Aquaporin-4 protein antibody-associated optic neuritis related to neuroendocrine tumor after receiving an inactive COVID-19 vaccine

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Neuromyelitis optica (NMO), also known as Devic’s disease, is a rare, autoimmune, and recurrent demyelinating disorder that primarily affects the spinal cord and optic nerve. We report a case with recurrent optic neuritis caused by the paraneoplastic NMO spectrum disorder in the setting of a gastric neuroendocrine tumor 2 weeks after receiving an inactive COVID-19 vaccine.

**Key words:** Aquaporin-4 protein antibody, gastric neuroendocrine tumor, inactive COVID-19 vaccine, optic neuritis

Neuromyelitis optica (NMO) is an autoimmune, inflammatory, demyelinating central nervous system disease distinct from multiple sclerosis (MS) associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG).[1] Furthermore, a limited form of NMO called NMO-spectrum disorder (NMO-SD) with AQP4-IgG is characterized by clinical syndromes or MRI findings related to the optic nerve, spinal cord, area postrema, and other brainstem, diencephalic, or cerebral involvement.[3]

Herein, we present a case of a young man with recurrent unilateral optic neuritis (ON) associated with aquaporin-4 protein antibodies in the setting of a gastric neuroendocrine tumor (G-NET) 2 weeks after receiving a COVID-19 vaccine.

**Case Report**

A 32-year-old Caucasian man presented to the Ophthalmology Clinic with retrobulbar pain and blurred vision in the right eye (RE) for 5 days. The patient had Graves’ disease and a history of having the first inactive COVID-19 vaccine (CoronaVac, Sinovac, China) 2 weeks ago. His best-corrected visual acuity (BCVA) was 20/40 RE and 20/20 in the left eye (LE). There was a relative afferent pupillary defect (RAPD) in RE. Ishihara color plate results were 4/19 and 19/19 in the RE and LE, respectively. The extraocular motility, eyelids, anterior segment examinations, and intraocular pressures were normal. On fundus examination, the LE appeared normal while the RE showed mild swelling and blurry demarcation at the nasal side of the optic disc [Fig. 1a]. All relevant laboratory tests were ordered to differentiate infectious, inflammatory, and infiltrative optic neuropathies, and only serum NMO-IgG was positive.

In addition, Humphrey 24-2 SITA-Fast automated visual field testing (VFT) revealed an inferior arcuate scotoma [Fig. 2a].

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**Figure 1:** (a) Mild swelling and blurry demarcation at the nasal side of the optic disc in the right eye at first optic neuritis attack. (b) Fundus fluorescein angiography demonstrating right optic disc staining in the late phase at first optic neuritis attack. (c) Optic disc atrophy was observed in the right eye, while the left optic disc was normal on dilated fundus examination at 4 weeks after the second optic neuritis attack.

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late phase fluorescein angiogram demonstrated optic disc staining [Fig. 1b], and visual evoked potentials (VEPs) revealed prolonged latency in the RE. All of the test results were normal for the LE.

Magnetic resonance (MR) imaging of the brain, orbits, and spine with and without contrast revealed uniform contrast enhancement and thickening of the intraorbital part of the right optic nerve but no lesions in the white matter or other areas [Fig. 3].

In light of all these results, the case was diagnosed with ON due to NMO-SD, which developed after inactivated COVID-19 vaccine. The patient received 1000 mg/day intravenous methylprednisolone for 5 days, followed by 1 mg/kg/day of oral corticosteroids. At the 4th week of treatment, the patient’s ocular findings responded quite well. The BCVA returned to 20/20 and the color vision was 13/19. The mild blurriness of the right optic disc continued. However, severe stomachache and dyspepsia developed during the treatment. Upper gastrointestinal system endoscopy and gastric ablation were performed, and the biopsy result was well-differentiated type 1 NET. The patient’s immunosuppressive treatment was postponed for further investigation.

Two weeks later, the patient presented to the ophthalmology clinic again with sudden right visual loss (20/800 BCVA, 0/19 color vision). A generalized loss of sensitivity was observed as the second attack of ON, and high-dose intravenous methylprednisolone sodium (1000 mg/day) was given for 5 days, followed by oral prednisone 1 mg/kg/day for 6 weeks. At the last visit, BCVA was 20/400, color vision could not be evaluated, and disc atrophy was observed [Fig. 1c]. SD-OCT showed decreased peripapillary retinal nerve fiber layer thickness and macula ganglion cell loss in the RE [Fig. 4].

After the tumor was removed by an endoscopic approach and no distant metastases were observed, the patient was started on intravenous rituximab treatment.

Discussion

Carcinoid-related NMO-SD and NMO-IgG seropositivity has been reported in isolated cases. The underlying mechanism may be explained as the secretion of onconeural antigens from tumor cells that can trigger an aquaporin-4 immune response. Cytokines, especially interleukin-6 (IL-6), play a crucial role in the development of inflammation related to NMO when they are secreted directly from a carcinoid tumor. Patients with paraneoplastic NMO have generally presented after the age of 50 years. However, our 32-year-old case was suffering from antibody-mediated recurrent ON in the setting of a G-NET, in a manner that is consistent with a paraneoplastic phenomenon.

The potential of the virus to stimulate autoantibody production has been suggested by a patient with bilateral severe ON and myelitis associated with the MOG-antibody,
as observed in the context of SARS-COV-2. On the contrary, autoimmune disease induction or triggering by the inherent immunogenicity of COVID-19 vaccines is possible. Antibody-dependent enhancement (ADE) is a factor that should be considered when developing COVID-19 vaccines. A relationship between autoimmunity and vaccines has been demonstrated, although it is rarely encountered. ON has been reported after vaccination for rabies and influenza. However, ADE has not been observed in preclinical studies of the approved inactivated vaccines, and CoronaVac is believed to have a low risk of ADE. Therefore, it is difficult to speculate that NMO-SD can be induced by the CoronaVac vaccine. However, the young age of our patient and the autoimmune disorder (Graves’ disease) in the background indicate that vaccination may trigger the development of aquaporin-4 protein antibodies in the setting of a G-NET and this can be seen at a younger age than usual. It may, therefore, be possible for the COVID-19 vaccine to play a triggering role in patients with a potential risk of autoimmune reactions.

Conclusion

In conclusion, we presented a case of G-NET-associated NMO-SD who presented with clinical findings of ON 2 weeks after receiving an inactivated COVID-19 vaccine. Although it is too early to state without further evidence that the vaccine has the potential to cause an immune reaction leading to NET-related NMO-SD and the two conditions could be coincidental, we feel the possibility should be considered in light of the underlying common immune mechanisms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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