A Case With New-Onset Neuromyelitis Optica Spectrum Disorder Following COVID-19 mRNA BNT162b2 Vaccination

Ilay Caliskan, MD,* Eser Bulus, MD,† Nazire Afsar, MD,‡ and Ayse Altintas, MD*†§

Introduction: In the midst of the coronavirus disease of 2019 pandemic, active immunization by effective vaccination gained utmost importance in terms of global health. The messenger RNA (mRNA) vaccines are novel strategies requiring clinical surveillance for adverse events.

Case Report: We report a 43-year-old previously healthy female with an optic neuritis attack 24 hours following immunization with the second dose of coronavirus disease of 2019 mRNA BNT162b2 vaccine. A second transverse myelitis attack together with an elevated anti-AQP-4 antibody titer confirmed the diagnosis of neuromyelitis optica spectrum disorder.

Conclusion: Our case identifies the BNT162b2 vaccine as a possible trigger for neuromyelitis optica spectrum disorder. This rare and potentially coincidental event has no implications for vaccine administration practices. However, further research is needed to elucidate the effects of mRNA vaccines on humoral and cell-mediated immunity.

Key Words: NMOSD, BNT162b2, COVID-19, mRNA vaccine

Neuromyelitis optica spectrum disorder (NMOSD) is a rare astrocytopathy commonly associated with an autoantibody against aquaporin-4 (AQP-4) water channels on astrocyte end-feet.1 The binding of AQP-4 antibody activates the downstream pathways of complement-mediated cytotoxicity or antibody-dependent cell-mediated cytotoxicity, which results in astrocyte cell death with secondary demyelination.2 NMOSD progresses with relapses that are commonly triggered by acute respiratory infections,3 including several reports of coronavirus disease of 2019 (COVID-19) infection-associated NMOSD relapses.4,5 One of the most powerful tools against the COVID-19 infection have been the messenger RNA (mRNA) vaccines, which brought on an era of feasible vaccine production, along with questions regarding their safety.6 Briefly, their mechanism of action relies on cellular uptake and translation of SARS-CoV-2 mRNA for the spike protein, followed by antigen processing and presentation to local immune cells for subsequent neutralizing antibody production and T-cell-mediated immune response.7 For optimal efficacy, 2 dosages of COVID-19 mRNA BNT162b2 (Pfizer-BioNTech) vaccine is administered at least 3 weeks apart.8 Bell palsy and transverse myelitis have been reported as potential neurological complications.9 The immunologic adverse events following BNT162b2 in patients with no previous history of autoimmune disease include but not limited to myocarditis, pericarditis,10 acute pancreatitis,11 polymyalgia rheumatica, multiple sclerosis,12 and uveitis.13 The mechanisms of these events are unknown, but the current hypothesis includes molecular mimicry between spike protein and host antigens, predisposed host immunity, and altered cytokine expression profile.10

CASE PRESENTATION

A 43-year-old Caucasian female presented with blurred vision and movement-associated pain in the right eye. Her symptoms began 24 hours following immunization with the second dose of the COVID-19 mRNA BNT162b2 vaccine. The time interval between the administration of the first and second doses was 4 weeks. She did not experience any attack-like complaints before this presentation. Her medical history was unremarkable except for 2 gestations. She had a second-degree family history of systemic lupus erythematosus. Her vitals were normal on admission. A neurological exam revealed decreased visual acuity in the right eye. Brain magnetic resonance imaging (MRI) confirmed the diagnosis of right optic neuritis (Fig. 1). The cervical spinal MRI was normal. Lumbar puncture revealed positive oligoclonal bands, 6 monoclonal leukocytes, slightly elevated protein (40.1 mg/dL), normal glucose, and no atypical cells. One gram daily intravenous methylprednisolone was administered for 10 days, which resulted in complete symptom resolution.

One month following discharge, the patient experienced right axillary pain with a tingling sensation, which progressed into right hemiparesis in 1 week. Accompanying symptoms were urinary retention and constipation. On neurological examination, the patient was alert and oriented. Vital signs were normal. No meningeal signs were observed. Her vision was 20/50 bilaterally. Cranial nerve examination was normal. She had right hemihypesthesia at T2 dermatomal level and below. Vibration sense was diminished at the right upper and lower extremities. Muscle strength was diminished on the right side (4/5). Deep tendon reflexes were increased in all 4 extremities. Hoffmann sign was present bilaterally. Gait ataxia was observed with a positive Romberg sign. Cervical, thoracic, and brain MRI studies were performed (Fig. 1). The cranial MRI demonstrated 2 lesions, a contrast-enhancing lesion at the right peritrigonal and a contrast-enhancing lesion at the left crus cerebri. An expansile T1-hypointense and T2-hyperintense spinal cord lesion located between cervical 1 to mid-thoracic levels were present. A patchy contrast enhancement pattern was apparent.

Concerning the differential diagnosis of a patient with optic neuritis and myelitis attacks; autoimmune markers, viral serologies, and malignancy screening were ordered. Anti-nuclear antibody, anti-double-stranded DNA antibody, lupus anticoagulant, rheumatoid factor, anti-cardiolipin antibody, and anti-beta2 glycoprotein levels were within normal range.

From the *Koc University Graduate School of Health Sciences; †Koc University Hospital; ‡Acibadem University School of Medicine; and §Koc University Center for Translational Medicine, Istanbul, Turkey. Written informed consent was obtained from the patient for publication and any accompanying images. An ethical approval is not applicable for this case report.

The authors declare no conflict of interest.

Correspondence to: Ayse Altintas, MD, Koc Universitesi Hastanesi, Davutpasa Caddesi, No. 4, Zeytinburnu, Istanbul 34010, Turkey. E-mail: ayalintas@ku.edu.tr.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 2331-2637/22/2703-0147
DOI: 10.1097/NRL.0000000000000420

CASE REPORT/CASE SERIES

The Neurologist • Volume 27, Number 3, May 2022

www.theneurologist.org | 147

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.
Serum immunoglobulin levels for human immunodeficiency virus, cytomegalovirus, hepatitis viruses, and varicella-zoster virus were below detection level. On abdominal MRI, bilateral uniloculated ovarian cysts with peripheral contrast enhancement were present. Cancer antigens including CA 12-5, CA 19-9, CA 15-3, and human epididymis protein 4 were within normal limits. All in all, the rheumatologic, infectious, and neoplastic etiologies were excluded. The anti-AQP-4 antibody serology was obtained during both attacks and found to be elevated with a titer of 1:320 by cell-based assay. The anti-myelin oligodendrocyte glycoprotein antibody was negative (Euroimmun) (Fig. 1).

Together with the second attack, associated MRI findings, and the strongly positive anti-AQP4 antibody results, she fulfilled the International Panel for NMO Diagnosis 2015 criteria.14 The final diagnosis was NMOSD with an index optic neuritis attack possibly triggered by the administration of the COVID-19 mRNA-BNT162b2 vaccine. She was admitted for further inpatient management. An intravenous methylprednisolone regimen was initiated. On follow-up, she demonstrated inadequate clinical improvement which prompted 6 cycles of plasma exchange procedure on alternate days. During inpatient care, a urinary catheter was placed due to urinary retention and physical therapy was

FIGURE 1. The T2-hyperintense (left), contrast enhanced (right) right optic nerve on axial brain MRI, consistent with optic neuritis (A). Arrows indicate the anatomical location of right optic nerve, which has the pathological MRI changes as described. Sagittal and Axial T2-weighted (B) and T1-weighted (C) cervical MRI images performed during the second attack demonstrating a T2-hyperintense longitudinally extensive spinal cord lesion with patchy contrast enhancement. MRI indicates magnetic resonance imaging.
DISCUSSION

The mRNA vaccine technology became the leading prevention strategy during the COVID-19 pandemic. Specifically, the mRNA-BNT162b2 vaccine is shown to be efficacious in mounting an antibody-mediated immune response against SARS-CoV2 and successfully prevented or reduced the severity of COVID-19. Although considered a well-tolerated vaccine with rare serious adverse effects, recent reports on its autoimmune side effects signify the need for a bedside-to-bench approach to better understand its immunostimulatory mechanisms of action.

Among postvaccination demyelination cases, acute disseminated encephalomyelitis following COVID-19 immunization has also been reported after inactivated and mRNA vaccines, but a direct causality is difficult to establish due to unclear pathomechanism and confounding factors. Postvaccination relapses with tetanus/diptheria toxin and influenza vaccine may rarely occur in NMOSD patients. Of note, an index demyelinating attack rather than a relapse of NMOSD has been reported with seasonal influenza. Japanese encephalitis virus, inactivated SARS-CoV2, ChAdOx1 nCoV-19, and SARS-CoV2 mRNA-1273, and Sputnik V COVID-19 vaccine.

This report presents a middle-aged previously healthy female experiencing a new onset autoantibody-associated central nervous system inflammatory disease, a day following the second dose administration of the BNT162b2 vaccine. A unique feature of our case is the proximity of symptom onset and vaccination, which ranges from 4 days to 3 weeks in previous reports. This close temporal relationship is plausible based on previously reported BNT162b safety data. The systemic adverse events are usually observed within the first 24 to 48 hours after vaccination. Also, the systemic immune response is mainly stimulated with the administration of the second dose. A causal relationship cannot be concluded based on this temporal association; however, some speculations can be made. Initially, the promotion of a self-reactive autoantibody response is unlikely as the symptom onset is within 24 hours of vaccination, which is inadequate for mounting adaptive immunity. Instead, the mRNA molecule can be a trigger for innate immune cells to secrete proinflammatory cytokines by activating their pattern recognition receptors. Additionally, BNT162b2 induces specific CD4+ and CD8+ T-cell immune responses, with these cells expressing high levels of interferon-gamma and interleukin-2 (IL-2). Although these antigen-specific T cells are not specific for AQP-4, they can promote self-antigen presentation in host cells and activate the complement cascade.

Some clinical clues can also aid in our understanding of the post-vaccination NMOSD. The relatively lower incidence of vaccination-associated neurological worsening in NMOSD patients treated with B-cell depleting therapies can hint at a B-cell-mediated association mechanism. Interestingly, a paralleled increase in reports of NMOSD following COVID-19 infection and vaccination may suggest a shared mechanism, such as increased blood-brain barrier permeability, molecular mimicry, and bystander peripheral immune activation.

Finally, the factors that support the coincidental nature of this association should be highlighted. Our case’s age and sex demographics are appropriate for the NMOSD onset in the general population. In addition, positive AQP-4 antibody result is a potential risk factor for postvaccination attacks as this patient subgroup more commonly suffers from such relapses.

CONCLUSION

Despite any possible association between BNT162b2 vaccination and NMOSD, patients should be encouraged to receive the vaccination as this rare adverse event cannot possibly outweigh the benefits of immunization in the healthy population. Our case points out the need to continue the surveillance for autoimmune adverse events after the BNT162b2 vaccine and investigate the modes of immune system activation in the development of mRNA vaccine-related central nervous system autoimmunity.

ACKNOWLEDGMENTS

The authors thank Dr Yusuf Oner from Koc University Hospital Radiology Department for interpreting the magnetic resonance imaging studies.

REFERENCES

1. Lennon VA, Kryzer Tj, Pittock SJ, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005;202:473–477.
2. Ratelade J, Asavapanumas N, Richie AM, et al. Involvement of antibody-dependent cell-mediated cytotoxicity in inflammatory demyelination in a mouse model of neuromyelitis optica. Acta Neuropathol. 2013;126:699–709.
3. Jarius S, Paul F, Weinges AM, et al. Neuromyelitis optica. Nat Rev Dis Primers. 2020;6:85.
4. de Ruijter JS, Kramer G, Gons RAR, et al. Neuromyelitis optica spectrum disorder after presumed coronavirus (COVID-19) infection: a case report. Mult Scler Relat Disord. 2020;46:102474.
5. Correõa DG, de Souza Lima FC, da Cruz Bezzera D, et al. COVID-19 associated with encephalomyelocorticulitis and positive anti-aquaporin-4 antibodies: Cause or coincidence? Mult Scler J. 2020;27:973–976.
6. Viatiello A, Ferrara F. Brief review of the mRNA vaccines COVID-19. Inflammopharmacology. 2021;29:645–649.
7. Sewell HF, Agius RM, Kendrick D, et al. Covid-19 vaccines: delivering protective immunity. BMJ. 2020;371:m4838.
8. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med. 2020;383:2603–2615.
9. Correõa DG, Cañete LAQ, Dos Santos GAC, et al. Neurollogical symptoms and neuroimaging alterations related with COVID-19 vaccine: cause or coincidence? Clin Imaging. 2021;80:348–352.
10. Bozkurt B, Kamat I, Hotzej PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144:471–484.
11. Parkash O, Sharko A, Farooqi A, et al. Acute pancreatitis: a possible side effect of COVID-19 vaccine. Cureus. 2021;13:e14741.
12. Watad A, De Marco G, Mahajna H, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV2 vaccination. Vaccines (Basel). 2021;9:435.
13. Rabinovitch T, Ben-Arie-Weinrobt Y, Hareuveni-Blum T, et al. Uveitis following the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: a possible association. Retina. 2021;41:2462–2471.
14. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177–189.
15. Kyriakidis NC, López-Cortés A, González EV, et al. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines. 2021;6:28.
16. Vogel AB, Kanovsky I, Che Y, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. bioRxiv. 2020. [Epub ahead of print].
17. Baxter R, Lewis E, Goddard K, et al. Acute demyelinating events following vaccines: a case-centered analysis. *Clin Infect Dis*. 2016;63:1456–1462.
18. Kania K, Ambrosias W, Tokarz Kupczyk E, et al. Acute disseminated encephalomyelitis in a patient vaccinated against SARS-CoV-2. *Ann Clin Transl Neurol*. 2021;8:2000–2003.
19. Mealy MA, Cook LJ, Pache F, et al. Vaccines and the association with relapses in patients with neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord*. 2018;23:78–82.
20. Cho JH, Park Y, Woo N. A case of neuromyelitis optica spectrum disorder following seasonal influenza vaccination. *Mult Scler Relat Disord*. 2019;30:110–113.
21. Furukawa Y, Komai K, Yamada M. Neuromyelitis optica after Japanese encephalitis vaccination. *Eur J Neurol*. 2011;18:e26–e27.
22. Chen S, Fan X-R, He S, et al. Watch out for neuromyelitis optica spectrum disorder after inactivated virus vaccination for COVID-19. *Neuro Sci*. 2021;42:3537–3539.
23. Anamnart C, Tsavipat N, Owattanapanich W, et al. Newly diagnosed neuromyelitis optica spectrum disorders following vaccination: case report and systematic review. *Mult Scler Relat Disord*. 2021. [In press].
24. Fujikawa P, Shah FA, Braford M, et al. Neuromyelitis optica in a healthy female after severe acute respiratory syndrome coronavirus 2 mRNA-1273 vaccine. *Cureus*. 2021;13:e17961.
25. Badrawi N, Kumar N, Albastaki U. Post COVID-19 vaccination neuromyelitis optica spectrum disorder: case report & MRI findings. *Radiol Case Rep*. 2021;16:3864–3867.
26. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. 2020;586:589–593.
27. Linares-Fernández S, Lacroix C, Exposito JY, et al. Tailoring mRNA vaccine to balance innate/adaptive immune response. *Trends Mol Med*. 2020;26:311–323.
28. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. *Nature*. 2020;586:594–599.
29. Pohl M, Kawakami N, Kitić M, et al. T cell-activation in neuromyelitis optica lesions plays a role in their formation. *Acta Neuropathol Commun*. 2013;1:85.
30. Lotan I, Romanow G, Levy M. Patient-reported safety and tolerability of the COVID-19 vaccines in persons with rare neuroimmunological diseases. *Mult Scler Relat Disord*. 2021;55:103189.