


ARTIGO ORIGINAL/ORIGINAL ARTICLE

The Incidence of Guillain-Barré Syndrome during COVID-19 Pandemic: A Portuguese Multicentric Retrospective Study

A Incidência da Síndrome de Guillain-Barré durante a Pandemia a COVID-19: Estudo Multicêntrico Retrospectivo Português

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Abstract

Introduction: Guillain-Barré syndrome (GBS) is a rare peripheral nervous system inflammatory disease with an annual estimated incidence of 1-2/100 000. Several studies relate GBS with vaccination, especially against influenza. The literature is discordant on GBS incidence during the pandemic. Additionally, while vaccination is globally ongoing, GBS cases have been associated with an inoculation against SARS-CoV-2. Objective: To evaluate COVID-19 vaccination-associated Guillain-Barré syndrome cases and to establish their real incidence.

Methods: Multicenter retrospective study with analysis of the GBS incidence and clinical characteristics in the pre-pandemic period (PPP), the pandemic pre-vaccination period (PPVP), and the pandemic vaccination period (PVP).

Results: Forty-seven cases of GBS were identified: 13 in the PPP, 11 in the PPVP and 23 in the PVP. An increase in GBS cases (77%) was observed during the PVP when compared to the PPP, but it was not statistically significant ($p = 0.10$). Although an increase of the non-AIDP phenotype after vaccination period was observed (34.7%), a statistically significant relationship was not found.

Conclusion: This study is the first Portuguese multicentric study regarding the incidence of GBS and SARS-CoV-2 infection and vaccination. We hypothesize that the slight decrease in GBS during the pandemic pre-vaccination period is probably due to hygienic measures implemented during the COVID-19 pandemic. Moreover, we found a small increase in the number of GBS cases with a possible relationship with COVID-19 vaccination. Prospective studies are necessary to better characterize this relationship and take further conclusions.

Resumo

Introdução: A síndrome de Guillain-Barré (SGB) é uma doença inflamatória rara do sistema nervoso periférico com uma incidência anual estimada em 1-2/100 000. Vários estudos relacionam a SGB com a vacinação, especialmente contra a gripe. A literatura é discordante quanto à incidência da SGB durante a pandemia. Atualmente a vacinação contra a COVID-19 está a decorrer mundialmente, e estão a ser descritos alguns casos de SGB associados às inoculações.

O nosso objetivo foi avaliar os casos de síndrome de Guillain-Barré associados à vacinação contra a COVID-19 e estabelecer a sua real incidência.

Métodos: Estudo retrospectivo multicêntrico com análise da incidência e características clínicas da SGB no período pré-pandémico (PPP), no período pandémico pré-vacinação (PPVP) e no período de vacinação pandémica (PVP).

Resultados: Foram identificados 47 casos de SGB: 13 no PPP, 11 no PPVP e 23 no PVP. Observou-se um aumento de casos de SGB (77%) durante o PVP quando comparado com o PPP, mas não foi estatisticamente significativo ($p = 0,10$). Embora tenha sido observado um aumento do fenótipo não-AIDP após o período de vacinação (34,7%), não foi encontrada uma relação estatisticamente significativa.

Conclusão: Este estudo é o primeiro estudo multicêntrico português sobre a incidência da infeção por SGB e SARS-CoV-2 e a vacinação. A nossa hipótese é que a ligeira diminuição do SGB durante o período pré-vacinal da pandemia se deve provavelmente às medidas de higiene implementadas durante a pandemia da COVID-19. Além disso, encontramos um pequeno aumento no número de casos de SGB com uma possível relação com a vacinação contra a COVID-19. São necessários estudos prospetivos para caracterizar melhor esta relação e tirar mais conclusões.

Introduction

Guillain-Barré syndrome (GBS) is a rare peripheral nervous system inflammatory disease with an annual estimated incidence of 1-2/100 000.^{1,2} Classically, GBS presents with a progressive ascendent muscle weakness pattern, along with a sensitive involvement, although its clinical presentation can be quite variable.¹ It is hypothesized that GBS is due to an immune system dysregulation caused by an external trigger (such as an infection, surgery, or pregnancy) in genetically susceptible individuals.¹ Several studies relate GBS with vaccination, especially against influenza, but, until now, there are no recommendations against its use.³

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus.⁴ It can have multiple clinical presentations, and neurological manifestations have been reported, namely GBS's demyelinating phenotype.⁵

The literature is discordant on GBS incidence during the pandemic. Some authors point towards an increase in GBS cases during the pandemic, suggesting a favorable SARS-CoV-2 post-infectious mechanism (and not a para-infectious mechanism).^{6,7} Other authors, however, uphold that there does not seem to be any epidemiological or phenotypical differences that allow establishing a causal relationship between COVID-19 and GBS.⁸ These authors also theorize that GBS incidence has decreased during the pandemic due to sanitary preventive

measures applied to withhold the disease dissemination (such as hand washing, confinement, etc).⁸ It is not yet clear however that COVID-19 patients are at a higher risk to develop GBS, nor there is evidence that supports a worse prognosis if it happens.

On the other hand, while vaccination is globally ongoing, more GBS cases have been associated with an inoculation against SARS-CoV-2, which has raised the hypothesis of a molecular mimicry mechanism or a bystander activation. Until October 2022, to our best knowledge, more than 50 cases had been described in the literature,⁹⁻¹⁸ and many more had been reported to the specific pharmacovigilance entities.¹⁰

Although these cases seem to strengthen the evidence in favor of a causal relationship between COVID-19 vaccination and GBS, given the non-neglectable disparity between clinical presentations, GBS classification and outcomes using clear criteria, besides important differences in methodologies, it may be precocious to make such an association.¹⁹ It is therefore important to correctly evaluate the GBS incidence in large-scale studies to prevent deleterious consequences from associating a severe disease such as GBS with an important public health measure.

Although health authorities have made a tremendous effort towards global vaccination, there is still an important percentage of non-vaccination supporters,^{20,21} mainly supported by disinformation regarding vaccina-

tion development and by the reported side-effects.²¹⁻²³ It is urgent to achieve favorable group immunization status to diminish COVID-19 transmissibility. To do so it is important to increase population knowledge of possible side effects and their real prevalence through effective health communication strategies. As such, it is extremely important to evaluate vaccination associated GBS cases and to establish its real incidence.

Methods

Data Sources

Data sources were the databases from three Lisbon area tertiary hospitals.

Study design

This study has a retrospective design, which included the review of clinical charts of the patients identified on the hospital databases. The following periods were analyzed: the pre-pandemic period (PPP), the pandemic pre-vaccination period (PPVP), and the pandemic vaccination period (PVP). The PPP included patients diagnosed between March 2019 - February 2020, the PPVP included patients from March 2020 - February 2021, and the PVP included patients from March 2021 - February 2022.

Inclusion and exclusion criteria

Inclusion criteria comprised: adults (>18 years old) with clinical symptoms of GBS according to the Brighton Collaboration Diagnostic Criteria for Guillain-Barré Syndrome, with a time from symptoms-onset until the date of diagnosis \leq 4 weeks; electromyographic confirmation (conduction velocities >2 motor nerves and >1 sensitive nerve) and cerebrospinal fluid compatible with GBS.

Exclusion criteria included: CSF pleocytosis (>50 cells), previous polyneuropathy, severe diabetes and severe intensive care myopathy (based on clinical and electromyographic criteria).

Data collected

The following data were collected from the clinical charts: age, gender, date of diagnosis, symptom-onset date, the subtype of Guillain-Barré syndrome, neurologic exam concerning the involvement of cranial nerves, dysautonomia, Hughes score, serologies (*Campylobacter jejuni*, *Haemophilus influenzae*, Influenza virus, cytomeg-

alovirus, Epstein-Barr virus, anti-ganglioside antibodies), intensive care unit admission, comorbidities (hypertension, cardiac pathology, chronic obstructive lung disease, renal disease), modified Rankin score at discharge, positive COVID-19 serologic test and date, COVID-19 vaccine (number of doses, date of vaccine administration and vaccine manufacturer).

A presumptive association between SGB and COVID-19 infection was defined as symptoms onset within 4 weeks after a positive RT-PCR SARS-CoV-2 test (COVID-19 positive patients). A presumptive association between SGB and COVID-19 vaccination was defined as symptoms onset within 4 weeks after COVID-19 vaccine inoculation (COVID-19 vaccinated patients)

Statistical analysis

Descriptive data is presented as median values and interquartile range (1st – 3rd). Proportions were analyzed with a χ^2 test. Due to our small sample, non-parametric tests were used. Group comparisons were assessed with the Kruskal-Wallis H test. These analyses were performed in IBM SPSS for Microsoft Windows, version 26.0 (Armonk, NY: IBM Corp). A p-value < 0.05 was accepted as significant. The incidence of GBS was estimated according to PORDATA data regarding the population served by each of the three hospitals involved in this study and then calculated using Microsoft Office Excel®. PORDATA is an updated Portuguese-certified national statistics database available for search. Exact confidence intervals on Poisson relative risks were computed with Stata for Microsoft Windows, Version 17.0 (College Station, TX: StataCorp).

Results

Forty-seven cases of GBS were identified: 13 in the PPP, 11 in the PP and 23 in the PVP. The median age in the PPP group was 60.0 (IQR 34.0-74.0) years old versus 57.0 (IQR 37.0-62.0) years old in the PPVP and 52.0 (41.0-64.0) years old in the PVP. Except for the PPP, in which more than half of the patients were female (61.5%, N = 8), both in the PPVP and PVP most of the patients were male (63.2%, N = 7; 65.2%, N = 15). There were, however, no statistically significant differences regarding gender [$X^2(2, N=47) = 2.66, p=0.265$] and age [$H(2) = 0.562, p=0.755$] between GBS cases in the three time periods analyzed. Most patients diagnosed with GBS had at least one cardiovascu-

Table 1. Demographic data.

	PPP (N = 13)	PPVP (N = 11)	PVP (N = 23)
Age (median and IQR, y.)	60; 34-64	57; 37-62	52; 41-64
Gender (male, %)	38.5	63.2	65.2
Presence CDV Risk Factors (at least one,%)	66.7	63.6	50.0

PPP – pre-pandemic period; PPVP - pandemic pre-vaccination period; PVP - pandemic vaccination period; CDV - cardiovascular.

Table 2. Incidence.

Period	Cases	IR ^a	IRR (95 CI)	p-value
PPP	13	1.01	--	--
PPVP	11	0.86	0.85 (0.34–2.04)	0.69
PVP	23	1.79	1.77 (0.86-3.80)	0.10

^a Per 100 000 person-years.

PPP - pre-pandemic period; PPVP - pandemic pre-vaccination period; PVP - pandemic vaccination period; IR – incidence rate; IRR – incidence rate ratio.

lar risk factor (hypertension, diabetes, smoking, others). Demographic data is presented in **Table 1** and more detailed demographic analysis and clinical characterization is presented in the supplementary material (**Table A**).

The incidence rates for each period and incidence rate ratios regarding the pre-pandemic period are described in **Table 2**. An increase in GBS cases (77%) was observed during the PVP when compared to the PPP. However, this increase was not statistically significant ($p = 0.10$), corresponding to an increase of less than 1 excess case per 100 000 person-years during this period.

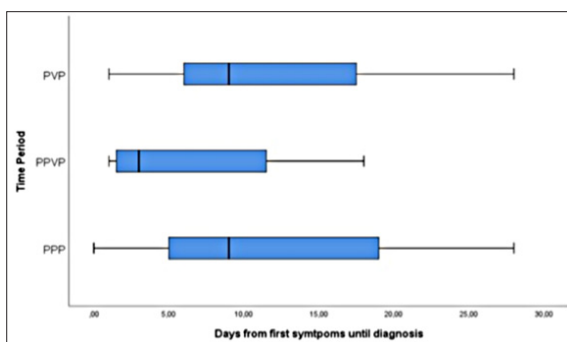
The median time between symptoms and diagnosis was 9.0 (IQR 5-19) days in the PPP, 3.0 (IQR 1-12) days in the PPVP and 9.0 days (IQR 6-19) in the PVP (**Fig. 1**). The difference in time to diagnosis between these periods was not statistically significant [$H(2) = 3.498, p=0.174$].

In the PPP, more than half of the patients presented with an acute inflammatory demyelinating polyneuropathy

(AIDP) phenotype (61.5%, $N = 8$), 23.0% ($N = 3$) had an acute motor axonal polyneuropathy (AMAN) phenotype and 11.1% ($N = 2$) presented with Miller-Fisher syndrome. No acute motor and sensory axonal neuropathy (AMSAN) was identified. Following the same tendency, in the PPVP, the majority (72.7%, $N = 8$) had an AIDP phenotype, but the three other observed phenotypes shared the same frequency ($N = 1$). During the PVP, AIDP was also the most frequent phenotype (56.5% were AIDP, $N = 13$), but a higher proportion of AMAN and AMSAN was documented (21.7% and 17.4%, respectively). Only 1 Miller-Fisher syndrome was reported. The detailed clinical characterization is presented in the supplementary material.

A further analysis was made, comparing phenotypes' frequencies in the PPP versus the PVP. Although there seemed to be a trend for an increase of the non-AIDP phenotype after vaccination started (13.9% vs 27.8%), a statistically significant difference between the aforementioned period and the PVP, when considering all patients in the group, was not found [$\chi^2(1, N=36) = 0.086, p = 0.769$]. Further subanalysis comparing only the vaccinated patients and the COVID-19-positive patients from the PVP group were also made, but no statistically significant difference was found.

Statistical analysis considering cranial nerve involvement, autonomic dysfunction, serologies, the severity of GBS, outcome and need for ICU admission no significant statistical differences were observed between the various phenotypes. No significant statistical differences were found in subsequent subanalysis for the COVID-19-positi-

**Figure 1.** Time variation until diagnosis.

PPP - pre-pandemic period; PPVP - pandemic pre-vaccination period; PVP - pandemic vaccination period.

tive patients and vaccinated patients. The full analysis can be found in the supplementary material (**Table B**).

Discussion

Concerning the apparent reduction in the incidence of GBS during the PPVP, several reasons can be hypothesized such as the underdiagnosis of mild GBS cases due to fear of COVID-19/health care services, the use of face masks, and lockdown measures, which have reduced the number of respiratory infections.²⁴ Moreover, the generalized use of hand sanitiser and the closure of restaurants also reduced the number of gastrointestinal infections.²⁴ The absence of a peak of GBS cases during the peak of SARS-CoV-2 infections appears to support the absence of a causal relationship between COVID-19 infection and GBS. Similar results were also found in a large UK study where the incidence of GBS fell during March and May 2020 when compared to the same months of 2016-2019.⁹

The slight increase found in the incidence of GBS during the PVP corresponds to an increase of less than 1 excess case per 100 000 person-years during this period. It is possible to hypothesize that, similarly to the influenza vaccine, which causes 1-2 additional cases per million of administered vaccine jabs,³ immunization against COVID-19 can also cause some additional cases of GBS. Several case reports of patients developing GBS after COVID-19 vaccination have been published.⁹⁻¹⁹ However, it is important to note that the published reports to date are highly heterogeneous in terms of methods, the accepted time between vaccine administration to consider a relationship, and the criteria to diagnose GBS.¹⁹ A reporting bias after the first reported cases of post-vaccination GBS cannot be excluded. Also, we highlight the importance of the efforts of vaccination worldwide as an absolute priority to save lives and this hypothesis should not reduce the efforts in vaccinating as many people as possible. It is also important to note that the vaccination period also includes several step-downs in confinement measures.

Another finding was the apparent smaller median time between symptoms and diagnosis in the PPVP (3.0 days), compared to 9.0 in the PPP and 9.0 in the PVP. These results, although not statistically significant, can possibly be explained by a lower number of neurologic inpatients during the pandemic due to COVID-19 pressure on healthcare services leading to a shorter time to diagnosis (especially faster electromyographic diagnosis).

A sub analysis considering only COVID-19-vaccinated patients versus patients from the pre-pandemic period did not confirm a statistically significant difference between non-AIDP phenotypes and vaccination. This result should be considered when analyzing previously published case reports and small case series concerning vaccination against COVID-19 and GBS, which reported this tendency.^{11,16-18}

It is very important to note that, when studying rare diseases, such as GBS, and trying to establish a relationship with a pandemic infection or a generalized mass vaccination, any relationship must be cautious regarding causality. The limitations of this study are a small sample of GBS cases, a retrospective study design and a vaccination effort still ongoing.

Conclusion

To conclude, we present the first Portuguese multicentric study regarding the incidence of GBS and SARS-CoV-2 infection and vaccination. We hypothesize that the slight decrease in GBS during the pandemic pre-vaccination period is probably due to hygienic measures implemented during the COVID-19 pandemic. We have also found a small increase in the number of GBS cases with a possible relationship with COVID-19 vaccination. Prospective studies are necessary to better characterize this relationship and take further conclusions. ■

Contributorship Statement / Declaração de Contribuição

JV and JMD: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Roles/Writing - original draft; Writing - review & editing.

CC, MOS, SC, JC, IC, MS: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing - review & editing.

JV, MC: Conceptualization; Methodology; Validation; Writing - review & editing.

IC: Conceptualization; Methodology; Supervision; Validation; Writing - review & editing.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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