EDITORIAL

SARS-CoV-2 Vaccination and Autoimmune Neuropathies

Rebalancing the Risk

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With every influenza vaccination, the question is asked: "Have you ever had Guillain-Barré syndrome?" If so, the potential vaccination recipient is advised to talk to their doctor before proceeding, and the physician will invariably recommend against it. The topic is widely discussed in patient and physician networks, with stakeholders holding firm convictions for or (more commonly) against vaccination. Naturally, with the emergence of the COVID-19 pandemic and the reality of administering billions of SARS-CoV-2 vaccinations across the globe, the anxiety within the inflammatory neuropathy community and among clinicians caring for patients with GBS and CIDP has been raised to new heights.

But why? What fuels this anxiety? In 1976, a looming swine influenza pandemic prompted the development of a national vaccination campaign program within the United States.[1] In its wake, an 8-fold increase in postvaccination GBS cases was observed (about 1 GBS case per 100,000 vaccinations), and the Institute of Medicine concluded that a causal relationship between the 1976 swine influenza vaccine and GBS was likely.[2] Coupled with the fact that the swine flu pandemic of 1976 never materialized, the foundation for vaccination hesitancy among patients with GBS/CIDP and their physicians was formed. However, since 1976, associations between seasonal vaccinations and GBS have been meager at best. Most studies have shown no increased risk[3] while others showed a marginal increased risk on the order of 1–2 additional cases of GBS per 1 million persons vaccinated.[4] To give these numbers more context, consider the stronger association observed between influenza infections and GBS where an estimated risk of about 17 GBS cases per 1 million patients hospitalized with influenza have been reported.[5]

Now enter the COVID-19 pandemic. Although much is still to be learned, there appears to be a small increased risk of GBS after COVID-19 infection[6] and probably an even smaller increase risk after some (but not all) of the SARS-CoV-2 vaccinations. GBS after the adenovirus vaccinations ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2 (Johnson & Johnson) ranges between 4-7 cases per million vaccinations.[7,8] No increased risk has been observed after the mRNA tozinameran (Pfizer-BioNTech) or 1 mRNA-1273 (Moderna) vaccines.[8]

So what is the patient with GBS/CIDP/MMN to do when faced with vaccination in the time of COVID-19? The threat of voluntarily doing something to worsen their disease can be terrifying, but so too is the prospect of developing a severe infection. Extrapolating from the influenza vaccine experience, patients are primed to be wary of vaccines. The information conveyed by support networks and sometimes physicians is often not reassuring and frequently inaccurate because it fails to balance risks of triggering relapse from vaccination with the risks from actually becoming infected.

In this issue of *Neurology*®, Baars et al. take on the timely issue of SARS-CoV-2 vaccination safety in patients with preexisting inflammatory neuropathies.[9] This prospective, multicenter cohort study included 406 patients with confirmed GBS, MMN, or CIDP who received a SARS-CoV-2 vaccination. Although disability and quality-of-life scales were collected, deterioration was loosely defined as any self-reported change in disease-related symptoms. Assessments were conducted 48 hours before vaccination and within 6 weeks to 4 months after vaccination.

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Symptoms experienced within 48 hours after vaccination were classified as vaccination side effects (i.e., not related to the immune-mediated neuropathy).

Among 162 patients with GBS, none experienced a GBS reoccurrence. Although 12 of 241 patients with CIDP or MMN reported worsening disease-related symptoms, the change prompted treatment modifications in only 6 patients, and in all, the symptoms resolved within 8 weeks. Also notably, in 10 of these 12 patients, other explanations for symptom exacerbation were present during or leading into the vaccination.

These results should provide much needed reassurance to inflammatory neuropathy patients in need of SARS-CoV-2 vaccination. In the unusual event that symptoms worsened, in most instances the setback was mild and self-limiting. Digging a bit further, a notable study limitation was how deterioration was defined. Objective documentation of neuropathy worsening with measures such as grip strength testing or neurologic examination was not feasible, and instead, there was a reliance on self-reported symptom changes to capture deterioration. Generally speaking, placebo and nocebo responses driven by anticipation and expectation are common in CIDP during changes in treatment or in the context of other life events.[10] This phenomena likely explains some of the self-reported deterioration in patients with CIDP and MMN observed in this study, rather than worsening of the neuropathy. In only 3 patients, did the change in disability scores reach the minimal clinically important difference, and in 10 of 12 patients, other explanations were observed that may explain the change in symptom status. Just as objectification of inflammatory neuropathy relapse was a challenge in this study, so too is it a struggle during clinical practice. Although it may be attractive to attribute any change in the postvaccination period to worsening neuropathy, it is critical to objectify changes and identify confounding explanations before assigning causation.

Extremely rare events are challenging to capture in relatively small prospective studies of this kind. It is even more difficult to understand if the mRNA and adenovirus vaccinations confer different levels of risk, as seems to be the case in the general population.[7,8] Although this study is unable to exclude associations between SARS-CoV-2 vaccination and worsening inflammatory neuropathy, it can now be confidently state that if there is a risk it is likely to be very small and almost certainly less than the risk of an infection-triggered relapse. The time is now to rebalance the risk of vaccination in our patients with GBS, CIDP, and MMN. It is overdue for influenza vaccination. Let us not make the same mistake with COVID-19.

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