COVID-19 vaccine take-up rate and safety in adults with epilepsy: data from a multicentre study in China

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Summary

Objective

To investigate the COVID-19 vaccine uptake rate and possible post-vaccination effects in adults with epilepsy.

Methods

We invited adults with epilepsy attending three centres in China from 24 July to 31 August 2021 to participate in this study. Age and sex-matched controls were recruited among people attending for other chronic neuropsychiatric conditions, and healthy controls accompanying people with illness attending the hospitals were also asked to participate. We excluded people who had contradictions to vaccination under the national guidelines. Participants were interviewed face-to-face using questionnaires. Vaccine uptake and post-vaccine adverse events among the people with epilepsy (PWE) were compared with those from people with neuropsychiatric conditions and healthy controls. We also compared the willingness and reasons for hesitancy among unvaccinated participants.

Results

We enrolled 981people, among whom 491 were PWE 217 had other neuropsychiatric conditions, and 273 were healthy controls. Forty-two percent of PWE had had the first dose of a vaccine compared with 93% of the healthy controls and 84% of the people with neuropsychiatric conditions ($P<0.0001$). The majority(93.8%) of the vaccinated had in-activated vaccines. Among the unvaccinated PWE, 59.6% were willing to injected. Their main hesitations were potential adverse effects (53.3%) and unsatisfied seizure controls (47.0%). The incidence of adverse events in the epilepsy group was similar to the controls. Two controls had the first-ever seizure without causation of the vaccines. Nineteen people with epilepsy reported an increased seizure frequency. No episode of status epilepticus or prolonged seizures were reported.

Significance

The vaccine update rate in PWE was lower than their same-age controls. The post-vaccination effect was no higher than in controls. We found no evidence suggested worsening of seizures after vaccination. Measurement and education focused on increasing the vaccination rate in epilepsy are warranted.

Keyword: SARS-CoV-2; Vaccine; real-word investigation; Seizure

Key points:

1. Adults with epilepsy had a much lower vaccine uptake than their age-matched controls
2. Vaccines were well-tolerated in adults with epilepsy, and post-vaccination effects no worse than in controls
3. Post-vaccination increase in seizures was rare
4. Evidence-based recommendations and detailed individual education are required to provide the best vaccine decision making.

Introduction

With the ongoing COVID-19 pandemic, the only hope for reestablishing pre-pandemic routines is deploying effective vaccines with high take-up rates worldwide. In December 2020, the US Food and Drug Administration (FDA) authorised the emergency use of two mRNA vaccines[1, 2], starting the first-ever vaccination program in adults. Since then, WHO has evaluated six vaccines meeting the criteria for safety and efficacy[3]. These are the mRNA vaccines from Moderna and Pfizer/Bion Tech, the viral vector vaccines from Johnson & Johnson and Oxford/AstraZeneca and the inactivated vaccines from Sinopharm and Sinovac.

The safety and efficacy of the COVID-19 vaccines have raised concerns amongst people with epilepsy. In guidelines for other vaccines[4] such as Diphtheria- tetanus-pertussis (DTP) and measles, mumps, and rubella (MMR), epilepsy is not a contraindication. Specific evidence about the COVID-19 vaccines in epilepsy is, however, still lacking. Reports from Germany[5] and Kuwait[6] based on relatively small cohorts suggest good tolerance of COVID-19 vaccines. Based on the current evidence, the International League against Epilepsy (ILAE) stated that no available evidence suggested that having epilepsy was associated with a higher risk of side effects from a COVID-19 vaccine. Conversely, in China, the early national guideline listed severe neurological disorders, including uncontrolled epilepsy, as contraindications[7].

We assessed whether there was a difference in the vaccination rate and post-vaccination adverse effects between people with epilepsy and controls or people with other neuropsychiatric conditions. We also explored seizure-related changes after vaccination in people with epilepsy.

Methods

The Ethics Committee of West China Hospital, Sichuan University (2020[100]) approved this crossectional multicentre study. All participants provided written consent.

The study was conducted in three tertiary hospitals (West China Hospital (Sichuan University), Henan Provincial People's Hospital and Chongqing University Three Gorges Hospital) from 24 July to 31 August 2021. People 18 years or older previously diagnosed with epilepsy attending neurological clinics were invited to participate. Other visitors to the hospital were invited to participate and divided into two groups: people with other neuropsychiatric conditions and healthy controls (recruited amongst healthy visitors). People were excluded if they had any conditions listed as contraindications in the national vaccination guideline, including pregnancy, allergy to vaccine products or severe allergy history, severe neurological disorders and febrile illness.

The data was gathered through face-to-face interviews. We designed a questionnaire (supplementary material) to acquire demographic data, diagnosis, medication, history of febrile convulsions, and vaccine-related information such as contraindications and willingness to be vaccinated. We asked about vaccine type and related adverse effects for those who had had a vaccine. A different questionnaire was used for people with epilepsy to include information about epilepsy, seizure frequency data, and seizure-related changes after vaccination. Seizure frequency was measured in two ways. The first is a grading variable listing as one-year seizure-free, at least once a year, once every six months, once every three months, once every month, once every week, once every day. Participants were asked to choose the most fitted ranking of the frequency.The second is the seizure-free interval between vaccination and the previous seizure. The seizure frequency change were recorded from the first injection to one week after the completion of vaccination. According to national guidelines,

complete vaccination was defined as having had full immunisation according to the schedule required by the corresponding vaccine. The subunit vaccine requires three doses, the inactivated platforms require two injections, and the viral vector vaccine only requires one injection. Postvaccine fever was defined as a temperature higher than 38.5°in the seven days after the vaccination. Drug-resistant epilepsy was defined as people not seizure-free in the previous 12 months despite having had treatment trials of two or more anti-seizure medications[8].

We used IBM SPSS Statistics(V25.0, 64-digital) for the analysis. ANOVA test, Chi-Squared test were used based on the variables. Results were considered statistically significant at a p-value of <0.05.

Results

We enrolled 981 individuals, including 491 people with epilepsy, 273 healthy controls and 217 with other neuropsychiatric conditions. None of the participants had a COVID-19 infection by the study endpoint. None in the epilepsy group had an epileptic encephalopathy. The cumulative 1st dose rate among the three groups from December 2020 to study end is shown in Figure 1.

Table 1 shows the demographics, febrile seizure history, vaccination rate, and willingness to be vaccinated in the unvaccinated population. In the unvaccinated population, vaccination willingness was similar between those with epilepsy and those with neuropsychiatric conditions. The healthy control group reported a higher willingness rate. The main reasons for vaccine hesitancy in people with epilepsy and other neuropsychiatric conditions are provided in Table 2. Despite fewer concerns about disease-vaccine interaction in those were unvaccinated in the healthy group (N=20), their main reasons

were concerns of potential adverse events (n=6) and scheduling conflicts at the time of the vaccine appointment (N=11).

For people with epilepsy, the clinical features of those vaccinated and those not vaccinated are shown in Table 3.

Adverse events reported by people with epilepsy and controls are provided in Table 4. Fever was only reported by two after the 1st injection, and none had a fever in subsequent injections. While only the subunit vaccine required three injections, there were seventeen people in the controls, seven in the other neurological group and eight participants in the epilepsy group who had the third injection. They reported three local reactions and two muscle pain.

Among controls, two participants visited the clinic for post-vaccine seizure-like symptoms. The first was a 29-year-old female with no specific history who reported one seizure after her second inactivated vaccine injection. The other was a 37-year-old male who reported a seizure while playing mahjong five days after vaccination. He was diagnosed with reflex epilepsy after a subsequent seizure also when playing mahjong. After investigation by disease control and prevention administration neither of the seizure incidences was considered vaccine-induced. No status epilepticus or prolonged seizures were reported.

During the vaccination period, nineteen participants with epilepsy reported increased seizure frequency after vaccination—two experienced seizure recurrence after more than two-years seizure-free. Two participants had a first ever convulsive seizure. Six withdrew medication, while two had add-on anti-

seizure medications(ASMs) during the vaccination for seizure control. The median seizure-free interval for them was three months. The longest interval was 58 months.

Discussion

We report a dramatically lower first dose coverage of COIVD-19 vaccination in adults with epilepsy than people with other neuropsychiatric conditions and healthy controls. The general adverse effects were no higher in the epilepsy group, and no evidence of seizure worsening or status epilepticus was seen.

We found significant lower vaccination rate and hesitancy in people with epilepsy compared to non-epilepsy groups. We could not find data from other regions addressing this issue, apart from two uncontrolled cross-sectional studies. One report from Germany suggested that fewer than a fifth of people with epilepsy had at least one dose, and a Kuwaiti report was similar[5, 6].

The difference might be multifactorial. Firstly, access and the population priority of vaccination might be significant due to the limited availability of vaccines. To date, three-quarters of the world population have not yet been fully vaccinated, despite the unprecedented worldwide vaccination campaign [9]. The recommendation from ILAE suggests that the risk of COVID-19 infection far outweighed the risk of adverse effects from vaccines[10]. Different countries announced widely differing regulations, however, adapted to the local situation and culture. For example, people with epilepsy were listed as a priority group in the UK and other European countries, but in the US and Thailand, epilepsy was not on the priority lists[5, 11-13]. In China, with almost no new domestic cases since last May, severe neurological diseases, including people with “uncontrolled seizures”, were listed as a contradiction during our study

period [7]. Although it would be unlikely to have a direct link to the willingness in people with epilepsy, since the main readership of the guideline were healthcare professions. It might have an indirect influence upon the willingness of people with epilepsy during their clinic visits. Moreover, the uncontrolled epilepsy was not clearly defined, nor was the minimal seizure frequency threshold set so that the guidance may have been over-interpreted. These uncertainty and ambiguity might harm promoting vaccinations in people with epilepsy.

Secondly, fear of seizure worsening was another factor. Our study suggests that compared to people with other chronic neuropsychiatric conditions such as depression, people with epilepsy had more concerns about safety and were worried about seizure exacerbation. This is in agreement with a previous study about vaccination safety, where efficacy and fear of epilepsy worsening were the two most common causes of vaccination hesitancy[14].

Thirdly, in these two studies, data acquisition was four to five months previously so that rates may have changed since[5, 6].

The potential for adverse effects was another critical issue influencing vaccination coverage. Thus far, no report has provided data comparing the vaccination rate among people with epilepsy and controls. The premarketing data of the currently used vaccines suggest good tolerance in the general population. Until recently, no real-world data were available, but now two single-centre reports exist with generally similar results from relatively small groups of epilepsy [5, 6]. Our data also showed an equal distribution and prevalence of general adverse effects in epilepsy and non-epilepsy groups, other than a slightly higher rate of post-vaccination headache in the epilepsy group. The most common adverse effects were injection site pain, myalgia and fatigue, consistent with the previous two studies[5, 6]. In the earlier

studies, most had mRNA or adenoviral vector-based vaccines, while most had inactivated vaccines in our study.

Interestingly, one healthy control reported a seizure-like event with no fever or other provoking factors and another one was diagnosed with reflex epilepsy after vaccination. A case report from India stated that a healthy older male had the first-ever seizure following the first dose of the vaccine[15]. Investigations after the event showed normal electroencephalography for age, but ASM was started as mild periventricular leukoaraiosis was seen in the brain MRI. No further seizure was reported at the subsequent one-month follow-up. Only one person with new-onset seizures in vaccinated individuals was reported in the premarketing phase of Chinese vaccines. We reported the second case of a seizure and the first case of reflex epilepsy in healthy subjects. Long term follow-up and larger cohorts are warranted to test causality.

For people with epilepsy, whether the vaccination will trigger a seizure or cause other epilepsy-specific side effects was a frequently asked question. No case of status epilepticus was reported after vaccination. Fewer than 10% reported seizure increase after vaccination, which might be coincidental. There was no evidence of seizure worsening in the group as whole and it's hard to interprete the causality because the absence of the data from unvaccinated control. Nearly one-third of those reporting an increase had stopped or reduced their ASM, fearing potential interaction with vaccinations. The reasons for the rise in seizures in the others remain unclear. Previous reports also reported a few people with seizure increases or status epilepticus for unknown reasons after vaccination[5]. Though the safety of vaccines requires long-term studies, current evidence suggests they

are likely to be safe. Intensive education programs are urgently needed to improve the coverage of the vaccine

Our study has several limitations: Firstly, the questionnaires were retrospective and self-reported, introducing bias. Secondly, participating hospitals were tertiary centres which might not represent the general population of people with epilepsy. Thirdly, the generalisation of our results to other populations should be cautious, as the vaccination types and guidelines vary. For example, this present study could not fully reflect the tolerability of mRNA vaccines. We only enrolled adults, and most had inactivated vaccines. Even though we have a relatively large group of people interviewed, we did not perform further analysis in seizure worsening, for the small number of people who reported seizure worsening and the lack of data in frenquncy change in unvaccinated people with epilepsy. In the future, studies with a larger cohort focusing on particular groups such as children or people with comorbidities are warranted to provide a clearer picture of vaccination safety in people with epilepsy.

Conclusion

Our data from a multicentre study in China suggest that the take-up rate of vaccines in people with epilepsy was far behind their age-matched counterparts. The general post-vaccination effect including local injection site skin adverse events, muscle pain, fatigue, was no higher than in controls, which should generate with caution. No evidence suggested seizure worsening due to the vaccination. Despite the generalisation of our results to other populations with different vaccine types and guidlines should be cautious, education focused on increasing the vaccine coverage in people with epilepsy is warranted.

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Ethical Publication Statement

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

Disclosure

Neither of the authors has any conflict of interest to disclose.

Reference

1. U.S. Food & Drug adminisstration. Pfizer-BioNTech COVID-19 Vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine. Accessed 2021/08/21.
2. U.S. Food & Drug Administration. Moderna COVID-19 Vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine. Accessed 2021/08/21.
3. World Health Organization. COVID-19 advice for the public: Getting vaccinated. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice. Accessed 2021/08/21.
4. Pruna D, Balestri P, Zamponi N, Grosso S, Gobbi G, Romeo A, et al. Epilepsy and vaccinations: Italian guidelines Epilepsia. 2013 Oct;54 Suppl 7:13-22.
5. 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 & behavior. 2021 Jun 21;122:108160.
6. 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 Aug 6;92:2-9.
7. Chinese Center for Disease Control and Prevention. Technical Guidelines for COVID-19 Vaccination (First Edition). Available at: http://www.nhc.gov.cn/xcs/yqfkdt/202103/c2febfd04fc5498f916b1be080905771.shtml. Accessed 24 Aug 2021.
8. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy.New England Journal of Medicine. 2011;365(10):919-926.
9. Vaccinations by location. Available at: https://ourworldindata.org/covid-vaccinations?country=OWID_WRL. Accessed 24 Aug 2021.
10. The International League Against Epilepsy. COVID-19 vaccines and people with epilepsy. Available at: https://www.ilae.org/patient-care/covid-19-and-epilepsy/covid-19-vaccines-and-people-with-epilepsy
Accessed 24 Aug 2021.
11. Department of Disease Control. Covid vaccination guideline(updated August 2021) 2021.
12. COVID-19 vaccination first phase priority groups. Available at: https://www.gov.uk/government/publications/covid-19-vaccination-care-home-and-healthcare-settings-posters/covid-19-vaccination-first-phase-priority-groups. Accessed 24 August 2021.

13. Vaccines for COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html. Accessed 24 August 2021.
14. Puteikis K, Mameniskiene R. Factors Associated with COVID-19 Vaccine Hesitancy among People with Epilepsy in Lithuania. International journal of environmental research and public health. 2021 Apr 20;18(8).
15. Ghosh R, Dubey S, Roy D, Mandal A, Naga D, Benito-Leon J. Focal onset non-motor seizure following COVID-19 vaccination: A mere coincidence? Diabetes Metab Syndr. 2021 May-Jun;15(3):1023-1024.

Figure Legend

Figure 1. The COVID-19 vaccine programme started in December 2020. The first injection rate among people with epilepsy (in grey) is lower than in the other two control groups throughout the whole period.