eNeurologicalSci 31 (2023) 100455

Contents lists available at ScienceDirect

eNeurologicalSci

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

Relapse of neuromyelitis optica spectrum disorder after BNT162b2 mRNA Covid-19 vaccination

Dear editors,

Neuromyelitis optica spectrum disorder (NMOSD) is a rare yet severe demyelinating autoimmune inflammatory disease affecting the central nervous system, specifically the myelin of the spinal cord and the optic nerves. With the introduction of COVID-19 vaccines worldwide, it is important to consider vaccination immunogenicity, safety, and efficacy in patients with neuroimmune disorders such as NMOSD. Approximately o.19% of COVID-19-vaccinated cases have reported complications involving the central nervous system [1]. There have been several reported cases of NMOSD recurrence after vaccination against influenza, hepatitis or tetanus and diphtheria (Table 1) [2]. There was also one case of new relapse of NMOSD as a potential adverse event of AstraZeneca AZD1222 vaccination for COVID-19 [3]. In this report, we describe a case of severe relapse of NMOSD after BNT162b2 mRNA Covid-19 vaccination which has not been reported previously.

In September 2008, a previously healthy 68-year-old woman developed decreased visual acuity (4/40) with an arcuate field defect on the left eye (Fig. 1A) which improved to 4/10 after steroid injection. Eight years later, she was admitted due to continuous hiccups and visual loss in the same left eye. Visual acuity was no light perception (NLP) and optic disc in the left eye was pale and atrophied (Fig. 1B and C). Neuroimaging studies showed enhancement of the orbital segment of the left optic nerve (Fig. 1D), and hyperintensity in the lower medullar involving the area postrema on T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI (Fig. 1E). AQP4-IgG antibody was positive with a titer of 1:10. After intravenous methylprednisolone injections, the hiccups resolved but visual impairment of the left eye remained with NLP. Until 2021, she showed neither clinical nor radiological progression of disease while on azathioprine 100 mg/day. In May 2021, she presented to the emergency department with weakness and numbness of the right lower leg. She denied any history of trauma, but she had received a second dose of the BNT162b2 mRNA COVID-19 vaccine five days before presentation. There was an eight-week gap between the first and second dose. Examination revealed weakness in the right lower limb with grade 2/5 proximal and 1/5 distal, and sensation of pain and temperature was reduced below the 10^{th} thoracic level with hyperreflexia in the right knee. Optic disc was pale and atrophic with NLP in the left eye (Fig. 1F and G). Serum AQP4-IgG antibody was positive with a titer of 1:40. Newly identified multifocal cerebral hemispheric lesions on T2-weighted FLAIR (Fig. 1H), and extensive longitudinal lesions between T8 and T11 with accompanying enhancement on spinal MRI (Fig. 1I). After five sessions of plasmapheresis and intravenous methylprednisolone, her motor symptoms improved bilaterally to nearly normal but without improvement with her vision.

The exact mechanism behind the relapse of neuroimmunological disorders after COVID-19 vaccination remains unclear. However, a combination of vaccine-related factors and the disease activity of the patients could be involved. There are several immunological processes that are involved in both anti-infectious immune response and autoreactivity, such as antigen presentation, cytokines production, anti-idiotypic networks, bystander activation, epitope spreading, and polyclonal activation of B cells [4]. The cross-reactivity between viral antigens and AQP-4 has been found to be associated with viral infection and viral vaccinations like influenza, human papilloma virus, hepatitis A or B, rabies [5]. The molecular mimicry between the viral proteins used in vaccines and self-antigens and the similarity between evolutionarily-conserved molecules and the immunologic adjuvants that are used in vaccines to enhance antigen-specific immune responses could be reasons for this cross-reactivity. Another interesting report using an experimental model showed that the SARS-CoV-2 spike protein (S protein) was able to cross the blood-brain barrier (BBB) [6]. Studies using radioiodinated S proteins have found that they have the potential to cross the BBB by a vesicle-dependent mechanism of adsorbent transcytosis [6]. Both the Pfizer-BNT162b2 and the Moderna COVID-19 vaccines use mRNA, which is immediately broken down after delivering instructions for how to make the S protein. Another important factor in the immunopathogenic process is activating bystander autoreactive lymphocytes by activation of toll-like receptors and production of type I interferon. In addition to this bystander activation, macrophages secreting cytokines can result in local inflammation and additional recruitment of T-helper cells.

Moreover, there have been reports regarding new onset, symptom flares, and recurrence of neuroimmunological conditions. Surveys targeting patients with multiple sclerosis (MS) showed that 15.1% (36/239) and 16.7% (73/438) of participants reported new or worsening neurological symptoms following COVID-19 vaccination, respectively. Relapses or exacerbations of pre-existing MS after mRNA-1273, AZD1222 or BNT162b2 COVID-19 vaccines were also reported. There was one case who presented with a new relapse after an eight-year period of NMOSD stability after an interval of 7 days following the first dose of AZD1222. However, the Pfizer-BNT162b2 COVID-19 vaccine was not reported to increase relapse rate in MS in two different studies involving a large number of patients [7]. Likewise, no increase in relapse rate was observed in NMOSD in a study involving patients from several countries who had received four different COVID-19 vaccines.

Appropriate management of immunosuppressive therapy was found important for balancing the risk of COVID-19 vaccine-related relapse of NMOSD and for protection of NMOSD patients against SARS-CoV-2 infections. In a retrospective analysis of relapse among patients with NMOSD, 81.25% of vaccine-associated relapses were in patients not on immunotherapy; their data also indicated that immunosuppressive therapy at the time of vaccination can reduce the risk of vaccination-associated relapses [8]. Thus, in the case of COVID-19 immunization, strict monitoring of disease activity following vaccination,

https://doi.org/10.1016/j.ensci.2023.100455
Received 14 June 2022; Received in revised form 10 February 2023; Accepted 25 February 2023
Available online 5 March 2023

Table 1
Reported cases of NMOSD with a relapse in close temporal relation to a vaccine.

Type of vaccine	Number of cases	Average vaccine-to-event days	Clinical manifestation of relapse	Background immunosuppression
Influenza	9	41.6	Myelitis [5]; Myelitis & Optic neuritis [2]; Optic neuritis [2]	Azathioprine [1]; None [8]
Td	2	38	Myelitis [2]	None [2]
Tdap	3	16	Myelitis [1]	Mycophenolate mofetil [1]; None [1]; unavailable [1]
Hepatitis A	1	13	Myelitis [1]	None [1]
Hepatitis B	1	44	Myelitis [1]	Glatiramer acetate [1]
Pneumococcal	2	54 (1); unavailable [1]	Optic neuritis [1]; progressive bilateral visual loss, paraplegia, and hiccups [1]	None [1]; IVMP [1]
COVID-19 (AZD1222)	1	7	Loss of vision in the left eye [1]	Azathioprine [1]
COVID-19 (BNT162b2)*	1	2	Right leg weakness and both legs hypesthesia [1]	Azathioprine [1]

* Our case; NMOSD: neuromyelitis optica spectrum disorders; IVMP = intravenous methylprednisolone.

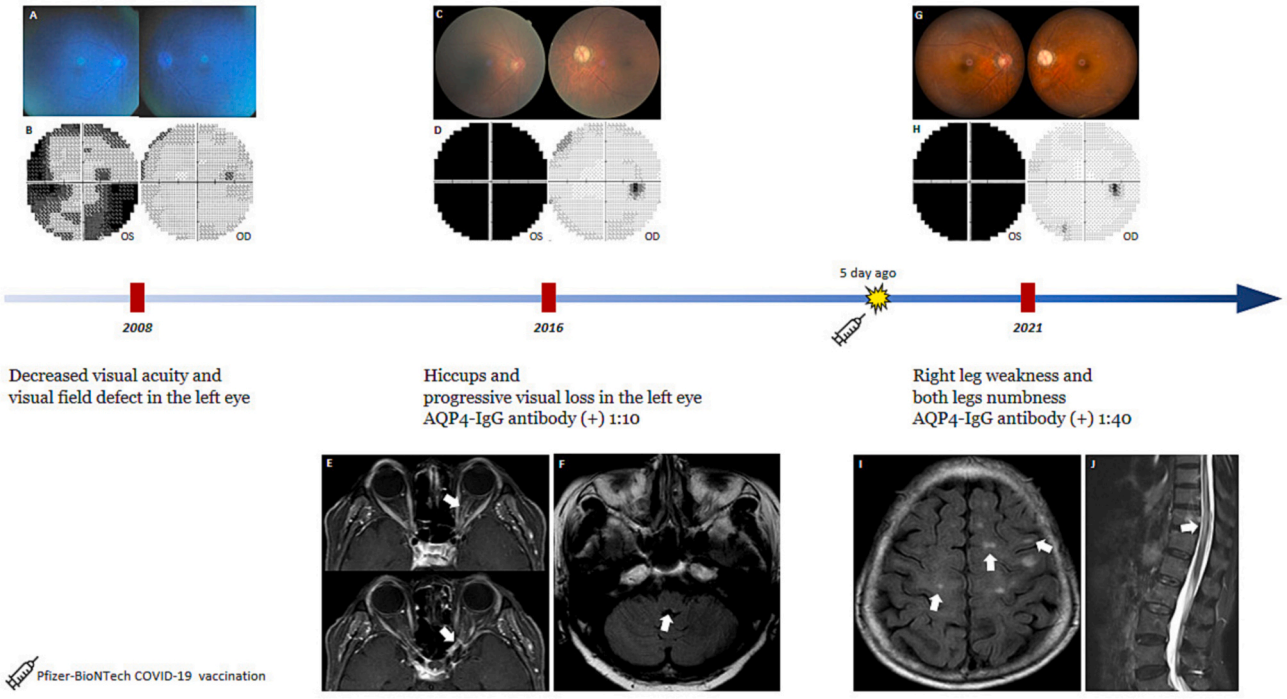

Fig. 1. Chronology of clinical and radiological findings in the current patient with NMOSD. Fundus examination showed moderate optic disc swelling in her left eye (A), and automated visual field examination revealed an arcuate visual field defect in the left eye (B). In 2016, fundus examination demonstrated pallor of the left optic disc (C) with global visual field defects in the left eye (D). T1-weighted axial magnetic resonance image of the brain revealed left retrobulbar optic nerve enhancement (arrows) (E), and T2-weighted fluid-attenuated inversion recovery (FLAIR) image demonstrated bilateral lesions in the area postrema (arrow) (F). In 2021, two days after BNT162b2 COVID-19 vaccination, optic disc pallor was confirmed on fundoscopy in the left eye (G), and a visual field defect was maintained over the entire visual field of the left eye (H). Newly identified high signal multifocal lesions were seen on T2-weighted FLAIR brain MRI (arrows) (I), and longitudinally extensive lesions over three vertebral segments ranging from the T8 to T11 level were demonstrated on spinal MRI (arrow) (J).
OS = Oculus sinister; OD = Oculus dexter.

immunosuppressive management, and infection prevention education should be taken into consideration.

Although vaccination-induced NMOSD cases or relapses have been reported, these studies demonstrate that vaccination can accelerate the transition to overt disease in patients with subclinical autoimmune disease [9]. Therefore, it is still difficult to conclude whether the interaction between vaccinations and the autoimmune diseases is causal or coincidental. However, there is convincing evidence that infection can induce relapses in autoimmune diseases, and SARS-CoV2 infection has already been demonstrated as a risk factor for NMOSD relapses,10 which suggest that patients with NMOSD are recommended to reduce their risk of infections by receiving COVID-19 vaccines [10].

Author contributions

QW and J-JK wrote and structured the manuscript. YB wrote sections of the manuscript. S-YO contributed to conception, design and manuscript revision. All authors read and approved the submitted version.

CRediT authorship contribution statement

Qi Wang: Writing – original draft, Writing – review & editing. **Jin-Ju Kang:** Writing – original draft, Writing – review & editing. **Yutong Bai:** Writing – review & editing. **Sun-Young Oh:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT) (No. 2022R1A2B5B01001933) and by the Biomedical Research Institute Fund, Jeonbuk National University Hospital.

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