Received: 12 April 2024 | Accepted: 26 July 2024
DOI: 10.1111/ene.16439

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

A nationwide Guillain–Barré syndrome epidemiological study in Spain during the COVID-19 years

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Funding information
GBS/CIDP Foundation International, Grant/Award Number: Personal grant Benson Fellowship to EP-G; Instituto de Salud Carlos III, Grant/Award Number: FIS PI22/00387, INT23/00066, Juan Rodés grant JR21/00060 - personal grant to L and Rio Hortega grant CM21/00101 - personal grant to M

Abstract

Background and purpose: The purpose was to perform a nationwide epidemiological study of Guillain–Barré syndrome (GBS) in Spain, analysing background incidences and seasonal variation and trying to identify incidence changes during the coronavirus disease 2019 (COVID-19) years.

Methods: This was an observational study collecting all GBS diagnoses from the National Epidemiological Surveillance Network collected by the Ministry of Health. Patients discharged with GBS as the main diagnosis and admitted during 2018–2021 were included. Data on the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were obtained from the National Epidemiology Centre.

Results: In total, 3147 cases were included, 832 in 2018, 861 in 2019, 670 in 2020 and 784 in 2021. Nationwide hospital incidence was 1.78 in 2018, 1.71 in 2019, 1.41 in 2020 and 1.66 in 2021, with an increased frequency in males, the elderly population and in the winter season. Eleven per cent of GBS patients needed ventilatory support. GBS and SARS-CoV-2 incidences did not correlate with one another ($r = -0.29$, $p = 0.36$). GBS incidence decreased during 2020 and during the COVID-19 lockdown period in comparison to the same months of 2018–2019.

Conclusions: The incidence of GBS in Spain is similar to that of other countries. Despite prior reports describing a significant increase in COVID-19-associated GBS in Spain, a significant drop of GBS incidence during the SARS-CoV-2 pandemic was detected, probably due to prevention measures.

KEYWORDS
COVID-19, epidemiology, Guillain–Barré syndrome, Spain, vaccines

Marina Blanco-Ruiz and Lorena Martín-Aguilar contributed equally and are also co-first authors.

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy [1], occurring a few days to 4 weeks after an infectious process [2]. GBS incidence ranges from 0.44 cases per 100,000 population in Japan to 2.2 cases per 100,000 population in the United States [3, 4]. In Spain, Cuadrado et al. [5, 6] described the epidemiology of GBS in the 1990s, using data from 11 public centres distributed throughout the country, and found an incidence of 1.26 cases per 100,000 inhabitants. Other studies from smaller regions of the country described variable incidences, from 0.95 cases per 100,000 inhabitants in Cantabria [7] to 2.07 cases per 100,000 inhabitants in Osona [8]. However, there are no studies describing nationwide GBS incidence in Spain since previous studies only covered some specific regional areas.

During the initial stages of the coronavirus disease 2019 (COVID-19) pandemic, several reports were published suggesting an association between COVID-19 and specific neurological syndromes, including GBS [9–14]. These reports mostly included small and medium size case series [15–17]. One Spanish study estimated a 5-fold increase in GBS incidence during March and April 2020 compared to the previous year, reaching 9.44 cases per 100,000 people per year [18]. The authors also concluded that the relative frequency of GBS with COVID-19 was significantly higher than GBS without it. However, whilst it may be plausible that coronavirus infection triggers GBS, it is not clear whether the COVID-19 pandemic has led to an overall increase in GBS incidence, as happened with other viral outbreaks such as the Zika virus pandemic [19]. In fact, a large national study of the UK population found a decrease in GBS incidence during the COVID-19 pandemic and found no association between GBS and COVID-19, but this study was performed based on the UK Immunoglobulin Database and therefore excluded patients treated with plasma exchange or not treated due to minor symptoms. Furthermore, one national study in Singapore showed a decreased incidence of GBS during the pandemic year, and failed to find a definitive link between GBS and COVID-19 infection [20]. On the other hand, a recent Italian study found an increase of GBS in northern Italy in the COVID-19 era compared to the previous year [21].

Mass severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination campaigns began in 2021 raising again concerns on the possibility of an increase in GBS incidence. Several SARS-CoV-2 vaccine-associated GBS cases were reported [22–24], especially with ChadOx1-S/nCoV-19 [25] and Ad26.COV2.S vaccines [26], and, indeed, three national cohort studies in the UK, France and the United States and one meta-analysis have found that first-dose ChAdOx1-S/nCoV-19 and Ad26.COV2.S vaccinations were associated with an increased GBS risk [27–30].

To clarify whether the COVID-19 pandemic influenced GBS incidence rates, the first nationwide epidemiological study of GBS was developed describing background GBS incidences in Spain, reporting regional and seasonal variations and aiming to identify background GBS incidence changes during the coronavirus pandemic.

METHODS

Study design and patients

This was a retrospective study extracting all patients with a primary diagnosis of GBS included in the National Epidemiological Surveillance Network of Spain (covering a population of 47 million people) during a 4-year period (2018–2021). This project has been approved by the Institutional Ethics Committee of the Hospital de la Santa Creu i Sant Pau (IIBSP-GSB-2023-151).

The source of information was the Spanish Minimum Basic Hospital Discharge Dataset, made available by the Ministry of Health. Diagnostic and procedural coding followed the International Classification of Diseases, Tenth Revision (ICD10). Patients with a main diagnosis at discharge of GBS (ICD10 classification, codes G61.0) were included. Duplicate entries arising from hospital admissions in different institutions for the same patient were merged into a single entry. Data on the incidence of SARS-CoV-2 infection were obtained from the National Epidemiology Centre (CNE) database, which is part of the Ministry of Health and the Ministry of Science and Innovation.

Statistical analysis

Continuous variables are described as mean ± SD or median (interquartile range). Categorical variables are described as percentages. To estimate the overall incidence of GBS, sex-specific incidence and age-specific incidence, the number of new cases each year was calculated and divided by the population at risk registered in the Spanish mid-term census, the source of the information being the National Statistics Institute.

Univariate analysis was performed with the chi-squared test or Fisher's exact test for dichotomous variables. Continuous variables were analysed with the *t* test or the Mann–Whitney *U* test when appropriate. To compare incidence between years, 95% confidence intervals (CIs) were calculated. Simple linear regression models were used to correlate the incidence of GBS with the incidence of SARS-CoV-2 infection. To compare GBS incidence and the relationship with SARS-CoV-2 infection a separate analysis was conducted using the months during the lockdown period in Spain (March–May) for SARS-CoV-2. Statistical significance for all analyses was set at 0.05 (two-sided). The analysis was carried out in the SPSS 27.0 (SPSS Inc., Chicago, IL, USA) programme for macOS. Ninety-five per cent CIs for incidences and proportions were performed with Stata v15.

RESULTS

Guillain–Barré syndrome incidence

A total of 3147 patients with GBS were detected, with the following yearly distribution: 832 in 2018, 861 in 2019, 670 in 2020 and 784 in 2021. Incidences and their 95% CIs are shown in Table 1.

The mean age was 53.2 years (SD 21.9) and 63.9% of patients were male. The average incidence of GBS in Spain for the years 2018–2021 was 1.67 cases per 100,000 population. The sex-specific incidence rates were 2.18 cases per 100,000 population for males and 1.18 cases per 100,000 for females (male-to-female ratio of 2.01: 1). The incidence of GBS increased with age, with the highest incidence detected at 70–79 years (3.26 [2.99–3.56]). Sex-specific and age-specific incidence rates with their 95% CIs are shown in Table 1.

The incidence in each region was also analysed, with País Vasco being the region with the highest incidence (2.02 cases per 100,000 inhabitants) and La Rioja the one with the lowest incidence (1.11 cases per 100,000 inhabitants). The distribution of incidences by regions can be seen in Figure 1 and Table S1.

TABLE 1 Incidence of GBS per year, sex-specific and age-specific incidences.

Variable	Number of cases (*n*, %)	Incidence per 100,000 (95% CI)
Year		
2018	832 (26.4%)	1.78 (1.66–1.91)
2019	861 (27.3%)	1.71 (1.71–1.95)
2020	670 (21.2%)	1.41 (1.31–1.53)
2021	784 (24.9%)	1.66 (1.53–1.77)
Sex		
Male	2012 (63.9%)	2.18 (2.08–2.27)
Female	1135 (36.1%)	1.18 (1.11–1.25)
Age		
0–9	168 (5.3%)	0.97 (0.83–1.13)
10–19	167 (5.3%)	0.85 (0.73–0.92)
20–29	179 (5.7%)	0.92 (0.79–1.70)
30–39	258 (8.2%)	1.06 (0.93–1.20)
40–49	401 (12.7%)	1.29 (1.16–1.42)
50–59	542 (17.2%)	1.93 (1.77–2.10)
60–69	636 (20.2%)	2.97 (2.74–3.21)
70–79	511 (16.2%)	3.26 (2.99–3.56)
80–89	260 (8.3%)	2.82 (2.48–3.18)
>90	14 (0.4%)	0.61 (0.34–1.03)

Abbreviations: CI, confidence interval; GBS, Guillain–Barré syndrome.

Guillain–Barré syndrome seasonality

A higher frequency of GBS was found during winter months (Table 2), without an overlap of their 95% CI incidences and an excess of almost 200 cases in winter (198.3). When months were divided according to the years, a significant drop in GBS was seen during the winter months of 2021, which coincides with the first winter after the pandemic (Figure 2).

Guillain–Barré syndrome features

No demographic differences between GBS patients from the different study years have been found. Average hospital stay was similar between years with a median of 13 (8–23) days. Eleven per cent of GBS patients needed mechanical ventilation during hospitalization and 10.4% required orotracheal intubation, with no differences between years. As for the comorbidities of the patients (Table S2), the most frequent were hypertension (32.1%), smoking (23.1%) and diabetes (14.6%), and the most frequent infections recorded during hospitalization were respiratory followed by urinary tract infections. Acute SARS-CoV-2 infection during hospitalization was found in less than 5% of GBS patients during 2020 and 2021 but this rate only captures concomitant and not preceding infection.

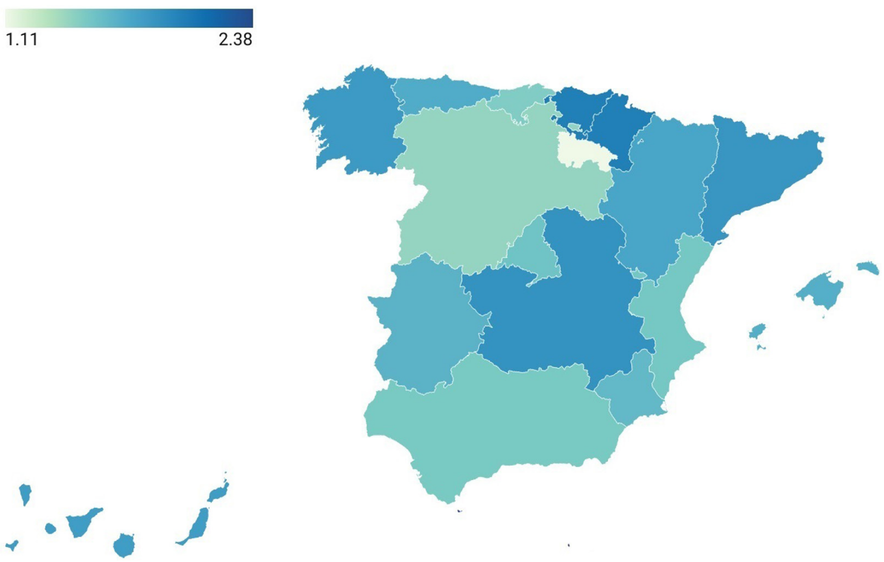

FIGURE 1 Heatmap of regional incidences of GBS.

TABLE 2 Seasonal variability in GBS.

	Number of GBS cases (*n*, %)	Proportion (95% CI)	*p*
Seasons			
Spring	754 (24%)	0.24 (0.22–0.25)	<0.0001
Summer	689 (21.9%)	0.22 (0.20–0.23)	
Autumn	724 (23%)	0.23 (0.22–0.25)	
Winter	980 (31.1%)	0.31 (0.30–0.33)	
Months			
January	379 (12%)	0.20 (0.18–0.22)	<0.0001
February	313 (9.9%)	0.17 (0.15–0.19)	
March	289 (9.2%)	0.15 (0.14–0.17)	
April	225 (7.1%)	0.12 (0.10–0.14)	
May	261 (8.3%)	0.14 (0.12–0.16)	
June	229 (7.3%)	0.12 (0.11–0.14)	
July	227 (7.2%)	0.12 (0.11–0.14)	
August	214 (6.8%)	0.11 (0.10–0.13)	
September	228 (7.2%)	0.12 (0.11–0.14)	
October	236 (7.5%)	0.13 (0.11–0.14)	
November	241 (7.7%)	0.13 (0.12–0.15)	
December	305 (9.7%)	0.16 (0.14–0.18)	

Abbreviations: CI, confidence interval; GBS, Guillain–Barré syndrome.

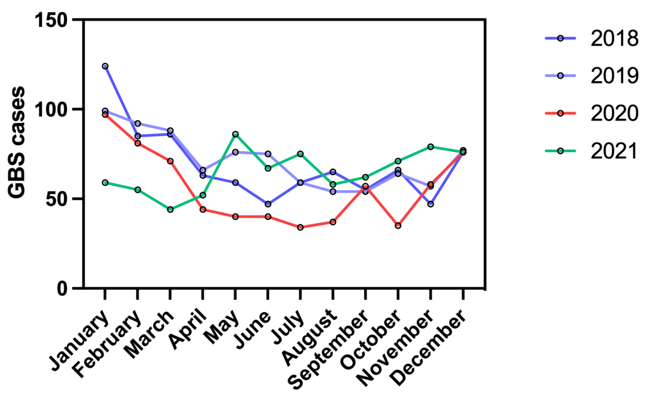

FIGURE 2 Seasonal distribution of GBS during the study years.

Coronavirus 2019 and GBS

Spain was one of the European countries most affected by the COVID-19 pandemic, with one of the highest incidence and mortality rates for SARS-CoV-2 in Europe, accounting for 172,541 confirmed cases and 18,056 deaths by the end of April 2020 [31]. A total of 498,789 patients (1.04% of the Spanish population) were admitted to hospitals with a diagnosis of COVID-19 in the first 2 years of the pandemic.

According to CNE 1,975,439 patients in 2020 and 4,751,798 patients in 2021 had a positive polymerase chain reaction (PCR) test for SARS-CoV-2. The lower result in 2020 is due to lower accessibility to detection tests for COVID-19, as a substantial proportion of people with symptoms compatible with COVID-19 were not tested by PCR and at least a third of infections determined by serology were asymptomatic [32]. In fact, it is estimated that, during the first weeks of the pandemic in Spain, only 1 in 10 cases were detected [33].

Guillain–Barré syndrome incidence was lower during the pandemic year (1.41 [1.31–1.53] in 2020 vs. 1.78 [1.66–1.91] in 2018 and 1.71 [1.71–1.95] in 2019) (Table 1), with 116 fewer cases than expected. A decrease in the incidence was also found when comparing incidences during the lockdown period (March–May 2020) with the same months in previous years (2018–2019) (Table 3). Moreover, the reduction of GBS incidence was observed in all regions, including those most affected by SARS-CoV-2 at the beginning (Table S3). GBS and SARS-CoV-2 incidences did not correlate with one another ($r = -0.29$, $p = 0.36$, Figure 3).

DISCUSSION

Our study shows that GBS incidence in Spain is similar to those reported in previous studies [4], with an increased frequency in males, in the elderly population and during the winter season. GBS incidence was lower during 2020 and during the lockdown period in comparison to the same months of previous years, and no association between SARS-CoV-2 infections and GBS incidences was found at the population level.

This is the first nationwide epidemiological GBS study in Spain. A GBS incidence of 1.67 cases per 100,000 population was found, similar to previous studies in other Western countries [4] and in Spain [5–8]. Our study found a significantly higher risk of GBS amongst males (male-to-female ratio 2:1), a finding that has been consistently demonstrated in previous studies [2, 4] and that differs to most autoimmune diseases, that usually are more frequent in women. An age-dependent increase in GBS frequency was also found, in line with previously published results describing a 20% increase every 10-year increase in age [4]. Incidence peaked at the 70–79 age range in our study. Thus, our study confirmed that male gender and older age are associated with GBS development [2–4].

An increased frequency was also found in winter months, which is also consistent with prior descriptions, since typical triggering infections also follow seasonal patterns [34]. This finding has been described in Western countries, the Far East and the Middle East, but not in the Indian subcontinent and Latin America. This lack of seasonality in some regions is partly explained by the influence of tropical climates and a greater predominance of a diarrhoeal prodrome or *Campylobacter jejuni* infection in low-income countries. Unfortunately, no data are available on previous infections in our study to correlate seasonality with an antecedent respiratory infection, but only concomitant infections during hospital admission.

Our study showed no relationship between SARS-CoV-2 infection and GBS incidences. There is some controversy about their relationship, as many cases and small series have been published suggesting a causal link; one national cohort study in northern Italy reported an increase in GBS cases during the pandemic year [21]

TABLE 3 GBS cases during SARS-CoV-2 lockdown period (March–May).

Year	Number of cases (*n*, %)	Study population	INC (95% CI)	*p*
2018	208 (35.1%)	46,728,814	0.45 (0.39–0.51)	0.001
2019	230 (38.8%)	47,105,358	0.49 (0.43–0.56)	
2020	155 (26.1%)	47,355,684	0.33 (0.28–0.38)	

Abbreviations: CI, confidence interval; GBS, Guillain–Barré syndrome; INC, incidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

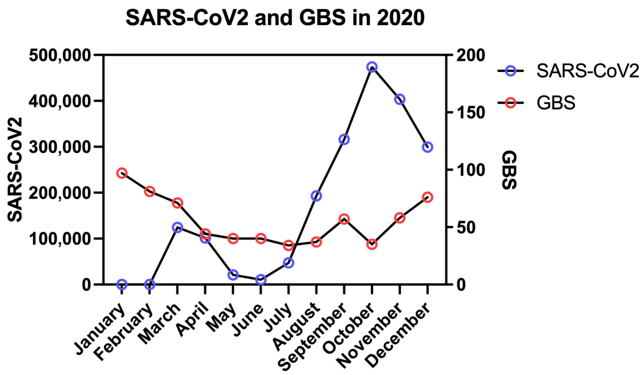

FIGURE 3 Relationship between GBS cases and SARS-CoV-2 in 2020.

and two national cohorts from the UK and Singapore reported a decrease [20, 27]. Our study, collecting all GBS cases admitted in Spain, a country in which the pandemic hit early and that reports one of the highest COVID-19-related excess mortality rates in Western countries [35], supports that there is no relationship between GBS and SARS-CoV-2 because (1) a decrease is observed in GBS incidence during the pandemic year, probably due to prevention measures, (2) a decrease was found during the lockdown period in comparison to the same months of previous years and (3) no correlation between GBS and SARS-CoV-2 infection incidences was found. Although the GBS incidence during March–April 2020 was estimated at 9.44/100,000 [18] in a previous Spanish study from emergency departments in COVID-19 patients, incidences remained significantly lower than the estimate (0.33/100,000) in all Spanish regions, including those with higher SARS-CoV-2 incidence. Data on GBS features were not available, but no difference was found in demographics, comorbidities, average hospital stay or need of ventilation in the different years studied, suggesting that the GBS pattern and the comorbidity profiles of GBS patients of the pandemic years are similar to those of non-pandemic years. Also, less than 5% of hospitalized GBS patients during 2020 and 2021 had a concomitant SARS-CoV-2 infection, far from the 50% of patients reported in the Italian cohort [21, 36], although information on antecedent infections was not systematically collected in our study.

In addition, although this study was not designed to detect the association of GBS with vaccines, our study did not find a population-wide increase in GBS cases during 2021, when massive SARS-CoV-2 vaccination occurred. Other studies designed specifically to detect vaccine-associated GBS found an association between adenovirus-vectored vaccines and GBS but not with mRNA-based vaccines, which were the ones used in the vast majority of the population in Spain [27, 28, 30].

Several considerations and limitations should be noted in our study. First, the cohort of patients comes from the codification of diagnosis at discharge in each hospital. These diagnoses are not confirmed later on and, thus, our cohort may include some potentially misdiagnosed cases. However, it is likely that misdiagnosis rates are low in GBS, that they remain stable across the years, and that the validity of our findings is not compromised by this limitation. Also, prior GBS diagnosis (unrelated to the current admission) may also have been reported in the registry. To minimize this bias, only patients with GBS as the main diagnosis of the active admission were selected, excluding all patients with a prior history of GBS. Furthermore, considering data are lacking on previous infections or vaccines at the individual level, the lack of association of SARS-CoV-2 infection and GBS at the description level must be interpreted without inferring any lack of causality. Finally, data on clinical variants, electrophysiological subtypes or functional outcome are also lacking which, with such a large cohort, would have helped to define the seasonal or yearly differences in GBS features.

In summary, this is the first nationwide epidemiological GBS study performed in Spain. Our study supports that the COVID-19 pandemic did not increase the incidence of GBS in our country. Implementation of similar, nationwide registries, particularly if they also collect real-time and more granular, individualized information, would help in understanding deviations in expected incidences in important diseases in the event of public health emergencies, including severe post-infectious disorders such as GBS.

AUTHOR CONTRIBUTIONS

Marina Blanco-Ruiz: Writing – review and editing; writing – original draft; investigation; methodology; formal analysis; data curation. **Lorena Martín-Aguilar:** Writing – review and editing; writing – original draft; investigation; methodology; formal analysis; data curation. **Marta Caballero-Ávila:** Writing – review and editing. **Cinta Lleixà:** Writing – review and editing. **Elba Pascual-Goñi:** Writing – review and editing. **Roger Collet-Vidiella:** Writing – review and editing. **Clara Tejada-Illa:** Writing – review and editing. **Janina Turon-Sans:** Writing – review and editing. **Álvaro Carbayo:** Writing – review and editing. **Laura Llansó:** Writing – review and editing. **Elena Cortés:** Writing – review and editing. **Laura Amaya Pascasio:** Writing – review and editing; methodology. **Luis Querol:** Conceptualization; writing – review and editing; investigation; supervision; resources.

ACKNOWLEDGEMENTS

The authors would like to thank the Registry of Specialized Health Care (RAE-CMBD) of the Ministry of Health and the Area of Health Information and Statistics of the General Subdirectorate of Health Information (MSAN). Some authors of this publication are members of the European Reference Network for rare neuromuscular diseases (EURONMD).

FUNDING INFORMATION

This work is supported by Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III, Spain, under grant FIS PI22/00387 and INT23/00066. LM-A was supported by a personal Juan Rodés grant JR21/00060. MC-A was supported by a personal Rio Hortega grant CM21/00101. EP-G was supported by GBS/CIDP Foundation International under personal grant Benson Fellowship.

CONFLICT OF INTEREST STATEMENT

LQ received research grants from Instituto de Salud Carlos III—Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grífols, received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi-Genzyme, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, ArgenX, UCB, LFB, Octapharma and Roche, serves at the Clinical Trial Steering Committee for Sanofi-Genzyme and Roche and is Principal Investigator for UCB's CIDP01 trial. The other authors report no disclosures.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Anonymized data not published within this article will be made available on request from any qualified investigator.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Blanco-Ruiz M, Martín-Aguilar L, Caballero-Ávila M, et al. A nationwide Guillain–Barré syndrome epidemiological study in Spain during the COVID-19 years. *Eur J Neurol*. 2024;31:e16439. doi:10.1111/ene.16439