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Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine

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ABSTRACT

Vaccines are the most effective strategy to mitigate the global impact of COVID-19. However, vaccine hesitancy is common, particularly among minorities. Guillain-Barré syndrome (GBS) is the most common autoimmune illness of the peripheral nervous system, occurring at an incidence of 1.1/100,000 worldwide. A causal link between mRNA vaccines and GBS has not been previously evaluated. We analyzed a cohort of 3,890,250 Hispanic/Latinx recipients of the BNT162b2 mRNA vaccine (613,780 of whom had already received both doses) for incident GBS occurring within 30 days from vaccine administration. Seven cases of GBS were detected among first-dose recipients, for an observed incidence of 0.18/100,000 administered doses during the prespecified timeframe of 30 days. No cases were reported after second-dose administration. Our data suggest that, among recipients of the BNT162b2 mRNA vaccine, GBS may occur at the expected community-based rate; however, this should be taken with caution as the current incidence of GBS among the unvaccinated population against COVID-19 is still undetermined. We hope that this preliminary data will increase the public perception of safety toward mRNA-based vaccines and reduce vaccine hesitancy.

1. Introduction

Within months after the first case of SARS-CoV-2 infection was detected, two mRNA vaccines, BNT162b2 (*Pfizer-BioNTech*) [1] and mRNA-1273 (*Moderna*) [2] have demonstrated to reduce COVID-19 incidence and severity effectively [3]. Despite the magnitude of the pandemic or the availability of effective vaccines, hesitancy toward vaccines is not uncommon, particularly, but not exclusively among minorities [4–6]. Hypothetically, vaccines may lead to the loss of self-tolerance and autoimmune disease and cause neural tissue damage, although, with current vaccines, the association is neither supported by empirical nor epidemiological [7,8].

Guillain-Barré syndrome (GBS) is the most common autoimmune disorder of the peripheral nervous system, resulting in flaccid paralysis and areflexia [9]. GBS may occur spontaneously after bacterial or viral infections, and it has been historically linked to several vaccines, but epidemiological studies have not found a direct association between current vaccines and GBS [10,11]. Globally, the annual estimated incidence rate of GBS in adults ranges from 0.84–1.91/100,000 persons/year [9,12]. In Mexico, the reported incidence ranges from 0.2 to 0.71/100,000 persons/year [9,13]; in a preliminary report, we observed an incidence of 0.43/100,000 administered doses among 704,003 recipients of the first dose of BNT162b2 vaccine [14]. Here, we report an update on the incidence of GBS among recipients of the BNT162b2

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Table 1
Characteristics of Guillain-Barré syndrome cases after the first dose of the BNT162b2 mRNA COVID-19 vaccine.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Sex/age, years	M/33	M/25	F/53	M/72	M/31	F/67	F/81
Medical history	Inverse psoriasis Food allergy	Food allergy	Drug allergy	None	None	None	Smoking Hypertension CKD (hemodialysis)
History of COVID-19	No	No	Yes	No	No	No	No
Current COVID-19	No	No	No	No	No	No	No
Preceding diarrhea (≤ 4 weeks)	No	Yes	Yes	Yes	No	No	No
Associated trigger[a]/ temporality	Acute hepatitis A/25 days	Gastrointestinal infection/8 days	Norovirus/2 days	Acute hepatitis A/56 days	None documented	None documented	Influenza vaccine/ 40 days
Interval vaccine-GBS-symptoms	28 days	12 days	6 days	4 days	11 days	4 days	3 days
GBS signs and symptoms[b]	Facial diplegia and loss of deep tendon reflexes.	Symmetric weakness (MRS 2/5) and paraesthesia of hands and feet.	Quadriparesis and loss of deep tendon reflexes.	Quadriparesis and decreased deep tendon reflexes (+).	Symmetric weakness (MRS 2/5) and loss of deep tendon reflexes.	Quadriparesis, loss of deep tendon reflexes, and respiratory failure.	Asymmetric weakness (arms MRS 3/5; legs MRC 1/5) and loss of deep tendon reflexes.
Admission GBS disability score	1	4	5	4	4	5	4
EGRIS	3	3	5	5	4	6	3
CSF findings/days GBS-symptoms to lumbar puncture	Proteins: 67.1 mg/dL, WBC: 0, glucose: 61 mg/dL/7 days	Proteins: 64 mg/dL, WBC: 20, glucose: 54 mg/dL/5 days	Proteins: 15 mg/ dL, WBC: 0, glucose: 84 mg/ dL/3 days	Not performed	Not performed	Proteins: 30 mg/ dL, WBC: 22, glucose: 84 mg/dL/ 2 days	Proteins: 414 mg/ dL, WBC: 0, glucose: 65 mg/dL/13 days
Electrophysiological variant	AIDP	AIDP	AMAN	AMAN	AIDP	AMAN	AIDP
Treatment	IVIg	IVIg	IVIg	IVIg	IVIg	IVIg	IVIg
Brighton Collaboration group certainty level	Level 1	Level 1	Level 2	Level 2	Level 2	Level 2	Level 1
Invasive mechanical ventilation	No	No	Yes	No	No	Yes	No
1-week mEGOS	0	7	6	8	6	11	5
Hospital LOS	10 days	7 days	119 days	11 days	8 days	17 days	10 days
Current status	Discharged home	Discharged home	Hospitalized (IMV)	Discharged home	Discharged home	Dead	Discharged home
GBS disability score at discharge	1	3	5 (BPAP)	4	3	6	4

M, male. F, female. COVID-19, coronavirus disease 2019. CKD, chronic kidney disease. GBS, Guillain-Barré syndrome. MRC, Medical Research Council Muscle Strength Grading System. EGRIS, Erasmus GBS respiratory insufficiency score. CSF, cerebrospinal fluid. AIDP, acute inflammatory demyelinating polyradiculoneuropathy. AMAN, acute motor axonal neuropathy. mEGOS, modified Erasmus GBS outcome score. LOS, length of stay. IVIg, intravenous immunoglobulin. IMV invasive mechanical ventilation. NA, not applicable; BPAP, Bilevel positive airway pressure.

[a] Before Guillain-Barré syndrome symptoms.

[b] On admission.

mRNA COVID-19 vaccine in Mexico in a larger nationwide cohort of ~3.9 million recipients, including recipients of one or both doses of the vaccine.

2. Material and methods

2.1. Study design

We conducted a nationwide, retrospective, observational cohort study evaluating GBS incidence among recipients of the BNT162b2 mRNA COVID-19 vaccine in Mexico. Cases were also classified according to the Brighton Collaboration Diagnostic Criteria for GBS presenting as an AEFI [15].

2.2. Cohort description

The Mexican Ministry of Health (*Dirección General de Epidemiología; Secretaría de Salud, Gobierno de México*) monitors and collects information on adverse events following immunization (AEFI); this database is updated every 24 h and includes every adverse event reported to the local, state, or federal authorities nationwide. Surveillance is carried out for 30 days after vaccine administration; vaccine-specific, clinical, and epidemiological data are recorded. This passive system relies on reports by the healthcare providers as well as vaccine recipients themselves.

2.3. Study interval

We included all cases of GBS reported to the Mexican Ministry of Health by recipients of the BNT162b2 mRNA COVID-19 vaccine between December 24, 2020, and March 19, 2021.

2.4. Ethics and data management

The study was revised and approved by the Ethics and Research Committees of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (Ref. NER-3667-20-21-1).

3. Results

During the study period, a total of 3,890,250 persons had received at least one dose of the BNT162b2 mRNA COVID-19 vaccine, and 613,780 had received both doses in Mexico [16]; among them, seven cases of GBS following immunization were reported nationwide, all after the first dose of the vaccine, for an observed incidence of 0.18/100,000 administered doses. Demographic information, pre-existing medical conditions, clinical presentation, treatment, and outcome data are summarized in Table 1. In four cases, a gastrointestinal or systemic infection preceded the appearance of neurologic symptoms; in two of those, infections were still present at GBS onset. In three cases, viral

infections were confirmed; one patient (case two) had self-limited diarrhea of infectious characteristics shortly before GBS onset, but an infectious agent could not be identified by stool culture or molecular methods during the in-hospital stay. In two cases (cases five and six), an associated trigger could not be determined, and case number seven had previously received an influenza vaccine 40 days before GBS symptoms onset. As of the day of this report, there has been only one death (case six), which was related to ventilator-associated pneumonia complicated with septic shock, and the remaining six patients had been discharged home.

4. Discussion

In this large (~3.9 million) and diverse cohort reflective of a population-wide immunization program, we observed that the BNT162b2 mRNA COVID-19 vaccine did might increase the risk of GBS when compared to the expected community-based incidence in Mexico [13]; however, this should be taken with caution as the current incidences of GBS among the unvaccinated population against COVID-19 are currently unknown. Also, a reduction of other infections due to public health mitigation strategies may have reduced the observed incidence in the non-immunized population [17].

Interestingly, in most cases, concurrent infectious triggers were detected, suggesting that gastrointestinal infections -and not vaccines- may be responsible for most cases. Among several infections that may increase the risk of GBS, *C. jejuni* is the most common, particularly in the acute motor axonal neuropathy (AMAN) form. None of the four cases evaluated for *C. jejuni* tested positive; however, in three cases, acute enteric viral infections known to induce GBS (hepatitis A in two cases, norovirus in one) were confirmed. One patient (case seven) had been immunized against influenza 40 days before GBS onset; while both vaccines may have synergistically triggered an autoimmune response, this observed association seems to be coincidental, as millions of healthy people have received both vaccines in short succession without a subsequent outbreak of GBS.

Concomitant infections -particularly gastrointestinal and respiratory- in temporal association to the vaccine may induce transient immune changes, resulting in cross-reactivity against peripheral nerve components[18,19]. For instance, mucosal T_H17 cells are necessary for normal protection against gastrointestinal infections, playing a crucial role in IgA responses. However, T_H17 cells can also magnify inflammation and reduce tolerance, resulting in autoimmune diseases [20].

Our study has limitations, including that we relied on a passive surveillance system for this report. While cases of GBS may have occurred and not been reported, due to the paralytic nature of GBS we think that is unlikely. However, milder cases may have not been reported by the patient or may have been misdiagnosed, hence misclassified.

5. Conclusions

Our data show that GBS is infrequent among recipients of the BNT162b2 vaccine. The presence of a concomitant trigger in most of our cases suggests a lack of mechanistic connection between mRNA vaccines and GBS. This data from a large and diverse cohort indicates that at least considering GBS, mRNA vaccines are safe. Vaccines are our fastest and safest public health strategy to counter the pandemic. We hope that this data will strengthen the public perception of vaccine safety, helping to reduce vaccine hesitancy.

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