Epilepsy & Behavior 139 (2023) 109070

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Immediate and 6-month seizure outcomes following first and second SARS-CoV2 mRNA vaccinations: A multicenter study with a nationwide survey

Megumi Nonaka [a], Shuichiro Neshige [a,b,*], Hidetada Yamada [a], Haruka Ishibashi [a], Yoshiko Takebayashi [a], Masahiro Nakamori [a], Shiro Aoki [a], Yu Yamazaki [a], Takeo Shishido [c], Dai Agari [d,e], Kazuhide Ochi [f], Koji Iida [b,g], Hirofumi Maruyama [a,b]

[a] Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Graduate School of Biomedical and Health Sciences, Japan
[b] Epilepsy Center, Hiroshima University Hospital, Japan
[c] Hiroshima City Asa Citizens Hospital, Japan
[d] Hiroshima City Hiroshima Citizens Hospital, Japan
[e] Hiroshima City Funairi Citizens Hospital, Japan
[f] Hiroshima Prefectural Hospital, Japan
[g] Department of Neurosurgery, Hiroshima University, Graduate School of Biomedical and Health Sciences, Japan

ARTICLE INFO

Article history:
Received 8 September 2022
Revised 23 December 2022
Accepted 23 December 2022
Available online 3 January 2023

Keywords:
Seizure worsening
SARS-CoV2 mRNA vaccination
Epidemic
Temporal lobe epilepsy
Focal impaired awareness seizure

ABSTRACT

Objective: This study aimed to identify seizure outcomes in people with epilepsy (PWE) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) messenger RNA vaccination.
Methods: We examined PWE (n = 332, age ≥ 14 years) treated in four tertiary hospitals between 2021 and 2022 to assess the incidence of seizure worsening following vaccination using closed questions. We identified the clinical factors associated with worsening and 6-month vaccination outcomes. We also conducted a nationwide survey on self-reported seizure worsening using open questions, to which 261 general practitioners from 99 institutes contributed.
Results: Of the 282 PWE vaccinated in the four hospitals, 16 (5.7%) exhibited seizure worsening; most of them emerged within 48 h of vaccination and were not sustained. Thus, all PWE were at baseline condition 6 months after their vaccination. PWE with seizure worsening were more significantly associated with focal impaired awareness seizures ($p < 0.001$), high seizure frequency ($p = 0.025$), and drug-resistant epilepsy ($p = 0.007$) at baseline compared to PWE without worsening. Multivariate logistic regression analysis revealed that focal impaired awareness seizures were independently associated with worsening (odds ratio, 7.0; 95% confidence interval, 1.50–32.77). A nationwide survey of 5156 PWE data (real-world data) confirmed an extremely low incidence rate of self-reported seizure worsening (0.43%).
Significance: Some PWE, particularly refractory focal epilepsy, exhibit seizure worsening. However, the worsening events were infrequent, non-sustainable, and probably under-reported by PWE, suggesting that there is little evidence that worsening seizures discourage current and future vaccinations.

1. Introduction

The novel coronavirus disease 2019 (COVID-19) epidemic has spread worldwide since 2019 and also in Japan since 2020 [1,2]. A vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was urgently developed and received the first temporary emergency use authorization in the United Kingdom on December 2, 2020, [3,4] and was subsequently approved in Japan in February 2021 [5]. The introduction of vaccines has radically changed the global infection situation. However, concerns about hesitancy to take vaccines have been noted in people with epilepsy (PWE). People with epilepsy occasionally exhibit worsening seizures due to major changes in social conditions, such as COVID-19 [6]. Thus, PWE need immediate management of seizures and mental health during social climate change. As COVID-19 vaccines have high efficacy against SARS-CoV-2 [7], it is crucial to determine

* Corresponding author at: Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minamiku, Hiroshima 734-8551, Japan.
E-mail address: s-neshige@hiroshima-u.ac.jp (S. Neshige).

https://doi.org/10.1016/j.yebeh.2022.109070
1525-5050/

whether vaccination is safe for PWE and to identify the risk of seizure exacerbation.

Recent studies have investigated the association between the COVID-19 vaccine and epileptic seizures [8–12]. They demonstrated that seizure exacerbations were observed after vaccination in 6.0% to 7.65% of PWE, suggesting that the risk of seizure exacerbations and adverse events did not outweigh the benefit of the infection-prevention effect of vaccination. However, little data are available concerning the medium- to long-term effects of vaccination on seizures. Given that PWE are a clinically diverse population, the effect of vaccination on seizures must be investigated based on multiple clinical epileptic parameters that have not been previously investigated [8–12]. Seizure exacerbation following vaccination other than the COVID-19 vaccine has also been demonstrated [13,14]. Thus, there is a clinical question regarding whether SARS-CoV2 messenger RNA (mRNA) vaccination has a specific effect on seizures. Additionally, fever due to adverse reactions to vaccines has frequently been reported after COVID-19 vaccination [4]. Thus, the association between adverse reactions and the worsening of seizures is important. Therefore, we conducted an observational multicenter study to determine the short- and mid-term effect of vaccination on seizures using comprehensive PWE data.

2. Methods

2.1. Study protocol and patient consent

We conducted a multicenter study with PWE who visited an epilepsy center in the Division of Neurology at four tertiary hospitals (Hiroshima University Hospital, Hiroshima City Asa Citizens Hospital, Hiroshima City Hiroshima Citizens Hospital, and Hiroshima City Funairi Citizens Hospital, which encompasses a medical area with a population of >1 million) to assess the incidence of seizure worsening following SARS-CoV2 mRNA vaccination and identified clinical factors that were associated with worsening and 6-month outcomes from the vaccination.

Intake of the SARS-CoV2 mRNA vaccine began in Japan in March 2021; most people with comorbidities, including epilepsy, received their first intake between April and September 2021. A second vaccine intake was available 1 month after the first intake. Thus, to confirm the 6-month outcome of seizure following the first and second vaccinations, we defined the observation period between April 2021 and March 2022. Additionally, we conducted a nationwide survey to identify the incidence of self-reported seizure exacerbations following vaccination. This study was approved by the Ethics Committee of Hiroshima University Hospital (No. E-2812 and E-2441-1). All patients provided informed consent to participate.

2.2. Inclusion and exclusion criterion

The inclusion criteria included consecutive PWE (1) whose medical history, including their seizure type and seizure frequency data, were available for all the observation periods and (2) whose vaccination history and 6-month outcomes from the vaccination were available. Epileptologists (SN, DA, and TS) confirmed the diagnosis of epilepsy in all the included patients based on the definition of epilepsy proposed by the International League Against Epilepsy classification in 2014 [15,16]. However, to conduct a comprehensive survey of patients with epilepsy or seizures, we also included patients with single seizures, that is, patients with suspected epilepsy. Including single seizures could theoretically reduce the time window for recurrence in patients who would ultimately develop epilepsy. Concomitantly, it is also important to note that patients with epilepsy and patients with single seizures may have similar or common concerns about vaccination. Therefore, we included patients with single seizures in this study.

We excluded patients with PWE aged <14 years. Additionally, we excluded PWE with dementia or intellectual disability. However, if seizure data were available from the caregivers, we did not exclude them.

2.3. Clinical factors related to epilepsy

We investigated the clinical data associated with epilepsy, that is, onset age, disease duration, seizure type, epilepsy classification, seizure frequency, medication, intellectual disability, comorbidity, and past histories. We also reviewed the findings of electroencephalography (EEG) and brain imaging (magnetic resonance imaging [MRI]) examined before the vaccination.

We examined the baseline seizure frequency for all PWE prior to vaccination. We used unprovoked habitual seizure data from the year before vaccination. If PWE had multiple seizure types, we evaluated each seizure frequency. The mean frequency of seizures was calculated for each PWE according to their habitual seizure frequency. For example, for PWE with a monthly seizure, we calculated the average seizure frequency several months prior.

2.4. COVID-2019 infection, vaccination, and adverse reactions

Three types of COVID-19 vaccines were approved in Japan during the study period: the BNT162b2 (Pfizer-BioNTech) [17] as an mRNA-based vaccine, mRNA-1273 (Moderna) [18] as an mRNA-based vaccine, and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) [19] as a viral vector-based vaccine.

We evaluated the vaccination rate, types of vaccines they vaccinated, and timing of vaccination in our cohort. We identified the incidence of adverse reactions based on the emergence of any adverse reaction, including mild (fever, headache, fatigue, and nausea) to severe (requiring medication or causing difficulties in daily activities) symptoms for all PWE vaccinated. However, local adverse reactions, such as injection site pain, were negligible in terms of the incidence of adverse reactions. We also investigated the incidence of fever (>37.0 °C) as an adverse reaction. The history of COVID-19 was also investigated during the study period.

2.5. Seizure worsening following vaccination and 6-month outcomes

To investigate whether receiving first, second or third doses of the vaccine resulted in changes to seizure frequency, severity, or type, data were gathered over two observational periods: "pre-vaccination," defined as the week prior to the date of vaccination, and "post-vaccination," defined as the week following vaccination. Changes in seizure rate were classified into three categories: neutral (increase by <50%), potential increase (increase by 50–100%), and increase (increase by >100%). We recorded seizures during routine visits by interviewing patients using "closed questions." However, we did not use special phone calls or a special diary. The period of 1 week was set as the observational period following the recent relevant studies, i.e., while the period ranged from 1 week to 90 days after vaccination, most of the seizure worsening was visible during the first 7 days after vaccination [8–12].

For PWE who had daily or weekly habitual seizures, we assessed changes in seizure rate using the number of seizure events that occurred during the two observational periods. However, for PWE who typically experienced seizures monthly or even less frequently, it was possible to have zero seizures in the "pre-vaccination period." For these cases, expected seizure frequency during a period of 1 week was used instead; this value was calculated based on the number of seizures that occurred during the

month (or year) prior to vaccination. For example, in PWE whose last seizure occurred 6 months prior to vaccination, the frequency of seizures during the pre-vaccination period was calculated to be 0.042 seizures per week.

We defined "definite seizure worsening" following vaccination as any of the following conditions: (1) more than 100% increase in habitual seizure frequency; (2) increased seizure severity resulting in atypical outcomes (e.g., seizure clustering, status epilepticus, or hospitalization); (3) emergence of unhabitual seizure, or (4) 50–100% increase in habitual seizure frequency when compared to pre- and post-vaccination periods accompanied by (2) or (3). However, for PWE who experienced seizures monthly or less frequently at baseline, an observation period of 1 week after vaccination (post-vaccination period) may not be representative. Thus, in addition to assessments 1 week before and after the vaccination, we calculated seizure increase by comparing seizures 1 month before and after vaccination to improve reliability.

Additionally, in some PWE, the seizure change after vaccination did not reach the threshold of our operational definition. Determining whether the number of seizures increased significantly was difficult in some cases. For example, a drug-resistant PWE who had daily to weekly seizures exhibited habitual seizures on the day of vaccination, and another PWE whose latest seizure emerged several years before vaccination exhibited seizure recurrence on the day after vaccination. Thus, we also defined "potential seizure worsening" as when a PWE exhibited an unexpected seizure on the day of vaccination or within 1 month of receiving the vaccination.

We did not include seizure worsening due to antiseizure medication (ASM) withdrawal and unhabitual seizures that were consistent with functional neurological disorders [20,21]. However, if PWE had a psychogenic nonepileptic seizure (PNES) as a habitual seizure and exhibited worsening of PNES in frequency or strength, we defined it as seizure worsening. Besides, we did not include patients with PNES alone. In PWE with worsening seizures, we examined seizure outcomes for more than 6 months after vaccination.

2.6. Nationwide survey for self-reported seizure worsening

We used "closed questions" in our multicenter study to collect any negative events related to seizures after vaccination, no matter how minimal. This was a sensitivity-oriented method of investigating the incidence of seizure worsening; this survey methodology may lead to an overvaluation of worsening. Conversely, PWE usually did not report all of their seizure-related incidences in an outpatient setting [22]. Thus, to investigate real-world data and to determine the number of PWE spontaneously reporting seizure worsening after vaccination without using the "closed questions," we conducted a national survey to investigate self-reported seizure worsening. The survey included 261 clinicians (mostly general clinical practitioners not specialized in epilepsy) from 99 institutes nationwide besides our multicenter evaluation with four tertiary hospitals (Supplementary data 1). We contacted clinicians via e-mail registered at nationwide online EEG lectures and open conferences for epilepsy held at our department [23]. We assessed the total number of PWE clinicians treated and investigated whether PWE spontaneously reported seizure deterioration related to vaccination. Clinicians were asked to report on anything related to seizures that might be associated with the vaccination reported by PWE. We then confirmed the incidence of self-reported seizure worsening. The causal association between vaccination and seizure worsening was dependent on the determinant of the physician in charge.

2.7. Data analysis

We performed a univariate analysis to identify the features of PWE who exhibited "definite seizure worsening" after vaccination. The statistical significance of intergroup differences was determined using Fisher's exact test for categorical variables. We used an unpaired Student's *t*-test for continuous variables. Significant clinical factors ($p < 0.05$) in the univariate analysis were selected for subsequent logistic regression analysis (force entry), and we estimated the likelihood ratio test to calculate the odds ratios (ORs). All statistical analyses were performed using the JMP software (JMP Pro version 16; SAS Institute, Cary, NC, USA).

3. Results

We evaluated 332 consecutive PWE who met the inclusion criteria; 168 were male (51.2%), and the mean age was 36.4 ± 17.2 years (Table 1). The majority of epilepsy classifications were focal,

Table 1
Clinical characteristics of people with epilepsy.

	People with epilepsy (n = 332)		
Age, years (mean ± SD)	36.4	±	17.2
Onset age, years (mean ± SD)	23.9	±	18.5
Disease duration (mean ± SD)	12.2	±	12.3
Sex, male (n, %)	168	,	51.2
Epilepsy classification (n, %)			
– Generalized epilepsy	81	,	24.4
– Focal epilepsy	200	,	60.2
– Temporal lobe epilepsy	82	,	24.7
– Frontal lobe epilepsy	51	,	15.4
– Unclassified	51	,	15.4
Seizure type (n, %)			
– FAS	68	,	20.5
– FIAS	142	,	42.8
– Myoclonic seizure	41	,	12.3
– FBTCS	125	,	37.7
– BTCS	95	,	28.6
– PNES	20	,	6.0
Seizure frequency (n, %)			
– Weekly or more	60	,	18.1
– Monthly	96	,	28.9
– Yearly or less	158	,	47.6
Drug-resistant epilepsy (n, %)*	101	,	30.4
Number of ASMs (mean ± SD)	1.8	±	1.2
Comorbidity (n, %)			
– ADHD/ASD	13	,	3.9
– intellectual disability	66	,	20.6
Etiology (n, %)			
– Autoimmune	13	,	3.9
– Structural	115	,	34.6
– Genetic	8	,	2.4
– Metabolic/infectious	2	,	0.6
– Unknown	195	,	58.7
Febrile seizure, yes (n, %)	40	,	12.1
MRI (n, %)			
– Normal	155	,	46.7
– Abnormal	127	,	38.3
– Hippocampal sclerosis, yes	24	,	7.2
– Unknown or not performed	50	,	15.1
Infection of COVID-19 (n, %)	5	,	1.5
SARS-CoV2 mRNA vaccination (n, %)			
– First dose	282	,	84.9
– Second dose	280	,	84.3
– Third dose	39	,	11.7
– Unvaccinated	50	,	15.1

FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; BTCS, bilateral tonic-clonic seizure; PNES, psychogenic nonepileptic seizure; ASM, antiseizure medication; ADHD/ASD, attention deficit hyperactive disorder/autism spectrum disorder; MRI, magnetic resonance imaging; PWE, people with epilepsy.
*Drug-resistant epilepsy is defined as PWE taking 2 or more ASMs with seizures monthly or more.

among which the highest was temporal lobe epilepsy (24.7%). The baseline habitual seizure frequency was variable. The mean number of current ASM use was 1.8 ± 1.2.

Among the included PWE in this study, 282 (84.9%) were vaccinated: 282 (84.9%), 280 (84.3%), and 39 (11.7%) received the first, second, and third doses of the vaccine, respectively. Most PWE (78.7%) were vaccinated with BNT162b2 (Pfizer-BioNTech), whereas none were vaccinated with ChAdOx1 nCoV-19 (Oxford-AstraZeneca). Adverse reactions were observed in 146 (51.8%) PWE, with fever in 123 PWE (43.6%) (Table 2). None of the PWE required hospitalization or specific treatment for adverse reactions. Conversely, 50 (15.1%) PWE were unvaccinated. The main reasons for refusing vaccination varied: low perceived benefit of vaccination, health concerns about an adverse reaction, information deficits about COVID-19, failure in scheduling, or low perceived risk of COVID-19 infection; but, none of PWE was concerned about seizure worsening after vaccination. Among the included PWE in this study, 5 (1.5%) PWE were infected with COVID-19 during the study period.

3.1. Incidence of seizure worsening

"Definite seizure worsening" was observed in sixteen (5.7%) PWE (Table 2). The presentation of worsening was variable: increased habitual seizure frequency (n = 12, 4.3%) (increase by >100% = 10; increase by 50–100% = 2), unhabitual seizure emergence (n = 3, 1.1%), and increased seizure severity (n = 6, 2.1%). Four (1.4%) PWE experienced seizures on the day of vaccination. Three (1.1%) PWE had a seizure for the first time in several years. Some PWE required hospitalization or exhibited status epilepticus or seizure clustering. However, most of these events were non-sustainable, and the seizure condition returned to the baseline level within 48 h of vaccination. Thus, all PWE returned to their baseline condition 6 months after the vaccination (only one patient who exhibited an unhabitual seizure took 1–2 months for seizures to return to normal levels using only ASMs). In addition, no PWE experienced worsening of PNES, and no one with a single seizure exhibited seizure worsening after vaccination. Conversely, there were nine (3.2%) PWE with "potential seizure worsening." Most of them exhibited seizures on the day of vaccination, but seizure frequency change was not evident.

Table 2
Outcomes of PWE following the SARS-CoV2 mRNA vaccination.

	PWE who were vaccinated (n = 282)
Type of vaccine for first and second dose (manufacturer) (n, %)	
– BNT162b2 (Pfizer-BioNTech)	222 , 78.7
– mRNA-1273 (Moderna)	40 , 14.2
Adverse reaction, yes (n, %)*	146 , 51.8
– Yes, after the first dose	63 , 22.3
– Yes, after the second dose	137 , 48.6
– Fever (>37.0 °C), yes	123 , 43.6
Seizure worsening (n, %)	25 , 8.9
– Definite seizure worsening	16 , 5.7
– Increased habitual seizure frequency	12 , 4.3
– increase by > 100%	10 , 3.5
– increase by 50–100%	2 , 0.7
– Increased seizure severity	6 , 2.1
– Unhabitual seizure emergence	3 , 1.1
– Seizures on the day of vaccination	4 , 1.4
– Seizure relapse in several years	3 , 1.1
– Hospitalized for seizure	5 , 1.8
– Status epilepticus	4 , 1.4
– Potential seizure worsening	9 , 3.2
Outcome of definite seizure worsening (n, %)	
– Prolongation of seizure worsening over 1 month	2 , 0.7
– Prolongation of seizure worsening over 6 months	0 , 0.0

*Adverse reactions are defined as symptoms occurring within 7 days of vaccination, including mild (fever, headache, fatigue, nausea, joint pain, muscle pain, or allergy) to severe (requiring medication or causing difficulties in daily activities) symptoms, not including local adverse reactions, such as injection site pain.

3.2. Factors associated with seizure worsening

People with epilepsy with definite seizure worsening were more significantly associated with focal impaired awareness seizure (FIAS) ($p < 0.001$), high seizure frequency ($p = 0.025$), and drug-resistant epilepsy ($p = 0.007$) at baseline compared to PWE without seizure worsening (Table 3). However, the incidence of adverse reactions including fever ($p = 0.37$), presence of fever (0.12), and history of febrile seizure ($p = 0.92$) was not significantly associated with seizure worsening.

Multivariate logistic regression analysis revealed that FIAS was the only factor independently associated with seizure worsening (OR, 7.0; 95% confidence interval, 1.50–32.77) (Table 4). After removing data for PWE with PNES (n = 20), the significance of FIAS (OR, 6.4; 95% confidence interval, 1.35–30.05) was reproduced in the univariate and multivariate sub-analyses (Supplementary Tables 1 and 2).

3.3. A nationwide survey for self-reported seizure worsening

A nationwide survey, to which 261 clinicians contributed, confirmed seizure status before and after the vaccination (Table 5). The incidence of self-reported seizure worsening was extremely low (22/5156, 0.43%). The following are examples of seizure exacerbation cases: there were several cases of seizure recurrence from the day of vaccination to within a few days, a man with post-

Table 3
Differences in clinical characteristics between PWE with or without seizure worsening following the vaccination.

	Seizure worsening (n = 16)	Without seizure worsening (n = 266)	P-value
Age, years (mean ± SD)	39.3 (17.1)	37.6 (17.7)	0.71
Onset age, years (mean ± SD)	22.1 (17.8)	25.2 (19.2)	0.53
Disease duration (mean ± SD)	17.3 (14.2)	12.0 (12.7)	0.11
Sex, male (n, %)	8 (50.0)	136 (51.7)	0.89
Epilepsy classification (n, %)			
– Generalized epilepsy	3 (18.8)	59 (22.2)	0.74
– Focal epilepsy	13 (81.3)	166(62.4)	0.11
– Temporal lobe epilepsy	6 (37.5)	69 (25.9)	0.33
– Frontal lobe epilepsy	1 (6.3)	46 (17.3)	0.20
Seizure type (n, %)			
– FAS	6 (37.5)	52 (19.6)	0.11
– FIAS	14 (87.5)	114 (42.9)	**<0.001**
– Myoclonic seizure	1 (6.3)	30 (11.3)	0.50
– FBTCS	8 (50.0)	99 (37.2)	0.31
– PNES	0 (0.0)	15 (5.6)	0.18
Seizure frequency, monthly or more (n, %)	12 (75.0)	124 (46.6)	**0.025**
Drug-resistant epilepsy (n, %)	10 (62.5)	76 (28.6)	**0.007**
EEG, spike (n, %)	7 (43.8)	124 (51.0)	0.57
MRI, hippocampal sclerosis (n, %)	2 (12.5)	21 (7.9)	0.54
Febrile seizure, yes (n, %)	2 (12.5)	31(11.7)	0.92
Type of vaccine for first and second doses, BNT162b2 (n, %)	14 (87.5)	208 (78.2)	0.35
Adverse reaction, yes (n, %)	10 (62.5)	136 (51.1)	0.37
– Fever, yes (n, %)	10 (62.5)	113 (42.5)	0.12

FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; PNES, psychogenic nonepileptic seizure; EEG, electroencephalography; MRI, magnetic resonance imaging; PWE, people with epilepsy; SD, standard deviation.

Table 4
Multivariate analysis of factors associated with seizure worsening.

	OR	95% CI	P-value
FIAS	7.0	1.50–32.77	**0.014**
Drug-resistant epilepsy	2.5	0.84–7.43	0.10

Multivariate analyses were performed using FIAS and drug-resistant epilepsy.

Table 5
Self-reported seizure outcome after the SARS-CoV2 mRNA vaccination in the nationwide questionnaire.

	Clinicians answered (n = 261)
Total number of PWE followed by clinicians	5156
Average monthly number of PWE followed by clinicians	7.0
Total number of PWE with seizure worsening	22/5156 (0.43%)

encephalitis epilepsy had a seizure recurrence the day after vaccination and required tracheal intubation due to convulsive status epilepticus, and a patient with a history of stroke experienced nonconvulsive status epilepticus 3 days after vaccination.

4. Discussion

Our multicenter epidemiological study, based on closed-question data from four tertiary hospitals, demonstrated that the incidence rate of seizure worsening after COVID-19 vaccination was 5.7%. Seizure worsening was observed in various ways, including changes in seizure severity, strength, and seizure type. Additionally, we confirmed that drug-resistant PWE with FIAS were at risk of worsening. However, seizure exacerbations were non-sustainable. Therefore, although some specific PWE should be notified of the risk of post-vaccination seizure exacerbation during future vaccination, the serious harm caused by post-vaccination seizure worsening to the patient's daily life might be minimal. In line with this, our nationwide survey demonstrated an extremely low incidence of self-reported seizure worsening, suggesting that unreported seizure worsening, which had little or no real-life effect, might exist.

4.1. Comparison with previous studies and strength of our data

Except for racial differences, the cohorts in the present and previous studies that investigated seizure worsening after vaccination were comparable; conversely, the vaccine intake rates and types of vaccines used differed among studies [8–12]. However, the incidence rate of seizure worsening following SARS-CoV2 mRNA vaccination in previous studies varied from 6 to 7.65% [8–12], which is comparable to or slightly higher than our findings. Seizures also reportedly worsened after vaccination with vaccines other than SARS-CoV2 mRNA [13,14]. These lines of evidence indicate that a slight, but still minor, worsening of seizures may occur during large-scale vaccination. Compared to previous studies, the present study more comprehensively investigated patient information, including MRI and EEG findings. In addition, we recorded data on seizure exacerbations more precisely and explored outcomes up to 6 months or more from vaccination. These real-world data are a strength of the present study.

4.2. Fever sensitivity

The mechanism underlying seizure exacerbation after vaccination is of great interest. Various adverse reactions to SARS-CoV2 mRNA vaccination have been described [24–26]. However, in our data, adverse reactions, including fever, were not directly associated with seizure worsening. In addition, a history of febrile seizures was not significantly associated with seizure worsening. Thus, temperature increase following immunization was not a major causative factor. Recent studies have reported that fever had no significant association with seizure exacerbation; one-third of the 19 PWE with increased seizure frequency had self-interrupted or reduced ASM, but the cause of exacerbation in the remaining two-thirds was unknown; some individuals exhibited seizure-like events without fever or other triggering factors [9]. In addition, two patients showed an increase in seizure frequency and a new seizure type after vaccination, without an association with fever [8]. There was also no evidence that vaccinations induced seizures and led to severe outcomes in PWE with fever sensitivity, for example, PWE with Dravet syndrome [27].

4.3. Potential mechanisms and clinical application

The PWE vaccinated in this study received either BNT162b2 or mRNA-1273. Both vaccines contain nucleoside-modified mRNA formulated in lipid nanoparticles. Once inside the host cells, the mRNA is translated into the SARS-CoV-2 spike protein, which is expressed on the surface of the host cells. The transient expression of this spike antigen induces neutralizing antibodies and cellular immune responses against it, which may confer protection against COVID-19 [3,28]. In this process, a vaccine can trigger an adaptive immune response to display its protective effect, which may stimulate a hyperinflammatory condition [29,30]. Thus, we hypothesized that such inflammation might have transiently contributed to the lowering of the seizure threshold.

The limbic system is probably more susceptible to hyperinflammatory conditions than other brain regions because the limbic system is frequently the primary lesion in the etiology of inflammatory encephalitis [31]. Thus, if inflammation produced by vaccination is possible, it may have a substantial effect on the limbic system compared to other brain regions. This hypothesis agrees with our results that PWE whose seizure type was FIAS were at risk of seizure worsening. Conversely, idiopathic generalized epilepsy, which is a group of seizures that are easily induced by lack of sleep or lazy medication, had little association with worsening. Additionally, differences in comorbidities and background factors were not associated with seizures worsening in this study.

COVID-19 vaccine-related skepticism has been reported in PWE [32]. As we demonstrated that PWE with drug resistance and FIAS are more likely to exhibit seizure exacerbation during vaccination, some specific PWE should acknowledge the risk. Although determining a causal association between seizure exacerbation and vaccination was beyond the scope of the current investigation, the unhabitual events occurred within a few days of vaccination; there were certain cases with unusual events that were highly likely to be associated. While supposedly the vaccine lowered the seizure threshold, all seizure worsening events were transient and did not affect 6-month outcomes, suggesting that it did not have a role in causing an irreversible epileptogenic change. Therefore, seizure worsening was considered a transient response and may be classified as an adverse reaction to vaccination. In addition, our results do not provide a basis for refraining from future vaccination for PWE. SARS-CoV2 mRNA vaccination was reported to be well-tolerated in PWE[33]. Thus, notifying PWE of the likelihood of seizure worsening following vaccination may allow PWE to avoid unanticipated events.

4.4. Limitations

The epidemiological difference that the spread of COVID-19 infection is smaller in Japan than in other countries should be

acknowledged when applying the data of this study to other countries [34]. Conversely, the vaccination coverage rate in Japan was 77% on December 3, 2021, and a similar vaccination rate was obtained in our dataset. Vaccination coverage rates in other countries ranged from 59 to 73% [35]. Our cohort was based on data from tertiary hospitals with epilepsy centers. Thus, the proportion of drug-resistant PWE might differ from that in general clinical practice. In this regard, our nationwide survey data might be true for PWE in general clinical practice.

Several nervous system adverse effects of COVID-19 vaccination involve some neurocritical conditions, such as neuropathy, vaccine-induced immune thrombotic thrombocytopenia, and encephalitis [36,37]. However, adenovirus vector vaccination against COVID-19 has not yet been used in our population. Therefore, these serious neurological conditions were not observed in the present study.

Since we included patients with single seizures in this study, the seizure worsening rate could have been different compared to the results when we included only PWE. Additionally, in the nationwide survey for self-reported seizure worsening, the number of PWE with seizure worsening relied on patients' spontaneous reports. These limitations may skew the data regarding true seizure worsening and interpreting the related factors.

5. Conclusion

Our multicenter study confirmed the emergence of a number of seizure exacerbations after SARS-CoV2 mRNA vaccination. The risk of worsening was prominent within a few days after vaccination, which should be acknowledged, especially for drug-resistant PWE with FIAS. However, seizure worsening was a monophasic course, such as a feature of adverse reaction to vaccination, and there were no cases with poor outcomes after 6 months of follow-up. Thus, we find no reason to discourage vaccination in PWE, also in the future, when social conditions change and new vaccination is required.

Funding Sources

This report was partly funded by JSPS KAKENHI, Grant Number 20K16601 (Grant-in-Aid for Early-Career Scientists).

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that the present report is consistent with those guidelines.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval statement

This study was approved by the Ethics Committee of Hiroshima University Hospital (No. E-2812 and E-2441-1).

Patient consent statement

All patients provided informed consent to participate.

Clinical trial registration

Not available.

CRediT authorship contribution statement

Megumi Nonaka: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Shuichiro Neshige:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Hidetada Yamada:** Writing – review & editing. **Haruka Ishibashi:** Writing – review & editing. **Yoshiko Takebayashi:** Writing – review & editing. **Masahiro Nakamori:** Writing – review & editing. **Shiro Aoki:** Writing – review & editing. **Yu Yamazaki:** Writing – review & editing. **Takeo Shishido:** Data curation, Writing – review & editing. **Dai Agari:** Data curation, Writing – review & editing. **Kazuhide Ochi:** Writing – review & editing. **Koji Iida:** Writing – review & editing. **Hirofumi Maruyama:** Writing – review & editing.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We appreciate our patients for their participation in this study. We also thank all the physicians who contributed to our nationwide survey (Supplementary data 1).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.109070.

References

[1] Wang D, Mao Z. A comparative study of public health and social measures of COVID-19 advocated in different countries. Health Policy 2021;125:957–71.
[2] Amengual O, Atsumi T. COVID-19 pandemic in Japan. Rheumatol Int 2021;41:1–5.
[3] Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First Approval. Drugs 2021;81:495–501.
[4] Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci 2021;25:1663–9.
[5] Iguchi T, Umeda H, Kojima M, Kanno Y, Tanaka Y, Kinoshita N, et al. Cumulative Adverse Event Reporting of Anaphylaxis After mRNA COVID-19 Vaccine (Pfizer-BioNTech) Injections in Japan: The First-Month Report. Drug Saf 2021;44:1209–14.
[6] Miller WR, Von Gaudecker J, Tanner A, Buelow JM. Epilepsy self-management during a pandemic: Experiences of people with epilepsy. Epilepsy Behav 2020;111:107238.
[7] Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect 2022;28:202–21.
[8] von Wrede R, Pukropski J, Moskau-Hartmann S, Surges R, Baumgartner T. COVID-19 vaccination in patients with epilepsy: First experiences in a German tertiary epilepsy center. Epilepsy Behav 2021;122:108160.
[9] Lu L, Zhang Q, Xiao J, Zhang Y, Peng W, Han X, et al. COVID-19 vaccine take-up rate and safety in adults with epilepsy: Data from a multicenter study in China. Epilepsia 2022;63:244–51. https://doi.org/10.1111/epi.17138.

[10] Massoud F, Ahmad SF, Hassan AM, Alexander KJ, Al-Hashel J, Arabi M. Safety and tolerability of the novel 2019 coronavirus disease (COVID-19) vaccines among people with epilepsy (PwE): A cross-sectional study. Seizure 2021;92:2–9.
[11] Romozzi M, Rollo E, Quintieri P, Dono F, Evangelista G, Consoli S, et al. Impact of COVID-19 vaccine on epilepsy in adult subjects: an Italian multicentric experience. Neurol Sci 2022. https://doi.org/10.1007/s10072-022-06100-0.
[12] Martinez-Fernandez I, Sanchez-Larsen A, Gonzalez-Villar E, Martínez-Martín Á, von Quednow E, Del Valle-Pérez JA, et al. Observational retrospective analysis of vaccination against SARS-CoV-2 and seizures: VACCI-COVID registry. Epilepsy Behav 2022;134:108808.
[13] Top KA, Righolt CH, Hawken S, Donelle J, Pabla G, Brna P, et al. Adverse Events Following Immunization Among Children With Epilepsy: A Self-Controlled Case Series. Pediatr Infect Dis J 2020;39:454–9.
[14] Top KA, Brna P, Ye L, Smith B. Risk of seizures after immunization in children with epilepsy: a risk interval analysis. BMC Pediatr 2018;18:134. https://doi.org/10.1186/s12887-018-1112-0.
[15] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[16] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–30.
[17] Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med 2021;385:1761–73. https://doi.org/10.1056/NEJMoa2034577.
[18] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403–16. https://doi.org/10.1056/NEJMoa2035389.
[19] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med 2021;384:1885–98. https://doi.org/10.1056/NEJMoa2102214.
[20] Kim DD, Kung CS, Perez DL. Helping the Public Understand Adverse Events Associated With COVID-19 Vaccinations: Lessons Learned From Functional Neurological Disorder. J Am Med AssocNeurol 2021;78:789–90.
[21] Hull M, Parnes M. Tics and TikTok: Functional Tics Spread Through Social Media. Mov Disord Clin Pract 2021;8:1248–52.
[22] Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol 2007;64:1595–9.
[23] Neshige S, Ono N, Iryo T, Watanabe T, Yamada H, Mine N, et al. Nationwide online EEG education during coronavirus disease 2019 pandemic. Clin Neurophysiol 2021;132:2763–5.
[24] Team CC-R, Administration FaD. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep 2021;70:46–51. https://doi.org/10.15585/mmwr.mm7002e1.
[25] Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607.
[26] Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. J Am Med AssocNetw Open 2021;4:e2140364.
[27] Clayton LM, Balestrini S, Cross JH, Wilson G, Eldred C, Evans H, et al. The impact of SARS-CoV-2 vaccination in Dravet syndrome: A UK survey. Epilepsy Behav 2021;124:108258.
[28] Mascellino MT, Di Timoteo F, De Angelis M, Oliva A. Overview of the Main Anti-SARS-CoV-2 Vaccines: Mechanism of Action. Efficacy Safety Infect Drug Resist 2021;14:3459–76.
[29] Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology 2022;165:386–401. https://doi.org/10.1111/imm.13443.
[30] Garrido I, Lopes S, Simões MS, Liberal R, Lopes J, Carneiro F, et al. Autoimmune hepatitis after COVID-19 vaccine - more than a coincidence. J Autoimmun 2021;125:102741.
[31] Leypoldt F, Wandinger KP, Bien CG, Dalmau J. Autoimmune Encephalitis. Eur Neurol Rev 2013;8:31–7. https://doi.org/10.17925/ENR.2013.08.01.31.
[32] Qiao S, Zhang RR, Yang TT, Wang ZH, Fang XQ, Fang CY, et al. Attitudes to Being Vaccinated Against COVID-19: A Survey of People With Epilepsy in China. Front Neurol 2021;12:. https://doi.org/10.3389/fneur.2021.743110743110.
[33] Lin K, Huang H, Fang S, Zheng G, Fu K, Liu N, et al. Should patients with epilepsy be vaccinated against coronavirus disease 2019? A systematic review and meta-analysis. Epilepsy Behav 2022;134:108822.
[34] Bulut C, Kato Y. Epidemiology of COVID-19: What changed in one year? Turk J Med Sci 2021;51:3253–61.
[35] Papagiannis D, Malli F, Gourgoulianis KI. Registry Systems for COVID-19 Vaccines and Rate of Acceptability for Vaccination Before and After Availability of Vaccines in 12 Countries: A Narrative Review. Infect Dis Rep 2022;14:121–33.
[36] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021;384:2124–30.
[37] Maramattom BV, Krishnan P, Paul R, Padmanabhan S, Cherukudal Vishnu Nampoothiri S, Syed AA, et al. Guillain-Barré Syndrome following ChAdOx1-S/nCoV-19 Vaccine. Ann Neurol 2021;90:312–4.