Underestimating the Prevalence of SARS-CoV-2 Associated Guillain-Barre Syndrome is Multicausal

**Keywords:** SARS-CoV-2, coronavirus, COVID-19, polyradiculitis, GBS, neuropathy.

**LETTER TO THE EDITOR**

With interest we read the article by Keddie et al., (2021) about the prevalence of Guillain-Barre syndrome (GBS) in Great Britain between January and May 2020 (retrospective, epidemiological part) and between March and May 2020 collecting data from 81 centers all over Britain (prospective part) (Keddie, S. et al., 2021). It was concluded that neither the epidemiological nor the prospective cohort study supports a causal link between COVID-19 and GBS (Keddie, S. et al., 2021). The study is appealing but raises concerns and comments.

Though there are indications that SARS-CoV-2 infections can be complicated by GBS (Finsterer, J. & Scorza, F. A. 2021), the index study found that the prevalence of GBS has not increased during the period January to May 2020 (Keddie, S. et al., 2021). This obvious contradiction may be due to several reasons. First, it may be due to unawareness of the association between COVID-19 and GBS. Though GBS may be diagnosed correctly, the causal relation with COVID-19 may go unrecognised due to a long interval between onset of COVID-19 and onset of GBS, or due to only mild or asymptomatic COVID-19 infection. If patients with GBS in the absence of classical symptoms of COVID-19 do not undergo PCR or antibody tests, the viral infection may go unrecognised as the trigger of the neurologic compromise. 2. Work-up for GBS and diagnosed criteria applied may not be standardised for all participating centers. If the diagnostic criteria are not the same for all participating centers, there may be a number of false positive and false negative cases. If the false negatives outweigh the false positives, GBS may remain underdiagnosed. 3. Those not receiving intravenous immunoglobulins (IVIGs) may not show up in specific databases, why the number of GBS patients may be underestimated as well. 4. Mild cases of GBS may go unrecognised because of restricted access to hospitals or ambulatory units during the pandemic. 5. SARS-CoV-2 associated GBS may remain undiagnosed in patients with severe COVID-19 being sedated and mechanically ventilated on an intensive care unit (ICU). If a patient is immobilised, muscle weakness may remain undetected and work-up for GBS may not be initiated. 6. The Brighton criteria for diagnosing GBS are applicable to GBS subtypes acute, inflammatory, demyelinating neuropathy (AIDP), acute, motor, axonal neuropathy (AMAN), and acute, motor and sensory, axonal neuropathy (AMSAN). These criteria, however, are not applicable to GBS subtypes Miller-Fisher syndrome (MFS), mono- or polyneuritis cranialis (PNC), the pharyngeal, cervical, and brachial (PCB) variant, and to Bickerstaff encephalitis (BFE). If patients with GBS more frequently develop subtypes not covered by the Brighton criteria, they may go undiagnosed, why the prevalence of SARS-CoV-2 associated GBS may remain low.

Arguments for a causal relation between SARS-CoV-2 and GBS are the increasing number of publications about patients developing GBS within a certain timeframe after onset of COVID-19 (Finsterer, J., & Scorza, F. A. 2021), the increasing number of publications about patients who develop GBS after SARS-CoV-2 vaccinations and cerebro-spinal fluid (CSF) studies demonstrating increased levels of cytokines in patients with SARS-CoV-2 associated CNS disease (Benamer, K. et al., 2020). Arguments against a causal relation are that no epitope homology has been yet established and that the onset of GBS can precede that of COVID-19.

**Article History**

Received: 31.07.2021
Revision: 10.08.2021
Accepted: 20.08.2021
Published: 31.08.2021

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**How to Cite the Article:**


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DOI: 10.47310/srjcms.2021.v01i02.001

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COVID-19 is not only associated with headache, anosmia, dysgeusia, stroke, meningo-encephalitis, acute disseminated encephalo-myelitis (ADEM) and GBS, but with a much wider spectrum of neurological disease. This includes cerebellitis, acute, hemorrhagic, necrotising encephalitis (AHNE), myoclonus syndrome, limbic encephalitis, posterior reversible encephalopathy syndrome (PRES), intracerebral bleeding, subarachnoid bleeding, venous sinus thrombosis, transverse myelitis, cerebral vasculitis, cerebral vasocostriction syndrome, epilepsy, psychosis, delirium, insomnia, carotid artery dissection, mono- and polyneuritis cranialis, myositis/dermatomyositis, and myasthenia (Finsterer, J. 2021). Additionally, damage of the central and peripheral nervous system (CNS/PNS) due to anti-COVID-19 therapy should be considered.

A limitation of the study is that probable COVID-19 cases were included. Without confirmation of the infection by documentation of virus RNA or antibodies against the virus, SARS-CoV-2 associated GBS should not be diagnosed.

A further limitation is that the prevalence of GBS was calculated upon data from an IVIG registry (NHSE immunoglobulin database) (Keddie, S. et al., 2021). Since this database did include Scotland and since IVIGs may be given in indications other than GBS, figures deriving from this registry may be unreliable.

According to the method section only patients developing GBS within 6 weeks after onset of COVID-19 were included (Keddie, S. et al., 2021). However, in the results section a time interval between onset of COVID-19 and onset of GBS of 52 days in probable COVID-19 cases is mentioned (Keddie, S. et al., 2021). This discrepancy should be clarified.

Overall, the study has several limitations which challenge the results and their interpretation. Considering causes for underestimation of the true prevalence, the number of SARS-CoV-2 associated GBS cases is most probably higher than calculated. Particularly mild GBS cases, GBS subtypes not fulfilling the Brighton criteria, and cases with severe COVID-19 and GBS requiring mechanical ventilation may go unrecognised.

DEclarations
Acknowledgement: none
Statement of ethics: was in accordance if ethical guidelines
Conflicts of interest: none
Funding sources: no funding was received
Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval,
Informed consent: was obtained
The study was approved by the institutional review board

REFERENCES