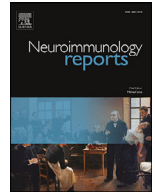




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# Optic neuropathy after COVID-19 vaccination: Case report and systematic review

Abid Haseeb<sup>a</sup>, Abdelrahman M. Elhusseiny<sup>b</sup>, Muhammad Z. Chauhan<sup>b</sup>, Ayman G. Elnahry<sup>c,d,\*</sup>

<sup>a</sup> Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL, USA

<sup>b</sup> Department of Ophthalmology, Harvey and Bernice Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA

<sup>c</sup> Department of Ophthalmology, Faculty of Medicine, Cairo University, Cairo, Egypt

<sup>d</sup> Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

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## ABSTRACT

**Purpose:** : To report a case of anterior ischemic optic neuropathy (AION) following COVID-19 vaccination and provide a systematic review of all published cases of optic neuropathy following COVID-19 vaccination.

**Methods:** : A systematic literature search was performed using PubMed and Ovid MEDLINE for cases of optic neuropathy following COVID-19 vaccination. Terms used in the search included “COVID-19 vaccination”, “optic neuropathy”, “optic neuritis”, and “ischemic optic neuropathy”. Titles and abstracts were initially screened then full texts of eligible studies were reviewed for data extraction. Only cases published in the English language, peer reviewed, and that included details on optic nerve involvement were included. All study types were eligible for inclusion.

**Results:** : Including our patient, a total of 10 patients (8 females) were identified as developing optic neuropathy following COVID-19 vaccination. Five patients (50.0%) were diagnosed with AION, while 4 (40.0%) were diagnosed with optic neuritis. One patient was diagnosed with papillitis and neuroretinitis. Three patients (30.0%) had bilateral involvement. Mean age of patients was 48.5±19.7 years. Mean time from vaccination to onset of ophthalmic symptoms was 6.5±6.4 days. Median (IQR) presenting visual acuity was logMAR 0.3 (0-1). For the 8 eyes which had both presenting and final follow-up visual acuity, median (IQR) presenting vision was logMAR 0.2 (0-0.7) and at final follow-up was logMAR 0 (0-0.05) (P=0.184).

**Conclusion:** : COVID-19 vaccination may result in optic neuropathy in the form of optic neuritis and ischemic optic neuropathy. Further studies are needed to determine the incidence, management, and prognosis of optic neuropathies associated with COVID-19 vaccination.

## Introduction

During 2021, vaccination against severe acute respiratory failure coronavirus 2 (SARS-CoV-2) emerged as a primary focus of public health efforts to mitigate the COVID-19 pandemic. Although generally found to be safe and effective in several large clinical trials, COVID-19 vaccines have been the subject of considerable scrutiny and analysis since the time of their introduction into the public sphere.

COVID-19 disease itself has impacted patient vision in numerous ways. Previous research has demonstrated a link between COVID-19 infection and ocular complications, direct or indirect. It has been reported that inflammatory conditions such as conjunctivitis, scleritis, orbital inflammatory disease, keratoconjunctivitis and retinal involvement may

occur in COVID-19 infection (Singh et al., 2021; Barros et al., 2021; Wang et al., 2021; Rokohl et al., 2021; Loffredo et al., 2020; Ahuja et al., 2020; Elhusseiny et al., 2021; Eleiwa et al., 2021; Eleiwa et al., 2021). In terms of indirect impact, Elhusseiny et al. and Salanha et al. reported on the impact of increased screen time and its relationship with eye strain and dry eye symptoms in pediatric and adult populations, respectively (Elhusseiny et al., 2021; Sawalha et al., 2020).

Since their introduction, COVID-19 vaccines have been associated with an assortment of ophthalmologic manifestations (Eleiwa et al., 2021; Ng et al., 2021). Separately, these events have included orbital (Bayas et al., 2021), corneal (Crnej et al., 2021; Phylactou et al., 2021), uveitic (Rabinovitch et al., 2021; ElSheikh et al., 2021), neuro-ophthalmologic (Elhusseiny et al., 2021; Elnahry et al., 2021), reti-

**Abbreviations:** AION, anterior ischemic optic neuropathy; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory failure coronavirus 2; MR, magnetic resonance; NAION, non-arteritic anterior ischemic optic neuropathy; OCT, optical coherence tomography.

\* Corresponding author at: Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, 10 Center Dr, Room 10D45, Bethesda, MD, 20892-2510, USA.

E-mail address: [ayman\\_elnahry@hotmail.com](mailto:ayman_elnahry@hotmail.com) (A.G. Elnahry).

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nal (Bohler et al., 2021; Book et al., 2021), and thrombotic events (Endo et al., 2021). Regarding neuro-ophthalmologic manifestations in particular, several cranial nerve palsies have been reported, including oculomotor (Pappaterra et al., 2021), abducens (Reyes-Capo et al., 2021), and facial (Bell's) nerve palsy (Khouri et al., 2021; Ozonoff et al., 2021; Shibli et al., 2021; Wong et al., 2021). To date, a limited number of reports have been made of optic neuropathy following COVID-19 vaccination (Elnahry et al., 2021; Garcia-Estrada et al., 2021; Girbardt et al., 2021; Leber et al., 2021; Pawar et al., 2021), and a few of them have been designated as anterior ischemic optic neuropathy (AION); three non-arteritic (NAION) (Garcia-Estrada et al., 2021; Girbardt et al., 2021; Nachbor et al., 2021), and one arteritic (AAION) (Maleki et al., 2021). In this report, we describe a case of ischemic optic neuropathy following vaccination with the BNT162b2 COVID-19 vaccination (Pfizer-BioNTech, New York, NY), discuss the pathophysiology for the development of optic nerve ischemia following vaccination, and provide a systematic review of all cases of optic neuropathy following COVID-19 vaccination published to date.

## Methods

A systematic literature search was performed using PubMed and Ovid MEDLINE on January 20, 2022, for cases of optic neuropathy following COVID-19 vaccination. Terms used in the search included "COVID-19 vaccination", "optic neuropathy", "optic neuritis", "papillitis", "retrobulbar optic neuritis", "ischemic optic neuropathy", and "neuroretinitis". Titles and abstracts were initially screened for identification of studies, then full texts were retrieved for eligible studies for review and possible inclusion in the final analysis. References of identified studies were also screened for eligible studies for inclusion. Only cases that were published in the English language, peer reviewed, and that included details on optic nerve involvement were included. There were no restrictions on study type, and all studies, including case reports and case series, were eligible for inclusion. Exclusion criteria included insufficient evidence or details of optic nerve involvement.

### Data extraction and statistical analysis

The following data was extracted from included studies: patient age, sex, vaccine type, vaccination dose, duration between vaccination and onset of ocular symptoms, presenting and final visual acuity, presenting symptoms, diagnoses, and treatment course. For continuous variables, mean was reported as mean  $\pm$  one standard deviation, while median was reported as median with interquartile range. Comparisons of populations were made, when appropriate, using a two-tailed two-sample t-test for means.  $P < 0.05$  was considered statistically significant.

## Results

Including our patient, a total of 10 patients (8 female, 2 male) were identified as developing optic neuropathy following COVID-19 vaccination (Table 1). Five patients (50.0%) were diagnosed with AION, while 4 patients (40.0%) were diagnosed with optic neuritis. One patient was diagnosed with papillitis in one eye and neuroretinitis in the other. Another two patients (30.0% in total) also had bilateral involvement, one with bilateral AAION and the other with bilateral optic neuritis. The mean age for all patients was  $48.5 \pm 19.7$  years (Range: 19-79 years). The mean age for AION patients was  $61 \pm 14.5$  years (Range: 40-79 years), while the mean age for optic neuritis patients was  $27.8 \pm 6.1$  years (Range: 19-32 years) ( $P = 0.004$ ). The mean time from vaccination to onset of ophthalmic symptoms was  $6.5 \pm 6.4$  days (Range: 0-21 days). For the 10 patients (13 eyes) found to have optic neuropathy following COVID-19 vaccination, the median (IQR) presenting visual acuity was logMAR 0.3 (0-1). For the 8 eyes which had both presenting and final follow-up visual acuity, the median (IQR) presenting visual acuity was logMAR 0.2 (0-0.7) and at final follow-up was logMAR 0 (0-0.05)

( $P = 0.184$ ). For the 4 cases with NAION (4 eyes), the median (IQR) presenting visual acuity was logMAR 0.45 (0.225-0.7), comparable to the 4 patients (5 eyes) with optic neuritis, who had median (IQR) presenting visual acuity of logMAR 0.4 (0-0.8).

## Case report

### Present illness

A 40-year-old male patient presented to us with acute-onset diminution of vision in his left eye of stationary course for 5 days. He also complained of an inferior visual field defect. Nine days earlier, he had received his first dose of the BNT162b2 COVID-19 vaccination (Pfizer-BioNTech, New York, NY), which was followed by mild constitutional symptoms including mild fever and myalgias which were treated with acetaminophen.

### Past illness

His past medical history included type 2 diabetes mellitus for 7 years treated by oral hypoglycemic drugs and diet. His last HbA1C was 7.8%.

### Relevant ophthalmic exam findings

Examination revealed a best corrected visual acuity of 20/20 in the right eye (OD) and 20/40 in the left eye (OS). There was a left relative afferent pupillary defect. External ocular exam, ocular motility and balance, intraocular pressure, and anterior segment examination was normal in both eyes. Posterior segment examination OS revealed a swollen, pale optic disc with blurred edges and splinter hemorrhages (Fig. 1A). Posterior segment exam OD was normal. Fluorescein angiography was performed and showed early leakage from the left optic disc with late staining and few microaneurysms (Fig. 1B). Optical coherence tomography (OCT) allowed quantitative analysis of disc edema (Fig. 2A). OCT angiography was done and showed peripapillary flow void areas OS indicating mild ischemia (Fig. 2B). Visual field testing revealed an inferior altitudinal field defect OS (Fig. 3) and normal visual field OD.

### Imaging

Magnetic resonance (MR) imaging of the brain and cervical spine with contrast as well as MR venography were unrevealing. Chest x-ray was normal.

### Laboratory testing

The patient underwent extensive laboratory investigations including complete blood count, erythrocyte sedimentation rate, C-reactive protein, angiotensin converting enzyme levels, interferon gamma release essays for tuberculosis, rapid plasma reagin, anti-nuclear antibodies, anti-dsDNA antibodies, anti-neutrophil cytoplasmic antibodies, and anti-aquaporin-4 antibodies which were all normal. SARS-CoV-2 PCR was negative. Lumbar puncture was performed and revealed a normal cerebrospinal fluid opening pressure with normal analysis.

### Outcome

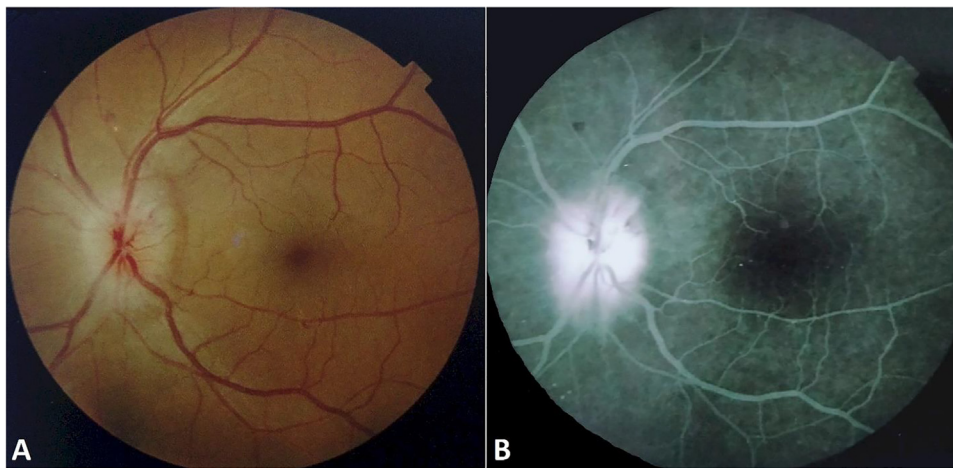
The patient was diagnosed with left anterior ischemic optic neuropathy secondary to COVID-19 vaccination. He was prescribed low dose aspirin and referred for more strict control of his blood sugar levels and cardiovascular systemic risk factors. Follow-up over 2 months revealed improvement of the optic disc swelling with pallor and minimal visual field improvement.

**Table 1**  
Summary of reports of optic neuropathies following COVID-19 vaccination.

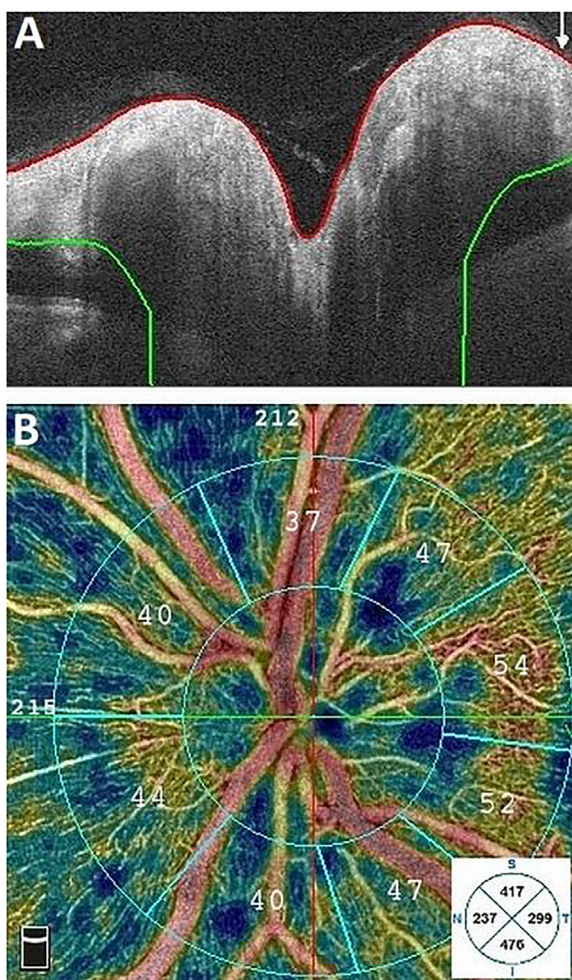
Author	Age	Sex	Vaccine	Time from Vaccine to Symptoms (days)	Presenting VA	Side	Manifestations	Outcome
Current Study	40	M	BNT162b2, #1	4	20/40	OS	Vision loss OS, with exam revealing RAPD OS and a swollen, pale optic disc with blurred edges and splinter hemorrhages. FA with early leakage OS with late staining, OCT with disc edema. <b>NAION</b> OS was diagnosed.	Control of systemic risk factors led to improvement of the optic disc swelling with pallor and minimal visual field improvement.
Elnahry et al. 2021	69	F	BNT162b2, #2	16	CF	OD	Blurry vision OU with immediate OS clearing but persistent blurring OD. Examination with optic nerve head edema (OD>OS) and RAPD OD on exam. RNFL imaging confirmed a diagnosis of <b>CNS inflammatory syndrome with papillitis and neuroretinitis</b> .	Significant improvement including decreased optic nerve swelling after 5 days of IV methylprednisolone.
	32	F	CoviShield, #1	4	20/20 20/30	OS OS	Blurred vision with superior field defect OS. Examination revealed left optic disc swelling and RAPD with decreased RNFL thickness. MRI was diagnostic of left <b>optic neuritis</b> .	Significant improvement including decreased optic nerve swelling after 3 days of IV methylprednisolone followed by PO prednisone.
Leber et al. 2021	32	F	Corona Vac, #2	0	20/200	OS	Rapidly progressive worsening vision and pain with EOM OS. Examination revealed RAPD OS and disc swelling OD and OS. Labs revealed thyroiditis and MRI revealed bilateral <b>optic neuritis</b> .	Improvement in symptoms and vision following 5 days of IV methylprednisolone 1g and intravenous corticosteroid therapy to reduce TSH level.
Maleki et al. 2021	79	F	BNT162b2, #2	2	20/20	OD	Bilateral sudden loss of vision, OD>OS, with 3+ afferent pupillary defect OD. OCT, FA, and ICG consistent with generalized disc pallor OD and inferior pallor OS, consistent with bilateral <b>arteritic anterior ischemic optic neuropathy (AAION)</b> .	Patient was initiated on subcutaneous tocilizumab 162mg weekly. Results were NR.
					20/1250	OD		
Pawar et al. 2021	28	F	NR	21	20/40 20/120	OS OS	Sudden vision loss OS, with examination revealing mild blurring of the optic disc margin. MRI was consistent with <b>optic neuritis</b> .	Resolution of symptoms after IV methylprednisolone followed by PO steroid course.
Nachbor et al. 2021	64	F	BNT162b2, #1	6	20/80	OS	Acute, painless, unilateral vision loss with superior sectoral optic disc edema OS after 1st dose. After 2nd dose, VA was CF with persistent APD OS. RNFL OCT showed diffuse thickening OS. <b>NAION</b> was diagnosed.	Improvement of symptoms with PO prednisone 1mg/kg/day over one week. Resolution of optic disc edema OS and diffuse pallor of optic nerve OS.
Tsukii et al. 2021	55	F	BNT162b2, #1	3	20/20	OD	Visual disturbance with RAPD OD. Fundoscopy revealed diffuse optic disc swelling OD which was confirmed on OCT. Goldmann visual field testing revealed an inferior visual field defect OD. A diagnosis of <b>NAION</b> was made.	No treatment was initiated. At a two-month follow-up, vision remained normal and there was diffuse pallor of the right eye.
Garcia-Estrada et al. 2021	19	F	Ad26.COV2.S, #1	7	20/20	OD	Ocular pain and vision loss OS, with examination revealing amaurosis, APD, and papillitis, all OS. Diagnosis of <b>optic neuritis</b> was made.	Resolution of symptoms and papillitis with five days of IV methylprednisolone followed by a PO prednisolone taper.
Girbardt et al. 2021	67	M	Vaxveria, #1	2	20/200	OD	Decreased vision and scotomas OD with examination revealing an elevated, congested optic nerve head with surrounding intraretinal hemorrhages and cotton-wool spots and probable intraretinal fluid. OCT consistent with <b>NAION</b> .	NR

*Note.* VA = visual acuity, OD = right eye, OS = left eye, OU = both eyes, RAPD = relative afferent pupillary defect, RNFL = retinal nerve fiber layer, CNS = central nervous system, IV = intravenous, PO = oral, OCT = ocular coherence tomography, ESR = erythrocyte sedimentation rate, NR = not reported. #1 indicates that the event occurred following the first dose of vaccination, while #2 indicates that it occurred following the second dose.





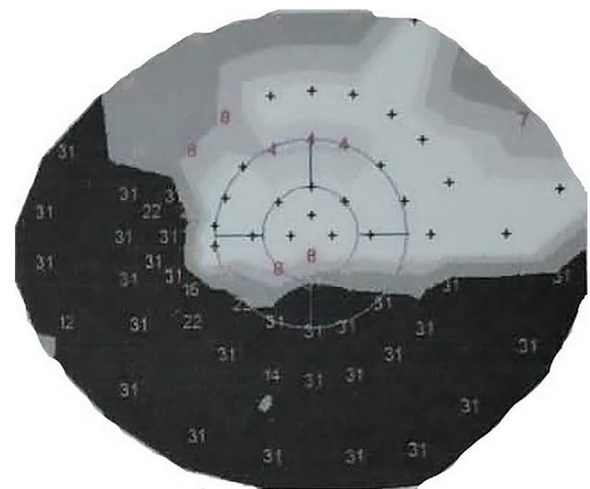
**Fig. 1.** At presentation, fundus examination of the left eye revealed optic disc swelling with pallor together with blurred edges and splinter hemorrhages (A). Fluorescein angiography revealed optic disc leakage with staining and scattered capillary microaneurysms (B).



**Fig. 2.** OCT at presentation revealed left optic disc elevation with retinal nerve fiber layer thickening (A). OCT angiography showed peripapillary flow void areas with decreased vascular density indicating mild ischemia (B) [insert showing corresponding retinal nerve fiber layer thickness in each peripapillary quadrant].

**Discussion**

Anterior ischemic optic neuropathy is an important cause of vision loss in adults divided into arteritic (AAION) and non-arteritic (NAION) categories. Previously, the incidences per 100,000 individu-



**Fig. 3.** Visual field testing of the left eye at presentation showed an inferior altitudinal field defect with enlargement of the blind spot.

als for NAION and AION, respectively, were reported as 2.30 and 0.36 (Hattenhauer et al., 1997). In terms of pathogenesis, AAION results from inflammatory changes and thrombosis of the short posterior ciliary arteries, which causes infarction of the optic nerve head (Hayreh, 2009, 1997). AAION is an ophthalmic emergency and treatment with systemic corticosteroids is standard (Hayreh, 2009). NAION is typically idiopathic (Hayreh, 2009), though there is an association with sleep apnea syndrome (Wu et al., 2016; Aptel et al., 2015; Mojon et al., 2002), medications including interferon alpha and sildenafil (Sharif et al., 2017; Purvin, 1995; Gupta et al., 2002), and the presence of optic disc drusen (Purvin et al., 2004; Newman and Dorrell, 1996; Elnahry, 2019). It commonly presents with an altitudinal field defect. Post-vaccination NAION has also been previously reported following influenza vaccination (Kawasaki et al., 1998; Manasseh et al., 2014).

Previous studies have demonstrated a female predominance of incident optic neuritis, with one large study in the United Kingdom demonstrating that 69.4% of new cases over 22 years were in females (Braithwaite et al., 2020). However, Lee et al. previously demonstrated in a cohort of diabetic patients that male gender increases the risk of developing AION by 32% (Lee et al., 2011).

Optic neuropathy has been reported rarely in the literature following vaccination against COVID-19. Only a total of 8 reports on 9 patients have been published to date, 8 (88.9%) of whom were females (Table 1). The currently reported case is the second case of post-COVID-19 vaccination optic neuropathy in a male, and the first case of post-BNT162b2

COVID-19 vaccine (Pfizer-BioNTech) optic neuropathy in a male. In a relatively large multinational study of ocular inflammatory events following COVID-19 vaccination, 70 patients were reported to develop ocular inflammation within 14 days of COVID-19 vaccination, but only 2 (2.9%) patients were diagnosed with optic neuritis (Testi et al., 2022). This indicates that the incidence of optic neuropathy following COVID-19 vaccination could be low. The latter study, however, did not provide specific details on cases with optic nerve involvement. Elnahry et al. previously reported on a pair of patients, one of whom was a 69-year-old woman who developed CNS inflammatory syndrome with neuroretinitis and papillitis following vaccination with the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech), and the other of whom was a 32-year-old woman who developed retrobulbar optic neuritis following vaccination with the CoviShield COVID-19 vaccine (AstraZeneca/University of Oxford, Cambridge, UK) (Elnahry et al., 2021). Only the patient who developed retrobulbar optic neuritis demonstrated significant improvement with IV methylprednisolone. Elsewhere, Leber et al. (Leber et al., 2021), Pawar et al. (Pawar et al., 2021), and Garcia-Estrada et al. (Garcia-Estrada et al., 2021) all reported cases of optic neuritis in women aged 32, 21, and 19, respectively. All three patients demonstrated improvement with IV methylprednisolone therapy.

The remaining cases reported in the literature were cases of AAION or NAION. Nachbor et al. reported on a 64-year-old woman who developed acute, unilateral vision loss 6 days after receiving her first dose of the BNT162b2 vaccine (Nachbor et al., 2021). Examination revealed superior sectoral optic disc edema at that time. While waiting for ophthalmologic follow-up, the patient received her second dose of the vaccine three weeks after her first dose. She awoke the next morning with painless, near-complete vision loss, with visual acuity on presentation being counting fingers at 2 feet. Examination revealed peripapillary splinter hemorrhages in the optic nerve OS and Humphrey visual field testing revealed dense constriction OS. OCT showed diffuse thickening of the retinal nerve fiber layer OS. All examination findings were normal OD. The patient was diagnosed with NAION and treated with one week of oral prednisone 1 mg/kg/day. At a six-week follow-up, visual acuity was 20/100 OS with resolved optic disc edema replaced by diffuse pallor, consistent with NAION.

Tsukii et al. reported on a 55-year-old woman who presented with visual field disturbance which developed three days after the first dose of the BNT162b2 vaccine (Tsukii et al., 2021). Although VA was 20/20 OD and OS at presentation, funduscopy revealed diffuse optic disc swelling and Goldmann visual field testing revealed an inferior visual field defect. A diagnosis of NAION was made. The patient received no treatment. At follow-up, vision remained unchanged and there was only residual diffuse optic nerve pallor.

We have previously described that an autoimmune mechanism underlies the development of optic neuropathies following vaccination (Eleiwa et al., 2021). Previously, Stübgen et al. reported that there is no long-term risk of developing optic neuropathy following vaccination, but that the presence of adjuvants contributes to the process (Stubgen, 2013). However, in the absence of adjuvants in several of the COVID-19 vaccines, this explanation is insufficient (Elnahry et al., 2021). Clinically, it is challenging to differentiate between AION and optic neuritis, and the diagnosis is usually based on both clinical impression and multimodal imaging findings (Levin et al., 1996; Elnahry and Elnahry, 2020; Raina et al., 2020). Some differentiating features include an older age of onset, altitudinal visual field defect, and worse visual outcome in patients with AION which was also found in our study, however, these features cannot confidently distinguish between both conditions (Levin et al., 1996). Furthermore, the pathophysiology (and treatment) of both types of optic neuropathies is postulated to be different and it is not currently clear why some patients develop AION while others develop optic neuritis following vaccination. Documented risk factors for NAION include diabetes, small cup-to-disc ratio, hyperlipidemia, and hypertension and it is likely that the development of NAION is a multifactorial process which includes pre-existing structural compromise of

the optic nerve (Hayreh, 2009; Behbehani et al., 2021; Tsai et al., 1998; Elhusseiny et al., 2022).

Our patient had the risk factor of type 2 diabetes, and the transient pro-inflammatory and hypercoagulable state following vaccination may have led to the development of AION. Nachbor et al. also endorsed this hypothesis for their patient with NAION (Nachbor et al., 2021). Tsukii et al. also proposed that neutralizing antibodies directed against SARS-CoV-2 spike proteins after vaccination may cross-react with proteins in the retinal vasculature and retinal pigment epithelial cells, a mechanism also endorsed by Maleki et al. (Maleki et al., 2021, Tsukii et al., 2021). It is conceivable that both processes may have played a role in the development of AION in our patient. Another possible explanation for the development of post-vaccination optic neuropathy that could link the occurrence of inflammation and ischemia was recently elucidated by Francis and colleagues in patients developing optic neuropathy in association with immune checkpoint inhibitors used for cancer treatment (Francis et al., 2020). These immunotherapy agents, like vaccines, enhance the adaptive immune response which may result in a range of adverse inflammatory events including ophthalmic and neurologic phenomenon (Francis et al., 2020). Francis and colleagues indicated that this class of drugs may result in optic papillitis, a specific type of optic neuritis that involves inflammation of the optic nerve head, leading to ischemia of the optic nerve head and a picture similar to AION (Francis et al., 2020; Francis et al., 2020).

In conclusion, several cases of optic neuropathy have been reported following the administration of COVID-19 vaccines. Nevertheless, the benefits of vaccination against SARS-CoV-2 have been substantial and probably outweigh the associated risks. Furthermore, most of the reported cases were self-limiting and had a good prognosis with available treatments. Future studies should aim to evaluate for risk factors, both ocular and systemic, which may contribute to the development of optic neuropathy after COVID-19 vaccination, and to elucidate the mechanisms underlying the development of these conditions in order to optimize their follow-up and treatment.

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## Relevant disclosures

The authors have no relevant financial disclosures.

## Consent for publication

The patient signed a written informed consent to publish this information and associated images.

## Ethics approval and consent to participate

This report was approved by Cairo University Research Ethics Committee and followed the tenets of the Declaration of Helsinki. No consent to participate was required as this was retrospective study, but consent was obtained from the patient to publish this information and associated images.

## Authors' contributions

AH and AME drafted the manuscript and reviewed the literature. AGE diagnosed and treated the patient and revised the manuscript. All authors read and approved the final version of the manuscript.

## Data availability

Data used in this study is available from corresponding author upon reasonable request.



## 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.

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