Effect of COVID-19 Vaccination on Seizures in Patients With Epilepsy: a Multicenter, Retrospective Study

Xiqin Fang
Shandong University Qilu Hospital
Shan Qiao
The First Affiliated Hospital of Shandong First Medical University
Ranran Zhang
Shandong University Qilu Hospital
Tingting Yang
Shandong University Qilu Hospital
Zhihao Wang
Shandong University Qilu Hospital
Qingxia Kong
Affiliated Hospital of Jining Medical College
Meihua Sun
Tengzhou Central People's Hospital
Jianhong Geng
Affiliated Hospital of Weifang Medical University
Chunyan Fang
Zhucheng People's Hospital
Yanxiu Chen
Liaocheng People's Hospital
Yanping Sun
The Affiliated Hospital of Qingdao University
Dongmei Zhang
Linyi People's Hospital
Lixin Qu
Dezhou People's Hospital
Wei Shang
Second Hospital of Shandong University
Jianguo Wang
Jinan Central Hospital
Xuewu Liu (snlxw1966@163.com)

Shandong University Qilu Hospital https://orcid.org/0000-0002-9982-1065

Research

Keywords: seizure, retrospective, vaccine, COVID-19, EEG

Posted Date: November 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-965045/v1

Abstract

Background: Previous study have shown that seizures may occur as a result of vaccination. This study aimed to evaluate the risk and correlative factors of seizures in patients with epilepsy (PWE) after being vaccinated with COVID-19 and to provide reference opinions for PWE to receive COVID-19 vaccine.

Methods: We retrospectively enrolled PWE patients who were vaccinated against COVID-19 in the epilepsy centers of nine hospitals in China. The binary logistic regression analysis included variables with a P-value less than 0.1 in the univariate analysis.

Results: The study included 290 patients, of which 40 (13.8%) developed seizures within 14 days after vaccination, whereas 250 (86.2%) remained seizure-free. The binary logistic regression analysis revealed statistical significance in seizures within three months before vaccination (P<0.001, OR=10.121, 95% CI: 4.301-23.816) and withdrawal or reduction of anti-seizures medications (ASM) during the peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768). In addition, 32 of 33 patients (97.0%) who were seizure-free within three months before vaccination and had normal EEG results before vaccination did not have any seizures within 14 days following vaccination.

Conclusions: SARS-CoV-2 may induce epilepsy through an inflammatory cascade. It is recommended to provide the COVID-19 vaccine to seizure-free patients for at least three months before vaccination, and the vaccination is safer if EEG result is normal. During peri-vaccination period, all PWE should be prohibited from reducing ASM dosage. PWE with well-controlled seizures who have discontinued ASM might consider resuming ASM during the peri-vaccination period if their EEG results are aberrant.

Background

COVID-19 emerged as a zoonotic virus at the end of 2019. Its pathogen is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection can lead to various clinical outcomes, ranging from asymptomatic infection to severe acute respiratory distress and death.[1] According to relevant data, over 200 million patients were diagnosed worldwide as of the end of August 2021. The most effective solution to end this pandemic is by administering safe and effective vaccines. With the release of the viral genome in January 2020,[2] developing various vaccines was started.

Patients with epilepsy (PWE) are a special group of people, and vaccination may have a certain impact on their condition. Existing studies indicated that diphtheria, tetanus, pertussis vaccines (DTP) and measles, mumps, rubella vaccines (MMR), the two long-lived vaccinations could significantly increase the risk of febrile convulsions and seizures.[3,4] In addition, some COVID-19 vaccines currently approved on the market have been associated with many adverse reactions, including severe neurological adverse reactions such as transverse myelitis.[5] This has prompted neurologists and PWE to consider whether PWE should be vaccinated against COVID-19. According to an investigation, most neurologists would recommend injections for PWE only when COVID-19 vaccine was safe and reliable.[6] Another study

revealed that approximately one-third of PWE were unwilling to receive COVID-19 vaccine for fear of worsening their seizures.[7] On the one hand, neurologists and PWE are concerned that vaccination may increase the risk of seizures. On the other hand, they are concerned that PWE lacks vaccine protection, making them susceptible to SARS-CoV-2 spread. However, since studies have demonstrated that COVID19 epidemic will worsen the physical and psychological conditions of PWE, ultimately resulting in seizure aggravation,[8,9] COVID-19 vaccination seems to be imperative for PWE. Therefore, clinical evidence of the risk of seizures in PWE after COVID-19 vaccination is critical in guiding PWE to vaccinate. Therefore, we designed this multicenter, retrospective study to evaluate the impact of COVID-19 vaccination on seizures in PWE, aiming to provide reference opinions for neurologists and PWE.

Methods

Patients and study design

From May 1st 2021 to August 1st 2021, patients who were vaccinated with COVID-19 vaccine (regardless of the vaccine type) and diagnosed with epilepsy according to the criteria proposed by ILAE in 2017 were collected retrospectively from the epilepsy centers of nine hospitals in China (Qilu Hospital of Shandong University, Provincial Hospital Affiliated to Shandong First Medical University, Affiliated Hospital of Jining Medical College, Affiliated Hospital of Weifang Medical College, Linyi People's Hospital, Dezhou People's Hospital, Affiliated Hospital of Qingdao University, Liaocheng People's Hospital, and Zhucheng People's Hospital). Patients were divided into two groups based on whether they experienced seizures within 14 days of vaccination: patients with seizures were assigned to the SAV group, while the remaining patients were assigned to the SFAV group. The current major vaccines in China included Sinopharm COVID-19 vaccine (inactivated vaccine, two doses) and Sinovac COVID-19 vaccine (inactivated vaccine, two doses). The interval between the two vaccine doses was generally 14-28 days. We did not impose any restrictions on the type of COVID-19 vaccine that patients received.

Exclusion criteria

The patients are excluded from the study if the following conditions occur: 1. the patients or their guardians refused to sign the informed consent; 2. patients failed to inject COVID-19 vaccines as required or violated post-vaccination regulations; 3. patients cannot cooperate to complete the questionnaire or follow-up; 4. patients are unable to provide an accurate history of seizures (including before and after vaccination); and 5. patients were lost to follow-up, or withdraw from the study by themselves.

Collection of patients’ data

All patients included in the study will fill out a questionnaire. In addition to the basic information and related information about vaccination, the questionnaire also contained the status of epilepsy control before vaccination, the type of seizure, the cause of epilepsy, the anti-seizures medications (ASM) taken and their adverse reactions, the results of the last electroencephalogram (EEG) before vaccination, seizures within 14 days after vaccination, the medication after vaccination, as well as the adverse

reactions and their severity of vaccination. If the patients were vaccinated for less than 14 days, they would be followed up by telephone to obtain relevant data. Before vaccination, we divided patients into five levels based on their seizure-free duration: I. less than three months, II. three months to six months, III. six months to one year, IV. one year to two years, and V. more than two years. The types of seizures were classified according to ILAE 2017 standard.

Primary observation indicator

Seizures that occur within 14 days after vaccination are highly correlated with vaccination.[10–14] Therefore, the primary observation indicator was whether patients experienced seizures within 14 days after vaccination (for a multi-dose vaccine, patients are classified into SAV group as long as they experienced seizures within 14 days after any dose). Based on this, we defined the peri-vaccination period as 14 days before and after any dose of vaccination

Secondary observation indicator

The secondary observation indicators included frequency and severity of non-epileptic adverse events following vaccination.

Statistical Analysis

The Chi-square test or Fisher's exact test was used to analyze the difference of categorical variables between two groups, while differences within a group were analyzed using Bonferroni correction. Kolmogorov-Smirnov test was employed to determine whether the continuous variable was conformed to normal distribution. The independent sample t-test was utilized for the continuous variable conforming to normal distribution, and the Mann-Whitney U test was deployed for the continuous variable that did not conform to normal distribution. A binary logistic regression analysis was performed for the factors with P-value less than 0.1 in the univariate analysis. If the P-value was less than 0.05, it was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 26.

Results

Demographics

In our study, we collected 323 patients, of which 33 were excluded because due to the following reasons: (1) inability to complete the questionnaire or follow-up, (2) inability to fully answer the questions in the questionnaire, and (3) inability to provide accurate seizure information. As a result, this analysis included data from 290 patients. A total of 40 (13.8%) patients were assigned to the SAV group, while the remaining 250 (86.2%) patients were assigned to the SFAV group.

The age range of 290 patients was 14 to 80 years, including 158 (54.5%) males and 132 (45.5%) females. A total of 84 (29.0%) patients had a clear cause of epilepsy and 47 (16.2%) stopped taking ASM or reduced its dose during peri-vaccination period. There were 40 (13.8%), 44 (15.2%), 37 (12.8%), 57 (19.7%), and 112 (38.6%) patients had seizure-free duration grades of I, II, III, IV and V, respectively. The

most frequent type of seizures(214, 73.8%)was focal seizures (with or without impaired awareness). Frequent ASM included valproate (87, 30%), oxcarbazepine (76, 26.2%), levetiracetam (69, 23.8%), carbamazepine (59, 20.3%), lamotrigine (41, 14.1%), topiramate (15, 5.2%), lacosamide (16, 5.5%), and perampanel (12, 4.1%). There were 36 (12.4%), 150 (51.7%), 81 (27.9%), and 23 (7.9%) patients taking 0, 1, 2, and more than 2 types of ASM, respectively. Table 1 compares epilepsy-related indexes between SAV and SFAV groups.

Table 1

Demographics

Valiables	SAV（n=40）	SFAV（n=250）
Age,year（n%）		
≦ 18	1（2.5）	19（7.6）
> 18 and ≦ 30	18（45.0）	112（44.8）
> 30 and ≦ 40	9（22.5）	63（25.2）
> 40 and ≦ 50	9（22.5）	32（12.8）
> 50 and ≦ 60	2（5.0）	13（5.2）
> 60	1（2.5）	11（4.4）
Male （n%）	24（60）	134（53.6）
Epileptic etiology （n%）		
Unknown	28（70.0）	178（71.2）
Trauma	5（12.5）	32（12.8）
Heredity	3（7.5）	15（6.0）
Inflammation	1（2.5）	7（2.8）
Tumor	1（2.5）	5（2.0）
Vascular	2（5.0）	10（4.0）
Metabolism	0（0）	3（1.2）
Withdrawl or reduction of ASM（n%）	13（32.5）	34（13.6）
Duration of seizure free （n%）		
Grade I	20（50）	20（8）
Grade II	6（15）	38（15.2）
Grade III	3（7.5）	34（13.6）
Grade IV	3（7.5）	54（21.6）
Grade V	8（20.0）	104（41.6）
Seizure type （n%）		

Focal (with or without impaired awareness)	31（77.5）	183（73.2）
Generalized	4（10）	30（12）
Unkonwn	5（12.5）	37（14.8）
Use of ASM （n%）		
Valproate	13（32.5）	74（29.6）
Carbamazepine	9（22.5）	50（77.5）
Oxcarbazepine	11（27.5）	65（26.0）
Levetiracetam	5（12.5）	64（25.6）
Lamotrigine	1（2.5）	40（16.0）
Topiramate	3（7.5）	12（4.8）
Perampanel	4（10）	8（3.2）
Lacosamide	5（12.5）	11（4.4）
Number of ASM （n%）		
None	10（25）	26（10.4）
1	13（32.5）	137（54.8）
2	11（27.5）	70（28）
3 or more than 3	6（15.0）	17（6.8）
Abbreviation: ASM, anti-seizures medications.		

Univariate analysis

Univariate analysis of the above factors revealed that duration of seizure-free ($P < 0.001$), or taking lacosamide ($P=0.025$), and number of ASM taken ($P=0.007$) differed significantly between the two groups (Table 2). In addition, we performed a within-group analysis on seizure-free duration and found that the proportion of patients with seizure-free grades II, III, IV, and V who experienced seizures following vaccination was significantly lower than that of patients with grade I ($P < 0.05$), but there was no significant difference between grades II, III, IV, and V ($P > 0.05$).

Table 2
Result of univariate analysis

Valiables	P value
Age	0.622
Sex	0.281
Epileptic etiology	0.981
Withdrawl or reduction of ASM	0.005
Duration of seizure free	<0.001
Seizure type	0.886
Use of ASM	
Valproate	0.713
Carbamazepine	0.677
Oxcarbazepine	0.848
Levetiracetam	0.075
Lamotrigine	0.025
Topiramate	0.444
Perampanel	0.068
Lacosamide	0.053
Number of ASM	0.007
Abbreviation: ASM, anti-seizures medications.	

Binary logistic regression analysis

In the univariate analysis, we performed a binary logistic regression analysis on the factors with P-value less than 0.1. For seizure-free duration, based on univariate analysis results (no significant difference existed between seizure-free grades II, III, IV, and V), we incorporated it as a binary variable with a three-month limit. The results revealed that seizures within three months before vaccination (P<0.001, OR=10.121, 95% CI: 4.301-23.816) and withdrawal or reduction of ASM during the peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768) were found to be statistically significant correlation factors (Table 3). A total of 8% (20/250) patients who were seizure-free within three months before vaccination experienced seizures following vaccination, compared with 50% (20/40) patients with seizures within three months before vaccination (Figure 1). Seizures occurred in 27.7% (13/47) of patients who withdraw or reduced ASM compared with 11.1% (27/243) of those who did not withdraw or reduce ASM.

Table 3
Result of multivariate analysis

Valiables	Ods ratio	95% CI	P value
Seizure within three months before vaccination	10.121	4.301-23.816	<0.001
Withdrawl or reduce the dosage	4.452	1.182-16.768	0.027
Lamotrigine	0.118	0.013-1.073	0.058
Levetiracetam	0.327	0.093-1.147	0.081
Number of ASM			0.095
0	1		
1	1.086	0.245-4.816	
2	1.872	0.405-8.646	
3 or more	8.221	1.051-64.285	
Abbreviation: ASM, anti-seizures medications.			

Results of the last EEG before vaccination of some patients

We obtained the results of the last EEG performed by 69 patients before vaccination (Figure 2). Among these 69 patients, 36 had normal EEG results, of which 3 were in the SAV group; 33 patients had abnormal EEG results, of which 6 were in the SAV group. The proportion of patients with normal EEG results having seizures after vaccination was lower than those with abnormal EEG results (8.3% vs. 18.2%), but the difference was not statistically significant (P=0.294). Notably, 32 of 33 patients (97.0%) who had no seizures within three months before vaccination and whose EEG results were normal before vaccination did not develop any seizure within 14 days after vaccination.

Non-epileptic side reactions

A total of 62 (21.4%) patients experienced non-epileptic side reactions after vaccination. A total of 46 (15.9%) patients experienced pain or itching at the injection site; 7 (2.4%) developed lumps or induration at the injection site; 3 (1.0%) experienced low-grade fever (37.1°C-38°C) after vaccination, although none of these three patients experienced seizures; 20 (7.0%) patients felt tired, 14 (4.8%) experienced dizziness or headache, 13 (4.5%) had muscle soreness, 4 (1.7%) had nausea or vomit, and 1 (0.4%) experienced stomachache or diarrhea. Patients with these adverse reactions can tolerate and did not require medical intervention. Only two patients (0.7%) experienced different serious adverse reactions: syncope and generalized rash (Figure 3). However, these adverse reactions were not significantly different between SAV and SFAV groups (P>0.05).

Discussion

This study provided important data about the impact of COVID-19 vaccine on seizures in PWE. Our results indicated that seizure (within 14 days after vaccination) was a frequent side reaction (13.8%) in PWE after vaccination. The binary logistic regression analysis revealed that seizures within three months before vaccination and withdrawal or reduction of ASM during the peri-vaccination period were correlative factors. In addition, vaccination may be safer for patients with normal EEG results. As far as we know, no studies have been conducted to evaluate the risk of seizures in PWE after COVID-19 vaccination. As the first study to assess the risk of seizures after COVID-19 vaccination, our findings provide critical guidance to PWE regarding vaccination.

This study chose seizures within 14 days after vaccination as the primary observation index rather than seizure frequency. This was because PWE with frequent seizures were not allowed to be vaccinated against COVID-19 in China. Therefore, for PWE with infrequent seizures, no appropriate comparison target for seizure frequency existed. Although taking perampanel or lacosamide was statistically significant in univariate analysis, we excluded them from the binary logistic regression analysis. This was because we believed that demographic characteristics of patients who took these two drugs were significantly different from those taking other ASM. We analyzed the distribution of seizure-free duration grades in patients treated with these two drugs and found statistically significant differences. These two medications were only recently approved in China, and few patients used them for more than two years, let alone seizure-free for more than two years (in fact, none of patients taking perampanel or lacosamide in our study was seizure-free for more than two years).

At present, a large-scale injection of COVID-19 vaccine in China has just started, and many people, including PWE, are skeptical about the vaccine's safety. Our results revealed that the safety of COVID-19 vaccine was worthy of recognition. Among 290 patients, 62 (21.4%) experienced mild non-epileptic side reactions, while only 2 (0.7%) had serious side reactions. However, for the special population of PWE, whether to vaccinate against COVID-19 still needs to be considered. In our study, 13.8% of PWE experienced seizures within 14 days after vaccination, which is much higher than previous studies of other vaccines; by contrast, even in patients with Dravet syndrome, the rate of seizures after MMR vaccination was only 2.3%.[15] Karina et al. found that the risk of seizures following vaccination with various vaccines did not even increase.[16] In our study, the high seizure rate after COVID-19 vaccination may be due to the following reasons: 1. first, most patients in the SAV group have a seizure-free duration of less than three months. For these patients whose epilepsy control status was not ideal, the seizures after vaccination may be derived from the characteristics of epilepsy itself, but not vaccination. 2. Verbeek et al. found that the longer the use of ASM, the higher the risk of post-vaccination seizures in children with epilepsy.[15] In our study, the minimum age of patients was 14, implying that our patients used ASM for a longer time than childhood epilepsy patients; demographic characteristics may lead to such results. 3. Mental disorders can promote the onset of epilepsy.[17] Unlike vaccines such as DTP and MMR, COVID-19 vaccination has not started too long. PWE continues to have concerns about the vaccine's safety and effectiveness, resulting in mental health problems in PWE following vaccination and then increasing seizures.

Unsurprisingly, injecting COVID-19 vaccine can induce seizures. Aladdin et al. once reported a case of refractory status epilepticus after ChAdOx1 nCoV-19 vaccine injection.[18] Although DTP and MMR can promote seizures by inducing additional fever,[3,13] in our study, the three patients who developed a fever after vaccination did not experience seizures. Therefore, the mechanism by which COVID-19 vaccine promotes seizures may not be correlated with fever induction. Existing studies have proved that coronaviruses, particularly β-coronavirus to which SARS-CoV-2 belongs, were not limited to infecting the respiratory tract but often invaded the central nervous system (CNS).[19] SARS-CoV-2 virus can enter CNS through a variety of ways: spreads through blood and crosses blood-brain barrier (BBB); spreads across synapses; and enters through blood-cerebrospinal fluid or structures around ventricles.[20] After entering CNS, the virus mainly binds to various nerve cells through angiotensin-converting enzyme 2 (ACE2).[20] Coronavirus mainly infected neurons in the brainstem associated with cardiopulmonary control; damage to these areas may aggravate respiratory depression and even lead to respiratory failure,[19] and can also increase the risk of sudden epileptic death.[21] In addition, SARS-CoV-2 infection can induce a systemic inflammatory storm and release many pro-inflammatory factors, resulting in BBB destruction, damage of glia limitans, activation of Toll-like receptors in microglia, and astrocytes, and ultimately promoted neuroinflammation, which may severely disrupt brain homeostasis and cause neuronal death.[22,23] On the one hand, many studies have revealed that activating Toll-like receptors can cause epilepsy;[24,25] On the other hand, BBB disruption can cause entry of immune cells and serum proteins from peripheral blood into the brain, promoting the occurrence of epilepsy.[25,26] Finally, SARS-CoV-2 transcriptome had molecular similarities with the epitopes of human CNS protein, producing various autoantibodies and may eventually trigger autoimmunity to aggravate inflammatory storms.[20] Overall, we imply that SARS-CoV-2 induces epilepsy mainly through an inflammatory cascade. Given the potential epileptogenic capacity of SARS-CoV-2, we do not propose injecting attenuated vaccines in PWE.

In the binary logistic regression analysis, seizures within three months before vaccination were a correlative factor with statistical significance. The results revealed that, in the three months before vaccination, the risk of seizures in patients with seizures was 10.121 times that of those who were seizure-free (P<0.001, 95% CI: 4.301-23.816). Therefore, PWE who are seizure-free for at least three months can be considered for vaccination. In China, "uncontrolled epilepsy" was a contraindication to COVID-19 vaccination, but no accurate definition for "uncontrolled epilepsy" existed. A study defined it as having a seizure within 12 months.[27] However, in univariate analysis, we found that for patients with a seizure-free duration of more than three months, as duration was further extended, the seizure rate after vaccination would not change significantly. Therefore, we considered "uncontrolled epilepsy" as having any seizure within three months. However, it should be noted that 7.8% of patients who were seizure-free for more than three months experienced seizures after vaccination. Another correlative factor with statistical significance was withdrawal of reduction of ASM during peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768). According to this, we suggest that ASM reduction should be forbidden during peri-vaccination period. For patients with well-controlled seizures who have withdrawn, whether

they need to retake ASM should be based on EEG results. Finally, regardless of EEG results, patients who withdraw by themselves must retake ASM.

Our study included a factor that was not statistically significant but worthy of attention. Although EEG results of 69 patients were not significantly different between the two groups, 32 of 33 patients (97.0%) who had no seizures within three months before vaccination and had normal EEG results did not experience any seizure following vaccination. According to a meta-analysis by Lamberink et al., abnormal EEG before drug withdrawal was a risk factor for epilepsy recurrence in PWE after drug withdrawal.[28] This means that compared with PWE who have abnormal EEG, PWE with normal EEG have a better seizure control status and are therefore less likely to develop seizures induced by various factors. Therefore, for PWE who are seizure-free for at least three months and whose EEG results are normal before vaccination, it will be safer to vaccinate against COVID-19.

Additionally, our study had some limitations. First, this was a retrospective study, with small sample size and lack of control. Second, the patients' seizure information was mainly obtained from patients themselves or their relatives, ignoring seizures in some PWE. Third, we only divided seizure-free duration into five levels, and too large intervals may affect the accuracy of our results. Finally, because patients were received inactivated vaccinations, our conclusions may not be generalizable to other types of vaccines. In the future, prospective randomized controlled studies with a large sample may be required to further evaluate the impact of COVID-19 vaccination on seizures in PWE.

Conclusions

In summary, our findings indicate that although seizure is a common adverse event in PWE vaccinated with COVID-19, the benefits of COVID-19 vaccination far outweigh the risks for PWE who are seizure-free for more than three months before vaccination. In addition, vaccination is safer if EEG result is normal. Finally, PWE who withdraw or reduce their ASM during the peri-vaccination period are at higher risk of vaccination, demonstrating that ASM regimen should be appropriately adjusted in this population.

Abbreviations

ASM	Anti-seizures medications
PWE	Patients with epilepsy
DTP	Diphtheria, tetanus, pertussis vaccines
MMR	Measles, mumps, rubella vaccines
CNS	Central nervous system
BBB	Blood-brain barrier
ACE2	Angiotensin-converting enzyme 2

Declarations

Acknowledgements

We would like to thank all the authors above for their contributions to this research. In addition, we would also like to thank Lili Cao (Qilu Hospital of Shandong University), Zhaofu Chi (Qilu Hospital of Shandong University), Liling Yang (Provincial Hospital Affiliated to Shandong First Medical University), Huaikuan Wu (The First Affiliated Hospital of Shandong First Medical University) for providing the data.

Author's contributions

XF,SQ and XL designed the study,XF, SQ, RZ, TY, ZW, QK, MS, JG, CF, YC, YL, YS, DZ, LQ, WS, JW and XL provided or collected the data. XF and XL analysed the data. XF and XL wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The experiment was approved by the Medical Ethics Committee of Qilu Hospital of Shandong University (2021035).All patients or their guardians who agreed to participate in this study signed an informed consent form.

Consent for publication

All patients or their guardians agreed to publish their information related to the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was supported by the National Natural Science Foundation of China.

References

1. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug 15;396(10249):467-478. doi: 10.1016/S0140-6736(20)31604-4.
2. Wu F, Zhao S, Yu B,et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579(7798):265-269. doi: 10.1038/s41586-020-2008-3.

3. Pruna D, Balestri P, Zamponi N, et al. Epilepsy and vaccinations: Italian guidelines. Epilepsia. 2013 Oct;54 Suppl 7:13-22. doi: 10.1111/epi.12306.
4. Rowhani-Rahbar A, Fireman B, Lewis E, et al. Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children. JAMA Pediatr. 2013 Dec;167(12):1111-7. doi: 10.1001/jamapediatrics.2013.2745.
5. Khan E, Shrestha AK, Colantonio MA, Liberio RN, Sriwastava S. Acute transverse myelitis following SARS-CoV-2 vaccination: a case report and review of literature. J Neurol. 2021 Sep 5:1–12. doi: 10.1007/s00415-021-10785-2.
6. Asadi-Pooya AA, Sahraian A, Badv RS, Sahraian MA. Physicians' opinions on the necessity of COVID-19 vaccination in patients with epilepsy. Epileptic Disord. 2021 May 31. doi: 10.1684/epd.2021.1282.
7. Puteikis K, Mameniškienė R. Factors Associated with COVID-19 Vaccine Hesitancy among People with Epilepsy in Lithuania. Int J Environ Res Public Health. 2021 Apr 20;18(8):4374. doi: 10.3390/ijerph18084374.
8. Huang S, Wu C, Jia Y, et al. COVID-19 outbreak: The impact of stress on seizures in patients with epilepsy. Epilepsia. 2020 Sep;61(9):1884-1893. doi: 10.1111/epi.16635.
9. Assenza G, Lanzone J, Brigo F, et al. Epilepsy Care in the Time of COVID-19 Pandemic in Italy: Risk Factors for Seizure Worsening. Front Neurol. 2020 Jul 3;11:737. doi: 10.3389/fneur.2020.00737.
10. Tartof SY, Tseng HF, Liu AL, et al. Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. Vaccine. 2014 May 7;32(22):2574-81. doi: 10.1016/j.
11. Deng L, Danchin M, Lewis G, et al. Revaccination outcomes of children with vaccine proximate seizures. Vaccine. 2021 Mar 12;39(11):1565-1571. doi: 10.1016/j.
12. Top KA, Righolt CH, Hawken S, et al. Adverse Events Following Immunization Among Children With Epilepsy: A Self-Controlled Case Series. Pediatr Infect Dis J. 2020 May;39(5):454-459. doi: 10.1097/INF.0000000000002553.
13. Vestergaard M, Hviid A, Madsen KM, et al. MMR Vaccination and Febrile Seizures: Evaluation of Susceptible Subgroups and Long-term Prognosis. JAMA. 2004;292(3):351–357. doi:10.1001/jama.292.3.351.
14. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001 Aug 30;345(9):656-61. doi: 10.1056/NEJMoa003077.
15. Verbeek NE, van der Maas NA, Sonsma AC, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology. 2015 Aug 18;85(7):596-603. doi: 10.1212/WNL.0000000000001855.
16. Top KA, Brna P, Ye L, Smith B. Risk of seizures after immunization in children with epilepsy: a risk interval analysis. BMC Pediatr. 2018 Apr 11;18(1):134. doi: 10.1186/s12887-018-1112-0.
17. Kanner AM. Depression and epilepsy: A bidirectional relation? Epilepsia. 2011 Jan;52 Suppl 1:21-7. doi: 10.1111/j.1528-1167.2010.02907.x.

18. Aladdin Y, Shirah B. New-onset refractory status epilepticus following the ChAdOx1 nCoV-19 vaccine. J Neuroimmunol. 2021 Aug 15;357:577629. doi: 10.1016/j.jneuroim.2021.577629.
19. Steardo L, Steardo L Jr, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol (Oxf). 2020 Jul;229(3):e13473. doi: 10.1111/apha.13473.
20. Gupta M, Weaver DF. COVID-19 as a Trigger of Brain Autoimmunity. ACS Chem Neurosci. 2021 Jul 2. doi: 10.1021/acschemneuro.1c00403.
21. Liu J, Peedicail JS, Gaxiola-Valdez I, et al. Postictal brainstem hypoperfusion and risk factors for sudden unexpected death in epilepsy. Neurology. 2020 Sep 22;95(12):e1694-e1705. doi: 10.1212/WNL.0000000000010360.
22. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
23. Kumar D, Jahan S, Khan A, et al. Neurological Manifestation of SARS-CoV-2 Induced Inflammation and Possible Therapeutic Strategies Against COVID-19. Mol Neurobiol. 2021 Jul;58(7):3417-3434. doi: 10.1007/s12035-021-02318-9.
24. Paudel YN, Angelopoulou E, Akyuz E, Piperi C, Othman I, Shaikh MF. Role of Innate Immune Receptor TLR4 and its endogenous ligands in epileptogenesis. Pharmacol Res. 2020 Oct;160:105172. doi: 10.1016/j.phrs.2020.105172.
25. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol. 2019 Aug;15(8):459-472. doi: 10.1038/s41582-019-0217-x.
26. Librizzi L, Vila Verde D, Colciaghi F, et al. Peripheral blood mononuclear cell activation sustains seizure activity. Epilepsia. 2021 Jun 1. doi: 10.1111/epi.16935.
27. Willems LM, Reif PS, Knake S, et al. Noncompliance of patients with driving restrictions due to uncontrolled epilepsy. Epilepsy Behav. 2019 Feb;91:86-89. doi: 10.1016/j.yebeh.2018.04.008.
28. Lamberink HJ, Otte WM, Geerts AT, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. Lancet Neurol. 2017 Jul;16(7):523-531. doi: 10.1016/S1474-4422(17)30114-X.

Figures

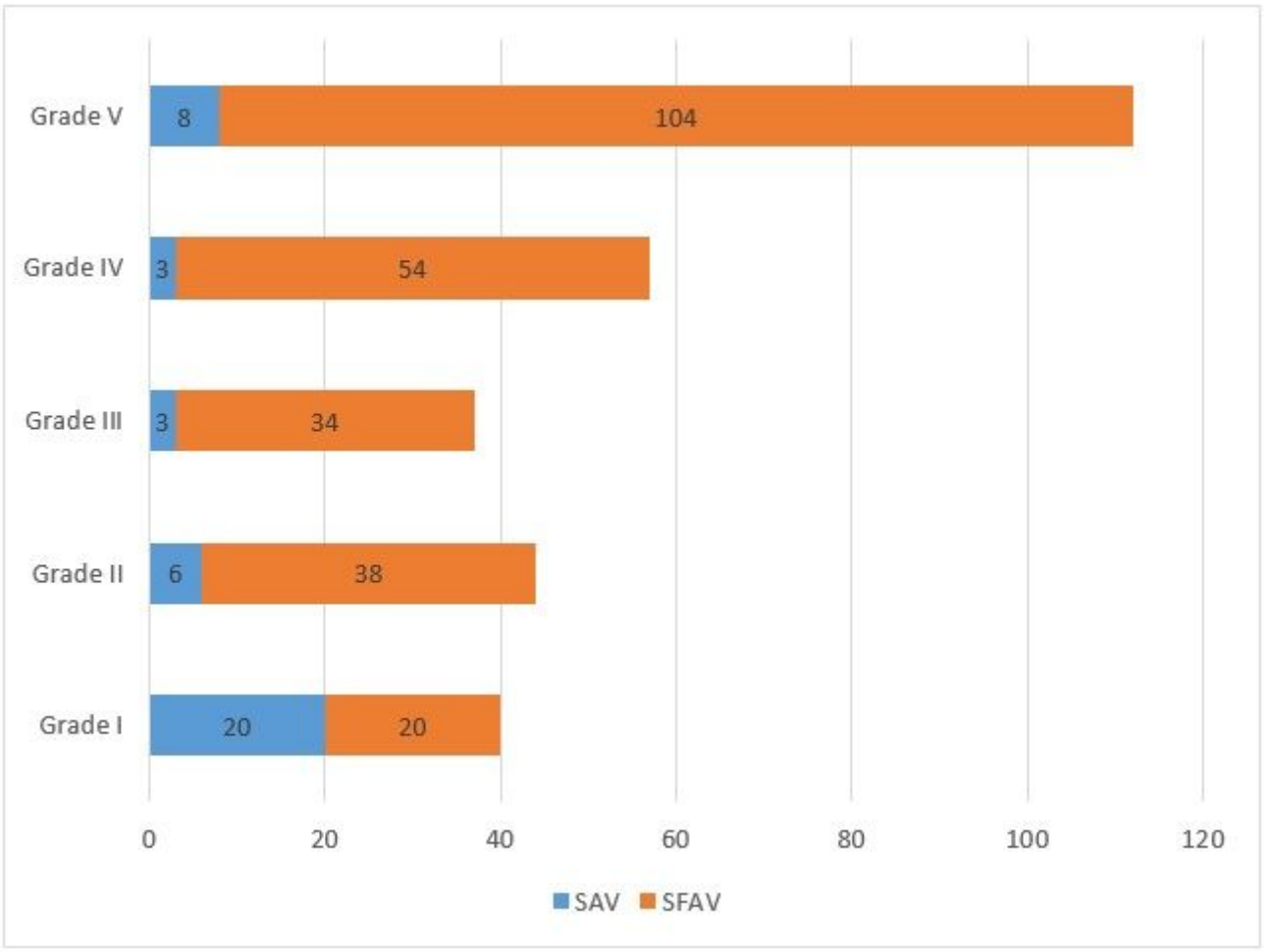

Figure 1

The distribution of different seizure-free grades of patients in the two groups

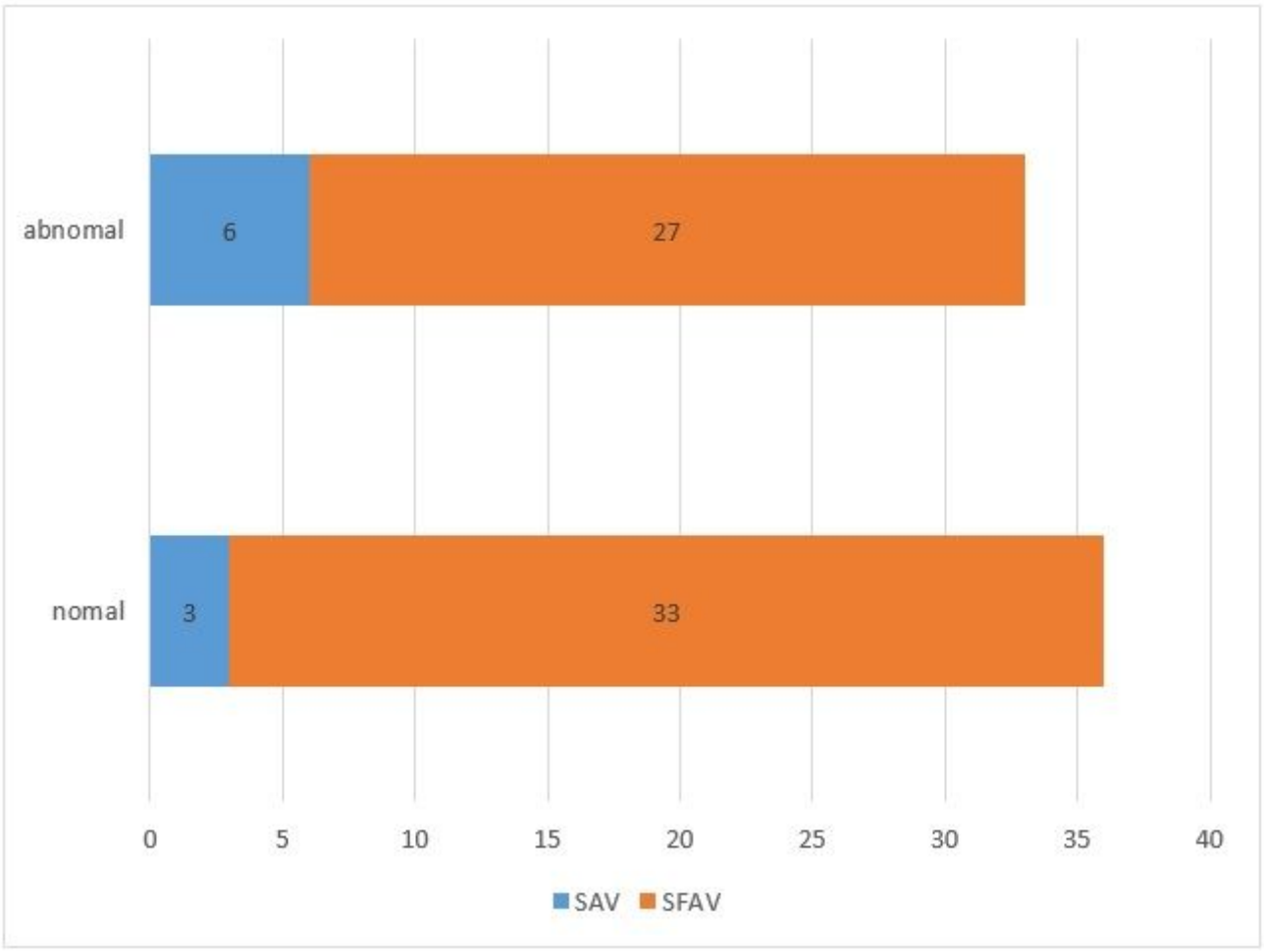

Figure 2

Result of electroencephalogram

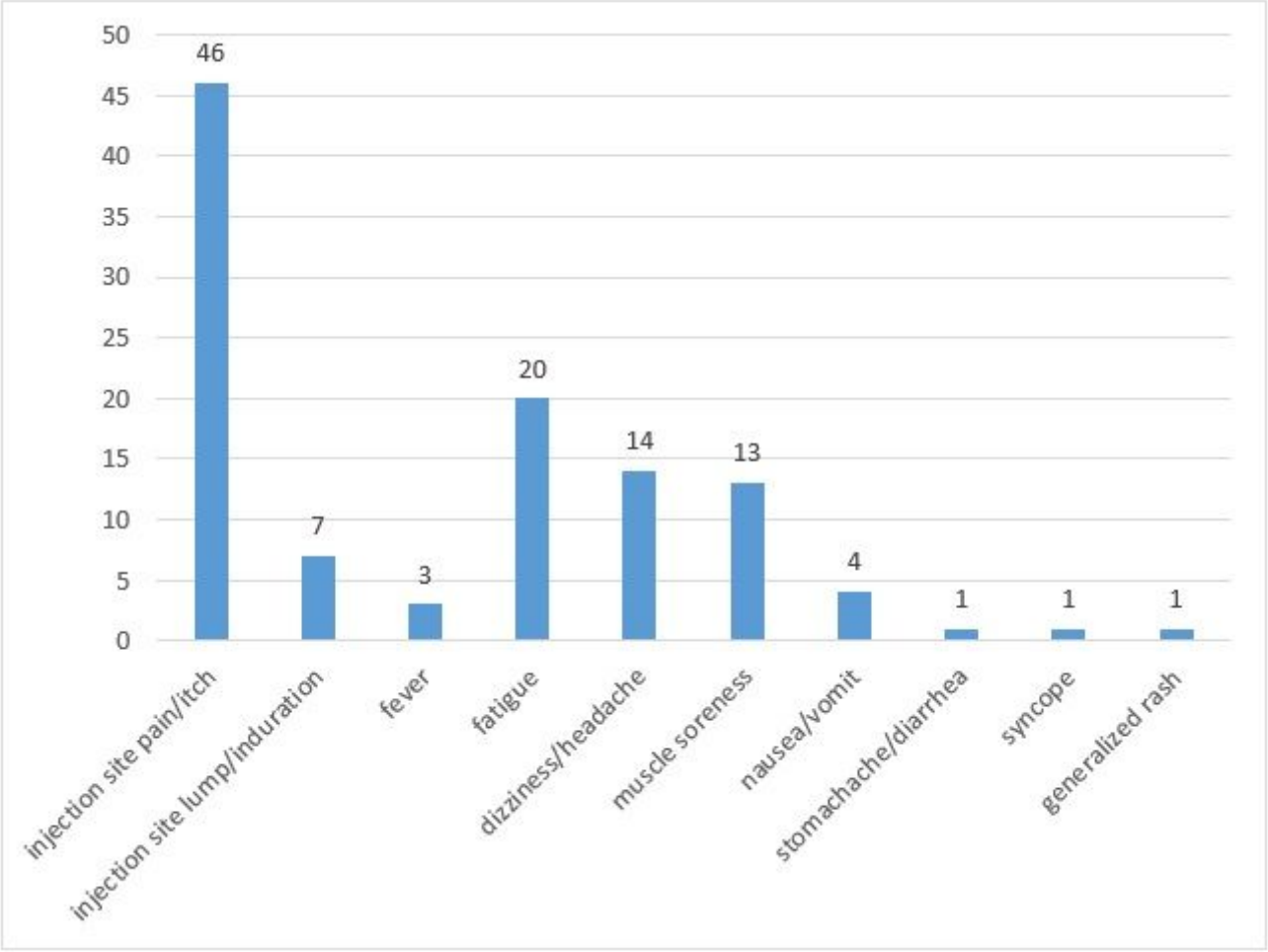

Figure 3

Non-epileptic adverse reactions