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Decreased Incidence of Guillain-Barré Syndrome during the COVID-19 Pandemic: A Retrospective Population-Based Study

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Keywords
Guillain-Barré syndrome · COVID-19 · Incidence · Population-based studies · Vaccine

Abstract
Background: Guillain-Barré syndrome is an immune-mediated acute inflammatory polyneuropathy that is associated with various triggers, including certain infections and vaccines. It has been suggested that both SARS-CoV-2 infection and vaccination may be triggering factors for Guillain-Barré syndrome, but evidence remains equivocal. Here, we conducted a population-based incidence study of Guillain-Barré syndrome spanning the 3 years immediately prior to and the 2 years during the pandemic. ***Methods:*** Cases were identified by searching a regional diagnostic database for the ICD-10 code for Guillain-Barré syndrome. Individuals who fulfilled the Brighton criteria for Guillain-Barré syndrome were included. Information on clinical presentation, laboratory values, and vaccination status were retrieved from medical records. We calculated the incidence immediately prior to and during the pandemic. ***Results:*** The Guillain-Barré syndrome incidence rate was 1.35/100,000 person-years for the pre-pandemic period and 0.66/100,000 person-years for the pandemic period (incidence rate ratio: 0.49; $p = 0.003$). Three cases were temporally associated with SARS-CoV-2 infection and 1 case each to the AstraZeneca and Pfizer-BioNTech COVID-19 vaccines. ***Conclusions:*** Our results show that the incidence of Guillain-Barré syndrome decreased during the pandemic. This is most likely due to decreased prevalence of triggering infections due to social restrictions. Our findings do not support a causal relationship between Guillain-Barré syndrome and COVID-19.

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated acute inflammatory polyneuropathy with a monophasic disease course. The reported incidence from Europe and North America is 0.8–1.9 per 100,000 person-years. Most cases are preceded by a presumed triggering event, primarily infections. Several microbial pathogens have been identified as triggers, including *Campylobacter jejuni*, Zika virus, and cytomegalovirus. The underlying mechanism is believed to be molecular mimicry, which is well-established in the case of *Campylobacter jejuni* [1]. GBS has also been reported following vaccination, most notably after the influenza H1N1 vaccine in 1976 [2].

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It has been suggested that COVID-19 may trigger GBS, but the evidence remains equivocal. The first case of GBS associated with SARS-CoV-2 infection appeared as early as in January 2020 [3]. Since then, numerous case reports have been published [4], and a few incidence studies have been conducted. Early in the pandemic, Filosto et al. [5] reported a 2.6-fold increase of GBS incidence in seven cities in Northern Italy during March and April 2020, compared to those same months in the previous year. Among 34 cases, 30 (88%) tested positive for SARS-CoV-2 at diagnosis, either by nasopharyngeal swab or serum antibodies. Most of the cases had concomitant active COVID-19 and GBS, suggesting a parainfectious neuropathy rather than the classical postinfectious GBS.

During the first 6 months of the pandemic, Keddie et al. [6] reported a decreased incidence of GBS in the UK. Furthermore, they found no similarities between the human genome and the SARS-CoV-2 proteome that could support molecular mimicry. Umapathi et al. [7] reported decreased GBS hospital admissions in Singapore during the first 10 months of the pandemic and found no association between hospitalization for GBS and COVID-19 notifications in the Ministry of Health surveillance system for infectious diseases.

The COVID-19 vaccine clinical trials did not report an increased risk of GBS following vaccination; however, since the start of worldwide mass vaccination, numerous GBS cases have been reported, mostly associated with the AstraZeneca vaccine (ChAdOx1 nCoV-19) [8]. A nationwide study in the UK identified all GBS cases occurring within 6 weeks of vaccination against COVID-19. The study compared information regarding all persons receiving intravenous immunoglobulins (IVIG) and all receiving vaccinations in the UK. They reported an excess risk of 0.576 GBS cases per 100,000 after receiving the first dose of the AstraZeneca vaccine. No risk increase was associated with the first dose of the tozinameran vaccine or with the second doses of any COVID-19 vaccine [9]. Here, we investigated the incidence of GBS during a 5-year period, including the 3 years immediately prior to the pandemic and 2 years during the pandemic.

Methods

Study Population

This study was conducted in the region of Västra Götaland, Sweden. During the study period, the area was home to an average of 1,682,625 residents, with a stable age distribution over time [10]. The study period was from January 1, 2017, to December 31, 2021, and was divided into pre-pandemic and pandemic. March 13, 2020, was selected as the beginning of the pandemic because that was the date social restrictions were implemented in Sweden. The pre-pandemic period lasted 38½ months, and the pandemic period lasted 21½ months.

Table 1. Demographics and clinical subgroups before and during the pandemic

	Pre-pandemic (n = 73)	During pandemic (n = 20)
Age at diagnosis, mean (range)	55.3 (9–89)	55.6 (5–85)
Male, % (n)	58 (42)	65 (13)
Brighton criteria, % (n)		
Level 1	38 (28)	45 (9)
Level 2	40 (29)	45 (9)
Level 3	22 (16)	10 (2)
Subgroup, % (n)		
AIDP	56 (40)	60 (12)
AMAN	8 (6)	10 (2)
AMSAN	4 (3)	5 (1)
MF	7 (5)	5 (1)
Unknown	26 (19)	20 (4)

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory neuropathy; MF, Miller Fisher variant.

Data Collection

Cases were identified by searching the regional diagnosis database for the ICD-10 code for GBS, G61.0, among all admissions to the four hospitals. This study included all patients who fulfilled level 1–3 of the Brighton diagnostic criteria for GBS [11]. From patient records, we retrieved information regarding age, sex, symptoms, vaccination status, results of laboratory analyses and neurophysiological studies, duration of hospitalization, and need for intensive care and mechanical ventilation. COVID-19 infections were confirmed by polymerase chain reaction (PCR). The Guillain-Barré disability scale was used to score symptoms at diagnosis, at the height of the illness (nadir), and after 1 year if available [12].

Statistical Analysis

Statistical analysis was carried out using Microsoft Excel (version 16.58) and IBM SPSS Statistics (version 28.0.1.0). Categorical nominal variables are presented as percentages. Quantitative variables that are normally distributed are presented as mean and range. Variables with a skew distribution are presented as median and interquartile range. Incidence rate (IR) was calculated using midyear populations, with the number of GBS cases as the numerator, and person-years (PY) as the denominator. Confidence intervals (CIs) of IR ratio were calculated using the exact Poisson method [13]. The p value for the comparison of rate is the double-sided mid-p value. Two-tailed Mann-Whitney U test for independent samples was used to determine differences in GBS score, length of interval between symptom debut and hospital admission, duration of hospital stay, intensive care, and mechanical ventilation before and during the pandemic. A p value of <0.05 is considered statistically significant.

Table 2. IR according to age before and during the pandemic

Age group, years	Pre-pandemic IR (95% CI)	During pandemic IR (95% CI)	IRR
0–29	0.45 (0.21–0.85)	0.27 (0.06–0.78)	0.57
30–59	1.36 (0.9–1.96)	0.42 (0.14–0.98)	0.31
60–99	2.65 (1.85–3.67)	1.53 (0.8–2.67)	0.60

IR, incidence rate; CI, confidence interval; IRR, incidence rate ratio.

Results

Cases

Out of 136 patients with the ICD-10 code for GBS during the study period, 93 fulfilled the inclusion criteria: 73 in the pre-pandemic period and 20 during the pandemic. Thirty-five patients were coded incorrectly or turned out to have alternative diagnosis; 7 patients who were considered to have GBS did not fulfill the Brighton criteria, level 1, 2, or 3. Table 1 shows the demographics and clinical subgroups of the patients before and during the pandemic.

Incidence

The IR was 1.35/100,000 PY (95% CI, 1.06–1.70) for the pre-pandemic period and 0.66/100,000 PY (95% CI, 0.41–1.02) for the pandemic period. The IR ratio was 0.49 ($p = 0.003$). The largest difference in IR was found in the 30–59 years age group (Table 2).

COVID-19 Infection and Vaccination as Possible Triggers

All 20 GBS cases during the pandemic period were tested for SARS-CoV-2 upon admission with nasal swab PCR, and 2 cases (10%) were positive. One additional patient had been PCR-positive for COVID-19 in the 6 weeks prior. Of these 3 patients, one had been vaccinated with the AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19) within 6 weeks prior to presenting with GBS. One additional patient had received the Pfizer-BioNTech COVID-19 vaccine (BNT-162b2) less than 6 weeks prior to presenting with GBS. A number of possible triggering infectious events were noted for both the pre-pandemic and pandemic groups (Table 3).

Disease Course and Prognosis

The GBS disability scores at diagnosis, nadir, and 1 year following discharge (Table 4) were comparable be-

Table 3. Possible triggering infectious events before and during the pandemic, reported by patients or in medical records

	Pre-pandemic ($n = 73$), % (n)	During pandemic ($n = 20$), % (n)
None	29 (21)	35 (7)
URI	32 (23)	15 (3)
Influenza	6 (4)	0 (0)
Pneumonia	3 (2)	0 (0)
HSV	1 (1)	0 (0)
Fever	6 (4)	10 (2)
Varicella	1 (1)	0 (0)
Tick bite[a]	6 (4)	0 (0)
Gastroenteritis	14 (10)	5 (1)
UTI	4 (3)	5 (1)
Mononucleosis	0 (0)	5 (1)
Sepsis[b]	0 (0)	10 (2)
Covid-19[c]	0 (0)	15 (3)

URI, upper respiratory infection; HSV, herpes simplex virus; UTI, urinary tract infection. [a] Two with positive serology for *Borrelia burgdorferi*. [b] *E. coli* and cytomegalovirus. [c] Positive PCR test.

Table 4. Guillain-Barré disability score at diagnosis, nadir, and at 1-year follow-up

	Pre-pandemic, % (n)	During pandemic, % (n)	p value
Diagnosis	$n = 70$	$n = 20$	
0	0 (0)	0 (0)	0.443
1	21 (15)	25 (5)	
2	40 (28)	20 (4)	
3	29 (20)	40 (8)	
4	9 (6)	15 (3)	
5	1 (1)	0 (0)	
6	0 (0)	0 (0)	
Nadir	$n = 73$	$n = 20$	
0	0 (0)	0 (0)	0.935
1	7 (5)	10 (2)	
2	21 (15)	15 (3)	
3	26 (19)	30 (6)	
4	26 (19)	20 (4)	
5	19 (14)	25 (5)	
6	1 (1)	0 (0)	
After 1 year	$n = 63$	$n = 14$	
0	41 (26)	57 (8)	0.399
1	33 (21)	14 (2)	
2	13 (8)	29 (4)	
3	5 (3)	0 (0)	
4	5 (3)	0 (0)	
5	0 (0)	0 (0)	
6	3 (2)	0 (0)	

Guillain-Barré disability score: 0 = no symptoms, 1 = minor signs or symptoms, 2 = able to walk unaided but unable to run, 3 = able to walk with aid, 4 = confined to bed or chair, 5 = requiring assisted ventilation, 6 = death.

Table 5. Treatment given pre-pandemic and during the pandemic

	Pre-pandemic, % (*n*) (*n* = 73)	Pandemic, % (*n*) (*n* = 20)
IVIG single round	62 (45)	80 (16)
Plasmapheresis single round	8 (6)	0 (0)
No treatment	4 (3)	0 (0)
Treatment 2nd round[a]	22 (16)	10 (2)
Treatment 3rd round[a]	4 (3)	10 (2)

[a] Either IVIG alone or combination of plasmapheresis and IVIG.

Table 6. Comparison of days from debut to admission, in the hospital, in intensive care, and of mechanical ventilation, between the pre-pandemic and during pandemic groups

	Pre-pandemic, median (IQR)	During pandemic, median (IQR)	*p* value
Days from debut to admission	4 (1–7)	5 (2–7)	0.595
Days at hospital	18 (11–29)	12 (9–22)	0.299
Days in ICU	25 (10–56)	15 (3–30)	0.604
Days on respirator	34 (10–64)	60 (32–67)	0.586

IQR, interquartile range.

Table 7. Incidence per 100,000 person-years of *Campylobacter jejuni* and *Haemophilus influenzae* during the study period

	2017	2018	2019	2020	2021
C. jejuni	97.94	84.86	72.6	32.63	40.81
H. influenzae	2.25	2.22	3.07	1.04	0.69

tween the pre-pandemic and pandemic groups. Intensive care unit (ICU) admission was required for 26% of cases during the pre-pandemic period and 35% during the pandemic period ($p = 0.50$). Mechanical ventilation was required for 22% of cases during the pre-pandemic period and 25% during the pandemic period. Table 5 shows the treatments administered during the pre-pandemic and pandemic periods. The pre-pandemic and pandemic groups did not differ in the length of time from symptom onset until hospital admission, number of days in the hospital, number of days in the ICU, or use of mechanical ventilation (Table 6).

Discussion

We report a large (50%) reduction in the incidence of GBS during the COVID-19 pandemic compared to the rate during the 3 years immediately preceding the pandemic. During the pre-pandemic period, the incidence was stable and consistent with previously reported data from countries with similar demographics. Jiang et al. [14] reported an incidence of 1.84/100,000 PY in Stockholm during the period 1978–1991, compared to 1.35/100,000 PY in our study. The use of different diagnostic criteria might explain the difference at least partly; Jiang and colleagues used the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria, while the Brighton criteria were applied in our study. Fluctuations of incidence between years might be a contributor since the present study covers a relatively short time period compared to the Stockholm study. There might also be a difference in the prevalence of GBS-associated infections during the two study periods that are 30 years apart.

During the pandemic period, 15% (3/20) of the GBS patients had COVID-19 as a potential trigger, and 10% (2/20) had GBS symptoms following a COVID-19 vaccination. It is possible that the number of postinfectious cases associated with COVID-19 was underestimated in the beginning of the pandemic due to lack of testing; however, from the middle of June 2020, PCR testing for SARS-CoV-2 was readily available and recommended to the public. Our results are similar to previously reported findings from the UK by Keddie et al. [6] and from Singapore by Umapathi et al. [7].

The decreased incidence of GBS during the pandemic may be explained by several factors. According to the Public Health Agency of Sweden, the incidence of notifiable communicable diseases – including known GBS triggers – has decreased during the pandemic. As an example, Table 7 shows the IRs of *Campylobacter jejuni* and *Haemophilus influenzae* infections during the years 2017–2021 [15]. Additionally, individuals with mild GBS may have been reluctant to seek medical attention during the pandemic. However, this possibility is not supported by the finding that the level of GBS disability score and duration of symptoms at diagnosis did not differ between the pre-pandemic and pandemic groups. Furthermore, GBS might have been underdiagnosed or misdiagnosed as critical illness polyneuropathy/myopathy in critically ill COVID-19 patients.

In a study from northern Italy, Filosto et al. [5] found a 2.6-fold increased incidence of GBS during March and April 2020, compared to during the same months in the previous year, with most of these cases co-occurring with COVID-19. This was a large study, involving around 1,400,000 PY of observation, and we do not have an explanation for the difference between our findings and theirs. However, the study was conducted over a relatively short period, and seasonal fluctuations in GBS incidence may have played a role. Additionally, their study was conducted early in the pandemic, possibly before the full effects of social restrictions were apparent.

The temporal relationship between GBS and COVID-19 has been variable among the reported cases, with COVID-19 infection having occurred both prior to and concomitantly with the GBS symptoms. Here, we described 2 cases of GBS in co-occurrence with COVID-19 and 1 case occurring a few weeks after SARS-CoV-2 infection. Considering the wide spread of COVID-19 during the period, this may have been due to chance rather than a true causal relationship.

Most reported vaccine-associated GBS cases have been followed vaccination with the Astra Zeneca vaccine. Notably, Keh et al. [9] reported an excess risk of 0.576 GBS cases per 100,000 first doses of the AstraZeneca vaccine. Public vaccination for COVID-19 in Sweden began in December 2020 and was mostly reserved for individuals of 65 years of age and older. By July 2021, 89% of the population in that age group had received two doses of vaccine, mostly with AstraZeneca [15]. We reported one case of GBS related to vaccination with the first dose of the AstraZeneca vaccine. Based on our study population, this is in line with what could be expected based on the findings of Keh et al. [9]. However, it is impossible to draw any conclusions regarding causality based on our data.

We found the biggest decrease in the age-specific incidence of GBS during the pandemic for individuals of 30–59 years of age, with less of a difference among younger and older persons. One possible explanation might be that the precipitating factors differ between the age-groups. For example, *Campylobacter jejuni* infections are more prevalent in middle-aged people and might be more susceptible to traveling restrictions and increased hygiene routines than other triggers more prevalent among the older ages [15]. A higher frequency of vaccination with the AstraZeneca vaccine in the oldest group may also contribute but cannot be the only explanation.

Some previously published data suggest an increased need of intensive care and mechanical ventilation for patients with COVID-19-related GBS [5, 16]. Our study included too few COVID-19-associated cases for such subgroup analysis. However, our findings do not show any differences in mechanical ventilation or ICU admissions among GBS patients before versus during the pandemic, despite decreased access to ICU care. During the pandemic, IVIG was experimentally used to treat COVID-19 patients, which led to a global deficiency in IVIG during the year 2021. However, we did not find any difference in IVIG treatment between the pre-pandemic and pandemic periods.

Conclusions

Our findings do not support a causal relationship between GBS and COVID-19. The incidence of GBS was significantly decreased during the pandemic compared to the years before, likely due to decreased spread of trigger infections. Our results indicated that the pandemic did not impact the care of GBS patients.

Statement of Ethics

This study was approved by the Swedish Ethical Review Agency, approval number 2020-02558 and 2021-04229.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Brynhildur Hafsteinsdóttir: conceptualization, design, data acquisition, analysis, interpretation, writing, reviewing, and editing. Ellen Dalemo: data acquisition, analysis, and interpretation. Ólöf Elíasdóttir: design, analysis, interpretation, reviewing, and editing. Elías Ólafsson: interpretation, reviewing, and editing. Markus Axelsson: conceptualization, design, analysis, interpretation, writing, reviewing, and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to information that could compromise patient privacy but are available from the corresponding author, B.H., upon reasonable request.

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