SARS-CoV-2 vaccination in paediatric patients with epilepsy: experience of a tertiary center in Colombia

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Aim. The objective of this study is to evaluate effects of SARS-CoV-2 vaccination on seizure pattern in paediatric patients with epilepsy that attended our tertiary center in the city of Bogotá, Colombia.

Patients and methods. Children with epilepsy who were treated at our center and have had SARS-CoV-2 vaccination and their caregivers were asked to report their experience following vaccination. We documented age, sex, age at onset of epilepsy, duration of epilepsy, epilepsy type, seizure frequency, number of medications, time from last crisis, vaccination schemes, and seizures two weeks after vaccination.

Results. One hundred and one patients with epilepsy were included (58%, male; and 42%, female). The average age was 11 years, 73% had focal epilepsy, and 27%, generalized. Twenty-one fulfilled criteria for refractory epilepsy and 11 had a personal history of febrile seizures. Forty-seven patients had been vaccinated with Sinovac's vaccine; 41 patients, with Pfizer's; 12 patients, with Moderna's; and one, with CoronaVac's. Three patients presented seizures 24 hours after the application of the vaccine with no clear relation between vaccination and seizure frequency, and one patient required admission to the hospital for a prolonged seizure.

Conclusion. Vaccination against SARS-CoV-2 in paediatric patients with epilepsy is safe. Approximately 3% of patients with epilepsy could eventually have seizures in the post-vaccination period.

Key words. Adverse reactions. COVID-19. COVID-19 vaccination. Epileptic status. Febrile seizures. Paediatric epilepsy.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a contagious virus responsible for COVID-19 disease, which was initially identified in Wuhan, China. SARS-CoV-2 spread quickly and was designated to be the cause of a pandemic by early 2020. SARS-CoV-2 was noted to have high transmissibility and it spread across wide geographical areas rapidly, resulting in high levels of morbidity and mortality [1].

SARS-CoV-2 is the third novel coronavirus to cause a large-scale epidemic in the twenty-first century, after SARS-CoV in 2003 [2] and the Middle East respiratory syndrome coronavirus in 2012 [3]. Coronavirus is a single stranded RNA virus that encodes different proteins including structural proteins such as: spike, nucleocapsid, envelope and glycoprotein; and also non-structural proteins such as RNA-dependent RNA polymerase and hemagglutinin as viral envelope glycoproteins [4].

The pandemic had a massive impact on global public health and the development of a safe and effective vaccine was a priority to control the virus and help restore normal social and economic life [5].

In 2020 and 2021, multiple treatment schemes were developed. Of those, only vaccines showed superior efficacy in reducing mortality and severity of presentation of coronavirus infection. At the time of writing, more than 190 vaccines have been developed, 74 vaccines have been evaluated in phase III clinical trials and 38 have been approved [6]. According to the World Health Organization's data, over 500 million confirmed cases and over six million deaths have been reported globally, of which 13,400 were children [7]. The strategy led by World Health Organization set two linked goals: to protect individual and public health, and to minimize societal and economic impact, by focusing vaccination efforts on the reduction of mortality, hospitalization, and severe disease [8].

Epilepsies are a group of chronic neurological diseases and are associated with increased morbidity and mortality. The average incidence of epilepsy is 61.4 per 100,000 people/year, and the incidence in low and middle-income countries is 139 per

100,000 people/year, while in high-income countries it is 48.9 per 100,000 people/year [9]. Acute symptomatic seizures are defined as clinical seizures occurring at the time of, or in close temporal relationship with, a documented central nervous system or systemic insult. The etiology of acute symptomatic seizures can be metabolic, toxic, structural, infectious, or inflammatory [10]. These seizures are a common reason for medical admission and require urgent investigation. SARS-CoV-2 vaccination can result in fever as a major adverse effect, and this is considered as one of the most prevalent triggers of acute symptomatic seizures [11].

In Colombia, the vaccination process against SARS-CoV-2 started in March 2021. From November 2021, the use of Sinovac and CoronaVac vaccines were authorized in children under 12 years of age, in addition to the previously approved schemes of Moderna and Pfizer.

There is evidence that some people with epilepsy, especially those with a history of febrile seizures, have concerns regarding the safety of vaccination against SARS-CoV-2 [12]. Based on the above, knowledge concerning SARS-CoV-2 vaccination, including tolerance and complications in people with epilepsy, became crucial in our routinary day, which is why we decided to share our clinical experience by analyzing 101 followed up patients.

Patients and methods

After SARS-CoV-2 vaccination was approved in the paediatric population, this study commenced and a follow-up of paediatric patients with epilepsy who were vaccinated was done in a tertiary epilepsy center.

A prospective, cross-sectional cohort study was conducted to identify the incidence of fever and seizures after the administration of the vaccine, and the presence of post-vaccination status epilepticus.

Our study criteria included patients aged 18 years or less who received care at outpatient or inpatient facility between December 2021 and April 2022. All people with a diagnosis of epilepsy, that was either controlled, active, or refractory, were included. Children with epilepsy not receiving pharmacological treatment for seizure control were also included.

Demographic data such as age and sex were recorded. Epilepsy variables including age at onset of epilepsy, duration of epilepsy, epilepsy type, seizure frequency, number of medications, time from last crisis, and vaccination schemes were also documented.

A period of up to two weeks after vaccination was determined to reflect vaccination-related events.

Results

During the study period, 101 patients visited the child neurology department of our tertiary center and were included. Clinical data and vaccination status was available in all cases. Fifty-nine were males and 42 females, and the average age was 11 years, ranging between 3 to 17 years.

Seventy-four patients had focal epilepsy, including one that had Panayiotopoulos syndrome. On the other hand, 27 patients had genetic generalized epilepsy; four, childhood absence epilepsy; three, juvenile myoclonic epilepsy; one, Jeavons syndrome; and one, Dravet syndrome. Twenty-one out of 101 fulfilled the criteria for refractory epilepsy and only 11 (10.8%) had a personal history of febrile seizures.

Of the 101 vaccinated patients, 33 had only one dose, while the remaining 68 had a complete vaccination scheme with two doses of the vaccine administered. 47 patients had been vaccinated with Sinovac's vaccine; 41 patients, with Pfizer's; 12 patients, with Moderna's; and one patient, with CoronaVac's.

Fifteen patients developed post-vaccination fever, with no seizures within two weeks of vaccination. Three children with epilepsy (2.97%) presented seizures in the 24-hour period after vaccine administration. These patients had a high seizure frequency (approximately, one crisis every two days), so the relationship between vaccination and the rate of recurrence of seizures was unclear.

One patient required admission to the hospital for a prolonged seizure and received management with intravenous benzodiazepines with no intensive care unit admission required. This patient was known to present prolonged non-epileptic paroxysmal events, however status epilepticus remained possible.

One of the participants was a known carrier of the SCN1A mutation, with a history of multiple episodes of febrile status epilepticus. It did not have increased seizures after vaccine application.

Another patient was a CDH2 mutation carrier with daily seizures and there was no change in its frequency or presence of status epilepticus (Table and Figure).

Discussion

Fear of vaccination in people with epilepsy has a

long history that has required extensive review and has motivated multiple studies in literature in order to provide evidence and support for it to be resolved. However, now-a-days reluctance to vaccination persists, in both the general population as well as in people with epilepsy, and this is why it has been an important focus for many study groups to address the reasons why hesitation continues.

In a study by Lu et al [12], 53% of adult patients reported fear in relation to the possible adverse effects of SARS-CoV-2 vaccination, and 47% had concerns about losing seizure control post-vaccination. Further, in a study by Massoud et al [13], one hundred and eleven people with epilepsy in Kuwait were assessed, and fear of adverse effects (42.9%) and worsening of epilepsy (23.8%) were the main reasons for vaccine hesitancy.

Asadi-Pooya et al [14] surveyed 582 people with epilepsy and other chronic conditions, and identified 11.3% who were not willing to receive a SARS-CoV-2 vaccine. This study demonstrated that comorbid psychiatric disorders and male sex were significantly associated with hesitancy, whereas Puteikis et al [15], in Lithuania, reported that the willingness to be vaccinated against SARS-CoV-2 among people with epilepsy and their caregivers was associated with receiving an influenza vaccine in 2020, belief in vaccine safety and as an effective means to acquire immunity.

Qiao et al [16] analyzed attitudes towards vaccination against SARS-CoV-2 in people with epilepsy in China and concluded that education level, urban living, and seizure freedom were significantly correlated with willingness to receive the vaccine.

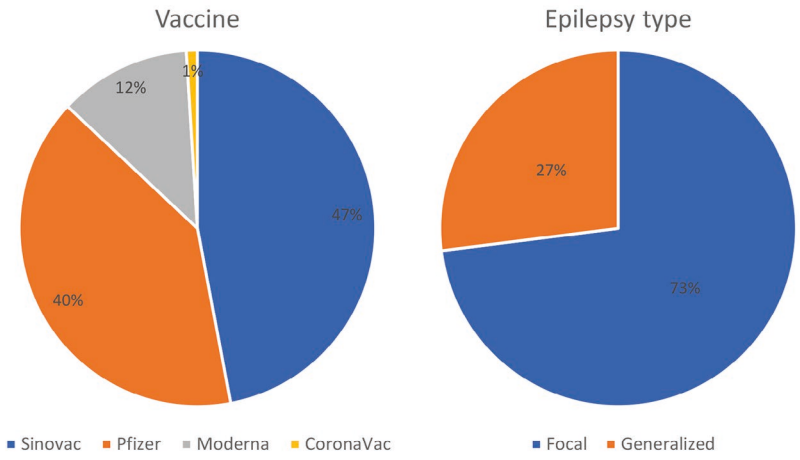
In a cohort of people with epilepsy from China, the causes of doubts related to vaccination were evaluated by Li et al [17]. Fifty eight percent of those evaluated were afraid of seizure worsening after vaccination, 22% were discouraged by medical personnel, who advised them not to be vaccinated, and 13% feared other potential effects of the vaccines. It is important to take into account the impact that medical personnel's knowledge and beliefs have in this matter. Asadi-Pooya et al [18] studied the opinion of physicians on the necessity of SARS-CoV-2 vaccination in people with epilepsy. One hundred and sixteen neurologists and 86 psychiatrists were included, and 74% confidently recommended SARS-CoV-2 vaccine. However, only 49% recommended it to all patients, and others would consider it in special populations only.

In terms of effects of vaccination on seizure pattern, Romozzi et al [19] studied the impact of SARS-CoV-2 vaccine on epilepsy in adults from It-

Table. Patients' characteristics (n = 101).

Demographic features	
Male/female	59 (58%)/42 (42%)
Age (years)	3-17 years (mean: 11 years)
Age at onset of epilepsy (years)	0.2-13 years (mean: 8 years)
Epilepsy syndrome	
Focal	74 (73%)
Panayiotopoulos	1 (1.3%)
Generalized	27 (27%)
Childhood absence epilepsy	4 (14%)
Juvenile myoclonic epilepsy	3 (11%)
Dravet syndrome	1 (4%)
Jeavons syndrome	1 (4%)
Seizure free	65 (64%)
Daily Seizure Frequency	1 (0.9%)
Medical therapy	
On antiseizure medication	78 (77%)
Use of ≥ 2 antiseizure medication	23 (23%)
Scheme	
One dose	33 (32.6%)
Two doses (complete scheme)	68 (37.4%)
Vaccines	
Sinovac	47 (46.5%)
Pfizer	41 (40.5%)
Moderna	12 (11.8%)
CoronaVac	1 (0.99%)
Post-vaccination symptoms	
Fever	15 (14.8%)
Seizures within 24 hours after vaccination	3 (2.97%)
Hospital admission for prolonged seizure	1 (0.9%)

Figure. Pie charts of SARS-CoV-2 vaccines used and epilepsy types.



aly. Of 358 participants, 92.4% did not experience an increase in seizure frequency, and those with seizure worsening had a higher pre-vaccine seizure frequency. This was similar in our study. Li et al [17] reported that none of the vaccinated patients in their study had a vaccine result in worsening of seizure control. Lu et al [12] carried another study in adults and registered 19 people out of 981 that had increased seizure frequency in the post-vaccination period, with no cases of status epilepticus.

Massoud et al [13] surveyed 111 people with epilepsy and, out of the vaccinated, 93.9% did not report seizure worsening after vaccination. The relative risk of seizure worsening after the first and second doses of Pfizer and the first dose of AstraZeneca vaccines was 1.027 (95% confidence interval: 0.891-1.183), 1.019 (95% confidence interval: 0.928-1.119) and 1.026 (95% confidence interval: 0.929-1.134), respectively, and only one patient reported status epilepticus. In Von Wrede et al study [20] 54 patients were evaluated and only one reported an increased seizure frequency after SARS-CoV-2 vaccination. Another patient reported a change in ictal semiology, with no reports of patients with epilepsy who developed post-vaccination status epilepticus.

In a study carried out by Özdemir et al [21] no increase in seizure frequency was found in patients with epilepsy who recorded their seizures one month before vaccination, in the period between doses of the vaccine, and one month after the last dose was applied. In a series of patients with Dravet syndrome, analyzed by Clayton et al [22], 3 of 15 patients were reported with increased seizure frequency after the first dose of the vaccine, without the same increase after the second. Hood et al [23] observed no status epilepticus cases in adult patients with Dravet syndrome after vaccination, and no worsening of seizures in temporal relation to vaccination in the majority of cases.

In the present study, in patients who presented seizures it was difficult to distinguish whether they were related to vaccination or due to high baseline seizure frequency. No direct link has been found between SARS-CoV-2 vaccines and epileptic seizures, and the majority of evidence supports that, even though some patients may experience fever, fever associated with the infection and the infection itself implies a higher risk in people with epilepsy.

One of the strengths of the present study was the inclusion of vaccines that are being used in low- and middle-income countries, as well as other vaccines already authorized by the United States Food and Drug Administration and European Medicines Agency. This vaccination spectrum, that includes types of vaccines different from those previously reported is essential, given that a large proportion of patients with epilepsy will be vaccinated with these agents in several regions of the world.

The evaluation of paediatric patients allows important and novel information to be considered as evidence to inform people with epilepsy. This is the first study, to our knowledge, that includes 44 patients under 11 years of age and with multiple types of epilepsy, demonstrating the safety of vaccination against SARS-CoV-2 in the youngest with epilepsy, even if they have heterogeneous etiologies for their epilepsy, frequency and patterns of seizures.

Limitations of the study include that the report of seizures depended mainly on parental reports and these could be affected by recall bias. However, the fact that resurgence of seizures is a traumatic event makes the report more authentic.

Conclusion

To conclude, based on this present review of the salient literature and from the results obtained from our study, vaccination against SARS-CoV-2 in paediatric patients with epilepsy is safe.

According to our data, approximately 3% of patients with epilepsy could eventually have seizures in the post-vaccination period, and status epilepticus is unlikely.

These results should be considered by medical personnel in order to support their knowledge, and guide the information provided to relatives of patients with epilepsy and paediatric patients with epilepsy, who may have doubts about getting the SARS-CoV-2 vaccine.

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Vacunación contra el SARS-CoV-2 en pacientes pediátricos con epilepsia: experiencia de un centro terciario en Colombia

Objetivo. El objetivo de este estudio es evaluar los efectos de la vacunación contra el SARS-CoV-2 sobre el patrón convulsivo en pacientes pediátricos con epilepsia que acudieron a nuestro centro terciario en la ciudad de Bogotá, Colombia.

Pacientes y métodos. Se pidió a los niños con epilepsia que fueron tratados en nuestro centro y que habían recibido la vacuna contra el SARS-CoV-2 y a sus cuidadores que informaran de su experiencia después de la vacunación. Se documentaron la edad, el sexo, la edad de inicio de la epilepsia, la duración de la epilepsia, el tipo de epilepsia, la frecuencia de las convulsiones, el número de medicamentos, el tiempo transcurrido desde la última crisis, los esquemas de vacunación y las convulsiones dos semanas después de la vacunación.

Resultados. Se incluyó a 101 pacientes con epilepsia (58%, hombres; y 42%, mujeres). La edad promedio fue de 11 años, el 73% tenía epilepsia focal, y el 27%, generalizada. Veintiuno cumplían los criterios para la epilepsia refractaria y 11 tenían antecedentes personales de convulsiones febriles. Cuarenta y siete pacientes habían sido vacunados con la vacuna de Sinovac; 41, con Pfizer; 12, con Moderna; y uno, con CoronaVac. Tres pacientes presentaron convulsiones 24 horas

después de la aplicación de la vacuna sin una relación clara entre la vacunación y la frecuencia de las convulsiones, y un paciente requirió ingreso en el hospital por una convulsión prolongada.

Conclusión. La vacunación contra el SARS-CoV-2 en pacientes pediátricos con epilepsia es segura. Aproximadamente el 3% de los pacientes con epilepsia podría eventualmente tener convulsiones en el período posterior a la vacunación.

Palabras clave. COVID-19. Crisis febriles. Epilepsia pediátrica. Estado epiléptico. Reacciones adversas. Vacunación contra la COVID-19.