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Guillain-Barré syndrome following SARS-CoV-2 vaccination: Is there a real association?

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ABSTRACT

Background: Guillain-Barre Syndrome (GBS) is the most common cause of acute flaccid paralysis, with an incidence of 0.81–1.89 cases per 100,000. With the SARS-CoV-2 virus pandemic, major international vaccination campaigns continue to be carried out to minimize the total burden of the disease. This study aims to report a case series of consecutive GBS patients after SARS-CoV-2 vaccination during the massive campaign in Mexico in 2021.

Methods: A single-center, observational study of consecutive GBS subjects diagnosed by Asbury criteria from January 1 to August 31, 2021. Including GBS-related symptoms on or after six weeks of vaccination record, both first and second doses.

Results: From a total of 53 GBS patients, eight had a history of SARS-CoV-2 vaccination, 87.5% male, the median vaccination-symptom onset and symptom-to-admission time were 15 (IQR 12.75–23.25), and 3.5 (IQR 1.5–8.25), all of them had GBS Disability Scale ≥3 at admission. Acute inflammatory demyelinating polyneuropathy (AIDP) was the most common electrophysiological variant encountered in this population. All patients received treatment Intravenous Immunoglobulin (IVIG) or Plasma Exchange (PE), 62.5% recovered independent walk at three months follow up.

Conclusion: The annual incidence of GBS cases associated with vaccination remains lower (0.81 - 1.89 cases / 100,000 persons) than non-vaccinated patients; this should encourage health authorities to continue promoting massive vaccination as benefits outweigh the risks.

Introduction

Guillain-Barre Syndrome (GBS) is the most common cause of acute flaccid paralysis globally, with an incidence of 0.81–1.89 cases per 100,000 individuals (McGrogan et al., 2009). This syndrome has two classic electrophysiological variants: acute inflammatory demyelinating polyneuropathy (AIDP) and axonal variants, such as acute motor axonal neuropathy (AMAN) and acute sensorimotor neuropathy (AMSAN) (Van den Berg et al., 2014). Although these variants have different epidemiological distribution, AIDP is more frequent in the United States and Europe in up to 90% of patients. In contrast, axonal variants remained the most prevalent forms in Latin American countries like Mexico with 45.4%, followed by 40.9% of AIDP cases (Van den Berg et al., 2014; López-Hernández et al., 2020).

GBS cases have been observed after massive vaccination campaigns, such as rabies, hepatitis A and B (HAV, HBV), and influenza viruses (Koike et al., 2021). With the SARS-CoV-2 virus pandemic, massive vaccination campaigns are ongoing worldwide to lower the significant disease burden. Several published reports describe a possible association of GBS after these vaccines, although causality is yet to be established (Trimboli et al., 2021). The first SARS-CoV2 vaccine-related case was reported in February 2021 in the US, followed by a Qatar case, both associated with the BNT162b2 vaccine (Razok et al., 2021).

We aim to report a case series of consecutive GBS patients after SARS-CoV-2 vaccination during the massive campaign in Mexico in 2021.

Material and methods

We carried out a single-center, observational study in a prospective cohort of consecutive GBS subjects diagnosed by Asbury criteria (Asbury and Cornblath, 1990) from January 1 to August 31, 2021. We included patients who presented with GBS-related symptoms on or after six weeks of vaccination record and first and second doses.

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We collected the following information: age, gender, previous infection history, vaccination-symptom onset (days from vaccination to GBS), GBS Disability Scale (GBD) and Medical Research Council (MRC) score upon admission, cranial nerve involvement, and applied treatment: Intravenous Immunoglobulin (IVIG), Plasma Exchange (PE). In addition, we performed lumbar puncture and nerve conduction studies (NCS). Rajabally criteria were applied (Hadden et al., 1998) to determine the mechanism of peripheral nerve damage, and Brighton criteria to establish the level of certainty of GBS (Sejvar et al., 2011).

Statistical analysis

According to data distribution, descriptive statistics are represented with frequencies and percentages for categorical variables and means (SD) or medians (IQR) for quantitative variables. We carried out data processing using SPSS version 22.0. The Local Ethics Committee approved the study protocol.

Results

Of a total of 53 GBS patients, thirteen had a history of SARS-CoV-2 vaccination, five of them had previous infection history. Finally, we included eight patients in the analysis with a median age of 50 (IQR 46.25–58.50) years, seven patients (84.6%) were male, the median vaccination-symptom onset and symptom-to-admission time were 15 (IQR 12.75–23.25) and 3.5 (IQR 1.5–8.25) days, respectively. Every patient had lost independent walk at admission; the MRC score was 25.25 ± 16.8 points. Tree vaccinated patients (37.5%) required invasive mechanical ventilation, with a mean duration of 34 (IQR 21–37.5) days.

Seven patients had a lumbar puncture performed; five patients (71.4%) had it done within a week from symptom onset, and four (57.1%) presented albumin-cytological dissociation. Nerve conduction studies were performed in 7 patients, 5 (71.4%) were AIDP, 1 (14.2%) inexcitable and 1 (14.2%) equivocal.

According to Brighton criteria, four patients (50%) fulfilled certainty level 1, two (25%) level 2, and two (25%) level 3. We show clinical characteristics in Table 1. We observed an increased incidence of AIDP-GBS in 2021 compared to the previous years (51.3% in 2021 vs. 48.9% in 2020 vs. 34.0% in 2019, $p = 0.20$). Electrophysiological variants distribution is depicted in Fig. 1.

All patients received treatment (six on IVIG and two with PE). At three months follow up, five (62.5%) patients recovered independent walk and improved MRC score to 42.5 ± 17.3.

We observed increased bimestrial distribution of GBS cases in January-February and July-August this year when compared to previous years 28.3% (2021), 7.6% (2020) and 8% (2019) ($p = 0.003$), and 32% (2021), 13.4% (2020) and 14%(2019) ($p = 0.025$) respectively. We show this data in Fig. 2.

Discussion

Guillain-Barré syndrome is produced by an aberrant immunological response to the peripheral nervous system, with an identified trigger in up to 70% of the cases, more commonly an infection (respiratory or gastrointestinal) and less likely after vaccination (Van den Berg et al., 2014). With this, we present eight GBS cases developed within six weeks from SARS-CoV-2 vaccination, similar to previous publications regarding COVID-19 vaccination and GBS appearance (Sejvar et al., 2011).

Only five patients (38.4%) reported a previous infection before GBS-related symptoms, comparable with a recent report (García-Grimshaw et al., 2021). AIDP was the most common electrophysiological variant encountered in this population, opposite to previous Mexican epidemiological reports, where axonal variants were more common in Mexican children (59% and 87.5%) (Jackson et al., 2014; Larrosa-

Table 1
Patient´s clinical and paraclinical studies.

	Gender/ age	Vaccine type and number of doses/vaccination-symptom onset.	Previous infection	GBD score at admission/MRC	GBD/MRC at 3 months	Cranial nerves affected	Hypo/ arreflexia	Clinical variant	Lumbar puncture: Proteins (mg/dL)/Cells (/mm3).	Electrophysiologic variant	Level of Certainty (Brighton Criteria)	Treatment type
Patient 1	M/59	2nd dose Gam-COVID-Vac/38	No	4/30	2/48	No	Yes	MS	34/9	AIDP	2	PE
Patient 2	F/57	1st dose Gam-COVID-Vac /24	No	5/4	4/12	Bulbar	Yes	MS.	32/1	AIDP	2	IVIG
Patient 3	M/46	1st dose ChAdOx1/21	No	4/30	1/60	Facial biparesis	Yes	MS.	116/3	AIDP	1	IVIG
Patient 4	M/52	2nd dose Gam-COVID-Vac /15	No	5/16	3/26	Facial biparesis	Yes	MS	49/1	Inexcitable	1	IVIG
Patient 5	M/47	1st dose BNT162b2 /15	No	4/32	2/60	No	Yes	MS	14/3	Equivocal	3	IVIG
Patient 6	M/61	2nd dose BNT162b2 /15	No	5/12	1/56	Facial biparesis, bulbar	Yes	MS	–	–	3	IVIG
Patient 7	M/25	1st dose BNT162b2 /12	No	3/33	1/53	No	Yes	MS	64/2	AIDP	1	IVIG
Patient 8	M/48	1st dose ChAdOx1/7	No	3/19	2/47	No	Yes	MS	113/0	AIDP	1	PE

Abbreviations: AIDP (Acute Inflammatory Demyelinating Polyneuropathy), GBD (Guillain-Barré Disability score), IVIG (Intravenous Immunoglobulin Type G), MS (Motor and sensitive), PE (Plasma Exchange).

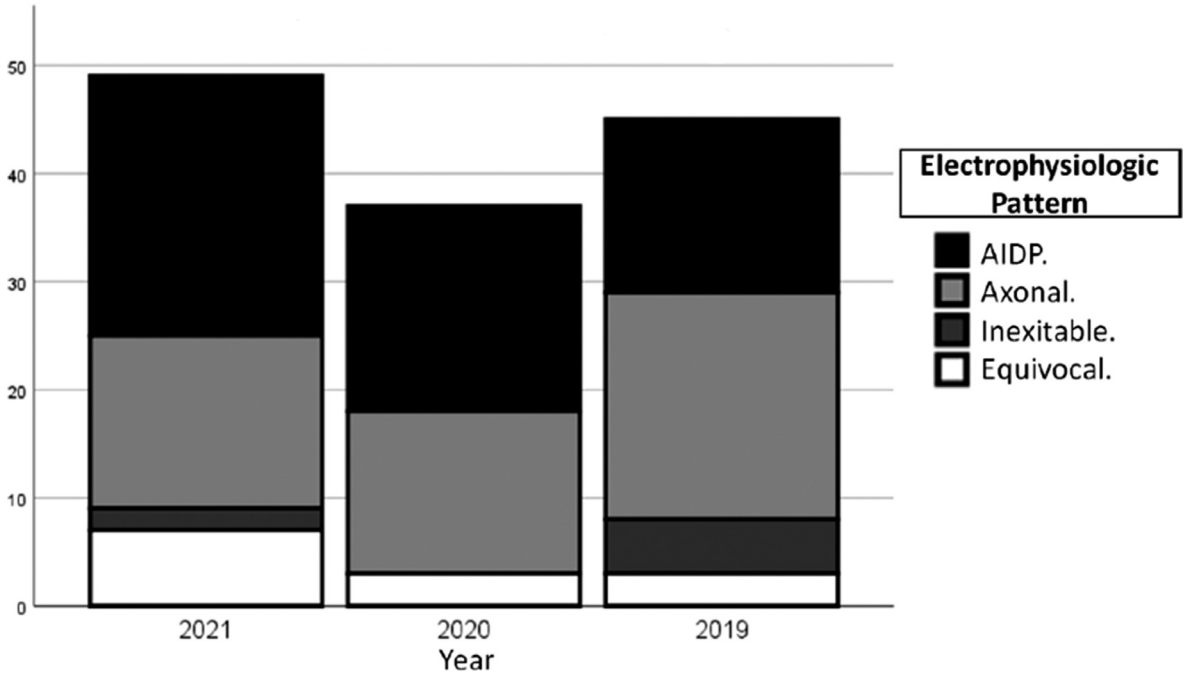

Fig. 1. Electrophysiological variants distribution by year.

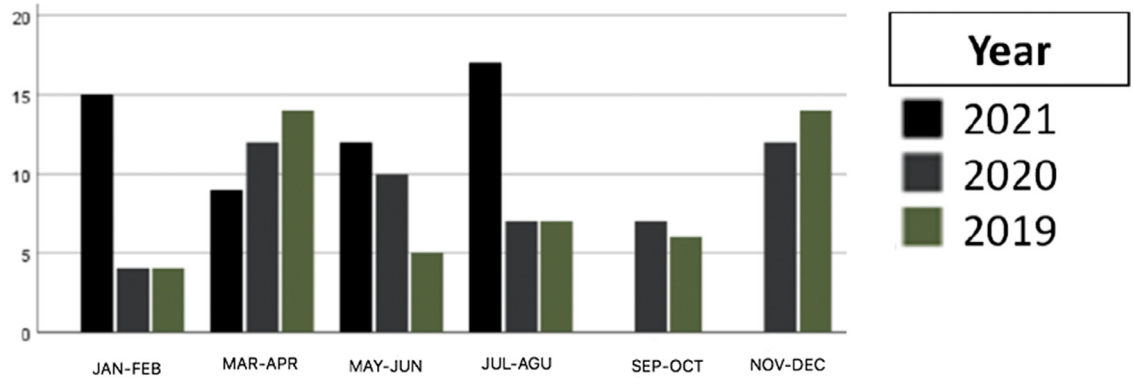

Fig. 2. Presentation of GBS cases per bimester period per year.

Haro et al., 2010). Moreover, bilateral facial palsy was observed in more than half of our patients, a feature commonly observed in demyelinating subtypes, as reported in other GBS patients following the COVID-19 vaccine (Bonifacio et al., 2021).

Four patients (50%) reached the first level of diagnostic certainty of Brighton criteria. Unfortunately, despite most patients presenting with the typical bilateral and flaccid weakness of limbs with decreased/absent deep tendon reflexes in a monophasic fashion, lumbar puncture was performed within a week of initial symptoms, decreasing the diagnostic yield of albumin-cytological dissociation and further decreasing the level of certainty using Brighton criteria (Van den Berg et al., 2014).

Currently, COVID-19 vaccines suggest at least 90% efficacy against symptomatic disease in clinical trials and are available in several countries; They project to prevent up to 60% of infections and 50% of deaths during a year (Swan et al., 2021). Furthermore, with a substantial decrease in SARS-CoV-2 infection, hospitalization, ICU admission, and overall mortality, it can rarely produce an aberrant immunological response such as Guillain-Barré syndrome; this has been observed in previous massive vaccination campaigns, such as with influenza viruses and poliovirus (Koike et al., 2021).

The potential association of vaccines and GBS was first brought to attention in 1976, following an influenza outbreak among new US Army recruits, revealing an almost 10-fold increased risk of development of GBS during the six weeks following vaccination (McKean and Chircop, 2021).

Nachamkin et al. hypothesized that the 1976 influenza vaccine, produced in hens' eggs, may contain contaminating proteins such as C. jejuni antigens that mimic human ganglioside, or the vaccine components may have elicited anti-ganglioside antibodies in some recipients. However, it was never proved (Nelson, 2012).

Several hypotheses not yet fully proven suggest a causal link between immunization against SARS-CoV 2 and GBS, one of them mentions that considering that COVID-19 vaccines induce immunization against SARS-CoV-2 spike proteins and SARS-CoV-2 spike protein can bind to sialic acid-containing glycoprotein and gangliosides on cell surfaces, an antibody cross-reaction may be the causal link between GBS and immunization to SARS-CoV-2 (Introna et al., 2021).

A slight increase in GBS cases was observed after the 2009 H1N1 monovalent influenza vaccines; however, the cumulative risk of GBS was significantly higher among the unvaccinated than the vaccinated population (9.2 vs. 6.6 per million persons), clearly outweighing the risks of vaccination (Vellozzi et al., 2014).

Moreover, COVID-19 vaccines and GBS reports are scarce, with no apparent association (Trimboli et al., 2021). However, another Mexican national health institute has reported seven GBS cases after 3890,250 people received at least one dose of BNT162b2Mrna (Pfizer) at the beginning of 2021, representing a low incidence of 0.18 per 100,000 vaccinated persons (García-Grimshaw et al., 2021).

Our tertiary care hospital comprises the primary referral center for neurological patients in Mexico City and the surrounding area. We usually attend 45–50 referred severe GBS cases a year. Interestingly, during the pandemic in 2020, we did not observe an increase in GBS cases, following a previous report from the UK (Keddie et al., 2021).

IVIG and PE are equally effective, and our center has experience with both treatment options; nevertheless, the final choice is mainly driven by the availability of any options at the time needed. (Sheikh, 2020)

Compared to European countries, the axonal variant is more common in Latin American patients due to poorer infection control (López-Hernández et al., 2020). Interestingly, we observed an increase in AIDP cases this year despite the axonal prevalence in our country (Van den Berg et al., 2014). We believe this change in electrophysiological variant relates to social distancing and public health measures implemented throughout the pandemic. Moreover, total GBS incidence has increased in our center this year, with 53 treated patients up to August 2021, contrary to local annual counts in 2019 and 2020.

Remarkably, we have seen more GBS cases reported with viral vector vaccines in our country (Oxford – AstraZeneca and Sputnik V) and other countries (Johnson & Johnson). GBS related to other vaccines that use vectors or attenuated viruses, such as influenza, tetanus, hepatitis B, and polio, has already been described (Lunn et al., 2021).

It will be more common soon to see GBS patients with a previous history of COVID-19 vaccination as public health measures become widely distributed throughout the country. However, the annual incidence of GBS cases associated with vaccination remains lower (0.81 – 1.89 cases/100,000 persons) than non-vaccinated patients, and this should not discourage health authorities from promoting massive vaccination as benefits outweigh the risks (McGrogan et al., 2009; Sheikh, 2020).

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Edwin Steven Vargas-Cañas, in behalf of all authors

References

McGrogan, A., Madle, G.C., Seaman, H.E., et al., 2009. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. Neuroepidemiology 32 (2), 150–163. doi:10.1159/000184748.

Van den Berg, B., Walgaard, C., Drenthen, J., et al., 2014. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat. Rev. Neurol. 10 (8), 469–482. doi:10.1038/nrneurol.2014.121.

López-Hernández, J.C., Colunga-Lozano, L.E., Garcia-Trejo, S., et al., 2020. Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience. J. Clin. Neurosci. 80, 292–297. doi:10.1016/j.jocn.2020.04.059.

Koike, H., Chiba, A., Katsuno, M, 2021. Emerging infection, vaccination, and Guillain-Barré syndrome: a review. Neurol. Ther. 12, 1–15. doi:10.1007/s40120-021-00261-4.

Trimboli, M., Zoleo, P., Arabia, G., et al., 2021. Guillain-Barré syndrome following BNT162b2 COVID-19 vaccine. Neurol. Sci. 4, 1–2. doi:10.1007/s10072-021-05523-5.

Razok, A., Shams, A., Almeer, A., et al., 2021. Post-COVID-19 vaccine Guillain-Barré syndrome; first reported case from Qatar. Ann. Med. Surg. (Lond.) 67, 102540. doi:10.1016/j.amsu.2021.102540.

Asbury, A.K., Cornblath, D.R., 1990. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann. Neurol. 27, S21–S24. doi:10.1002/ana.410270707, Suppl.

Hadden, R.D., Cornblath, D.R., Hughes, R.A., et al., 1998. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Plasma exchange/Sandoglobulin Guillain-Barré syndrome trial group. Ann. Neurol. 44 (5), 780–788. doi:10.1002/ana.410440512.

Sejvar, J.J., Kohl, K.S., Gidudu, J., et al., 2011. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29 (3), 599–612. doi:10.1016/j.vaccine.2010.06.003, 10.

García-Grimshaw, M., Michel-Chávez, A., Vera-Zertuche, J.M., et al., 2021. Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clin. Immunol. 230, 108818. doi:10.1016/j.clim.2021.108818.

Jackson, B.R., Alomia, J., López-Gatell, H., et al., 2014. Binational outbreak of Guillain-Barré syndrome associated with Campylobacter Jejuni infection, Mexico and USA, 2011. Epidemiol. Infect. 142 (5), 1089–1099. doi:10.1017/S0950268813001908.

Larrosa-Haro, A., Macias-Rosales, R., Sánchez-Ramírez, C., et al., 2010. Seasonal variation of enteropathogens in infants and preschoolers with acute diarrhea in western Mexico. J. Pediatr. Gastroenterol. Nutr. 51 (4), 534–536. doi:10.1097/MPG.0b013e3181df5b66.

Bonifacio, G.B., Patel, D., Cook, S., et al., 2021. Bilateral facial weakness with paraesthesia variant of Guillain-Barré syndrome following Vaxzevria COVID-19 vaccine. J. Neurol. Neurosurg. Psychiatry 14. doi:10.1136/jnnp-2021-327027, jnnp-2021-327027.

Swan, D.A., Bracis, C., Janes, H., et al., 2021. COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact. Sci. Rep. 11, 15531. doi:10.1038/s41598-021-94719-y.

McKean, N., Chircop, C., 2021. Guillain-Barré syndrome after COVID-19 vaccination. BMJ Case Rep. 14 (7), e244125. doi:10.1136/bcr-2021-244125, 30.

Nelson, K.E., 2012. Invited commentary: influenza vaccine and Guillain-Barre syndrome-is there a risk? Am. J. Epidemiol. 175 (11), 1129–1132. doi:10.1093/aje/kws194, 1.

Introna, A., Caputo, F., Santoro, C., et al., 2021. Guillain-Barré syndrome after AstraZeneca COVID-19-vaccination: a causal or casual association? Clin. Neurol. Neurosurg. 208, 106887. doi:10.1016/j.clineuro.2021.106887.

Vellozzi, C., Iqbal, S., Broder, K, 2014. Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin. Infect. Dis. 58 (8), 1149–1155. doi:10.1093/cid/ciu005.

Keddie S., Pakpoor J., Mousele C., 2021. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. 144(2):682–693. doi: 10.1093/brain/awaa433

Sheikh, K., 2020. Guillain-Barré Syndrome. Continuum (Minneap Minn) 26 (5), 1184–1204. doi:10.1212/CON.0000000000000929.

Lunn, M.P., Cornblath, D.R., Jacobs, B.C., et al., 2021. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. Brain 144 (2), 357–360. doi:10.1093/brain/awaa444, 3.