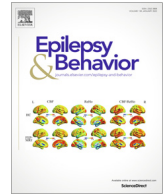




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Brief Communication

COVID-19 vaccination-related exacerbation of seizures in persons with epilepsy ☆

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ABSTRACT

Although vaccines are generally safe in persons with epilepsy (PWE), seizures can be associated with vaccination, including COVID-19. This study assessed the occurrence of COVID-19 vaccination-related seizure exacerbations in PWE.

Adult PWE who had received a COVID-19 vaccine were consecutively recruited at a tertiary epilepsy clinic between June 2021 and April 2022. Patient demographics, including epilepsy history, vaccination details, and reported adverse effects were recorded. Seizure exacerbation, defined as occurring within one week of vaccination, was assessed.

Five hundred and thirty PWE received the COVID-19 vaccine. 75 % received the Comirnaty (Pfizer) vaccine as their initial dose. Most patients (72 %) were taking ≥ 2 antiseizure medications (ASM) and had focal epilepsy (73 %). One-third were 12 months seizure free at their first vaccination. 13 patients (2.5 %) reported a seizure exacerbation following their first vaccination, three of whom required admission. None were seizure-free at baseline. Six of these patients (46 %) had a further exacerbation of seizures with their second vaccine. An additional four patients reported increased seizures only with the second vaccine dose.

Seizure exacerbations are infrequently associated with COVID-19 vaccination, mainly in patients with ongoing seizures. The likelihood of COVID-19 infection complications in PWE outweighs the risk of vaccination-related seizure exacerbations.

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1. Introduction

Twelve months after the national coronavirus-19 (COVID-19) vaccination rollout in Australia, over 94 % of the population over 16 years old were fully vaccinated [1]. Some people have reservations about the vaccination, including persons with epilepsy (PWE) despite the established safety of similar vaccinations in PWE [2]. Multiple factors may have fuelled vaccination hesitancy, including safety concerns, lack of trust in the information provided by government and pharmaceutical companies as well as conflicting opinions on social media platforms [3–4]. For PWE, one of the most common concerns contributing to vaccination hesitancy has been the potential for seizure exacerbation [5–7].

Several small reports have assessed the safety of the COVID-19 vaccine in PWE over the past 12 months. Two initial studies from Germany and Kuwait surveyed 52 and 82 patients respectively after their first COVID-19 vaccine [5,6]. Neither study demonstrated significant vaccine-related seizure exacerbations [5,6]. The few patients who had a vaccine-related seizure exacerbation were predominantly female, older, and on multiple antiseizure medications (ASM). However, given the small sample, the significance of these factors could not be assessed [5,6]. A recent study from China assessed COVID-19 vaccine take-up and vaccine side effects, including seizure exacerbation, in PWE compared to healthy controls and patients with neuropsychiatric comorbidities [7]. Only 204 of 491 PWE were vaccinated. While the incidence of adverse effects comparing PWE and controls was no different, 19 patients (9.3 %) reported an exacerbation of seizures, but limited details were provided [7].

Given ongoing uncertainty and the importance of providing COVID-19 vaccination to PWE, we aimed to assess the likelihood of COVID-19 vaccination-related seizure exacerbations in PWE and identify possible predictors.

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2. Materials and methods

PWE aged ≥ 18 years who had received at least one COVID-19 vaccine were consecutively recruited from a tertiary hospital epilepsy clinic in Perth, Western Australia, between June 2021 and April 2022. All enrolled patients had confirmed epilepsy based on clinical assessment and investigations, including neuroimaging (CT and/or MRI brain), routine EEG, and in many cases prolonged video-EEG monitoring prior to their first vaccine dose. Patients who did not have epilepsy were excluded. However, patients who had known epilepsy but concurrent psychogenic nonepileptic spells (PNES) clearly distinguishable from their epileptic seizures were included. Patient demographics, including age, gender, epilepsy characteristics, baseline seizure frequency, and current anti-seizure medications (ASMs) were recorded.

A paper-based survey assessing COVID-19 vaccination status and associated complications, including vaccine-related seizure exacerbations, was conducted during the in-person routine clinic appointments and was completed by the patient and/or their support person (in cases where the patient was unable to complete the survey; i.e. intellectual disability) and the treating clinician. For patients requiring telephone-based appointments, often due to COVID restrictions or remote or rural settings, the treating clinician conducted the survey via telephone and completed the paper-based form. Additional information about any seizure-related admissions was obtained through the computerized state-wide public hospital medical records system. The majority of patients documented their vaccine doses on the initial survey during a single clinic attendance. For patients who had multiple clinic reviews during the data-collection period and obtain sequential vaccine doses after their first survey, a second survey was completed to capture relevant information regarding their subsequent doses.

Seizure exacerbations were documented based on the patient's self-reported seizures (i.e. survey results and clinic reviews) or hospital presentations with seizures, seizure-related injuries, or status epilepticus. They were defined as an increase in seizures within one week of vaccination compared to the patient's baseline seizure frequency by utilizing seizure diaries and as determined by the treating clinician. Occurrence of other seizure-like events, including syncope and PNES, which were clarified by clinical assessment and where necessary EEG, was not considered a seizure exacerbation. Patients were also excluded if other external factors unrelated to vaccination were likely responsible for the seizure exacerbation (e.g. ASM non-compliance), based on clinical assessment by the treating epileptologist, at the time the survey was conducted. If a patient had a vaccine-associated seizure exacerbation, the timing and nature of increased seizures, treatment requirements, and need for hospital presentation or admission were recorded. The demographics and clinical features of PWE who developed COVID-19 vaccine-related seizure exacerbations were compared to those without seizure exacerbations.

Comparisons between groups were conducted using *t*-tests for normally distributed data and Mann-Whitney tests for non-normal data. Chi-square and Fisher exact tests were used for categorical data.

This study was approved by the Fiona Stanley Hospital Human Research Ethics Committee. Consent was obtained from all patients.

3. Results

3.1. Patient demographics and clinical features

530 PWE who had received the COVID-19 vaccine were identified over the 10-month recruitment period. Most patients (73 %) had focal epilepsy and 145 patients (27 %) had symptomatic generalized epilepsy (SGE). 177 patients (33 %) had been seizure free for 12 months at the time of their first vaccination. 222 of 353 patients (63 %) with ongoing seizures at baseline had multiple seizures a month. The median number of ASM was 2, with 72 % of patients taking 2 or more ASM (Table 1).

516 (97 %) received two COVID-19 vaccine doses. 14 patients only received a single dose for various reasons, including the wait required for the second dose at the time of the survey and patient choice. 400 patients (75 %) of patients received the Pfizer Comirnaty vaccine as their initial dose, reflecting vaccine availability in Western Australia. The median age at the first vaccine was 38 years (range 16 – 84 years, interquartile range 25).

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3.2. Seizure exacerbation after first COVID-19 vaccine dose

13 patients (2.5 %) reported a clear exacerbation of seizures following their first vaccination (Table 2). None were seizure free at the time of their initial vaccination, compared to 34 % of the control cohort ($p = 0.006$). Their demographics were otherwise similar to those without seizure exacerbation, including vaccination brand and number of ASM (Table 1).

Ten of the 13 patients (77 %) with a seizure exacerbation reported increasing seizures within 24 hours of their first vaccine dose, and the remainder within 72 hours. Six patients had a cluster of multiple seizures, with five patients reporting several consecutive days of increased recurrent seizures. One patient developed convulsive status epilepticus, which was terminated with out-of-hospital midazolam prior to arrival in the emergency department (ED). No patient required intensive care admission.

Five patients (38 %) presented to hospital because of a seizure exacerbation post-vaccination: two were discharged from ED after a short period of observation and three patients required hospital admission for 1 to 3 days. One patient sustained a seizure-related injury (foot fracture) which was conservatively managed.

Table 1

Demographics of patients with and without seizure exacerbation after first COVID vaccination.

	No seizure exacerbation N = 517	Seizure exacerbation N = 13	p-value
Sex: female n (%)	267 (52)	9 (69)	0.27
Median age at time of first dose, yrs (range)	38 (16–84)	37 (17–62)	0.54
Epilepsy type n (%)			
– focal	377 (73)	9 (69)	
– generalized	135 (26)	4 (31)	
– undifferentiated	5 (1)	–	0.88
Symptomatic generalized epilepsy n (%)	141 (27)	4 (31)	0.94
12 months seizure free at time of first dose	177 (33)	0	0.006
Seizure frequency at time of first dose			
– ≥ 1 seizure/day	52 (10)	4 (31)	
– ≥ 1 seizure/mo	161 (31)	5 (38)	
– ≥ 1 seizure/year	131 (25)	4 (31)	0.35
Median no. of ASM at time of first dose	2	3	0.16
2 or more ASM at time of first dose n (%)	372 (72)	11 (85)	0.53
3 or more ASM at time of first dose n (%)	225 (44)	8 (61)	0.26
Brand of first dose			
– Pfizer Comirnaty	391 (75)	10 (77)	
– Astra Zeneca	108 (21)	2 (15)	
– Moderna	17 (3)	1 (8)	
– Novavax	1 (<1)	–	0.93

Table 2
Vaccine-associated seizure exacerbation after 1st and 2nd vaccine doses.

	Seizure exacerbation after 1st vaccination	Seizure exacerbation after 2nd vaccination
Number of patients	13 patients	10 patients
Median time from vaccine to seizure (range)	1 day (0–3)	1 day (0–7)
Seizure on day of vaccine n (%)	4 (31)	5 (50)
Other vaccine side effects n (%)	5 (38)	4 (40)
Seizure cluster n (%)	6 (46)	4 (40)
Status epilepticus n (%)	1 (8)	0
Exacerbation with 2nd vaccination n (%)	6 (46)	–

ASM were escalated in only two patients, with increases in their regular ASM dosing and the commencement of a short course of additional clobazam.

Five of the 13 (38 %) had concurrent vaccination-related side effects including fatigue, fever, and headache. This was similar to the systemic side effect rate of the whole cohort (30.6 %). One patient with type 1 diabetes mellitus reported vomiting and diarrhea leading to metabolic disturbance and hypoglycemia, potentially contributing to their seizure exacerbation.

3.3. Seizure exacerbation after second COVID-19 vaccine dose

All 13 patients with seizure exacerbation after the first vaccination received a second vaccination (Table 2). Six of the 13 patients (46 %) reported an increase in seizures after their second vaccination, including one patient who had received pre-emptive clobazam. The median time from the second vaccine to seizure exacerbation was 1 day (range 1–7 days), with 4 of 6 patients having a seizure increase within 24 hours of their second vaccine dose. Only one patient reported an increase in seizures occurring over multiple days. None of these patients presented to hospital or required ASM escalation to manage their seizures.

A further four patients reported a vaccine-related seizure exacerbation only occurring after their second dose. The clinical features of these patients were similar to those who reported seizure exacerbations after the first vaccine; none were seizure-free at baseline. The median time from vaccine to seizure was 3.5 days (range 0–7 days) with half reporting seizure exacerbation within 24 hours of their second vaccine. Three of these four patients reported concurrent vaccine side effects, mild in all but one with high fevers and hypotension. Two patients (50 %) presented to the hospital, with one requiring multiday admission and ASM escalation.

4. Discussion

Of 1,046 COVID-19 vaccine doses administered in 530 PWE (530 initial doses and 516 second doses), only 23 (2 %) vaccine-associated seizure exacerbations occurred, exclusively in patients with ongoing seizures. The only predictor of *not* developing vaccine-associated seizures post-COVID vaccine was 12 months of seizure freedom at the time of the first dose. To date, this is the largest study assessing COVID-19 vaccine-associated seizure exacerbation in PWE.

The risk of increased seizures after vaccination is small, compared to the previous studies from Germany, China, and Kuwait that reported seizure exacerbation in 1.8 to 16 % of patients [5–7]. These differences may relate to differing sample sizes and study

populations. The combined number of patients from these studies is 338 patients compared to our cohort of 530 patients, and we also examined seizure exacerbations after the second vaccination [5–7]. Specific groups of PWE may differ in their vulnerability, for example, a study of 120 patients with Dravet Syndrome found 13 % of patients had a self-reported vaccine-associated seizure exacerbation [8].

This study demonstrates a small risk of seizure exacerbation due to the COVID-19 vaccinations, in contrast to the much higher risks associated with COVID-19 infection itself [9]. PWE are more likely to develop severe complications from COVID-19, including the requirement for mechanical ventilation and ICU admission, and death [9–10]. While COVID-19 may not worsen seizures in PWE directly, seizures can be triggered by fevers or other systemic factors, as with other infections [11]. Furthermore, COVID-19 may be associated with hypoxia, stroke, systemic inflammatory response syndrome, and encephalitis, all capable of precipitating acute symptomatic seizures in already vulnerable patients [8]. Therefore the risk of neurological and systemic complications of COVID infections far outweighs the low risk of vaccine-associated seizure exacerbation.

Our study has limitations. First, most patients had relatively refractory epilepsy, typical of a tertiary hospital epilepsy clinic. The risk of vaccine-associated seizure exacerbations in the general population of PWE may be lower than in our patients. Since most of our patients were not seizure free and required polytherapy with ≥ 2 ASMs, our data is relevant to drug-resistant PWE. Only a small number of our patients had not received a COVID vaccine at the time of the survey and therefore a comparison to assess spontaneous fluctuations in seizure frequency was not possible. We were only able to compare seizure exacerbation post-vaccination with each patient's historical baseline seizure frequencies prior to their vaccination. Nonetheless, if anything, our results, which demonstrate a low risk of seizure COVID-19 vaccine-associated seizure exacerbation risk and highlight vaccine safety in this population, may be an *overestimation* of seizure exacerbation risk, providing further reassurance for patients and clinicians when counseling about vaccine safety. The most common reason for the lack of vaccination was a concern about vaccine safety and the exclusion of these patients may have introduced an element of selection bias. Data regarding previous seizure exacerbations associated with other vaccinations (e.g. influenza vaccination) was not obtained. This may have influenced patients' decisions to receive the COVID vaccine and information on this may have helped delineate whether the exacerbations were COVID vaccine-specific or a complication of vaccinations in PWE as a whole. In addition, the majority (75 %) of our patients received the Pfizer Comirnaty vaccination, limiting the generalisability of our findings to other COVID-19 vaccines. As with other studies, we have relied on patient self-reported seizure increases which may be vulnerable to recall bias. Pre-emptive escalation of ASM prior to the first COVID-19 vaccine dose was not explored, nor was the potential protective role of this measure subsequently.

5. Conclusions

In summary, our findings indicate a very low likelihood of COVID-19 vaccine-related seizure exacerbations in PWE, usually occurring in patients with ongoing seizures, and major sequelae are very uncommon. This data can be utilized in counseling PWE regarding the safety of COVID-19 vaccination.

CRedit authorship contribution statement

E.W. Pang: Data curation, Formal analysis, Writing – original draft, Writing – review and editing. **N.D. Lawn:** Conceptualization,

Data curation, Formal analysis, Supervision, Writing – review and editing. **J. Chan:** Data curation, Writing – review and editing. **J. Lee:** Data curation, Formal analysis. **J.W. Dunne:** Conceptualization, Data curation, Formal analysis, Writing – review and editing.

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.

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