



Are COVID-19 vaccines safe for people with epilepsy? A cross-sectional study

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Abstract

Background COVID-19 disease was first seen in December 2019 and was declared a pandemic soon after. To fight the pandemic, there is an immense need for effective vaccines. The purposes of our study were to investigate the effect of coronavirus vaccines on seizures in people with epilepsy (PWE) and assess the adverse events of COVID-19 vaccine in PWE.

Methods This was a cross-sectional study. We included epilepsy patients who got vaccinated with two or three doses at least 1 month earlier. We gathered the data using a standardized form. The form contained questions about patients' demographic features, clinical features, and information about the vaccination and its adverse events. The questionnaire included questions about epilepsy-related adverse events.

Results We included 178 people with epilepsy in our study. The frequency of adverse events was lower than clinical studies of the vaccines. The mean number of seizures in the month before the vaccination was 1.62, between the doses was 1.61, and after vaccination was 1.64. There was no significant difference in the number of monthly seizures before the vaccination, the month between the doses, or the month after the vaccination ($p = 0.46$).

Conclusions The vaccines under consideration in our study were tolerated well by the epilepsy patients. The vaccines did not affect the monthly number of seizures of the PWE. A small number of patients had more seizures than normal after vaccination. We think that benefits of the vaccines outweigh the slightly increased possibility of having a seizure after vaccination.

Keywords Epilepsy · COVID-19 · Vaccine · Safety

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a contagious virus responsible for COVID-19 disease [1]. COVID-19 disease was first seen in December 2019 and was declared a pandemic soon after [1]. The pandemic affected people worldwide and caused millions of deaths [1]. To fight the pandemic, there is an immense need for effective vaccines [2].

Several COVID-19 vaccines with different mechanisms of action are in use nowadays, and several potential vaccines are in the development phases [2]. Since COVID-19 vaccines have been employed only recently, there is a lack of

experience in using them in patients with chronic diseases such as epilepsy [3].

Epilepsy is one of the most common chronic neurological disorders [4]. Clinical trials of the COVID-19 vaccines showed no severe neurological adverse event [5–7]. Furthermore, studies on other vaccines found that vaccination did not cause an increase in seizure risk except for the diphtheria, tetanus, and pertussis (DTP) vaccine and the measles, mumps, and rubella (MMR) vaccine [8]. However, real-life experience on this subject remains lacking.

The CoronaVac inactivated whole-virion vaccine and the Pfizer-BioNTech mRNA vaccine (BNT162b2) were licensed in Turkey for people aged over 15 years old [9]. The vaccines are administered in two doses separated by a 4-week interval [9]. People may have a third vaccine dose if they wish to [9]. People can choose either vaccine regardless of the vaccine they got fully vaccinated for the third dose, and, in this case, they can be vaccinated with different vaccines [9]. By November 2021, more than 118 million doses had been administered in Turkey [9].

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The purposes of our study were to investigate the effect of coronavirus vaccines on seizures in people with epilepsy (PWE) and assess the adverse events of COVID-19 vaccine in PWE. We aim to share our real-life experience on this subject.

Methods

This was a cross-sectional study. The study was conducted in Ege University Hospital, Department of Neurology. Ege University Hospital is a tertiary center in Turkey. Approximately five hundred PWEs are followed up regularly in Ege University Hospital, Department of Neurology. PWEs who presented to our tertiary center between January 7, 2021, and January 9, 2021, were evaluated for the study. We included those who met the following criteria: having a definite diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) Guideline, being older than 18 years old, being vaccinated with two or three doses at least 1 month earlier, and having a follow-up of at least 3 months [10]. Patients who had unconfirmed epilepsy diagnosis according to the ILAE Guideline, PWEs diagnosed with epilepsy less than 3 months ago, PWEs who do not visit the outpatient clinic regularly, PWEs with low drug compliance, PWEs with additional psychogenic nonepileptic seizures, and PWEs with severe comorbid diseases which can interfere the result were excluded.

We gathered the data using a standardized form. The form contained questions about patients' demographic features, clinical features, and information about the vaccination and its adverse events. Patients' demographic features including age, sex, and age at onset of epilepsy were asked. Patients' seizures were classified according to the ILAE Classification of Epilepsies 2017 Guideline [10]. Patients' most recent electroencephalography and magnetic resonance imaging findings were noted.

The following information about vaccination and vaccine-related systemic adverse events were recorded: vaccination date, vaccine type, vaccine-related adverse events after each dose, injection site redness or pain, fever (> 38 °C temperature), tiredness, headache, muscle pain, and chills. Serious adverse events were also questioned. The World Health Organization defined serious adverse events as the following: results in death, hospitalization, or compelling or persistent disability [11]. The patients' COVID-19 infection history was noted. Patients who had the history of detection of SARS-CoV-2 by molecular methods were assessed as PWEs with positive COVID-19 infection history.

The patients were questioned about the frequency of seizures in the month before vaccination, yearly frequency of seizures, and the types and doses of medication they were on at that time. The vaccination dates and type of

vaccine were noted. The questionnaire included questions about epilepsy-related adverse events: having more seizures in the first week after vaccination, frequency of seizures between the two doses, frequency of seizures in the month after the second and third doses, new-onset status epilepticus, and new seizure type. We utilized patients' seizure diaries to ascertain monthly seizure frequency. The seizures were recorded by PWEs in epilepsy diaries.

We divided the patients into three subgroups according to seizure frequency: seizure-free, lower seizure frequency, and higher seizure frequency. We used a Seizure-based Outcome Classification System (Duke) for this grouping [12]. Seizure-free was considered as freedom from all types of seizures for 12 months or three times the pre-intervention inter-seizure interval [13]. Moreover, the PWEs were divided into five groups according to age at onset of epilepsy. The age groups were determined in line with the milestones of the life span: infancy and toddlerhood 0–2 years, childhood 2–12 years, adolescence 12–18, adulthood 18–65, and late adulthood > 65 years of age. We compared these subgroups for vaccine-related adverse events. To assess the change in seizure frequency, we statistically compared the patients' monthly seizure frequencies before the vaccination, the month between the doses, and the month after vaccination. We completed the form for the mentally disabled patients with their caregivers.

The Local Ethical Committee of Ege University Medical School approved the study. Written informed consent was obtained from all participants.

Statistical analysis

The data were analyzed using SPSS version 25. Numeric variables, with a normal distribution, were defined with means and standard deviations, and those without a normal distribution were defined with median values. The Shapiro–Wilk test was used to test for normality of distribution. When comparing quantitative data to determine whether there was a difference between the groups, Student's *t*-test was used for data with a normal distribution and the Mann–Whitney *U* test for data without a normal distribution. To determine the differences between groups, the χ^2 and Fisher's exact test were used. The relations of numerical variables with each other were evaluated with Pearson correlation analysis for those with a normal distribution and Spearman's correlation analysis for those without one. The Friedman test was used to evaluate whether there were any statistically significant differences between the distributions of three or more paired groups. Values of $p < 0.05$ were considered statistically significant.

Results

In the abovementioned time span, 312 PWEs visited the outpatient clinic. We included 178 PWEs according to the inclusion criteria. While 91 PWEs (51.1%) were female, 87 PWEs (48.9%) were male. The mean age of the study population was 32.47 years ($SD = 12.76$). The median follow-up duration was 8 years (minimum = 0.5 years, maximum = 42 years). Only eight patients were older than 55 years old.

The number of the PWE who had epilepsy onset in infancy and toddlerhood was 23 (12.9%), in childhood was 54 (30.3%), in adolescence was 34 (19.1%), in adulthood was 64 (35.9%), and in late adulthood was 3 (1.8%). The majority of the PWEs in our study group had generalized epilepsy; 111 PWEs (62.3%) had generalized epilepsy, 27 PWEs (15.2%) had focal epilepsy, and 40 PWEs (22.5%) had combined epilepsy.

Seventy-four PWEs (41.6%) had abnormal EEG findings. In line with the distribution of the types of epilepsy in our

study group, generalized epileptiform activity was the most frequent EEG abnormality, followed by focal epileptiform activity. Forty-seven PWEs (26.4%) had generalized epileptiform activity and 14 PWEs (7.9%) had focal epileptiform activity. Eight PWEs (4.5%) showed focal and generalized epileptiform activity on different EEG traces. Four PWEs (2.3%) showed basic rhythm slowing and 1 (0.6%) showed a brush rhythm on EEG.

One hundred five participants (59%) were seizure-free. Thirty-four patients (19.1%) were grouped in the lower seizure frequency group, while 39 patients (21.9%) were grouped in the higher seizure frequency group. The mean number of seizures in the month before the vaccination was 1.62, between the doses was 1.61, and after vaccination was 1.64. There was not a statistically significant difference among the monthly number of seizures ($p = 0.46$). Only one patient (0.6%) was not on any anti-seizure medication (ASM). While 78 PWEs (43.8%) were on monotherapy, 99 PWEs (55.6%) were on polytherapy. The patients' clinical and demographic features are shown in Table 1.

Table 1 Patients' clinical and demographic features

	BNT162b2 ($n = 136$)	CoronaVac ($n = 35$)	Combination ($n = 7$)	Total ($n = 178$)
Gender				
Female	64 (35.9%)	22 (12.4%)	5 (2.8%)	91 (51.1%)
Male	72 (40.4%)	13 (7.3%)	2 (1.1%)	87 (48.9%)
Age (years),				
Median (range)	27 (18–55)	33 (18–81)	46 (23–69)	29 (18–81)
Epilepsy type				
Focal epilepsy	16 (8.9%)	9 (5.1%)	2 (1.1%)	27 (15.2%)
Generalized epilepsy	91 (51.1%)	17 (9.6%)	3 (1.7%)	111 (62.3%)
Combined epilepsy	29 (16.3%)	9 (5.1%)	2 (1.1%)	40 (22.5%)
Age at onset of epilepsy				
0–2 years	16 (8.9%)	7 (3.9%)	0	23 (12.9%)
2–12 years	46 (25.9%)	7 (3.9%)	1 (0.6%)	54 (30.3%)
12–18 years	28 (15.7%)	4 (2.2%)	2 (1.1%)	34 (19.1%)
18–65 years	46 (25.9%)	15 (8.4%)	3 (1.8%)	64 (35.9%)
> 65 years	0	2 (1.1%)	1 (0.6%)	3 (1.8%)
EEG abnormality				
Yes	55 (30.9%)	16 (8.9%)	3 (1.7%)	74 (41.6%)
No	81 (45.5%)	19 (10.7%)	4 (2.2%)	104 (58.4%)
Seizure frequency				
Seizure-free	82 (46.1%)	17 (9.6%)	6 (3.4%)	105 (59%)
Lower seizure frequency	29 (16.3%)	4 (2.2%)	1 (0.6%)	34 (19.1%)
Higher seizure frequency	25 (14.1%)	14 (7.8%)	0	39 (21.9%)
Number of ASMs				
On no medication	1 (0.6%)	0	0	1 (0.6%)
One drug	57 (32.1%)	15 (8.4%)	6 (3.4%)	78 (43.8%)
Two drugs	43 (24.2%)	8 (4.4%)	1 (0.6%)	52 (29.2%)
Three drugs	32 (17.9%)	10 (5.6%)	0	42 (23.6%)
Four or more drugs	3 (1.7%)	2 (1.1%)	0	5 (2.8%)
Number of seizures in the month before vaccination				
Mean (SD)	1.12 (3.5)	3.91 (7.37)	0	1.62 (4.59)

One hundred thirty-six PWEs (76.4%) were vaccinated with two doses of BNT162b2, 35 PWEs (19.7%) with two doses of CoronaVac, and 7 PWEs (3.9%) with a combination of the vaccines (one dose of BNT162b2 following two doses of CoronaVac). Eight PWEs (4.5%) had had COVID-19 infection before being vaccinated with CoronaVac.

Fifty-two PWEs (29.2%) had a local adverse event (injection site redness/pain) after the first dose of the vaccine. Forty-nine of the 136 (36%) PWEs vaccinated with BNT162b2 and 3 of the 42 (7.1%) PWEs who received CoronaVac had a local adverse event. Having a local adverse event is significantly more frequent with BNT162b2 ($p=0.003$). Fifty-eight PWEs (32.6%) had at least one

systemic adverse event after the first dose of the vaccine. There was not a significant difference for having a systemic adverse event (36% vs. 21.4%) between the BNT162b2 and CoronaVac groups ($p=0.07$). Detailed information about systemic adverse events is provided in Table 2. No severe adverse events were reported after the first dose of the vaccines.

We compared the clinical features of the PWE who had at least one adverse event and had no adverse event (Table 3). Epilepsy type and age at onset of epilepsy were not associated with local adverse events ($p=0.19$ and $p=0.44$, respectively). The number of drugs to treat epilepsy and seizure frequency were not related to the presence of local adverse events ($p=0.33$ and $p=0.59$, respectively). Moreover, having a systemic adverse event after the first dose of the vaccine was not associated with any of the clinical features of the PWE. Epilepsy type, age at onset of epilepsy, number of drugs to treat epilepsy, and seizure frequency were not associated with having systemic adverse events ($p=0.72$, $p=0.24$, $p=0.16$ and $p=0.25$, respectively).

Forty-three PWEs (24.1%) had a local adverse event after the second dose of the vaccine. The presence of a local adverse event was significantly more common in the BNT162b2 group than in the CoronaVac group (30.1% vs. 4.7%, $p=0.001$). Forty-six PWEs (25.8%) had at least one systemic adverse event. There was no significant difference between the frequency of systemic adverse events between the BNT162b2 group and the CoronaVac group (28.6% vs. 16.6%, $p=0.12$). The systemic adverse events after the

Table 2 The frequency of adverse events after the first dose of vaccines

	BNT162b2 ($n=136$)	CoronaVac ($n=42$)	p
Local adverse effects			
Injection site redness/pain	49 (36%)	3 (7.1%)	0.003*
General adverse effects			
Fatigue	25 (18.3%)	4 (9.5%)	0.17
Headache	19 (13.9%)	5 (11.9%)	0.73
Fever	16 (11.7%)	3 (7.1%)	0.39
Myalgia	11 (8%)	2 (4.7%)	0.46
Chills	9 (6.6%)	3 (7.1%)	0.90
Nausea	2 (1.4%)	1 (2.3%)	0.68
Dizziness	2 (1.4%)	2 (4.7%)	0.20
Diarrhea	2 (1.4%)	1 (2.3%)	0.68

Table 3 The association between patients' clinical features and adverse events after the first dose of vaccines

	Patient-reported local adverse effect		p	Patient-reported general adverse effect		p
	Present	Absent		Present	Absent	
	N (%)	N (%)		N (%)	N (%)	
Epilepsy type						
Focal epilepsy	6 (22.2)	21 (77.8)	0.19	7 (25.9)	20 (70.1)	0.72
Generalized epilepsy	38 (34.2)	73 (65.8)		37 (33.3)	74 (66.7)	
Combined epilepsy	8 (20)	32 (80)		14 (35)	26 (65)	
Age at onset of epilepsy						
0–2 years	6 (26.1)	17 (73.9)	0.44	8 (34.8)	15 (62.2)	0.24
2–12 years	16 (29.6)	38 (70.4)		17 (31.5)	37 (68.5)	
12–18 years	14 (41.2)	20 (58.8)		16 (47.1)	18 (52.9)	
18–65 years	16 (25)	48 (75)		17 (26.6)	47 (73.4)	
> 65 years	0 (0)	3 (100)		0 (0)	3 (100)	
Seizure frequency						
Seizure-free	28 (26.7)	77 (73.3)	0.59	30 (28.6)	75 (74.2)	0.25
Lower seizure frequency	12 (35.3)	22 (64.7)		15 (44.1)	19 (55.9)	
Higher seizure frequency	12 (30.8)	27 (67.9)		13 (33.3)	26 (66.7)	
Number of ASMs						
No medication	1 (100)	0	0.33	1 (100)	0 (0)	0.18
Monotherapy	26 (33.3)	52 (66.7)		25 (32.1)	53 (67.9)	
Polytherapy	25 (25.3)	74 (74.7)		32 (32.3)	67 (67.7)	

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second dose are shown in Table 4. No serious adverse events were recorded after the second dose of the vaccines.

The clinical characteristics of the PWE did not affect the frequency of the adverse events after the second vaccination dose. Epilepsy type, age at onset of epilepsy, number of drugs to treat epilepsy, and seizure frequency were not associated with having a local adverse event ($p=0.84$, $p=0.83$, $p=0.90$, and $p=0.08$, respectively) or systemic adverse events ($p=0.70$, $p=0.66$, $p=0.54$, and $p=0.64$, respectively) (Table 5).

We compared the monthly number of seizures. The mean number of seizures in the month before the vaccination was 1.62, between the doses was 1.61, and after vaccination was

1.64. There was no significant difference in the number of monthly seizures before the vaccination, the month between the doses, or the month after the vaccination ($p=0.46$). Seven patients were vaccinated with a combination of vaccines (2 doses of CoronaVac and one dose of BNT162b2). These seven patients were seizure-free and vaccination did not trigger any seizure. Eight patients had caught the COVID-19 infection before the vaccination. Four patients were in the seizure-free group, two patients were in the lower seizure frequency group, and two patients were in the higher seizure frequency group. Two PWEs in the higher seizure frequency group had seizures (one seizure per month). This may be expected since they were in a higher seizure frequency group.

Only four PWEs had more seizures than normal for patients. Three patients were male and one patient was female. All patients were younger than 40 years of age. They had had epilepsy for more than 10 years. All patients were on polytherapy. Three patients were vaccinated with BNT162b2 and one patient was vaccinated with CoronaVac. Seizures occurred within the first two days after the first dose of vaccine. It is important to emphasize that all patients had systemic adverse events, especially fever and seizures that occurred in the first two days after vaccination. One patient (patient 3 in Table 6) had two additional seizures after vaccination, and the remaining three patients had one additional seizure. No patient had status epilepticus. No adjustment of ASMs was made. Detailed information is provided in Table 6.

Table 4 The frequency of adverse effects after the second dose of vaccines

	BNT162b2 (n=136)	CoronaVac (n=42)	p
Local adverse effects			
Injection site redness/pain	41 (30.1%)	2 (4.7%)	0.001*
General adverse effects			
Fatigue	16 (11.7%)	3 (7.1%)	0.39
Headache	17 (12.5%)	4 (9.5%)	0.60
Fever	10 (7.3%)	1 (2.3%)	0.24
Myalgia	11 (8%)	2 (4.7%)	0.46
Chills	7 (5.1%)	2 (4.7%)	0.92
Nausea	2 (1.4%)	1 (2.3%)	0.68
Dizziness	3 (2.2%)	1 (2.3%)	0.94
Diarrhea	1	0	

Table 5 The association between patients' clinical features and side effects after the second dose of vaccines

	Patient-reported local adverse effect		p	Patient-reported general adverse effect		p
	Present	Absent		Present	Absent	
	N (%)	N (%)		N (%)	N (%)	
Epilepsy type						
Focal epilepsy	5 (18.5)	22 (81.5)	0.84	5 (18.5)	22 (81.5)	0.70
Generalized epilepsy	28 (25.2)	83 (74.8)		30 (27.1)	81 (72.9)	
Combined epilepsy	10 (25)	30 (75)		11 (27.5)	29 (72.5)	
Age at onset of epilepsy						
0–2 years	4 (17.4)	19 (82.6)	0.83	5 (21.7)	18 (72.3)	0.66
2–12 years	13 (24.1)	41 (75.9)		17 (31.4)	37 (68.6)	
12–18 years	10 (29.4)	24 (70.6)		10 (29.4)	24 (70.6)	
18–65 years	16 (25)	48 (75)		14 (21.9)	50 (78.1)	
> 65 years	0 (0)	3 (100)		0 (0)	3 (100)	
Seizure frequency						
Seizure-free	25 (23.8)	80 (76.2)	0.94	24 (22.9)	81 (77.1)	0.54
Lower seizure frequency	9 (26.4)	25 (73.6)		10 (29.4)	24 (70.6)	
Higher seizure frequency	9 (23.1)	30 (76.9)		12 (30.8)	27 (69.2)	
Number of ASMs						
No medication	1 (100)	0 (0)	0.08	1 (100)	0 (0)	0.64
Monotherapy	19 (24.4)	59 (76.6)		19 (24.4)	59 (76.6)	
Polytherapy	23 (22.4)	76 (77.6)		26 (25.5)	73 (74.5)	

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Table 6 Demographic and clinical features of patients who had more seizures than usual

	Age (years)	Gender	Epilepsy duration (years)	Vaccine/dose	Seizure type	Epilepsy type	Number of ASMs	Accompanying side effects
Patient 1	21	Male	10	CoronaVac/first	Generalized motor seizure	Generalized epilepsy	3	Fever Myalgia Fatigue
Patient 2	32	Male	14	BNT162b2/first	Generalized motor seizure	Combined epilepsy	2	Fever Fatigue
Patient 3	18	Female	10	BNT162b2/first	Focal seizure with impaired awareness	Combined epilepsy	3	Fever
Patient 4	35	Male	19	BNT162b2/first	Focal seizure with impaired awareness	Combined epilepsy	3	Fever

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Discussion

This cross-sectional study shows real-life data from our tertiary epilepsy clinic. The mean age of our patients was 32.47 years ($SD = 12.76$). It is lower than that of European peers, which was 47.9 ($SD = 20.1$) in a tertiary center in Germany and 48.2 ($SD = 19.8$) in a tertiary center in Spain [14, 15]. The demographic structure of the Turkish population can explain this difference. According to the Turkish Statistical Institute's official data, the proportion of the youth population in Turkey is the highest in Europe [16].

Epilepsy started in adulthood in 35.9% of the patients and late adulthood in 1.8%. Our statistics were similar to those of a multicenter study from France [17]. The majority of the patients in our study sample had generalized epilepsy. The distribution of epilepsy types may vary among centers [3, 14, 15]. The drug-resistant epilepsy rate was 19.1% in our patients, similar to the literature rates [18]. We evaluated the clinical features of our patients in accordance with the literature.

The rate of local adverse events was 36% after the first dose of BNT162b2 and 30.1% after the second dose of it. The incidence of local adverse events was lower than that of the clinical trials (83% after the first dose; 78% after the second dose) and a UK community-based observational study (71.9% after the first dose; 68.5% after the second dose) [5, 19].

The local adverse events were significantly more frequent in patients that had received BNT162b2 than in patients that had received CoronaVac for the first and second doses ($p = 0.003$ and $p = 0.001$, respectively). In the clinical trials of the vaccines, local adverse events occurred much more frequently in patients vaccinated with BNT162b2 (83% after the first dose; 78% after the second dose) than in those vaccinated with CoronaVac (2.7% overall) [5, 6]. The frequency of local adverse events after combined vaccines was 28.6%, similar to the frequency of adverse events after the first dose

of BNT162b2. A CombiVacS study found a similar adverse event profile with BNT162b2 following the ChAdOx1-S vaccine [20]. To the best of our knowledge, there are no data in the literature about the adverse event profile of BNT162b2 following CoronaVac.

There was no significant difference between the frequency of systemic adverse events between the BNT162b2 group and the CoronaVac group ($p = 0.07$ and $p = 0.12$, respectively). Our study's rate of having a systemic adverse event is lower than that of the clinical trial of the vaccines and community-based studies [5, 6, 19]. A cross-sectional study conducted with PWE in Germany found a rate of having a systemic adverse event of 33% [14]. In our study, the patients were questioned retrospectively about adverse events; recall bias can explain the difference for both local adverse events and systemic adverse events.

In our study, the most commonly reported adverse events were fatigue and headache for BNT162b2 and CoronaVac. Clinical trials showed that fatigue and headache were the most common systemic adverse events for BNT162b2 and CoronaVac [5, 6]. A real-life study from Czechia also found fatigue and headache as the most common adverse events [21]. The less prevalent adverse events in our study, such as fever, myalgia, and chills, were also less prevalent in the clinical and cross-sectional studies [5, 6, 21]. Almost all participants' local adverse events and systemic adverse events lasted less than 7 days, as the clinical trials and real-life studies stated [3, 5, 6].

The clinical trials showed that serious adverse events are infrequent with BNT162b2 and CoronaVac [5, 6]. The incidence of serious adverse events was 0.1% for both vaccines and no patient reported serious adverse events in our study.

We investigated the association between patients' clinical characteristics and having a vaccine adverse event. Our study did not find that any of the patients' epilepsy characteristics, including epilepsy type, age at onset of epilepsy, seizure frequency, and the number of ASMs patients were

using, were associated with having a vaccine-related adverse event. Von Wrede et al. indicated that having an earlier onset of epilepsy and using a lower number of ASMs can predict having a vaccine adverse event 83.3% correctly [14]. In contrast to a German study, Massoud et al. did not find an association between epilepsy duration and having a vaccine-related adverse event [3]. Moreover, Massoud et al. stated that receiving polytherapy was associated with a higher frequency of vaccine-related adverse events [3]. Since there are contrasting results in the literature, the relationship between the PWE's clinical characteristics and vaccine-related adverse events needs to be interpreted cautiously. Clinical trials showed that the vaccines under consideration in our study are safe for people with chronic diseases [5, 6]. Our data suggested no association between the PWE's clinical characteristics and adverse events [23]. We need more information to define an association between epilepsy treatment and having a systemic adverse event.

The vaccines under consideration did not affect the monthly number of seizures in our study. Vaccination is recommended for PWE [8]. Moreover, the ILAE specifically recommends vaccination against COVID-19 infection for PWE [22]. An elevated seizure risk was found only for the DTP vaccine and the MMR vaccine in the first three days after vaccination [8, 23]. It was hypothesized that fever caused by vaccination might trigger seizures [8, 23]. Fever can also trigger seizures in adults [24]. Fever presented as a systemic adverse event in all of our patients who had more seizures than normal after vaccination. Triggered seizures often occur in the first three days after vaccination [3, 8, 23]. Longer duration of epilepsy is also a risk factor for seizure triggering [25]. Although a high number of current ASMs were not a risk factor for seizure triggering, all of our patients who had seizures more than normal after vaccination were receiving polytherapy with ASMs [24, 25]. In the study by Massoud et al., patients who had more seizures than usual after being administered the COVID vaccine were receiving polytherapy and had had epilepsy for more than 2 years [3].

Our study has limitations. Adverse events were questioned retrospectively; this may have resulted in recall bias. The caregivers answered questions on behalf of the mentally disabled patients; some adverse events such as headaches, chills, and myalgia may be overlooked. We included the patients who visited the clinic; this may have caused bias as a result of the absence of patients with serious adverse events. Our study population was younger than those in the clinical trials of the vaccine; this might have affected the adverse event profile.

In conclusion, the vaccines under consideration in our study were tolerated well by the epilepsy patients. The vaccines did not affect the monthly number of seizures of the PWE. A small number of patients had more seizures than

normal after vaccination. Patients had the following common features: being on polytherapy, having epilepsy for more than 10 years, and having fever as a systemic adverse event. We think that benefits of the vaccines outweigh the slightly increased possibility of having a seizure after vaccination.

Declarations

Ethical approval The Local Ethical Committee of Ege University Medical School approved the study.

Consent to participate Written informed consent was obtained from all participants.

Competing interests The authors declare no competing interests.

References

- Hu B, Guo H, Zhou P, Shi ZL (2021) Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 19(3):141–154. <https://doi.org/10.1038/s41579-020-00459-7>
- Yan ZP, Yang M, Lai CL (2021) COVID-19 vaccines: a review of the safety and efficacy of current clinical trials. *Pharmaceuticals (Basel)* 14(5):406–434. <https://doi.org/10.3390/ph14050406>
- Massoud F, Ahmad SF, Hassan AM, Alexander KJ, Al-Hashel J, Arabi M (2021) Safety and tolerability of the novel 2019 coronavirus disease (COVID-19) vaccines among people with epilepsy (PwE): a cross-sectional study. *Seizure* 92:2–9. <https://doi.org/10.1016/j.seizure.2021.08.001>
- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388(10053):1545–1602. [https://doi.org/10.1016/S0140-6736\(16\)31678-6](https://doi.org/10.1016/S0140-6736(16)31678-6)
- Polack FP, Thomas SJ, Kitchin N et al (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 383(27):2603–2615. <https://doi.org/10.1056/NEJMoa2034577>
- Tanriover MD, Doğanay HL, Akova M et al (2021) Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 398(10296):213–222. [https://doi.org/10.1016/S0140-6736\(21\)01429-X](https://doi.org/10.1016/S0140-6736(21)01429-X)
- Lu L, Xiong W, Mu J et al (2021) The potential neurological effect of the COVID-19 vaccines: a review. *Acta Neurol Scand* 144(1):3–12. <https://doi.org/10.1111/ane.13417>
- Pruna D, Balestri P, Zamponi N et al (2013) Epilepsy and vaccinations: Italian guidelines. *Epilepsia* 54(7):13–22. <https://doi.org/10.1111/epi.12306>
- Republic Of Turkey Ministry Of Health (2021) COVID-19 vaccination information platform. https://covid19asi.saglik.gov.tr/?_Dil=2. Accessed 15 November 2021
- Scheffer IE, Berkovic S, Capovilla G et al (2017) ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58(4):512–521. <https://doi.org/10.1111/epi.13709>
- WHO Pharmacovigilance Team (2019) Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. World Health Organization, Geneva

12. Vickrey BG, Hays RD, Engel J Jr et al (1995) Outcome assessment for epilepsy surgery: the impact of measuring health-related quality of life. *Ann Neurol* 37(2):158–166. <https://doi.org/10.1002/ana.410370205>
13. Kwan P, Arzimanoglou A, Berg AT, et al (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies [published correction appears in *Epilepsia*. 2010 Sep;51(9):1922]. *Epilepsia* 51(6):1069–1077. <https://doi.org/10.1111/j.1528-1167.2009.02397.x>
14. von Wrede R, Pukropski J, Moskau-Hartmann S, Surges R, Baumgartner T (2021) COVID-19 vaccination in patients with epilepsy: first experiences in a German tertiary epilepsy center. *Epilepsy Behav* 122:1–4. <https://doi.org/10.1016/j.yebeh.2021.108160>
15. Fonseca E, Quintana M, Lallana S et al (2020) Epilepsy in time of COVID-19: a survey-based study. *Acta Neurol Scand* 142(6):545–554. <https://doi.org/10.1111/ane.13335>
16. Turkish Statistical Institute (2020) Youth in Statistics, 2020. <https://data.tuik.gov.tr/Bulten/Index?p=Youth-in-Statistics-2020-37242&dil=2>. Accessed 15 November 2021
17. Chipaux M, Szurhaj W, Vercueil L et al (2016) Epilepsy diagnostic and treatment needs identified with a collaborative database involving tertiary centers in France. *Epilepsia* 57(5):757–769. <https://doi.org/10.1111/epi.13368>
18. Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V (2018) The epidemiology of drug-resistant epilepsy: a systematic review and meta-analysis. *Epilepsia* 59(12):2179–2193. <https://doi.org/10.1111/epi.14596>
19. Menni C, Klaser K, May A et al (2021) Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis* 21(7):939–949. [https://doi.org/10.1016/S1473-3099\(21\)00224-3](https://doi.org/10.1016/S1473-3099(21)00224-3)
20. Borobia AM, Carcas AJ, Pérez-Olmeda M, et al (2021) Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial [published correction appears in *Lancet*. 2021 Aug 14;398(10300):582]. *Lancet* 398(10295):121–130. [https://doi.org/10.1016/S0140-6736\(21\)01420-3](https://doi.org/10.1016/S0140-6736(21)01420-3)
21. Riad A, Pokorná A, Attia S, Klugarová J, Koščík M, Klugar M (2021) Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech Republic. *J Clin Med* 10(7):1428–1446. <https://doi.org/10.3390/jcm10071428>
22. International League Against Epilepsy (2021) COVID-19 vaccines and people with epilepsy. <https://www.ilae.org/patient-care/covid-19-and-epilepsy/covid-19-vaccines-and-people-with-epilepsy>. Accessed 15 November 2021
23. Barlow WE, Davis RL, Glasser JW et al (2001) The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 345(9):656–661. <https://doi.org/10.1056/NEJMoa003077>
24. Balamurugan E, Aggarwal M, Lamba A, Dang N, Tripathi M (2013) Perceived trigger factors of seizures in persons with epilepsy. *Seizure* 22(9):743–747. <https://doi.org/10.1016/j.seizure.2013.05.018>
25. Wassenaar M, Kasteleijn-Nolst Trenité DG, de Haan GJ, Carpay JA, Leijten FS (2014) Seizure precipitants in a community-based epilepsy cohort. *J Neurol* 261(4):717–724. <https://doi.org/10.1007/s00415-014-7252-8>

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