	6(5.5)
1 month-1 year, *n* (%)	39(3.5)
Less than 1 year, *n* (%)	65(59.1)
EEG finding	
Normal, *n* (%)	38(34.5)
Generalized, *n* (%)	48(43.6)
Focal n, (%)	24(21.8)
The number of patients whose seizure frequency increased during the pandemic period, *n* (%)	7 (6.4)
Number of patients experiencing difficulties in drug supply during the pandemic period, *n* (%)	2 (1.8)

Mean values (standard deviation) and % (*n*) are reported for continuous and categorical variables, respectively.

Table 2
Total stigma and subgroup values before and during COVID-19 period.

	Before COVID-19	During COVID-19	*p*
Stigma total score (1–32)	50.06 ± 15.37	50.15 ± 16.39	0.96
Social isolation (7,9,10,11,15,16,19,23,24,25,27,29)	17.14 ± 6.86	17.38 ± 7.21	0.75
Discrimination (5,6,8,12,13,14,22,28,30)	15.49 ± 5.49	15.09 ± 5.66	0.42
Inadequacy (17,18,20,21,26)	6.61 ± 2.69	6.89 ± 3.35	0.49
False beliefs (1–4)	6.23 ± 2.03	6.01 ± 1.95	0.31
Stigma resistance (31–32)	4.54 ± 1.82	4.93 ± 1.71	0.11

Table 3
The Modified Morisky Scale values before and during the COVID-19 period.

	Before COVID-19 (n:110)	During COVID-19 (n:110)	*p*
Low motivation - low knowledge, *n* (%)	10 (9.1)	4 (3.6)	0.048
Low motivation - high knowledge, *n* (%)	14 (12.7)	14 (12.7)	
High motivation - low knowledge, *n* (%)	12 (10.9)	10 (9.1)	
High motivation - high knowledge, *n* (%)	74 (67.3)	82 (74.5)	

in the COVID-19 period are shown in Table 4. Seizure frequency, lack of access to medication, number of drugs, and duration of illness were evaluated in univariate analysis. In multivariate analysis, the number of drugs alone predicted an increase in seizure frequency during COVID-19 ($p = 0.005$). As the number of drugs used increases, the risk of seizure frequency increases in the period of COVID-19.

In correlation analysis, a negative correlation was found between the stigma total score during COVID-19 period and education level ($r = -0.382$, $p = 0.001$ <). A positive correlation was observed between the stigma total score during the COVID-19 period and the number of drugs used ($r = 0.303$, $p = 0.006$). The stigmatization of epilepsy patients increased as the education level decreased and the number of drugs used increased.

4. Discussion

In this survey study, we evaluated the impact of the COVİD-19 pandemic on drug compliance and stigmatization in epilepsy patients. We found no significant difference in stigmatization in the study. Regarding drug compliance, we reached higher motivation and higher information in the MMS during the pandemic period. In addition, an increase in the frequency of seizures was observed in a small number of patients during the pandemic period. To the best of our knowledge, our study contains the first information on this subject, as there is no other data on this subject in the literature.

Over the centuries, new strain of viruses such as the flu has produced pandemics in countries that increase disease, death, and disruption. The Spanish flu in 1918, Asian flu in 1957, Hong Kong flu in 1968, and swine flu in 2009 were known as pandemics with varying morbidity and mortality. As a result, pandemics bring many problems, both in individual and societal levels [3].

The neurotropic and neuroinvasive abilities of coronaviruses have been described in humans. Symptoms such as febrile seizures, convulsions, loss of consciousness, encephalomyelitis, and encephalitis can be observed in patients with coronavirus infection [10]. The angiotensin-converting enzyme suggested that the central nervous system could be a potential target of SARS-CoV-2, since two receptors were detected on the surface of glial cells and neurons [11]. However, the effects of COVID-19 on patients with epilepsy and the prevalence of new-onset epilepsy remain unclear [12]. Some sources on the pandemic show that people with epilepsy are neither more likely to be infected by the coronavirus nor are they more likely to have severe symptoms of COVID-19 because they suffer from epilepsy. However, the management of COVID-19 in patients with epilepsy is more complex than in other individuals [13]. Based on previous data, the rate of neurological comorbidity was not assumed to be higher for COVID-19 than for other respiratory viral infectious diseases. Epilepsy patients infected with COVID-19 or other infectious diseases may have fever and possibly trigger seizures.

The relationship between antiepileptic drugs (AEDs) and COVID-19 drugs should be considered. Drugs should be selected individually in clinical settings, and attention should be paid to drug interactions. Since the risk of COVID-19 infection may increase with the increase in seizure frequency and duration, it is not recommended to change the AEDs of patients whose seizures are well controlled. Huang et al. found that a small proportion of patients with epilepsy experienced seizure exacerbation during the COVID-19 outbreak. Stress is an independent precipitant for triggering seizures in these patients [14].

A stigma can be defined as a sign, mark or label that causes an individual to be rejected, viewed and excluded by the society [15]. Stigma has negative consequences for epilepsy patients in many areas. The deterioration in quality of life is one of these areas. Studies show that stigmatization in epilepsy has profound effects on a person's social functionality and social isolation [16]. Epilepsy

Table 4
Univariate and multivariate analyses for independent predictors an increase in seizure frequency in COVID-19 period.

	Univariate			Multivariate		
	OR	CI	*p*	OR	CI	*p*
Seizure frequency	3.833	1.195–12.289	**0.024**	0.958	0.198–4.619	0.96
The number of drugs used	10.139	2.603–39.498	**0.001**	**8.941**	**1.905–41.961**	**0.005**
Duration of illness	1.053	0.992–1.118	**0.090**	1.046	0.970–1.128	0.24
Lack of access to medication	17.00	0.943–306.34	**0.055**	25.750	0.095–6986	0.26

OR: odds ratio, CI: confidence interval.

patients described themselves as less valuable, unable to adapt, less reliable, less mature, more unstable, less successful, and less compatible. In addition, the stigma associated with epilepsy has been found to be associated with low self-perception, high anxiety level, and depression [17,18]. The age of the patient, the age of onset of the disease, the duration of the treatment, marital status, drug side effects, accompanying physical and psychiatric disorders, the education level of the patients and the level of knowledge about the disease are among the factors that affect the stigmatization [19]. Adverse outcomes are observed in many areas such as quality of life, treatment compliance, and social and occupational functionality. Stigmatized individuals are exposed to high risk due to both disease and stigmatization, and stigmatization reduces patients' access to preventive and therapeutic methods [20,21]. Disease progression is exacerbated by the stress from stigmatization. Therefore, stigmatization is an important factor that increases the severity of the disease [19]. In our study, the stigmatization of epilepsy patients increased as the education level decreased and the number of drugs used increased.

Pandemics can adversely affect chronic diseases, because patients may have problems reaching healthcare facilities and accessing medicines due to the epidemic. In our country, the drug reports of those with chronic diseases such as epilepsy have been extended, and specific pandemic hospitals have been established. Those with epilepsy and other chronic diseases did not have any problems in accessing healthcare facilities and accessing drugs from pharmacies. In our study, only two patients had difficulties in accessing their medication. Epilepsy patients isolate themselves from society because of stigma and fear of seizures in public. Social isolation reduces the chance of developing friendship relations, which leads to a decrease in marriages and problems in finding a job in epilepsy patients [22]. Epilepsy patients, who already tend to be isolated, are less affected by isolation than healthy people. Most of the patients in the study had a good education level, and the frequency of seizures was not very high. They did not have any difficulty in obtaining their medicines and provided more regular medication as they remained in forced social isolation at home. During the pandemic period, patients with epilepsy can reach higher levels of knowledge and motivation, although they spend more time with their families and feel safer with their families at home.

After the intensification of the COVID-19 epidemic in Iran, about one-third of patients with epilepsy stated that they had significant difficulties in obtaining their medicines. In this study, the frequency of seizures increased in 6% of patients during the 4-week COVID-19 period [23]. A study of 227 patients with epilepsy during the SARS epidemic in Taiwan in 2003 showed that 22% of patients did not take their medication due to a loss of contact with healthcare providers, and 12% of the patients experienced worsening seizure control during the epidemic [24]. During the current COVID-19 outbreak, in an Italy-based study with 456 epilepsy and 472 non-epilepsy patients, those with epilepsy experienced difficulties in follow-up, especially with an 18% increase in the number of seizures. Epilepsy patients had worse depressive and anxiety symptoms than those without epilepsy. Sleep quality was equally similar in both groups. The seizure increase was best related to the number of anti-seizure medications and sleep disturbances [25]. According to the Italy-based study, the increase in the frequency of seizures was less in our study because our patient group had a low seizure frequency (94.5% of individuals had a seizure frequency less than 1 per month). This made it difficult to evaluate its worsening in epilepsy patients in our study. Alkhotani et al. Reported an increase in seizure frequency in 29.5% of their patients during the COVID-19 period in a Saudi Arabia-based study [26]. They found that higher baseline seizure frequency, more AEDs, non-adherence, increased stress, and self-reported sleep changes were important factors associated with an increase in seizure frequency during the pandemic. In our study, while an increase in seizure frequency was found in seven patients (6.4%) during the 4-month period of COVID-19, a relationship was found between the increase in seizure frequency and the number of drugs used. Studies demonstrate the effectiveness of a structured training program in improving drug adherence in a cohort of epilepsy patients with a low educational background [27]. In the context of a pandemic, telemedicine, especially through video consultations, should be promoted and expanded to reduce the risk of disease transmission. It has been shown to improve access to treatment, especially for patients with epilepsy living in rural areas [28].

Limitations of the study: The first limitation is that it is a single center study and the number of patients is limited. Second, more valuable information would have been obtained if the study had been designed to compare epilepsy patients with healthy controls. Depression, quality of life and anxiety were not evaluated in our study. In our study, we used a 6-question MMS questionnaire, which is valid and reliable in our country. Modified Morisky Adaptation Scale-8, which was proven to be valid in the studies, was not used [27,29]. One of the limitations of our study in the regression analysis is low ratio of the number of patients with increased seizure frequency in the COVID-19 period to the total number of patients (7 vs 103).

5. Conclusion

Pandemics have many negative social and psychological effects on society and individuals. A slight increase in the frequency of seizures was observed in our patients during the pandemic period, and no significant problem was experienced in accessing drugs.

Epilepsy patients experience an intense feeling of stigma due to their illness. With the increasing number of patients stigmatized in the community due to the diagnosis of COVID-19, the idea that epilepsy patients are not alone has emerged. The idea is that stigmatization occurs not only in themselves but also in patients diagnosed with COVID-19. Therefore, in our patient group, the COVID-19 outbreak did not have a negative effect on stigmatization in epilepsy patients.

During the pandemic period, patients with epilepsy did not have any problems in drug compliance due to easy access to drugs and intensive training and information about COVID-19 in visual and printed media. Our patients had a higher level of motivation and knowledge.

Conflict of interest statement

Authors state no conflict of interest regarding the manuscript.

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