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Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

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Reports of Guillain-Barré syndrome (GBS) have emerged during the Coronavirus disease 2019 (COVID-19) pandemic. This epidemiological and cohort study sought to investigate any causative association between COVID-19 infection and GBS. The epidemiology of GBS cases reported to the UK National Immunoglobulin Database was studied from 2016 to 2019 and compared to cases reported during the COVID-19 pandemic. Data were stratified by hospital trust and region, with numbers of reported cases per month. UK population data for COVID-19 infection were collated from UK public health bodies. In parallel, but separately, members of the British Peripheral Nerve Society prospectively reported incident cases of GBS during the pandemic at their hospitals to a central register. The clinical features, investigation findings and outcomes of COVID-19 (definite or probable) and non-COVID-19 associated GBS cases in this cohort were compared. The incidence of GBS treated in UK hospitals from 2016 to 2019 was 1.65–1.88 per 100 000 individuals per year. GBS incidence fell between March and May 2020 compared to the same months of 2016–19. GBS and COVID-19 incidences during the pandemic also varied between regions and did not correlate with one another ($r = 0.06$, 95% confidence interval: –0.56 to 0.63, $P = 0.86$). In the independent cohort study, 47 GBS cases were reported (COVID-19 status: 13 definite, 12 probable, 22 non-COVID-19). There were no significant differences in the pattern of weakness, time to nadir, neurophysiology, CSF findings or outcome between these groups. Intubation was more frequent in the COVID-19 affected cohort (7/13, 54% versus 5/22, 23% in COVID-19-negative) attributed to COVID-19 pulmonary involvement. Although it is not possible to entirely rule out the possibility of a link, this study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS. GBS incidence has fallen during the pandemic, which may be the influence of lockdown measures reducing transmission of GBS inducing pathogens such as *Campylobacter jejuni* and respiratory viruses.

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Abbreviations: COVID-19 = Coronavirus disease 2019; GBS = Guillain-Barré syndrome; IGOS = International GBS Outcome Study; IVIg = intravenous immunoglobulin; NHSE = NHS England; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Introduction

The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported to the WHO in late 2019, and by March 2020 COVID-19 was pandemic. (WHO, 2020) SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) were previously associated with neurological sequelae (Li *et al.*, 2020). Early reports identified neurological symptoms of COVID-19 infection as headache, anosmia and dysgeusia (Mao *et al.*, 2020). Subsequently COVID-19 infection has been associated with stroke, meningoencephalitis, acute disseminated encephalomyelitis and Guillain-Barré syndrome (GBS) (Ghannam *et al.*, 2020; Paterson *et al.*, 2020; Varatharaj *et al.*, 2020). The first reported case of GBS questioned a possible link with COVID-19 and occurred in late January 2020 in a COVID-19 asymptomatic patient who developed COVID-19 symptoms at Day 8 of GBS (Zhao *et al.*, 2020). The first series of five patients with GBS following SARS-CoV-2 infection was reported in April 2020, (Toscano *et al.*, 2020) followed by a number of case reports, case series and collective reviews.

GBS is an acute, post-infectious immune mediated polyradiculoneuropathy typically arising a few days to 6 weeks after bacterial or viral infections including *Campylobacter jejuni*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, influenza, Epstein-Barr virus, cytomegalovirus, and more recently, Zika virus (Tam *et al.*, 2007; Lehmann *et al.*, 2010; Cao-Lormeau *et al.*, 2016). The pathogenesis of GBS following the majority of presumed causative infections is unknown, although humoral molecular mimicry is definitively established for *C. jejuni*-associated GBS, and may play a role in many or most cases of GBS (Willison and Yuki, 2002; Loshaj-Shala *et al.*, 2015). The pathological initiating event of *C. jejuni* GBS is the manufacture of antibodies to lipo-oligosaccharide surface epitopes of *C. jejuni* that cross-react with peripheral nerve glycolipids, resulting in complement fixation, macrophage attraction and resultant peripheral axon or myelin nerve damage (Yuki and Hartung, 2012). This mechanism may also occur with other bacterial and viral pathogens since anti-ganglioside antibodies are found in up to 60% of GBS cases (Kaida *et al.*, 2009), including those associated with viral infections; for example, anti-GM2 antibodies occur in CMV-associated GBS. GBS associated with ganglioside complexes increases the frequency of potential ganglioside related molecular mimicry, and the presence of antibodies to paranodal and juxtaparanodal antigens suggests an unproven post-infectious link to protein epitopes (Devaux *et al.*, 2012; Rinaldi *et al.*, 2013). Zika-associated GBS has such a close association to seroconversion that some cases may be due to direct but unproven neurotropic damage.

SARS CoV-2 is a single-stranded RNA enveloped virus. Open reading frames (ORF) encode for replicase proteins and the structural proteins, which are the spike (S), nucleocapsid (N), envelope (E) and membrane (M) proteins (Liu *et al.*, 2014). To date, we know of no homology between SARS-CoV-2 surface epitopes and peripheral nerve tissue.

Reports of varied anti-ganglioside antibodies in association with COVID-19 GBS suggest that a uniform CMV-like immune-mediated hypothesis is unsupported. More comprehensive epidemiological characterization is crucial to understanding any causal link. With over 50 million cases of COVID-19 infection worldwide by 1 December 2020 (European Centre for Disease Prevention and Control, 2020*b*), the question of whether COVID-19 infection is a cause of GBS or a coincidental finding remains to be answered.

This study aimed to investigate whether a causal relationship could be determined between COVID-19 and GBS, and was performed in three parts. First, we retrospectively explored UK population-based epidemiological datasets of cases with confirmed COVID-19 and compared that to patients hospitalized with GBS. Separately, but in parallel, we characterized a large cohort of the incident UK GBS cases presenting both with and without COVID-19 to explore timing of onset, and any identifying phenotypic characteristics that might hint towards a specific mechanistic link (as for example in sensory GBS associated with CMV). Finally, we explored any homology between SARS-CoV-2 and the human genome and proteome that would support a molecular mimicry mechanism.

Materials and methods

Epidemiological case reporting

Incident hospitalized cases of GBS were retrospectively ascertained from the UK National Immunoglobulin Database from 1 January to 31 May 2020, demonstrating the frequency of GBS cases across the year, pre and during the COVID-19 pandemic. NHS England (NHSE) procures the total intravenous immunoglobulin (IVIg) supply for England, Scotland and Northern Ireland. NHSE mandates that every IVIg prescription is approved by a clinical panel and is reported onto the database within 90 days. Recording compliance is almost 100% as hospital trusts are only reimbursed once records of dispensed volumes are submitted; these are retrospectively cross-checked against supply and returned stocks (Foster, 2017). To ensure complete reporting of cases, NHSE specifically mandated all users of the National Immunoglobulin Database to log any outstanding GBS cases by 30 June 2020 by email on 9 June 2020. Data retrieval was then performed on 7 July 2020 to allow time for reporting delay.

Current UK guidance for GBS treatment indicates IVIg or plasma exchange (PLEX) as first line therapy (Department of Health, 2011), but IVIg is, in practice, first line in most UK hospitals as PLEX is normally not as available. IVIg is also only authorized in the UK for patients with Hughes Grade $\geqslant 4$, progressing towards intubation and ventilation, with a high likelihood of respiratory support (mEGRIS score $\geqslant 3$) or a predicted poor prognosis (mEGOS $\geqslant 4$). The patients usually treated with IVIg in the UK are those who require admission, and although this under-ascertains the true incidence of GBS, it reduces the effects of attendance bias in a pandemic, whereby milder cases may not have attended hospital, but regardless would not have required treatment. IVIg is given to nearly all presenting GBS patients in Europe as illustrated by 86% (612/715) of European cases treated with IVIg in the International GBS Outcome Study (IGOS) (Doets *et al.*, 2018), and 88% (37/42) of 'COVID-19 GBS' in the literature until July (Uncini *et al.*, 2020).

We also searched the NHSE Immunglobulin Database for GBS cases from 1 January to 31 May in each of the years 2016 to 2019 to determine the incidence of non-COVID-19 reported cases of GBS to compare to the 2020 pandemic data. Data were stratified by hospital trust and region. UK population data for COVID-19 PCR confirmed infection were collated from Public Health England, Health Protection Scotland and the Public Health Agency of Northern Ireland. Because of the lack of available testing early in the pandemic, COVID-19 PCR confirmed cases were significantly fewer than the true incidence of infection across the UK (Connors and Sutherland, 2020). Therefore in addition, we obtained data from the NHS Blood Transfusion Service (NHSBT) (Public Health England, 2020*a*) of antibody seroprevalence across the UK to SARS-CoV-2, and used the London data to study the number of GBS cases that occurred according to the number of PCR confirmed cases and the number of seroconverted COVID-19 cases.

Cohort study

In parallel to the epidemiological study, we conducted a prospective cohort study to compare the demographic, phenotypic and infective associations of COVID-19 associated GBS (definite and probable) to COVID-19 negative GBS reported during the same study period.

Reports of GBS were submitted by members of the British Peripheral Nerve Society (BPNS), who cover 81 different UK sites. Members were emailed on a weekly basis to collect information on hospital presentations of GBS from 1 March to 31 May 2020. Reporting was restricted to BPNS members to achieve a comprehensively characterized sample of incident cases diagnosed by peripheral nerve experts. Data were entered to the International Neuromuscular COVID-19 database (www.ucl.ac.uk/centre-for-neuromuscular-diseases/news/2020/may/international-neuromuscular-covid-19-database), at the Centre for Neuromuscular Disease. Cohort study data collection ended on 1 July 2020 to allow time for retrospective case reporting. Anonymized clinical data of demographics and medical history, COVID-19 infection, symptoms and management were collected. Precipitating illness, clinical features of GBS, investigation findings including CSF and electrophysiology, management and outcomes were also collated.

Data collected from the cohort study were compared to the phenotypic characteristics of the published European International GBS Outcome Study cases to assess whether pandemic presentations (COVID-19 positive and negative) differed from a comparable cohort of non-pandemic phenotypes (Doets *et al.*, 2018).

Evidence of COVID-19

For the cohort study, GBS cases were stratified into three groups: definite COVID-19, probable COVID-19 and non-COVID-19. Definite cases had either a positive nasal or throat swab PCR for viral RNA or a subsequent positive serological test for anti-SARS-CoV-2 IgM or IgG irrespective of clinical

signs and symptoms. Probable cases were defined by the presence of clinical symptoms consistent with COVID-19 infection as per the European Centre for Disease Prevention and Control case definitions (European Center for Disease Prevention and Control, 2020*a*), or pulmonary imaging [chest X-ray (CXR) or CT] highly suggestive of COVID-19 (airway opacification typically bilateral, peripheral and basal in distribution) where PCR analysis was negative. Occurrence of GBS within 6 weeks of acute COVID-19 infection (clinically or on confirmed laboratory findings) was considered necessary to confirm a definite link, with longer time frames accepted but recorded in the data and classified as probable (Ellul *et al.*, 2020).

Search for homology between SARS-CoV-2 and human genome and proteome

At the time of this study relatively little is known of the epitope presentation and immunobiology of SARS-CoV-2. We searched for evidence of molecular mimicry between any SARS-CoV-2 proteins and human nerve axonal or myelin proteins and glycoproteins, recognizing that epitopes are not all protein and not necessarily all linear. We searched for human homologues of proteins encoded by the SARS-CoV-2 genome using the National Centre for Biotechnology Information (NCBI's) Basic Local Alignment Search Tool (BLAST) to identify common amino acid sequences in the human Reference Sequence Database (refseq_protein). The NCBI BLAST was also used to query the SARS-CoV-2 genome against the human genome for any significant alignments at specific genomic loci.

The expect value (E-value) quantifies the number of times a specific alignment can be 'expected' to occur in a database by chance. As the E-value decreases the significance of the alignment in the specified database increases. Any alignment with an E-value of $\leqslant 1 \times 10^{-4}$ was considered homologous to a human protein (error rate $<0.01\%$).

Statistical analysis

The incidence rates of GBS and COVID-19 (95% confidence intervals by Byar's approximation method) (Breslow and Day, 1987) were calculated by dividing regional cases and time period by the relevant mid-year population estimate. Mid-year population estimates at both regional and national level were obtained from the UK Office for National Statistics (Office for National Statistics, 2019). We explored any association between the incidence of GBS and the incidence of COVID-19 in UK regions in 2020 (January to May) using Pearson's correlation coefficient. The Shapiro-Wilk test was used to determine suitability of parametric tests.

COVID-19 definite and probable cases in the cohort were statistically compared against non-COVID-19 associated GBS. In addition, to determine whether characteristics differed between pandemic and non-pandemic GBS phenotypes, clinical characteristics of our study cohort were also compared to published IGOS study participants. We used Mann-Whitney U to test non-parametric continuous data, and the χ^2 or Fisher's exact test to compare proportions. IGOS data stratified to European/American cases ($n = 715$) were used in preference to the entire IGOS cohort ($n = 925$) where available (Doets *et al.*, 2018). R (4.0.0) and GraphPad prism (8.1.2) were used for analysis and figures.

Ethics

The UK Health Research Authority was consulted and advised the study did not require review by an NHS Research Ethics Committee as an analysis of previously collected non-identifiable information. The project was submitted as a 'Service Evaluation' to the Clinical Audit and Quality Improvement Subcommittee (CAQISC).

Data availability

Data are available upon request to the corresponding author.

Results

Epidemiological study

The NHSE Immunoglobulin Database reported a mean of 1098 (range 1021–1155) GBS cases per year in the UK (excluding Scotland) between 2016 and 2019 (monthly range 83–170 cases). This represents the UK GBS population who are admitted to hospital that are treated. As PLEX is seldom used and only patients with significant GBS are treated, IVIg treatments represent the vast majority of UK cases. Annual UK GBS incidence requiring treatment was therefore a minimum of 1.65–1.88 per 100 000 individuals each year across this period, consistent with the incidence of GBS in Europe and North America from a previous meta-analysis of 1643 GBS cases (range 0.81–1.89 cases per 100 000) (Sejvar *et al.*, 2011). These comparative figures along with the mandatory reporting supports the NHSE Immunoglobulin Database as the most comprehensive, complete and accurate resource for epidemiological analysis of GBS in the UK.

Although COVID-19 was first reported in the UK on 31 January 2020, significant numbers of daily new infections in the first wave (>1000 per day) did not occur until March, with the highest recorded daily count of 6201 confirmed cases prior to this report on 1 May 2020 (Public Health England, 2020*a*). Through April and May there were between 4000 and 6000 COVID-19 cases per day. If a strong causative and temporal association existed, COVID-19 GBS cases would be expected to rise in subsequent weeks (Fig. 1). However, even accounting for the consistent summer dip in GBS cases seen in 2016–2019, GBS cases in March (93), April (70) and May (56) of 2020 were significantly fewer than years 2016–19 [mean 132 (March), 116 (April) and 113 (May)] (Fig. 2). GBS and COVID-19 incidences varied across UK regions with no correlation between COVID-19 and GBS at a regional level ($r = 0.060$ 95% confidence interval −0.56 to 0.63, $P = 0.86$) (Fig. 3 and Supplementary Table 1).

By the 1 March 2020 there were only 17 PCR-positive confirmed COVID-19 cases in London, which increased to

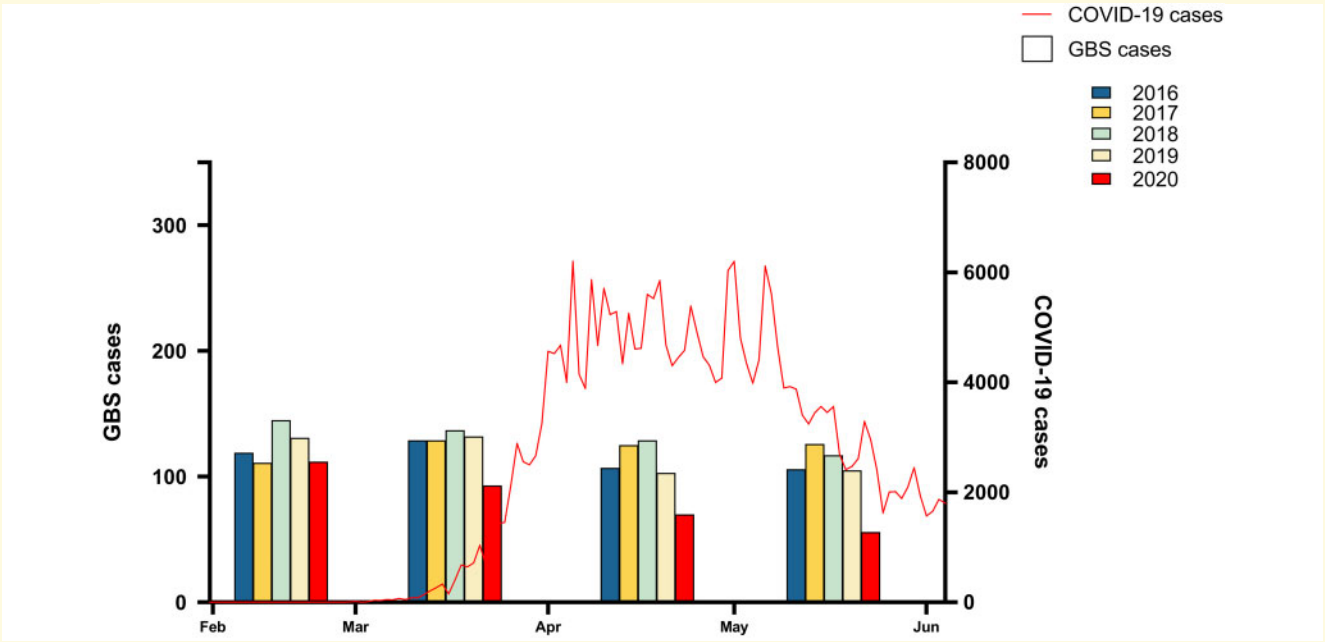

Figure 1 Numbers of new daily COVID-19 infections from February to May inclusive, 2020 (red line) compared to GBS cases in the UK between February to May inclusive from 2016 to 2020 (years depicted by colours in legend).

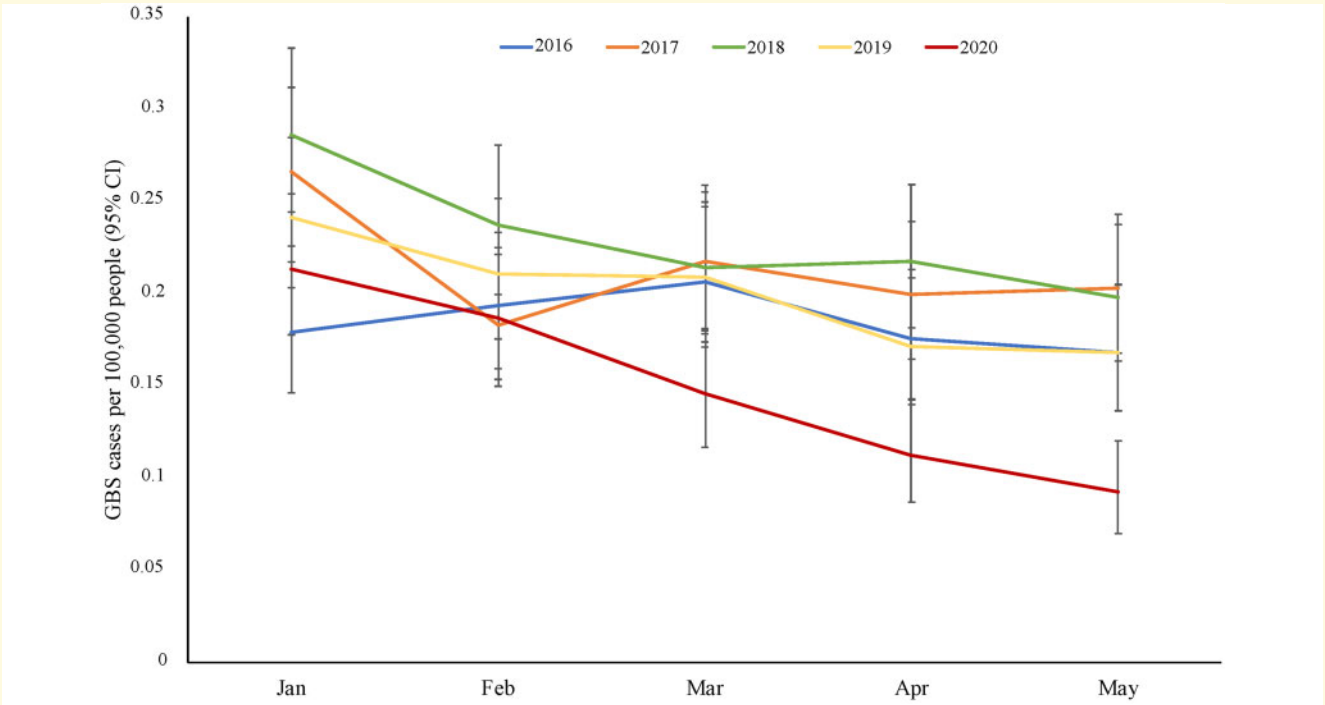

Figure 2 Monthly incidence of GBS per 100 000 individuals treated with IVIg in the UK between January and May inclusive for 2016–20.

26 798 by the 27 April 2020 (Public Health England, 2020*a*). In London there were 25 cases of GBS registered to the NHSE IVIg database during this time (138 in the rest of the UK). Using these figures for this period, the estimated occurrence rate is 0.82 GBS cases per 1000 COVID-19 infections. However, serological data from London blood donors on the 27 April 2020 reported the prevalence of prior SARS-CoV-2 infection in London as 17.5% (Public

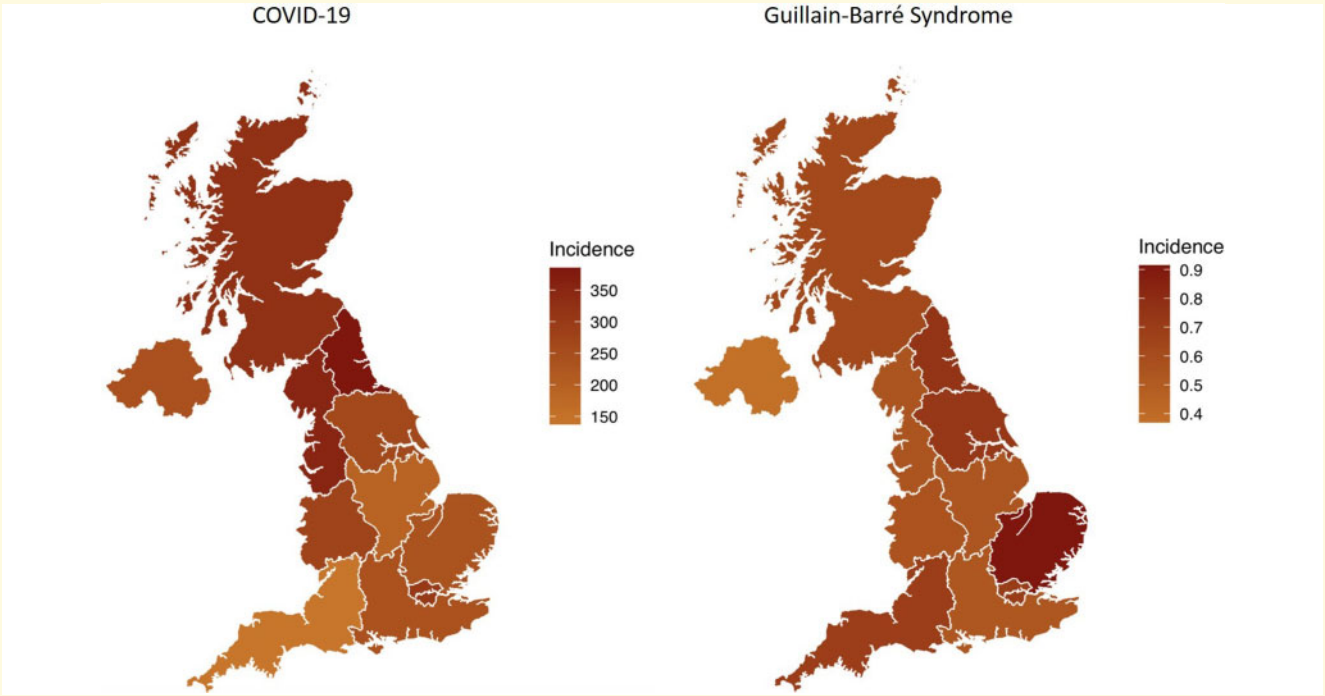

Figure 3 Heat map of regional incidences of GBS and COVID-19 infections per 100 000 across the UK from January to May inclusive, 2020.

Health England, 2020*b*), equivalent to 1 571 850 individuals having made a serological response to COVID-19. This is more likely to give the true estimate of COVID-19 infections in the community. Using 1 571 850 as the denominator for infection, the occurrence rate of GBS is more likely to be 0.016 cases per 1000 COVID-19 infections.

Cohort study

Forty-seven cases of GBS were reported to the cohort by BPNS members over a 12-week collection period. Patients were classified according to the Brighton Criteria ranging from high to low of diagnostic certainty (Sejvar *et al.*, 2011*b*). Twenty-two were level 1 (46%), 15/47 (32%) level 2, with four (9%) level 3 and six (13%) level 4, similar to previously reported large GBS cohorts (Fokke *et al.*, 2014). Of the 47 cases, 13 had definite COVID-19 infection, 12 were probable, and 22 had GBS with no evidence of COVID-19. Median age was 57 years [interquartile range (IQR) 19–88], 33 were male (70%) and 29 (66%) were Caucasian. The male:female ratio in the COVID-19 patients was 5.5 compared to 1.4 in the non-COVID (Table 1) and IGOS study (Table 2). Males are more likely to be significantly unwell and hospitalized with COVID-19 infection, which may partially or completely explain this difference (Docherty *et al.*, 2020; Williamson *et al.*, 2020).

The clinical characteristics of the patients with GBS are shown in Table 1 and Supplementary Table 2. For patients with COVID-19 infection, the median time between onset of infective symptoms and neurological weakness was 12 days for definite COVID-19 and 5 days for probable cases; however, the range of time intervals was very broad, ranging from 0 to 37 days in definite and –14 to 52 days in probable cases, with only one case in which GBS developed over 6 weeks following COVID-19 onset. Three probable cases developed symptoms of GBS without any clear COVID-19 symptoms, and had incidental imaging evidence of COVID-19 suggesting recent mild or asymptomatic infection. Numbers of non-COVID-19 GBS cases with symptoms of a precipitating illnesses, particularly gastroenteritis, were significantly fewer than that compared to the IGOS cohort [1/22, 5% in non-COVID-19 cases compared to 163/652 (25%) in the IGOS cohort, $P < 0.0001$, see Table 2]. This may be an effect of lockdown with improved hand hygiene reducing numbers of faecal-oral pathogen transmissions. The pattern of weakness and time to nadir were no different between COVID-19 associated GBS and non-COVID-19 GBS. Although not statistically significant, electrophysiological studies found a higher proportion of axonal GBS in the non-COVID-19 patients [four acute motor and sensory axonal neuropathy (AMSAN) and one acute motor axonal neuropathy (AMAN) 23%, compared to one with AMSAN only from the COVID-19-positive group]. Cranial nerve involvement was the only finding more frequent in the IGOS study compared to our cohort (Table 2).

The use of ventilation did not differ significantly between COVID-19 (definite and probable) cases versus non-COVID-19 GBS. However, the number of COVID-19 definite GBS cases that were ventilated was higher than all other groups (7/13, 54% compared to 0/12 probable and 5/22, 22% non-COVID-19). Despite this, the GBS disability score at 4 weeks was no different between all groups, suggesting

Table 1 Cohort study data demonstrating clinical characteristics of GBS with definite, probable and without COVID-19 infection

GBS features	COVID-19 definite	COVID-19 probable	Non-COVID-19	*P*-value
n	13/47 (28)	12/47 (26)	22/47 (47)	
Age, years [IQR]	60 [57–66]	57 [50–60]	54.5 [34–66]	0.528
Sex, male: female (ratio)	11:2 (5.5)	9:3 (3.0)	13:9 (1.4)	0.200
Ethnicity/origin (%)				
White	8 (62)	6 (50)	15 (68)	0.548
Black, Asian and minority ethnic	3 (23)	2 (17)	5 (23)	
Unknown	2 (15)	2 (17)	2 (9)	
Comorbidities (%)				
Hypertension	3 (23)	1 (8)	4 (18)	>0.999
Diabetes	1 (8)	1 (8)	3 (14)	>0.999
Cerebrovascular disease	1 (8)	0 (0)	1 (5)	>0.999
COPD/asthma	2 (15)	0 (0)	0 (0)	0.491
Severity and distribution of weakness (%)				
Tetraparesis	9 (69)	8 (67)	13 (59)	0.558
Weakness lower limbs only	2 (15)	3 (25)	5 (23)	>0.999
Weakness upper limbs only	0 (0)	0 (0)	0 (0)	>0.999
Unilateral limb weakness	1 (8)	0 (0)	0 (0)	>0.999
No limb weakness	1 (8)	1 (8)	2 (9)	>0.999
Other	0 (0)	0 (0)	2 (9)	0.213
GBS syndrome (%)				
Normal neurophysiology	0 (0)	1 (8)	1 (5)	0.084
AIDP	7 (54)	2(17)	12 (55)	0.248
Axonal (AMAN/AMSAN)	0 (0)	1 (8)	5 (23)	0.084
Miller Fisher	1 (8)	0 (0)	0 (0)	>0.999
Neurophysiology not assessed	5 (38)	8 (67)	4 (18)	**0.031**
Preceding illness (%)				
Upper respiratory tract infection	10 (77)	2(17)	6 (27)	0.229
Gastrointestinal infection	0 (0)	0 (0)	1 (5)	0.468
Presence of sensory deficit (%)	6 (46)	7 (58)	11 (50)	>0.999
Cranial nerve involvement (%)	3 (23)	6 (50)	6 (27)	0.550
CSF results				
Protein, g/l [IQR]	0.78 [0.50–0.99]	1.08 [0.69–1.66]	0.49 [0.33–1.23]	0.172
White cell count, cells/μl [IQR]	2 [0–5]	2 [0–13]	2 [0–38]	0.762
Positive gangliosides (%)	0 (0)	0 (0)	5 (10)	**0.017**
Time from COVID-19 symptoms to weakness, days [IQR]	12 [4–21]	5 [–7–19]	NA	
Time from weakness onset to nadir, days [IQR]	7 [4–11]	11 [5–17]	6 [4–9]	0.311
Invasive mechanical ventilation during illness (%)	7 (54)	0 (0)	5 (23)	0.747
ITU as the maximum level of care required (%)	7 (54)	1 (8)	9 (41)	0.558
HDU as the maximum level of care required (%)	3 (23)	0 (0)	1 (5)	0.611
GBS disability score at 4 weeks from admission [IQR]	3 [2–4]	2.5 [1.75–3]	3.5 [2–4]	0.990
0	0 (0)	2 (17)	1 (5)	
1	1 (8)	1 (8)	2 (9)	
2	2 (15)	3 (25)	4 (18)	
3	3 (23)	4 (33)	3 (14)	
4	4 (31)	2 (17)	8 (36)	
5	1 (8)	0 (0)	3 (14)	
GBS disability score on discharge [IQR]	3 [2–4]	2 [1.75–3]	3 [2–4]	0.658
0	1 (8)	1 (8)	1 (5)	
1	1 (8)	1 (8)	2 (9)	
2	2 (15)	4 (33)	5 (23)	
3	3 (23)	3 (25)	4 (18)	
4	2 (15)	1 (8)	4 (18)	
5	1 (8)	0 (0)	0 (0)	
Initial treatment type (%)				
IVIg	9 (69)	9 (75)	21(95)	0.052
PLEX	0 (0)	0 (0)	0 (0)	
Nil	4 (31)	3 (25)	1 (5)	0.052
Mortality (%)	1 (8)	0 (0)	0 (0)	>0.999

Data are presented as *n* (%) or median [IQR]. *P*-values represent a comparison between COVID-19 definite and COVID-19 probable to non-COVID-19 GBS. *P*-values below 0.05 are highlighted in bold. GBS disability score provided as median. 0 = healthy; 1 = minor symptoms and capable of running; 2 = able to walk 1 m without assistance but unable to run; 3 = able to walk 1 m across an open space with help; 4 = bedridden or chair bound; 5 = requiring assisted ventilation for at least part of the day; 6 = dead. AIDP = acute inflammatory demyelinating polyradiculopathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; COPD = chronic obstructive pulmonary disease; HDU = high dependency unit; ITI = intensive care unit.

Table 2 Clinical characteristics of COVID-19 pandemic GBS compared to the IGOS cohort

GBS features	Overall	IGOS Cohort 2018	*P*-value
n	47	**925**	
Age, years [IQR]	57 [19–88]	55 [37–67]	
Sex, male:female (ratio)	33:14 (2.36)	418:297 (1.41)	0.127
Severity and Distribution of weakness			
Tetraparesis	30/47 (64)	677/924 (73)	0.178
Weakness lower limbs only	10/47 (21)	105/924 (11)	0.059
Weakness upper limbs only	0/47 (0)	19/924 (2)	>0.999
Unilateral limb weakness	1/47 (2)	10/924 (1)	0.422
No limb weakness	4/47 (9)	15/924 (2)	**0.010**
GBS syndrome			
Normal neurophysiology	2/47 (4)	36/573 (6)	0.758
AIDP	21/47 (45)	312/573 (55)	0.224
Axonal (AMAN/AMSAN)	6/47 (12)	33/573 (6)	0.107
Preceding illness			
Upper respiratory tract infection	18/47 (38)	248/652 (38)	>0.999
Gastrointestinal infection	1/47 (2)	163/652 (25)	<**0.000**
Presence of sensory deficit	26/47 (55)	408/588 (69)	0.051
Cranial nerve involvement	15/47 (32)	304/620(49)	**0.033**
CSF results			
Protein g/l, median [IQR]	0.695 [0.24–4.16]	0.98 [0.59–1.84]	
<0.4 g/l	16/39 (41)	262/823 (32)	0.144
>0.4 g/l	23/39 (59)	561/823 (68)	0.225
White cell count, median [IQR]	2 [0–38]		
<5	30/35 (86)	641/823 (80)	0.401
5 to 50	5/35 (14)	149/823 (19)	0.659
>50	0/35 (0)	14/823 (2)	>0.999
Time of weakness to admission, days [IQR]	4 [–13–27]	3 [2–6]	
Number of patients requiring invasive mechanical ventilation during illness	12/47 (26)	121/715 (17)	0.162
Initial treatment type			
IVIg	39/47 (83)	612/715 (86)	0.668
PLEX	0/47 (0)	43/715 (6)	0.101
Mortality	1/47 (2)	44/659 (7)	0.352

Data are presented as *n* (%) or median [IQR]. *P*-values represent a comparison between the COVID-19 cohort (definite, probable and non-COVID-19) GBS compared to that of the IGOS study cohort. Note that IGOS denominator values reflect worldwide cases reported (*n* = 925) or once stratified for 'Europe/American' cases (*n* = 715) if available. AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy.

the requirement for initial ventilation was secondary to active COVID-19 pulmonary involvement rather than neuromuscular weakness in PCR-positive, definite COVID-19 cases.

There were no differences in the treatment of GBS subgroups. IVIg was the first therapy in 83% cases, and only one patient received PLEX as second line therapy. One patient received more than one course of IVIg. One patient (COVID-19 definite) died. Death was attributed to pulmonary complications rather than neuromuscular weakness.

Comparison between SARS-CoV-2 and human genome and proteome

When we examined the entire SARS CoV-2 genome [29 903 bases (b); NC_045512.2] as well as overlapping fragments of 1000 b (±500 b) and compared this to the human genome, we found no significant similarity.

We also explored individual proteins encoded by the SARS-CoV-2 genome comparing these against all referenced human proteins. Only the replicase ORF1ab/ORF1a polyprotein (7096 amino acids) produced a match with the human mono-ADP-ribosyltransferase (PARP14) protein. PARP14 belongs to an enzyme superfamily involved in histone modification during DNA damage and is ubiquitously expressed making it unlikely as a mimotope. These two proteins are 32% identical (E-value 3×10^{-6}) but have only one contiguous identical sequence of five or more amino acids (Val-Val-Val-Asn-Ala) that might act as a cross reactive linear peptide epitope. The remaining SARS-CoV-2 proteins including the spike/surface, envelope, membrane and nucleocapsid phosphoprotein have no significant similarity with any referenced human protein.

Discussion

Although it is profoundly difficult to prove no link in a rare disease, this retrospective epidemiological and prospective cohort study does not support any significant causal link

between COVID-19 infection and GBS (Lucas and McMichael, 2005). We have used several reliable sources of data to collate the best evidence from each to demonstrate the lack of likelihood of significant causation. The population-based data find no plausible temporal relationship between COVID-19 and GBS (Fig. 1), a reduction in cases of GBS in comparison to preceding years (Fig. 2) and no correlation between COVID and GBS incidence at regional level (Fig. 3). There are in addition no identifiable COVID-19-associated GBS features that differentiate it from GBS in non-pandemic circumstances, in this, the largest cohort reported to date. There are also no scientific data to support a molecular mimicry link of SARS-CoV-2 to GBS at the nucleic acid or protein level, other than a presumptive analogy to other known bacterial and viral GBS-causing pathogens. The lack of even a short, linear homology between the SARS-CoV-2 structure proteins and any axonal or myelin surface proteins reduces the likelihood that molecular mimicry with SARS-CoV-2 might be a putative mechanistic link of SARS-CoV-2 to GBS.

The UK has a single highly regulated IVIg supply. IVIg is routinely available for all patients with GBS, but every vial given for GBS is logged under a mandatory NHS-based system linked directly to clinicians and to subsequent payment. The mandatory reporting to the NHSE National Immunoglobulin Database correlates with audits and clinical data showing that nearly all GBS patients receive IVIg. GBS incidence calculated through this data source corresponds exactly with reported incidence rates from multinational population-based epidemiological studies, supporting the database as an appropriate repository for epidemiological analysis. Using this almost unique source we identified significantly fewer cases of GBS during the COVID-19 pandemic compared to previous years. This could, however, represent an under-ascertainment of cases during lockdown for several reasons, including incomplete IVIg prescription recording or patients avoiding hospital attendance.

UK Hospital Trusts are mandated to report all IVIg treatments to the database within 90 days and previous database analyses have shown 95% of cases were recorded within 30 days of treatment, and 98% within 90 days. We collected data from 1 January to 31 May 2020 on 7 July, thus allowing sufficient time to capture the majority of reported cases. A subsequent direct check of complete IVIg reporting, specific requests for clinicians to document cases and a cross check between clinical reports and IVIg prescribing data ensured we have as complete a dataset as possible.

Mildly symptomatic patients may have decided not to visit hospital for fear of contracting COVID-19. This issue was recognized in stroke and emergency medicine with declines in overall admissions worldwide (Aguiar de Sousa *et al.*, 2020; Markus and Brainin, 2020; Perry *et al.*, 2020; Public Health England, 2020*c*). Physicians' prescribing behaviour could also have changed during the pandemic, being more selective in providing treatments, including IVIg. The National Immunoglobulin Database only records treated GBS cases. The indication for IVIg treatment in GBS is for non-ambulant patients, and therefore it is unlikely such patients remained at home or would not be admitted to hospital. Even in 2016–19, only cases with significant disability and meeting criteria for treatment were recorded. This reduces the likelihood of a disparity resulting from mild disease attendance bias, as a result of COVID-19 explaining the decline. Furthermore, within our cohort study 83% of cases were treated with IVIg, providing cross validation of high treatment rates, but also the fact that milder patients continued to attend hospital to some extent.

We hypothesize that the lockdown measures introduced to prevent COVID-19 transmission have had secondary effects of reducing other common transmissible infective GBS triggers such as upper respiratory tract infections through social distancing and mask wearing, and gastrointestinal illnesses as fewer people dined out and stricter hand hygiene was adhered to. In our cohort of 47, only 1/47 (2%) reported diarrhoea preceding their GBS, significantly fewer than in the European IGOS patients at 25% (Doets *et al.*, 2018). This is speculative but consistent with our hypothesis. Other studies have reported significant reductions in airborne or faeco-oral transmissible infectious diseases during lockdown, supporting this assertion (Angoulvant *et al.*, 2020). Although the true impact of hygiene measures is unknown, the avoidance of *C. jejuni* and respiratory pathogens could conceivably reduce the incidence of GBS, and may explain the pandemic-related reduction of GBS cases. Successful interventions to lower *Campylobacter* contamination of fresh poultry meat have previously been reported to reduce hospitalizations for GBS by 13% (Baker *et al.*, 2012), and so this assertion is not impossible.

The true COVID-19 incidence in the UK is known to have been significantly under-reported. Until the end of March 2020, only patients admitted to hospital were tested for COVID-19 by PCR, and after this time it took 2 months for community testing to record symptomatic cases elsewhere. Only PCR confirmed cases were reported in the published data. Where a known link of GBS to an infectious agent exists, rates of occurrence have been published and are in the range of 0.2 to 2.2 cases per 1000 infections; for example GBS occurs at 0.25–0.65 per 1000 cases of *C. jejuni*, 0.6–2.2 per 1000 cases of primary cytomegalovirus, and 0.24 per 1000 Zika virus infections (Orlikowski *et al.*, 2011; Yuki and Hartung, 2012; Cao-Lormeau *et al.*, 2016). Utilizing PCR confirmed cases as a denominator to calculate the rate of GBS COVID occurrence suggests 0.82 cases per 1000 COVID-19 infections. As COVID-19 is a novel infection with no pre-existing seropositivity, it provides a unique opportunity to assess infection relationship rates. The true community infection rates of COVID were nearly 60× higher than the published PCR rate from the measured seroprevalence; furthermore, serological data may even still under-report the true COVID-19 infection rates as antibody responses are not detectable in all post COVID-19 infected cases, in which SARS-CoV-2 specific T-cell immune responses may occur (Sekine *et al.*, 2020). The COVID-19 seroprevalence estimated GBS incidence is 0.016 per 1000

COVID-19 infections (1.6 per 100 000, and equivalent to the usual incidence of GBS). Although it is difficult to entirely rule out a causative link, these data provide further evidence for a lack of strong relationship between COVID-19 and GBS compared to other recognized GBS-associated infective pathogens, and potential over-reporting of an association when using PCR confirmed cases only.

Whilst at an epidemiological level we found no increase in GBS linked to the COVID-19 epidemic, our data do not exclude the possibility that SARS-Cov-2 might be a driver of GBS in very rare cases, or that a significant reduction in non-COVID-19 GBS could mask a smaller spike of COVID GBS cases. However, other infective causes of GBS have been identified through demonstrating a spike in incidence temporally related to an increased incidence of the causative infective pathogen. With SARS-CoV-2 being one of the most prevalent infective pathogens in the past century, it is more conceivable that the absence of any increase in GBS cases during the pandemic is more likely due to a lack of causation. We have also shown that there is no significant homology between any SARS-CoV-2 genetic or linear protein structure and human linear protein structures, making a molecular mimicry causation less likely. The lack of homology does not exclude immunological similarity entirely as antibody epitopes are often non-linear. Furthermore, post-translational modification of viral proteins by their host cells can occur, which theoretically could result in the generation of immunogenic surface glycomolecules so far unknown (Mary *et al.*, 2019). Although molecular mimicry is the only fully proven pathogenic GBS mechanism, we acknowledge others could exist. More research is required to determine whether a causal relationship exists between SARS-CoV-2 and GBS.

Some small early series of COVID-19 associated GBS have been reported (Gigli *et al.*, 2020; Toscano *et al.*, 2020). The series of Gigli *et al.* (2020) reported eight patients, all of whom were swab negative, one seropositive only and only four with COVID symptoms. Another small cohort of five reported specific disease characteristics suggesting differences from typical AIDP (Toscano *et al.*, 2020). Our prospective cohort study compared 47 cases of GBS, 13 with definite COVID-19 infection, 12 probable, and 22 with no evidence of COVID-19. Although over half of cases in our clinical cohort of GBS had evidence of COVID-19 infection, reporting bias could have influenced these proportions. A similar effect will have influenced the medical literature with over-reporting of COVID-19 GBS cases in small studies creating an impression of significant co-existence of the two conditions. The purpose of the cohort study was to compare clinical characteristics of COVID-19 and non COVID-19 associated GBS and was not fully representative of the population. This cohort revealed no differences in the clinical and neurophysiological features, disease severity or outcomes of COVID-19 and non-COVID-19 associated GBS. A larger proportion of COVID-19 PCR-positive GBS cases required mechanical intervention compared to all other groups. The similar rate of neurological recovery across all groups suggests ventilation was more related to COVID-19 associated pulmonary involvement rather than neuromuscular deficit at nadir.

This population based epidemiological study has been able to demonstrate no relationship between GBS and COVID-19 infections across the UK through the interrogation of several complementary data sources. As we explore potential COVID-19 associated neurological disease, a measured analysis of the statistical probability of rare disease occurrence in the context of a pandemic is required to investigate causation appropriately, and continue to manage non-COVID-19 neurology with the associated challenges on healthcare resources. This study contradicts a growing number of reports postulating causation between SARS-CoV-2 and GBS, and indeed demonstrates a reduction of GBS cases. This paper alone cannot be considered definitive in ruling out SARS-CoV-2 as a cause of GBS, but further prospective data collection of COVID-19 associated GBS cases and laboratory research are required. Although prompt reporting of disease manifestations and potential associations of COVID-19 is important to inform public health decisions, robust scientific assessment to establish causality versus association is essential to evolve our understanding of this novel viral pathogen and its sequelae.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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