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.
Dear editor

In the context of coronavirus disease 2019 (COVID-19) vaccination, a recent review by Anamnart et al. (Anamnart et al., 2022) suggested a possible association between vaccination and the triggering anti-aquaporin-4 antibody (AQP4-Ab) formation causing neuromyelitis optica spectrum disorder (NMOSD). It was stated that temporal relationship and pathophysiological explanation might be a rational justification for post-COVID-19 vaccination NMOSD. However, this may be a coincidence; despite mass vaccination in many countries, such complications were not frequently reported. Nonetheless, the severity and the possible pathophysiology of postvaccination NMOSD make it a considerable complication, particularly in the case of mass vaccinations. Herein we present an unusual presentation of post-COVID-19 vaccination and want to add more robust evidence to the development of NMOSD following COVID-19 vaccination.

Our patient was a 70-year-old woman admitted to our clinic with a history of numbness and weakness in her left limbs, 7 days after receiving the third dose of a COVID-19 vaccine (Sinovac: CoronaVac, a whole inactivated virus). Her left-sided hypoesthesia and hemiparesis progressed rapidly to paraplegia. Her upper limbs paresis worsened in the next 3 days. Spinal cord magnetic resonance imaging (MRI) determined a high T2- and a low T1-weighted long segment hemorrhagic lesion in the cervical cord (C1- C7) with a peripheral rim-shaped enhancement in the post-Gadolinium T1 image (Fig. 1, A-C). A thoracic cord lesion (T1-T3) was also evident on MR image (Fig. 1D). Brain MRI was unremarkable. A biopsy of cervical cord lesion was taken to exclude the possible malignancy source for cervical lesion, which determined reactive gliosis. Biochemical and cytological analysis of cerebrospinal fluid (CSF), including oligoclonal band (OCB), was normal. Cell-based antibody assay for AQP-4-Ab was positive. Based on the international panel for NMO diagnosis (IPND) criteria (Wingerchuk et al., 2015), the diagnosis of NMOSD could be confirmed. A methylprednisolone pulse therapy was administered for five days (1000 mg/day). The patient did not benefit from pulse therapy, so we started a therapeutic plasma exchange (TPE). As she was non-responsive to the treatment, she developed respiratory insufficiency, and her symptoms escalated to quadriplegia, cyclophosphamide (600 mg on days 1, 2, and 9) (Awad and Stüve, 2009 Nov 28) was administered. The patient was non-responsive to the treatment and developed lymphopenia and fever following cyclophosphamide treatment without any clinical improvement. The patient died after 2 months of hospitalization.

NMOSD is a rare autoimmune disorder that usually does not affect people older than 50 years old (Krumholz et al., 2015 May 10). Our patient developed NMOSD in her 70s without any relevant past medical history of demyelinating or other autoimmune-related disorders. The previous report by Anamnart et al. included two female patients with new-onset NMOSD after COVID-19 vaccination at apparently younger ages than our patient (a 26- and 46-year-old woman). The age of onset in both patients in their report was in line with common age onset of NMOSD disorder. However, regardless of the close temporal relationship, a coincidental concurrency of vaccination and NMOSD presentation was probable. Considering the very late-onset of NMOSD in our patient following 7 days postvaccination, it is plausible that AQP4-Ab was triggered by vaccination. However, a previously asymptomatic seropositivity for AQP-4-Ab could not be excluded. Under such assumption, vaccination may provoke an NMOSD relapse even in the elderly. Anamnart et al. reported a favorable response to corticosteroids or corticosteroids and TPE in all post-COVID-19 vaccination NMOSD. Our patient had a fatal course of disease without any response to corticosteroids, TPE, and cyclophosphamide, which was in line with other reports about severe complications of the late-onset NMOSD (Krumholz et al., 2015 May 10).

The late-onset of NMOSD following COVID-19 vaccination makes this presentation a unique case that adds strong evidence to the alleged role of vaccination in the development or worsening of NMOSD. Further studies are required to elucidate if an etiologic relationship exists.

Ethics

Written informed consent has been obtained from the patient. This
study was approved by the Iranian national committee for ethics in biomedical research and performed in accordance with the Helsinki Declaration of 1964, and its later amendment.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**CRediT authorship contribution statement**

A.M, I.A, S.N, and V.S contributed to the conception and design of the research. A.M wrote the first draft of the manuscript. I.A, S.N, and V.S revised the manuscript. All the authors have read and approved the final version.

**Declaration of Interests**

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.

**Acknowledgments**

N/A.

**References**

Anamnart, C, Tisavipat, N, Owattanapanich, W, Apiwattanakul, M, Savangned, P, Prayoonwiwat, N, et al., 2022. Newly diagnosed neumyelitis optica spectrum disorders following vaccination: Case report and systematic review. Mult. Scler. Relat. Disord. 58, 103414. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2211034821006805.

Awad, A, Stüve, O., 2009. Review: Cyclophosphamide in multiple sclerosis—Scientific rationale, history and novel treatment paradigms. Ther. Adv. Neurol. Disord. 2 (6), 357–368. Available from: http://journals.sagepub.com/doi/10.1177/17562854093443475.

Krumbholz, M, Hofstadt-van Oy, U, Angstwurm, K, Kleiter, I, Jarius, S, Paul, F, et al., 2015. Very late-onset neumyelitis optica spectrum disorder beyond the age of 75. J. Neurol. 262 (5), 1379–1384. Available from: http://link.springer.com/10.1007/s00415-015-7766-8.

Wingerchuk, DM, Banwell, B, Bennett, JL, Cabre, P, Carroll, W, Chitnis, T, et al., 2015. International consensus diagnostic criteria for neumyelitis optica spectrum disorders. Neurology 85 (2), 177–189. Available from: https://www.neurology.org/lookup/doi/10.1212/WNL.0000000000001729.

Ali Motahharynia a, Saba Naghavi b,c, Vahid Shaygannejad a,b,c, Iman Adibi b,c,*

*Corresponding author at: Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

a Center for Translational Neuroscience, Isfahan University of Medical Sciences, Isfahan, Iran

b Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

c Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

E-mail address: i_adibi@med.mui.ac.ir (I. Adibi).