

Assessing Differences between SARS-CoV-2 Vaccination / Infection related and Unrelated GBS Patients Requires Appropriate Study Populations

Josef Finsterer¹ and Walter Strobl²

¹MD PhD, Neurology & Neurophysiology Center, Vienna, Austria, ORCID: 0000-0003-2839-7305

²MD, Dpt. of Health Sciences, Medicine and Research, Danube University Krems, and MOTIO, Vienna, Austria

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LETTER TO THE EDITOR

We read with interest the article by Martic, *et al.* about a retrospective, multicentre study of 109 patients with Guillain-Barre syndrome (GBS), due to SARS-CoV-2 infection (SC2I) (n=19), due to SARS-CoV-2 vaccination (SC2V) (n=17), and 74 patients with GBS due to other causes, in terms of age, latency between exposure to trigger and onset of clinical manifestations, the clinical presentation, and severity [Martic, V. *et al.*, 2023]. It was found that the three groups did not differ in age, latency between trigger and onset of clinical manifestations, severity, and outcome, except for an increased frequency of facial palsy in the GBS-SC2V group [Martic, V. *et al.*, 2023]. The study is excellent but has limitations that should be discussed.

The major limitation of the study is that the group sizes in the GBS-SC2V and GBS-SC2I groups were small and that control group and active groups differed significantly in size. It is also not mentioned whether the patient and control groups matched in terms of age and gender. These shortcomings can limit the statistical comparison and affect the validity of the results.

Another limitation is that the different subtypes of GBS were not evaluated separately. Although it is mentioned that the demyelinating form was predominant in all three groups [Martic, V. *et al.*, 2023], we should know how many patients in each group had acute, inflammatory demyelinating polyneuropathy (AIDP), how many acute, motor axonal neuropathy (AMAN), how many acute, motor and sensory axonal neuropathy (AMAN), how many Miller-Fisher syndrome, polyneuritis cranialis, pharyngo-cervico-brachial GBS (PCB), how many pure dysautonomia, and how many brain stem Bickerstaff encephalitis (BBE). It is important to know the subtype composition of each group as it could influence the results

A third limitation is that the clinical severity of GBS was only assessed using the Hughes disability scale [Martic, V. *et al.*, 2023]. The disadvantage of this scale is that it only assesses the motor functions of limb and respiratory muscles [Merkies, I. S. *et al.*, 2002]. Patients with MFS, pure dysautonomia, or PCN may be rated as zero (normal) on this scale. In addition, sensory or autonomic disturbances, which are common manifestations of GBS, are also not considered by this evaluation. Therefore, comparing GBS severity and outcome only on this score may lead to incorrect results.

A fourth limitation is that the observation period was reported as 1/2020 and 4/2022, but the vaccination was not available before 1/2021 [Martic, V. *et al.*, 2023]. Because the number of GBS-SC2I and GBS-SC2V patients was similar (19 vs 17), the incidence of GBS-SC2V appears to be much higher than that of GBS-SC2I. We should therefore know which SC2V brands were most common triggers of GBS.

We wonder how the authors determined the timing of “exposure to triggering factor” in GBS-SC2I patients. It is usually not possible to assess the exact time of onset of SC2I. The diagnosis is usually made either incidentally through a screening test or based on clinical suspicion and the performance of a PCR. In both cases, the exact day on which the virus entered the body cannot be determined.

We disagree that vaccinations are a rare cause of GBS [Martic, V. *et al.*, 2023]. On the contrary GBS has been repeatedly reported to be triggered by vaccinations against SARS-CoV-2, influenza (swine vaccine), poliomyelitis, tetanus, meningococcal (MCV4), and rabies (old formulations) [Haber, P. *et al.*, 2009].

Overall, the interesting study has limitations which challenge the results and their interpretation.

Addressing these limitations could further strengthen and reinforce the statement of the study. Before concluding that there is no difference between GBS-SC2V, GBS-SC2I, and GBS-SCV2 unrelated patients, large groups of GBS should be studied with its subtypes and valid scoring systems that cover all clinical manifestations of GBS. .

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