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LETTER TO THE EDITOR

Ongoing challenges in unravelling the association between COVID-19 and Guillain-Barré syndrome

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We read with great interest the cohort study by Keddie et al.[1] The authors questioned an epidemiological or phenotypic association between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and Guillain-Barré syndrome (GBS), by disclosing no increased incidence of GBS during the first coronavirus disease-2019 (COVID-19) outbreak in the UK.[1] Although the study was certainly carried out through a good methodology, our careful reading of the paper raised some points of discussion. First, as argued by the authors themselves, the incidence of pathogens with a well-known relationship with GBS (primarily *Mycoplasma pneumoniae* and *Campylobacter jejuni*)[2] could have indirectly decreased during the pandemic due to the widespread implementation of social distancing measures, hygiene or self-protective habits (e.g. mask-wearing, hand-washing), which could have interfered with their transmission.[1] Whereas the majority of published COVID-19-related GBS cases were tested negative for these infectious agents, the study by Keddie et al.[1] evaluated the global incidence of GBS without taking into account the single incidences according to distinct aetiological entities. Therefore, this factor could have significantly influenced the incidence of GBS in the UK, as well as in other countries, given also that the association between these pathogens and GBS is likely stronger compared to that with SARS-CoV-2. In this regard we cannot exclude the contribution of different immunological mechanisms (molecular mimicry versus para- or postinfectious dysimmunity, including cytokine dysregulation and production of autoantibodies, e.g. anti-glycan antibodies[3]) and individual (genetic?[4]) predisposition. In addition, epidemiological data showing the incidence of *M. pneumoniae* or *C. jejuni* infection during the pandemic are currently lacking.

On another issue, we agree with Keddie et al.[1] when they did not completely exclude a possible immunological similarity between SARS-CoV-2 and human proteome, which would support a molecular mimicry mechanism. Indeed, although the authors did not find any homology between SARS-CoV-2 genetic or linear protein structure and the human genome, non-linear antibody epitopes or post-translational modifications might theoretically lead to the generation of immunogenic proteins.[1] Indeed, COVID-19 patients showed abnormally high IgG and IgM antibodies to various self-glycans, including gangliosides, compared to control subjects.[3] These autoantibodies are also often found in GBS occurring after *C. jejuni*, cytomegalovirus and *M. pneumoniae* infections.[3] Moreover, a parainfectious mechanism may also play a role, given that many reported COVID-19-associated GBS cases seem to develop through a para-infectious rather than a post-infectious process.[5,6] Furthermore, given the abundance of gangliosides in olfactory nerves, and considering that SARS-CoV-2 enters the CNS by crossing the neural-mucosal interface in olfactory mucosa,[7] the ongoing inflammation and

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destruction of olfactory epithelium and olfactory sensorial cells may be a possible source of antigen expression.[7] In this regard, Fragiel et al.[7] observed a higher frequency of olfactory disturbances in COVID-19-associated GBS patients compared to non-COVID-19-associated GBS subjects. However, further studies are undoubtedly needed to clarify these issues.

Second, as suggested by the most extensive systematic review[5] and multicentre studies,[6,7] GBS seems to represent a complication of symptomatic COVID-19 (97.2%).[5] In contrast, asymptomatic and paucisymptomatic COVID-19 together account for more than 80% of all cases[8] and their incidence has quickly increased in the last months due to the refinement of diagnostic strategies and the development of systematic contact tracing. Such a phenomenon should theoretically lead to a progressive reduction in the incidence of neurological postinfectious syndromes, including GBS, over the course of time. Beyond that, in the prospective cohort by Keddie et al.[1] more than 50% of GBS patients had either probable or definite COVID-19.[1] Even when limiting the analysis to definite cases, the percentage (27.6%) remains strikingly high compared to that of other infections previously described to be associated with GBS (40% for *C. jejuni* and <25% for *M. pneumoniae*).[2] These data may suggest that patients with respiratory symptoms (related to COVID-19 or GBS) were more likely to seek medical advice, in turn leaving out from the cohort a significant proportion of mild cases. Additionally, some GBS cases could have been masked by more severe complications related to COVID-19 itself (e.g. immobilization due to severe pneumonia or concurrent septic events), or to the prolonged intensive care unit stay [e.g. critical illness myopathy/polyneuropathy (CIMP)]. A retrospective analysis taking into account concurrent complications (especially CIMP) as well as the setting and duration of the hospital recovery might help to clarify the impact of these factors, which could have potentially influenced the identification and treatment of COVID-19-related GBS cases.

Furthermore, we would address some statistical issues concerning the paper by Keddie et al.[1] In particular, Pearson's correlation is far from being the gold standard to prove a causal relationship in observational studies whilst more complex methods would be more suitable.[9] Similarly, when the authors claimed that an '$r = 0.06$, 95% CI: –0.56 to +0.63, $P = 0.86$' should support a lack of correlation,[1] they did not take into account that, based on this confidence interval (CI), higher correlation coefficients might also be possible when larger and/or different samples are considered. Moreover, Keddie et al.[1] calculated an occurrence rate of GBS of 0.016 cases per 1000 COVID-19 infections. This estimation is based on the report that the real prevalence of COVID-19 in the London area was remarkably higher than officially reported.[10] However, looking at up-to-date data (December 2020), COVID-19 seroprevalence seems, from one side, to vary quite a lot between different UK regions, while, from the other, estimated seroprevalences are often associated with wide 95% CIs.[10] Depending on these aspects, one could argue that COVID-19 might be either a risk factor or even protective for GBS.

On another issue, two recent multicentric studies conducted in northern Italy[7] and Spain,[8] two of the major hot spots of the pandemic's first wave, provided opposite results to those of Keddie et al., by showing an increase of GBS incidence in concomitance with the first COVID-19 outbreak and a higher relative frequency of GBS in COVID-19 patients. Thus, we would suggest more caution when ruling out a causal relationship between COVID-19 and GBS based on data collected in a single country.

Finally, the COVID-19 pandemic has led to significant changes in the neurological practice, clinical pathways and means of assessment. Outpatient clinics have been conducted almost entirely by telephone or video link, and most importantly direct physical examination has been minimized.[11] Indeed, since the onset of the pandemic, in keeping with many UK NHS Trust hospital policies, face-to-face clinics were performed in a very minimal percentage of the all-outpatient attendance with, in some cases, a lack of mechanism in place to allow urgent clinics for those patients who needed an immediate examination after a remote consultation. Generally, the COVID-19 pandemic led to a reorganization of the services at multiple levels.[12] Neurologists with recent experience in stroke medicine were redeployed to focus efforts on acute stroke management while neurologists with less experience in this field were mainly allocated to telephone clinics to reduce the likelihood of excessive caseloads. This model change could have impacted on a delayed involvement of a consultant neurologist, especially in District General Hospitals (DGH), with the possibility that GBS-related symptoms not requiring hospital admission have been under-recognized. Moreover, the methods of data collection for the prospective part by Keddie et al.[1] could be highly bias borne. Indeed, members of the British Peripheral Nerve Society represent selected experts of peripheral neuropathies, who might work only in tertiary centres and therefore not directly involved in the management of mild GBS cases. A more representative sample of GBS patients might be collected from hospital records of neurology departments or at least from those UK sites addressing the diagnosis of GBS. Weekly reports, using emails in the middle of a very chaotic time such as a pandemic, could have generated a bias through low response rate.

To conclude, we believe that the definitive proof of a possible causal association between COVID-19 and GBS could derive from two different efforts: (i) the conduction of rigorous case-control studies; and (ii) the systematic testing of all patients with GBS for anti-SARS-CoV-2 antibodies. This would allow us to avoid possible underestimation of COVID-19-related GBS by including patients tested negative with PCR whilst positive for untested anti-SARS-CoV-2

antibodies (a bias which reasonably cannot be excluded in the cohort by Keddie et al.[1]).

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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