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Is SARS-CoV-2 vaccination related Guillain-Barré syndrome really different from that due to other causes?

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Dear Editor,

We read with interest the article by Reddy et al. [1] on a literature review of 100 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination-related Guillain-Barré syndrome (GBS) who were compared with 61 patients with SARS-CoV-2 infection related GBS and 925 patients with GBS due to other causes from the International GBS Outcome Study (IGOS). Three-quarters of the vaccinees had limb weakness with sensory deficits, half of the vaccinees facial palsy, and a quarter each dysautonomia and respiratory insufficiency [1]. Severity and pain occurred more frequently with vector-based vaccines compared to messenger RNA-based vaccines [1]. It was concluded that SARS-CoV-2 vaccination-related GBS more commonly presents with facial palsy and sensory disturbances than GBS due to other causes [1]. The study is compelling but has limitations that should be discussed.

The major limitation of the study is the design. A literature review is not the ideal approach to assess whether the clinical presentation and outcome of SARS-CoV-2 vaccination-related GBS differ from the presentation and outcome of GBS due to other causes. A prospective, multicenter study would be more appropriate to answer the question of interest. Literature reviews also have the disadvantage that the data extracted are incomplete or that the methods used to generate the data differ between the included studies.

Another limitation of the study is that the vaccination group was inhomogeneous with regard to vaccine types [1]. Patients in this group had received six different types of vaccines [1]. Different vaccine types might elicit different immune responses and hence different clinical presentations. It is also conceivable that components of the vaccine other than the active ingredient itself could cause GBS. Because pharmaceutical companies use different types of stabilizers, solvents, and preservatives, it is conceivable that these components were responsible for different host immune reactions and hence for different clinical presentations.

A third limitation is that the IGOS cohort is heterogeneous regarding the cause of GBS. Homogeneous cohorts are required to compare clinical presentation between two groups. Furthermore, the vaccination group and the control groups should be matched for age, sex, comorbidities, and medications, which was not the case in the index study. GBS with cranial nerve involvement and sensory disturbances also occurs in GBS due to *Campylobacter jejuni*, cytomegaly, Zika, Epstein-Barr, or Dengue virus [2]. Thus, if other control groups had been used, differences between the cohorts

might not have been registered.

A fourth limitation is that several patients had normal or inconclusive nerve conduction velocity (NCV) findings. Normal NCV findings were reported in study-2, study-16, study-26, and study-45 [1]. Inconclusive NCV findings were reported in study-19, study-25, study-28, study-34, and study-42 [1]. Based on these results, it is questionable whether all included patients actually had GBS or rather plexopathy or polyneuropathy.

A fifth limitation is that the number of patients in the vaccination and the SARS-CoV-2 infection groups was low. Furthermore, the number of patients in the vaccination group and SARS-CoV-2 infection group was significantly lower than the number of patients in the IGOS cohort.

A sixth limitation is that Muscular Research Council sum scores, Erasmus GBS Respiratory Insufficiency Score, and Hughes grades were assessed by the authors if not stated in the article. This can lead to incorrect results.

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Whether SARS-CoV-2 vaccination-related GBS really presents in a different way as GBS due to SARS-CoV-2 infection or other causes should be investigated by well-powered studies with an appropriate design.

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