LETTER TO THE EDITOR

Currently available data regarding the potential association between COVID-19 and Guillain-Barre syndrome

Juan González del Castillo, Jesús Porta-Etessam and Óscar Miró on behalf of the Spanish Investigators on Emergency Situations TeAm (SIESTA) network

1 Emergency Department, Hospital Clínico San Carlos, IDISSC, Madrid, Spain
2 Neurology Department. Hospital Clínico San Carlos, Madrid, Spain
3 Emergency Department, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain

Correspondence to: Juan González del Castillo
Emergency Department, Hospital Clínico San Carlos. Profesor Martín Lagos s/n, 28040 Madrid, Spain
E-mail: jgonzalezcast@gmail.com

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Keddie et al.\textsuperscript{1} report a retrospective epidemiological study not supporting any significant causal link between COVID-19 infection and Guillain-Barre syndrome (GBS) based on a reduction in cases in 2020 in comparison to preceding years. Our group recently retrospectively reviewed all COVID-19 patients diagnosed with GBS in 61 Spanish emergency departments during the first 2-month period of the COVID-19 outbreak.\textsuperscript{2} This study forms part of the Unusual Manifestations of Covid-19 (UMC-19) project, a retrospective, case-controlled, emergency department-based, multicentre study investigating the potential relationship between COVID and 10 different entities that could be influenced by SARS-Cov-2 infection.\textsuperscript{3} Our study showed that GBS is rarely observed as a form of COVID-19 presentation (~0.15‰ cases). Nevertheless, in comparison with non-COVID-19 patients coming to the emergency department, patients with COVID presented a significantly higher relative frequency of GBS [odds ratio (OR) = 6.30, 95% confidence interval (CI) = 3.18–12.5]. Two additional previous reports\textsuperscript{4,5} provide epidemiological data of the frequency of GBS during the COVID-19 pandemic and compare the frequency of GBS in non-COVID patients and/or during the pre-COVID-19 years. These two studies were performed in Italian cohorts and also support an increased number of GBS in patients with COVID-19. Table 1 summarizes the main data of the four studies reported at the time this letter was written.

We would like to discuss some aspects related to the role of SARS-CoV-2 as a causative agent of GBS. Firstly, the four studies estimated standardized incidences of GBS in their general populations during the years prior to the COVID-19 pandemic (between 0.93 to 1.88 cases/100 000/year) similar to those classically reported in many Western countries (0.89 to 1.89/100 000/year),\textsuperscript{6} therefore conferring reliability to such estimations. Secondly, as commented by Keddie et al.\textsuperscript{1} population confinement and the tremendous increase in personal hygiene measures introduced during the lockdown probably reduced the transmission of other common infectious GBS triggers, especially respiratory or gastrointestinal infections. Therefore, the lack of difference in the estimated standardized incidences of GBS between the COVID and pre-COVID periods does not rule out the potential role of SARS-CoV-2 in GBS, especially if most of the GBS cases observed during the COVID-19 periods appeared in COVID-19 patients. In fact, in the other three studies aside of the Keddie et al.\textsuperscript{1} study, a high frequency of GBS cases occurred in COVID-19 patients during the COVID-19 period (between 52% and 88% of cases) (Table 1). We do not know if Keddie et al.\textsuperscript{1} could perform a similar analysis of their data to check if their findings agree with those from the other studies. Third, estimation of the standardized incidence of
GBS varies greatly depending on the strategy of GBS identification, case ascertainment and definitions. In this sense, it is of note that while the other three studies used a patient-based strategy to capture GBS cases, Keddie et al. based their estimations on immunoglobulin supply registered by the UK National Immunoglobulin database. Fourth, it is possible that the mildest cases of GBS stayed at home during the COVID period and did not come to the emergency department due to fear of contracting COVID-19 infection. In our study, the standardized incidence of GBS in the COVID-19 period was nearly half that of the pre-COVID period (0.42 versus 0.91). Although it can be hypothesized that this underestimation of GBS incidence had a similar impact on both COVID-19 and non-COVID-19 patients, this must be confirmed in further studies. And fifth, the estimation of GBS in COVID-19 and non-COVID-19 populations during the 2020 pandemic is not an easy task. On one hand, in several centres, COVID-19 diagnoses were exclusively performed on clinical grounds without microbiological confirmation due to the shortage of tests during March to April 2020. In Spain, during the worst weeks of the pandemic, only 43–78% of patients (depending on the geographical area) with a clinical diagnosis of COVID-19 were tested for SARS-CoV-2, and among the patients tested, microbiological confirmation was only possible in 73–78% of cases. Therefore, comparison of standardized incidences of GBS in COVID and non-COVID populations, which probably better approaches the relevance of SARS-CoV-2 in the development of GBS, also carries its own risk. On the other hand, seroprevalences have demonstrated that the spread of SARS-CoV-2 infection in European populations was higher than that officially reported based on microbiologically confirmed cases. As an example, the very high standardized incidence of GBS in COVID patients found by Filosto et al. (287/100 000/year) probably resulted from the use of confirmed cases of COVID-19 as the denominator instead of seroprevalences used by our group.

In conclusion, it is difficult to know the real incidence of GBS related to COVID-19 but, in our opinion, this relationship cannot be ruled out based on the current knowledge. Our data, as well as the previously mentioned publications and the neurotrophic and neuroinvasive characteristics of coronavirus would support this relationship.

**Data availability**

Data sharing is not applicable to this article as no new data were created or analysed in this study.
Competing interests

The authors report no competing interests.

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Table 1 Details of the four studies reporting epidemiological data on Guillain-Barre syndrome frequency in patients with COVID-19

| Study characteristics | Keddie et al.¹ | Fragiel et al.² | Filosto et al.⁴ | Gigli et al.⁵ |
|-----------------------|----------------|----------------|-----------------|--------------|
| Country (city)        | UK             | Spain          | Italy           | Italy (Udine)|
| Setting               | National Immunoglobulin Database | 61 Emergency Departments | Hospitalized patients in 12 hospitals | Neurology Unit in 1 referral hospital |
| Time period of 2020 included in the analysis | 1 January to 31 May | 1 March to 30 April | 1 March to 30 April | 1 March to 15 April |
| **Data for the 2020 analysed period** | | | | |
| Cases of GBS reported in the overall population | 408 | 21 | 34 | 7 |
| Cases of GBS reported in COVID-19 patients (%) | NR/NC | 11 (52%) | 30 (88%) | 5 (71%) |
| Standardized incidence in overall population (per 100 000/year) | 1.53 (1.65 255) | 0.87 (1:115 373) | 2.43 (1:41 177) | 10.5 (1:9 563) |
| Standardized incidence in COVID-19 population (per 100 000/year) | NR/NC | 9.44 (1:10 593) | 287.2 (1:348) | NR/NC |
| OR (95% CI) of GBS in COVID versus non-COVID populations in 2020 | NR/NC | 21.7 (15.3–30.8) | 998 (351–2833) | NR/NC |
| **Data for previous years (before 2020)** | | | | |
| Years used as comparator | 2016–19 | 2019 | 2019 | 2017–19 |
| Standardized incidence in overall population (per 100 000/year) | 1.65–1.88 (1.53 191 to 60 606) | 0.95 (1:105 340) | 0.93 (1:107 362) | 1.49 (1:66 939) |
| OR (95% CI) of GBS during COVID period respect to non-COVID period | From 0.82 (0.75–0.89) to 0.93 (0.85–1.01) | 0.91 (0.51–1.65) | 2.6 (1.4–5.0) | 7.0 (3.3–14.7) |

CI = confidence interval; GBS = Guillain-Barre syndrome; NR/NC = not reported/not calculable; OR = odds ratio.