LETTER TO THE EDITOR

Unclear association between COVID-19 and Guillain-Barré syndrome

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The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now rapidly disseminating throughout the world. Although it typically affects the respiratory system in the form of a viral pneumonia, extra-respiratory involvement has also been reported, including neurological manifestations.1 In particular, both para-infectious (anosmia, stroke and encephalopathy) and post-infectious, likely immune-mediated, complications [Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM)] have been observed.1,2

GBS represents the prototype of a post-infectious neurological disorder, as shown by the rapidly progressive course developing shortly (<1 month) after an infectious illness. Two-thirds of adult GBS patients report preceding symptoms compatible with a respiratory or gastrointestinal tract infection.3 The most common pathogen associated with GBS is Campylobacter jejuni, which can be found in 25–50% of patients. Aside from bacterial infections, several viral pathogens were also shown to be associated with GBS, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Zika virus (ZIKV).3

The association between SARS-CoV-2 and GBS was initially postulated based on case reports and small case series,2 and subsequently corroborated by the detection of concerning GBS clusters concomitantly with the first wave of COVID-19 in the Friuli-Venezia Giulia Region (northeastern Italy)4 and French-Swiss border.5 Subsequently, epidemiological studies from Italy6 and Spain7 provided further large-scale data to support the association between SARS-CoV-2 and GBS.

In contrast to the abovementioned studies, a recent UK population-based study published in Brain found an overall reduction of GBS incidence in the period March–May 2020 (period of the first COVID-19 wave in the UK) as compared...
to the same months in 2016–19. These results led the authors to conclude that this study ‘contradicts a growing number of reports postulating causation between SARS-CoV-2 and GBS’. By examining the data presented, we believe that this study is extremely interesting and well conducted, but we arrive at different conclusions.

First, a net reduction of GBS incidence during the first wave of COVID-19 may be the effect of lockdown, social distancing, and improved hand hygiene, as proposed by the authors, representing more a measure of reduced C. jejuni-associated GBS (and possibly also of GBS due to other pathogens), rather than proof of the absence of a link between SARS-CoV-2 and GBS. In agreement with this hypothesis, numbers of non-COVID-19 GBS cases with symptoms of a precipitating infectious illnesses, particularly gastroenteritis, were significantly lower than that of pre-pandemic studies (1/47, 2% versus 163/652, 25% in the International GBS Outcome Study). In other words, when a disease has multiple possible causes, the relative contribution of one aetiology can be inferred by the variation in the total number of cases registered only when the other predisposing factors remain stable, which is not the case here. Using the same logic, we cannot conclude that smoking is not associated with lung cancer if we simply compare the incidence of this neoplasia in the same geographical area before and after the industrial revolution, for example.

Second, the finding by the authors that more than half (25/47, 53%) of the incident GBS cases detected during the pandemic had either definite (PCR-proven) or probable (clinically compatible) COVID-19 is impressive, and this is a much higher percentage than that of the seroprevalence of SARS-CoV-2 in the UK or other western countries. Similarly, in the cluster of eight cases detected in Friuli-Venezia Giulia in March–April 2020, four cases had COVID-19 symptoms and one asymptomatic patient had interstitial pneumonia on thoracic CT, that would signify a temporal link.

In conclusion, the study by Keddie et al. provides several important findings on the epidemiology of GBS in the COVID-19 era, but we think that caution should be exerted in interpreting their results as proof of the lack of association between the two. Conversely, in our eyes, the findings of Keddie et al. might corroborate the hypothesis of an association between COVID-19 and GBS. More studies are needed to find more direct evidence of this possible association.

**Data availability**

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

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**Competing interests**

The authors report no competing interests.

**References**

1. Meppiel E, Peiffer-Smadel N, Maury A, et al. Neurologic manifestations associated with COVID-19: A multicentre registry. *Clin Microbiol Infect*. 2020;27:458–466.
2. Camdessanche J-P, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barré syndrome. *Rev Neurol (Paris)*. 2020;176:516–518.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet*. 2016;388:717–727.
4. Gigli GL, Bax F, Marini A, et al. Guillain-Barré syndrome in the COVID-19 era: Another occasional cluster? [published online Jun 23, 2020] *Neurology*. doi:10.1212/WNL.0000000000009981.
5. Tatu L, Nono S, Grácio S, Koçer S. Guillain-Barré syndrome in the COVID-19 era: Another occasional cluster? [published online Jun 23, 2020] *Neurology*. doi:10.1212/WNL.0000000000009981.
6. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: An observational multicentre study from two Italian hotspot regions [published online Nov 6, 2020]. *J Neurol Neurosurg Psychiatry*. doi:10.1136/jnnp-2020-324837.
7. Fragili M, Miró O, Llorens P, et al. Incidence, clinical characteristics, risk factors and outcomes of Guillain-Barré syndrome in patients with COVID-19. *Ann Neurol*. 2020;89:598–603.
8. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain*. 2021;144:682–693.
9. Gigli GL, Vogrig A, Nilø A, et al. HLA and immunological features of SARS-CoV-2-induced Guillain-Barré syndrome. *Neurology*. 2020;41:3391–3394.
10. Lucchese G, Floel A. SARS-CoV-2 and Guillain-Barré syndrome: Molecular mimicry with human heat shock proteins as potential pathogenic mechanism. *Cell Stress Chaperones*. 2020;25:731–735.

11. Dalakas MC. Guillain-Barré syndrome: The first documented COVID-19-triggered autoimmune neurologic disease: More to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e781.

12. Muñiz-Castrillo S, Vogrig A, Honnorat J. Associations between HLA and autoimmune neurological diseases with autoantibodies. *Auto Immun Highlights*. 2020;11:2.