Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

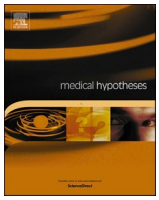
Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Medical Hypotheses 160 (2022) 110792

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Letter to Editors

Post-adenoviral-based vaccines Guillain-Barre Syndrome: A proposed mechanism

ARTICLE INFO

Keywords
COVID-19
Vaccine
Adenovirus
Guillain-Barre syndrome

ABSTRACT

Despite great public health advances achieved by COVID-19 vaccines, rare side effects may impact the public acceptance. Guillain-Barre Syndrome has increasingly been reported with adenoviral-based vaccines. This perspective proposes a possible mechanism underlying this rare but clinically significant side effect thereby providing insights for improving our current vaccines against COVID-19.

Notwithstanding massive success in reducing the burden of infection and disease achieved by coronavirus disease 2019 (COVID-19) vaccines, concerns regarding their safety still remain. Although exceedingly rare, certain adverse effects can be associated with significant morbidity and mortality smearing this major global public health triumph. There have recently been a number of post adenoviral-based vaccine cases of Guillain-Barre syndrome (GBS) reported in the literature [1–4] and to regulatory agencies. GBS and its variants have been reported after a range of bacterial and viral infections, *Campylobacter jejuni*, cytomegalovirus, influenza, Mycoplasma pneumoniae, and flaviviruses such as Zika and dengue viruses among others [2]. GBS has also been repeatedly described shortly after the onset of COVID-19 signs and symptoms [5,6]. Given the proclivity and association of COVID-19 with GBS and its clinical variants compared with the rarity of post-adenoviral COVID-19 vaccine administration [7], it is inconceivable to reliably attribute causality to the adenoviral vectors used in COVID-19 vaccines; therefore, the search for the smoking gun must continue. Recently, the possibility of molecular mimicry has been investigated in which several SARS-CoV-2 short amino acid sequences showed homology to a range of proteins expressed in the human body [8]. Among several amino acid stretches found within SARS-CoV-2′s spike protein, VYSTGSN heptapeptide near the furin cleavage site, was also found in human neural cell adhesion molecule (NCAM) L1-like protein (aa. 391–397). In addition to the central nervous system, NCAM L1-like protein is also expressed in the peripheral nervous system including in Schwann cells [8]. NCAM L1-like protein has also been proposed to be linked to GBS and COVID-19 [9]. This heptapeptide is predicted to be part of RVYSTGSNVFQ peptide which is a B cell epitope, namely it is recognized by antibodies. Specific or cross-reactive antibodies, therefore, can bind to it and recruit classical complement to the site leading to demyelination and *in situ* destruction of nerves [10]. This may at least partly explain as to why most, if not all, of these cases have no detectable anti-gangliosides antibodies.

Adenovirus-based COVID-19 vaccines generate pre-fusion trimeric spike proteins that all carry the afore-mentioned peptides. This region is shared, to a great extent, with other common coronaviruses. After infection with SARS-CoV-2, COVID-19 vaccination, or infection with common coronaviruses, strong anamnestic humoral immune responses against the shared epitopes in spike protein are elicited [11]. This may precipitate GBS or GBS-like signs and symptoms as is the case with the reported cases that typically occur within 14 days post-vaccination. The short timeframe post-vaccination within which GBS manifests is reminiscent of the kinetics of an anamnestic immune response. This may particularly be the case in those with a conducive genetic background, HLA-A*68 and HLA-DQA1/HLA-DQB1 haplotypes [9], among others, hence the rarity of this phenomenon. That adenoviruses can trigger stronger innate immune responses such as interferons compared with RNA-bases vaccines, may in turn, stimulate a wide range of cells to up their surface expression of HLA, further setting the stage for a more rigorous immune response.

All in all, this proposed mechanism needs substantiating. Mitigation strategies would include knocking out this peptide region from the vaccines, as long as the tertiary structure of the spike is preserved, so no anamnestic immune response against this epitope arises.

Funding statement

Funding not received for the study

Consent statement/ethical approval

Not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Finsterer J. Exacerbating Guillain-Barré Syndrome Eight Days after Vector-Based COVID-19 Vaccination. Case Rep Infect Dis 2021;2021:3619131.
[2] Hasan T, Khan M, Khan F, Hamza G. Case of Guillain-Barré syndrome following COVID-19 vaccine. BMJ Case Rep 2021;14(6):e243629. https://doi.org/10.1136/bcr-2021-243629.
[3] Leung C. Guillain-Barre syndrome should be monitored upon mass vaccination against SARS-CoV-2. Hum Vaccin Immunother 2021;17(9):2957–8.

https://doi.org/10.1016/j.mehy.2022.110792
Received 26 November 2021; Accepted 9 February 2022
Available online 12 February 2022
0306-9877/© 2022 Elsevier Ltd. All rights reserved.

[4] Maramattom BV, et al. Guillain-Barré Syndrome following ChAdOx1-S/nCoV-19 Vaccine. Ann Neurol 2021.
[5] Finsterer J, Scorza FA. Guillain-Barre syndrome in 220 patients with COVID-19. Egypt J Neurol Psychiatr Neurosurg 2021;57(1):55.
[6] Shoraka S, et al. SARS-CoV-2 Infection and Guillain-Barré Syndrome: A Review on Potential Pathogenic Mechanisms. Front Immunol 2021;12:674922.
[7] Márquez Loza AM, Holroyd KB, Johnson SA, Pilgrim DM, Amato AA. Guillain-Barré Syndrome in the Placebo and Active Arms of a COVID-19 Vaccine Clinical Trial: Temporal Associations Do Not Imply Causality. Neurology 2021;96(22):1052–4.
[8] Gammazza AM. *Molecular mimicry in the post-COVID-19 signs and symptoms of neurovegetative disorders?* Lancet Microbe 2021.
[9] Morsy S. NCAM protein and SARS-COV-2 surface proteins: In-silico hypothetical evidence for the immunopathogenesis of Guillain-Barré syndrome. Med Hypotheses 2020;145:110342.
[10] Nobile-Orazio E. The complement story in Guillain-Barré syndrome: from pathogenesis to therapy. Lancet Neurol 2018;17(6):483–5.
[11] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581(7809):465–9.

Kamran Kadkhoda*
Immunopathology Laboratory, Robert J. Tomsich Pathology & Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA
Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, USA

* Address: Immunopathology, Cleveland Clinic, Clinical Professor of Pathology, CCLCM, CWRU, LL3-150, 10300 Carnegie Ave., Cleveland, OH 44106, USA.
E-mail address: kadkhok@ccf.org.