

CASE REPORT



## Atypical Optic Neuritis After Inactivated Influenza Vaccination

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### ABSTRACT

The existence of vaccine-associated optic neuritis is essentially based on the temporal relationship between the administration of a vaccine and the development of optic neuritis in patients with no other known aetiologies for infectious or non-infectious inflammation that could account for the optic neuritis. Influenza vaccine (inactivated or live attenuated) is considered to be one of vaccines that could be related to optic neuritis. The authors describe a rare case of bilateral asymmetric optic neuritis with leptomeningeal enhancement on magnetic resonance imaging (MRI) in a previously healthy young woman who received inactivated influenza vaccination 2 weeks before the onset of symptoms.

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### Introduction

The existence of vaccine-associated optic neuritis is essentially based on the temporal relationship between the administration of a vaccine and the development of optic neuritis in patients with no other known aetiologies for infectious or non-infectious inflammation that could account for the optic neuritis. Influenza vaccine (inactivated or live attenuated) is considered to be one of vaccines that could be related to optic neuritis. There are three different influenza vaccines (egg based, cell based, and recombinant) approved by the US Food and Drug Administration (FDA). The egg-based manufacturing process is the most common and has existed for more than 70 years. It is used to make both inactivated (killed) vaccine (flu shot) and live-attenuated vaccine (nasal spray). Attenuated (weakened) live viruses cannot cause flu illness. The weakened viruses are cold-adapted, which means they are designed to only cause infection at the cooler temperatures found within the nose. The live viruses in the nasal spray cannot infect the lungs or other areas where warmer temperatures exist. Cell-based influenza vaccine also uses egg-grown viruses but does not require large numbers of chicken eggs because the viruses are

grown in animal cells and it takes slightly less time to manufacture cell-based influenza vaccines than egg-based vaccines. Recombinant influenza vaccine, approved in 2013, is the only 100% egg-free vaccine on the US market.

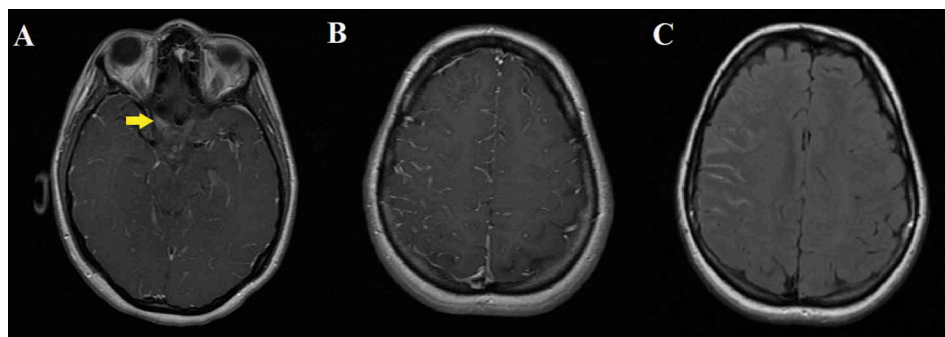
We describe a rare case of bilateral asymmetric optic neuritis with leptomeningeal enhancement on magnetic resonance imaging (MRI) in a previously healthy young woman who received inactivated influenza vaccination 2 weeks before the onset of symptoms.

### Case report

A 23-year-old Indian woman presented to the neuro-ophthalmology clinic because of a 5-day history of right frontal headache and a 3-day history of blurred vision and pain on eye movement of the right eye. She recently arrived in the United States from India and as a requirement for college admission received an influenza vaccination 2 weeks prior to the development of symptoms. She had no other constitutional symptoms such as skin rash, fever, and muscle aches and no recent history of febrile illness or tick exposure. Initial ophthalmologic examination of the right eye

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**Figure 1.** Magnetic resonance imaging (MRI) of the brain with and without gadolinium. (A) T1 axial with contrast showed enhancement of the right optic nerve (arrow). (B) T1 axial with contrast showed enhancement of the leptomeninges on the right frontoparietal lobes. (C) FLAIR axial showed increased intensity of the leptomeninges on the right frontoparietal lobes.

showed reduced visual acuity (20/40), dyschromatopsia (4/10 on Hardy-Rand-Rittler [HRR] test), a visual field defect (constriction of peripheral visual field) on Humphrey automated perimetry, a relative afferent pupillary defect, and optic disc swelling suggestive of optic neuritis. The left eye was normal on examination, and neurologic examination was otherwise unremarkable. MRI of the brain and orbits with and without gadolinium showed enhancement of the right retrobulbar optic nerve and right hemispheric leptomeninges (Figure 1).

Given the atypical presentation of optic neuritis, further evaluation was performed. Serologic studies showed increased erythrocyte sedimentation rate (37 mm/h) and C-reactive protein (1.7 mg/L), mildly elevated immunoglobulin G4 (IgG4) (112.7 mg/dL) and low vitamin D; however, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-Ro/La, C3/4, aquaporin 4 (AQ4) antibody, angiotensin-converting enzyme (ACE), Lyme, syphilis, human immunodeficiency virus (HIV), *Bartonella*, *Brucella*, and quantiferon gold were negative. Vitamins B<sub>1</sub>, B<sub>6</sub>, B<sub>12</sub>, and E levels were normal. Opening pressure on lumbar puncture was 23 cm H<sub>2</sub>O, and cerebrospinal fluid (CSF) showed leukocytosis (45/ $\mu$ L; mononuclear dominant), normal protein and glucose levels, no oligoclonal IgG, negative tests for cytomegalovirus, Epstein-Bar virus, herpes simplex virus, and varicella-zoster virus, and negative cultures for *Mycobacterium* and other fungi. Chest computed tomography was normal except for a small thyroid nodule. Positron emission tomography (PET) scan showed no lesion outside the brain and orbit. Her vision of the right eye started

improving, and she deferred treatment and did not receive corticosteroid.

About 3 weeks after the initial visit, the patient developed mild pain and blurred vision in the fellow (left) eye. Repeat brain MRI with and without gadolinium showed new abnormal enhancement of the left optic nerve. Given the atypical presentation of the inflammatory optic neuritis and the involvement of fellow eye, she underwent meningeal and brain biopsies with craniotomy from the right frontal lobe, which showed reactive astrogliosis with lymphocytic infiltration without evidence of neoplasm, granulomas, or vasculitis. Her vision started improving at hospital day 4 and had improved to 20/20 in both eyes by the time of discharge. She deferred intravenous corticosteroid therapy but received oral corticosteroid for 14 days with tapering. A week after completing the course of oral corticosteroids, she experienced worsening of the vision in her right eye (counting fingers at 3 ft). Repeat brain and spinal MRI showed enhancement of the right optic nerve. Repeated rheumatologic work-up, infectious disease work-up, CSF analysis, and paraneoplastic antibody assay, including repeated AQ4 antibody, were unremarkable or negative. She received a 3-day course of intravenous corticosteroid, with minimal improvement of her vision, and then received 5-day plasmapheresis. Her vision of the right eye recovered to 20/25 in 2 weeks after the completion of the treatment and in 3 weeks after recurrence of vision loss.

## Discussion

This is a rare case of idiopathic, atypical, sequential, bilateral optic neuritis with leptomeningeal

**Table 1.** Case reports of unilateral or bilateral optic neuritis following influenza vaccination.

Year of report	First author	Type of influenza vaccine	Age/Sex	Interval between vaccination and symptom onset	Treatment	Outcome
1971	Wells <sup>2</sup>	Inactivated	26/M	2 weeks	PO steroids	Full recovery in 2 months
1977	Bienfang <sup>3</sup>	Inactivated	27/M	3 weeks	PO steroids	Full recovery in 3 weeks
1979	Perry <sup>4</sup>	Inactivated	58/M	6 days	PO steroids	Full recovery in 12 months
1980	Cangemi <sup>5</sup>	Inactivated	38/M	3 weeks	None	Optic atrophy at 3 months
1982	Macoul <sup>6</sup>	Inactivated	31/M	3 weeks	None	Optic atrophy at 26 months
1996	Ray <sup>7</sup>	Inactivated	61/F	3 weeks	IV steroids	Partial recovery in 12 months
1997	Hull <sup>8</sup>	Inactivated	59/F	2 weeks	IV steroids	No improvement
2010	Tan <sup>9</sup>	Inactivated	55/F	3 weeks	IV/PO steroids	Full recovery in 6 months
2012	Crawford <sup>10</sup>	Live attenuated	13/M	2 weeks	IV steroids	Full recovery in 3 months
2012	Rubinov <sup>11</sup>	Inactivated	18/M	2 weeks	IV/PO steroids	Full recovery in 3 months

Note. PO = oral; IV = intravenous.

enhancement on MRI in a young woman who had no previous medical history other than influenza vaccination about 2 weeks prior to the development of visual disturbance.

Numerous reports suggest that demyelination may be associated with various types of vaccine, including MMR (measles, mumps, and rubella), hepatitis, diphtheria, pertussis, tetanus and influenza vaccines. There are various case reports describing an association of optic neuritis and influenza vaccination based on the temporal relationship (Table 1).<sup>1–12</sup> Both the inactivated and live-attenuated vaccine have been temporally related to the development of optic neuritis. However, reports of such cases should not be interpreted as a proof of cause. A recent review<sup>13</sup> regarding adverse effects of vaccines stated that it is inadequate to accept or reject a causal relationship between influenza vaccine and optic neuritis. The temporal relationship between vaccine administration and the onset of acute optic neuritis in the absence of known infectious or non-infectious inflammatory aetiologies, coupled with some evidence from biological plausibility studies, suggests that the concept of an immune-mediated attack against optic nerves after vaccination in genetically susceptible individuals does exist, and the possible link should be considered. Here we present a case of optic neuritis that could be linked to alteration of immune system by influenza vaccination.

The exact pathophysiologic mechanism of post-vaccination optic neuritis is not clearly defined. It could be triggered by a common denominator such as an adjuvant<sup>14</sup> used in the vaccine to enhance the antigen-specific immune response, which perhaps induces the release of inflammatory cytokines and

interacts with Toll-like receptors and NLRP (NOD-like receptor protein) inflammasomes. Post-vaccination optic neuritis and other post-vaccination autoimmune phenomena could be understood as among the autoimmune/inflammatory clinical syndromes induced by adjuvants (ASIA),<sup>15</sup> which include macrophagic myofasciitis, Gulf War syndrome, silicosis, and other post-vaccination phenomena. Post-vaccination autoimmune responses are characterised by hyperactive immune responses to a common pathogenic denominator and accompanied by a similar complex of signs and symptoms. However, with some vaccines, the weakened or inactivated virus stimulates a strong immune response so no additional adjuvant is needed for protection against infection. In the United States, most vaccines against measles, mumps, rubella, chickenpox, rotavirus, polio, and seasonal influenza do not contain added adjuvants. In 2015, the US Food and Drug Administration (FDA) approved the first seasonal influenza vaccine containing adjuvant. Called FLUAD, this trivalent vaccine is produced from three influenza virus strains (two subtypes A and one type B), is manufactured using an egg-based process, and is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil. It might be interesting to observe as data accumulate on this vaccine if it is associated with an increased occurrence of post-influenza vaccination autoimmune clinical syndromes, including optic neuritis.

Post-influenza vaccination optic neuritis is uncommon. The pathophysiology of development is presumably immune-mediated. Based on a review of most of the reported cases (including ours), optic neuritis usually develops around 2 to 3 weeks after influenza vaccination. Systemic corticosteroid therapy may

facilitate recovery and prevent vision loss. To prove the causality between influenza vaccine and optic neuritis, extensive epidemiological studies would be required, but the rare occurrence of influenza vaccine-associated optic neuritis and the underreporting of such cases might be a limitation in collecting data to support such causality. Well-designed animal studies may help reveal the causality and understand the pathophysiologic mechanism of development of post-influenza vaccination optic neuritis.

### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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