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COMMENTARY

Guillain-Barre syndrome should be monitored upon mass vaccination against SARS-CoV-2

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ABSTRACT

In response to the recent pandemic, vaccines have been developed for large-scale immunization. Despite safety and efficacy verified by health authorities, Guillain-Barre syndrome (GBS) remains a risk of unexpected adverse reactions. Since COVID-19-related GBS cases have largely been reported in Europe, vaccines involving viral genetic materials can potentially trigger GBS, as demonstrated in clinical trials in the Americas. Therefore, medical professionals should be aware of GBS as a potential adverse reaction in SARS-CoV-2 vaccination. Consultation with a neurologist may be needed. Nevertheless, this is not to say that the use of vaccines against SARS-CoV-2 should be suspended and that the association between GBS and the vaccine is confirmed or excluded. The benefits of vaccine still outweigh potential adverse effects.

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Amid the ongoing pandemic, vaccines against SARS-CoV-2 have been developed for large-scale immunization. While the safety and efficacy requirements of these vaccines have been met, risks of unexpected adverse reactions remain, Guillain-Barre syndrome (GBS), for example. Since GBS cases associated with SARS-CoV-2 infection have been reported globally, vaccines involving viral genetic materials can potentially trigger GBS, as demonstrated in two clinical trials of viral vector-based and inactivated vaccines in the Americas. Therefore, health-care professionals should be aware of GBS as an adverse reaction upon mass vaccination. However, this is not to say that the use of vaccines against SARS-CoV-2 should be suspended and that the association between GBS and the vaccine is confirmed or excluded. The benefits of vaccine still outweigh potential adverse effects.

GBS is a post-infectious peripheral neuropathy consisting of a group of acute immune-mediated disorders. It is characterized by the elevated level of cerebrospinal fluid (CSF) protein as well as tingling and/or weakness in lower extremities, followed by progressive paralysis. Nevertheless, symptoms vary between individuals and can be difficult to diagnose in the early stages. It can be fatal as paralysis can spread to the diaphragm, leading to fatal respiratory failure. There are still no sufficient biomarkers for GBS; antiganglioside antibodies are not always detected in GBS patients. Consequently, diagnosis relies on nerve conduction studies, electromyography and CSF analysis. Intravenous immunoglobulin and plasma exchanges are commonly used treatments. GBS has a global annual incidence of 0.62–2.66 cases per 100,000 per year[1] and can affect any age groups.

While the etiology is not fully understood, the observation of antecedent infection in most GBS cases has given rise to the hypothesis of molecular mimicry, the sharing of sequence between the host and the foreign antigen leading to cross-reactive immune responses. It is generally believed that the tight junction comprised of transmembrane proteins, such as claudin and occludin to regulate the passage of molecules in the blood-nerve barrier, is disrupted. Autoantibodies cross the tight junction and attack the myelin or axonal membrane, depending on the subtype of GBS. To confirm that an agent triggers GBS by molecular mimicry, four strict criteria must be met, including epidemiological evidence, detection of antibodies against host target antigens, the demonstration of microbial mimic of target antigen, and reproduction in an animal model.[2] So far, *C. jejuni* has been the only commonly accepted triggering agent for GBS, meeting all four criteria with a similar oligosaccharide structure shared with GM1 ganglioside that is highly expressed in nerve cell membranes. Other triggering agents, such as Zika virus[3] and influenza vaccine,[4] have also been proposed. In the former, increased incidence of GBS during the epidemic of an infectious disease is usually observed,[3] whereas the latter relies on differential diagnosis to identify possible triggering agents. Similar observations were also made in Europe during the current pandemic, suggestive of SARS-CoV-2 triggering GBS.[5] In Italy, a 5.4-fold increase in the incidence of GBS was observed during the pandemic.[5] It is then suspected that vaccines against SARS-CoV-2 may be associated with GBS.[6] In a clinical trial of a viral vector-based vaccine, two cases of GBS were reported with one in the placebo group. The investigator suggested that it is possibly related to the vaccine and, according to the assessment by the Food and Drug Administration, it is unlikely related to the vaccine, but a causal relationship cannot be definitively excluded.[7]

While there is not yet evidence confirming the other three criteria, the result of an amino acid sequence analysis does not completely rule out the potential molecular mimicry between GBS and SARS-CoV-2 infection. Following the method used in Lucchese et al.[8] where polypeptides (at least pentapeptides because five amino acid residues can induce highly specific antibodies) shared between human proteins and the viral

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peptides provide some evidence of molecular homology, a total of 5 heptapeptides were found shared between the proteins of SARS-CoV-2 and GBS-related human proteins, namely GPPGTGK, LDDFVEI, LKELLQN, PPGTGKS, and VDNSSLT. The method involves a total of 286 GBS-related human proteins consisting of 210201 peptides found in UniProt with search terms "myelin OR demyelination OR axonal neuropathy" and 7096 peptides identified in SARS-CoV-2 from GenBank (accession number NC_045512). The resulted theoretical probability E is calculated to be 9.10×10^{-1}°, indicating a very low chance of co-incidence. It is, however, important to note that this is a necessary yet not a sufficient condition for molecular mimicry.

Having said that there is not yet a confirmed association between GBS and COVID-19 and that further investigations are strongly needed, just like that between GBS and Zika. However, amid the ongoing global vaccination programs, medical professionals should recognize GBS as a potential adverse reaction. Hospitalization for further clinical investigation by neurologists may be required because some of the adverse reactions reported in studies on vaccine trials resemble the symptoms of GBS, making diagnosis very difficult. For instance, four cases of Bell's palsy were observed in the vaccine group, compared with none in the placebo group.[9] Characterized by elevation of the CSF protein and weakness in extremities, transverse myelitis was observed in participants receiving the vaccine[10] In addition, medical professionals should also be aware of the increased demand for medical resources. For example, competing use of mechanical ventilation may be seen because it is common in severe COVID-19 and is required for about 30% patients with GBS.[11] Also, many GBS patients can take weeks to months to recover, further stretching hospital resources.

Despite results and findings from phase 2/3 trials demonstrating the efficacy of the vaccine, the epidemiology of mRNA vaccines and pathogenesis of GBS remain elusive and medical professionals should be aware of GBS as a potential adverse reaction in SARS-CoV-2 vaccination. Consultation with a neurologist may be needed and the demand for medical resources such as mechanical ventilation that is common for severe COVID-19 and GBS may heighten.

Disclosure of potential conflicts of interest

The authors confirm that there are no known conflicts of interest associated with this publication.

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