ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Review Article

Impact of COVID-19 Vaccines on Eye

Shalini Kumari[1]*, Raj Anand[2], Bhumika Sambyal[3], Yudhyavir Singh[4], Pradeep Rangappa[5] and Simant Kumar Jha[3]

[1]*Department of Ophthalmology, Alfalah School of Medical Science and Research Centre, Faridabad, India*

[2]*Department of Ophthalmology, EYE 7 Hospital, New Delhi, India*

[3]*Department of Critical Care Medicine, PSRI, New Delhi, India*

[4]*Department of Anaesthesiology and Critical Care, AIIMS, New Delhi, India*

[5]*Department of Critical Care Medicine, Manipal Hospital, Bangalore, India*

***Corresponding Author:** Shalini Kumari, Department of Ophthalmology, Alfalah School of Medical Science and Research Centre, Faridabad, India.

Received: January 17, 2022; **Published:** February 28, 2022

DOI: 10.31080/ecop.2022.13.00877

Abstract

The COVID-19 pandemic has led to development and roll-out of several vaccines world-wide at unprecedented pace. Various adverse events of COVID-19 vaccines on eye have also been reported.

This review has been undertaken to spread awareness among general physicians and ophthalmologists about the possible adverse effects in the eye following COVID-19 vaccination.

A literature search was performed on 7th January 2022 through PUBMED and Google scholar for publications on ocular adverse effects after COVID-19 vaccination.

One retrospective cohort study, two brief communications, one photo essay, four retrospective case series, fourteen case reports, and five letters to editor were included.

Ocular manifestations most commonly appear in the posterior segment of eye i.e. uvea and retinal vasculature, and in cranial nerves innervating the eye. Other manifestations are also seen on eyelid, cornea and ocular surface.

The incidence rate of these manifestations is quite low after COVID-19 vaccinations. Most of these effects are transient and resolve without any sequalae.

The risk of having ocular adverse effects after taking COVID-19 vaccine is far less in comparison to the benefits of it in curbing the pandemic.

Keywords: *COVID-19; SARS-COV-2; Coronavirus; Vaccination; Ocular Adverse Effects; Uveitis; Eyelid; Cornea; Ocular Surface; Retinopathy; Nerve Palsy; Thrombosis*

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2; AAION: Arteritic Anterior Ischemic Optic Neuropathy; AMN: Acute Macular Neuroretinopathy; AZOOR: Acute Zonal Occult Outer Retinopathy; CSCR: Central Serous Chorioretinopathy; CNV: Choroidal Neovascularization; DSAEK:

Descemet Stripping Automated Endothelial Keratoplasty; DMEK: Descemet Membrane Endothelial Keratoplasty; ITP: Immune Thrombocytopenia; NAION: Non-Arteritic Anterior Ischemic Optic Neuropathy; MRI: Magnetic Resonance Imaging; MEWDS: Multiple Evanescent White Dot Syndromes; N: No of Cases; OCT: Ocular Coherence Tomography; PKP: Penetrating Keratoplasty; PAMM: Paracentral Acute Middle Maculopathy; RVO: Retinal Vein Occlusion; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SOVT: Superior Ophthalmic Vein Thrombosis; VKH: Vogt-Koyanagi-Harada Disease; VITT: Vaccine Induced Thrombocytopenic Thrombosis; VZV: Varicella Zoster Virus

Introduction

Corona virus disease, COVID-19, caused by SARS-CoV2 virus has lead to a pandemic with unprecedented effects on human lives and lifestyle. It's grippling effect on human civilization has forced scientific community to work at breathtaking speed.

Following vaccines have been approved so far globally on emergency basis. BNT162b2 is a mRNA vaccine produced by Pfizer-BioNTech.

ChAdOx1(AZD1222) is a non-replicating viral vector vaccine developed by AstraZeneca, Serum Institute of India.

BBIBP-CorV is an inactivated virus COVID -19 vaccine developed by Sinopharm. Few other vaccines approved are as follows:

- Sputnik V is an adenoviral-based vaccine produced in Russia initially. mRNA-1273 is developed by Moderna Inc.
- Ad26.COV2.S is a non-replicating viral vector vaccine developed by Janssen, Johnson and Johnson. BBV152 (COVAXIN) is an inactivated vaccine developed by Bharat Biotech, India.
- CoronaVac is an inactivated vaccine produced by Sinovac in China.

The latest vaccine added in this list, NVX-CoV2373 is a protein subunit vaccine, developed by Novavax. The efficacy of Vaccines have been found to be 94% - 95% [1-3].

As the data from all over world is pouring, several adverse events, including ophthalmic manifestations, of these vaccines are being reported.

In this review, we analyze reported ophthalmic side effects of these vaccines.

Methods

For this review, a literature search was done for relevant articles through a computerized search on PubMed and Google scholar on 7th January 2022.

The following keywords: 'COVID-19', 'SARS-COV-2', 'coronavirus', 'vaccination', 'ocular adverse effects', 'uveitis', 'eyelid', 'cornea', 'ocular surface', 'retinopathy', 'nerve palsy', thrombosis' were searched.

Articles were screened for relevance. Few reference articles of these were further looked for thorough information.

This search was made for articles published worldwide in English language.

Study	Type	Vaccine	Dose	Duration between Vaccine and Ocular symptoms [Days]	Diagnosis	No of Cases [N]
Austria., *et al*. [4]	Letter to editor	BNT162b2	1st/ 2nd	1-2	Eyelid edema and erythema	[N = 3]
Mazzatenta., *et al*. [5]	Letter to editor	BNT162b2	1st/ 2nd	10-25	Purpuric lesions on eyelid	[N = 3]
Rehman., *et al*. [8]	Case report	ChAdOx1	NA	3-28	Herpes zoster ophthalmicus	[N =2]
Parmar., *et al*. [10]	Case report	ChAdOx1	1st	2	Acute graft rejection in a repeat PKP	[N=1]
Nioi., *et al*. [14]	Case report	BNT162b2	1st	13	Dual graft rejection in post-PK in 6months Follow up	[N=1]
Ravichandran., *et al*. [15]	Photo assay	ChAdO×1	1st	21	Corneal graft rejection in PKP	[N = 1]
Crnej., *et al*. [17]	Letter to editor	BNT162b2	1st	7	Acute endothelial rejection after DMEK	[N = 1]
Rallis., *et al*. [18]	Brief Communication	BNT162b2	1st	3	Corneal graft rejection in PKP	[N=1]
Wasser., *et al*. [19]	Case report	BNT162b2	1st	14	Acute corneal graft rejection in PKP	[N=2]
Papasavvas., *et al*. [20]	Case report	BNT162b2	2nd	42	Reactivation of VKH	[N= 1]
Testi., *et al*. [21]	Case series	BNT162b2 ChAdOx1 m RNA-1273 BBIBP-CorV BBV152	1st/2nd	1- 14	Anterior uveitis Posterior uveitis Scleritis	[N=70]
Pan., *et al*. [27]	Case report	Inactivated COVID-19 Vaccine	NA	5	Bilateral choroditis	[N=1]
Bolletta., *et al*. [28]	Retrospective Case Series	BNT162b2 ChAdOx1 m RNA-1273 Ad26COV2.S	1st/2nd	1-30	Uveitis and other complications	[N=34]
Maleki., *et al*.[30]	Case report	BNT162b2 mRNA-1273	2nd	2-10	Bilateral AAION and AZOOR	[N=2]
Renisi., *et al*. [34]	Case report	BNT162b2	2nd	14	Anterior uveitis	[N=1]

Bøhler., *et al.*[36]	Brief Communication	ChAdOx1	1st	2	AMN	[N=1]
Vinzamuri., *et al.* [38]	Case report	ChAdOx1	2nd	30	PAMM and AMN	[N=1]
Lee., *et al.* [39]	Letter to Editor	ChAdOx1	1st	2	Disc edema and CSCR	[N=1]
Girbardt., *et al.* [41]	Retrospective Case series	BNT162b2 ChAdOx1 m RNA-1273	1st/2nd	2-12	Retinal vascular occlusion Venous stasis retinopathy NAION Nerve fiber layer infarction Bilateral AMN	[N=6]
Pichi., *et al.* [42]	Retrospective Case series	BBIBP-CorV	1st	1-10	Episcleritis Anterior scleritis AMN PAMM Forme fruste of CSR	[N=7]
Colella., *et al.* [43]	Letter to editor	BNT162b2	1st	5	Bell's palsy	[N=1]
Shibli., *et al.* [44]	Retrospective Cohort Study	BNT162b2	1st/2nd	1-30	Bell's palsy	
Pawar., *et al.* [45]	Case report	ChAdOx1	1st	7	Abducen's nerve palsy	[N=1]
Estrada., *et al.*[46]	Case report	Ad26COV2.S	1st	7	Optic Neuritis	[N=1]
Tsukii., *et al.* [50]	Case report	BNT162b2	1st	7	NAION	[N=1]
Bayas., *et al.* [51]	Case report	ChAdOx1	1st	10	Bilateral superior ophthalmic vein thrombosis, ITP and Ischemic stroke	[N=1]
Lui., *et al.* [52]	Case report	BNT162b2	2nd	35	Grave's Disease	[N=1]

Results

Most of the adverse effects in the eyes post Covid vaccination are secondary to the immune dysregulation triggered by the antigens associated with respective vaccines. Depending on the clinical site, patients predisposition to a particular immune disorder and some yet unknown factors these adverse reactions have varied clinical presentations in different patients.

Eyelid swelling

Three patients presented with unilateral lid edema and erythema, more in upper than lower, on day 1 or 2 following first or second dose of Pfizer COVID -19 mRNA vaccine [4]. They had no other associated ocular, adnexal, or systemic findings. These symptoms resolved fully in 1 - 2 days without any sequalae with observation, antihistamines, and oral steroids, respectively.

A hypothesis was proposed that reactivation of an autoimmune response was triggered by the mRNA vaccine which lead to these symptoms.

Eyelid purpuric lesions

Three cases of localized purpuric and ecchymotic eyelid reaction after BNT162b2 mRNA COVID-19 vaccine was reported [5]. The lesions appeared after a median of 14 days post injection. There were no symptoms. Spontaneous clearing occurred after 10 - 15 days.

Both BNT162b2 mRNA and ChAdOx1 adenovirus vaccine are associated with several new potential adverse events. Symptomatic and asymptomatic thrombocytopenia have also been reported with BNT162b2 vaccine [6]. Thrombotic thrombocytopenic disease is a life threatening condition. The heparin-induced thrombocytopenia resembles it. This condition has been attributed to ChAdOx1. A new term has been coined for this, vaccine-induced thrombocytopenic thrombosis (VITT) [7].

A very mild and localized form of vaccine-induced microangiopathy could be the reason behind the appearance of purpuric and ecchymotic lesions on eyelids after receiving BNT162b2 mRNA vaccine.

Herpes zoster ophthalmicus

Two young immunocompetent individuals developed HZO after receiving a live vaccine, ChAdOx1, Covishield vaccine (developed by Oxford-AstraZeneca and manufactured in India by Serum Institute of India). The time duration between receiving the injection and appearance of symptoms was 3 days and 28 days respectively. Involvement of tip of nose and occurrence of HZO on the ipsilateral side of the vaccinated arm were seen in both patients. Their symptoms responded to the standard treatment regimen. The authors attributed the reactivation of latent VZV to immune dysregulation after vaccination in both these immunocompetent cases as a direct causal relationship could not be established [8].

Previous case reports are of individuals at higher risk of VZV reactivation due to systemic comorbidities, advanced age, or autoimmune disorders [9].

Corneal graft rejection

A patient complained of diminution of vision in left eye within 2 days of COVID-19 vaccination (ChAdOx1, viral vector vaccine). He had a history of repeat penetrating keratoplasty of same eye. A diagnosis of acute graft rejection post vaccination was made [10]. An improvement of visual acuity and corneal graft clarity was achieved with topical and systemic immunosuppression therapy.

The immune privilege of cornea is attributed to its avascularity. The corneal host bed lacks lymph vessels. Major histocompatibility complex (MHC) class II antigen-presenting cells are absent [11]. This is the basis of acceptance of the allogenic donor tissue by recipient corneal bed without rejection. However, vaccination triggers increased generalized immunological response. Subsequent rejection of allograft follows due to immunological reaction towards it. Induction of Class II MHC complex antigens in all layers of the cornea is seen post vaccination. The similar pathomechanism of rejection is seen with influenza vaccine [12,13].

A 44-year-old woman presented with features of acute corneal graft rejection after 25 years of corneal transplantation for keratoconus. She had received BNT162b2 vaccine (Comirnaty, BioNTech/Pfizer) 13 days ago. She was put under regular follow up. In a span of 6 months, the inflammation in cornea appeared twice. A diagnosis of biphasic corneal graft rejection was established [14]. Supplementation of Vitamin D was given in view of deficiency in this case. She was put on standard regimen of topical therapy as well.

This case highlights the possibility of dual corneal graft rejection post vaccination, concomitant vitamin D deficiency, immunomodulatory role of vitamin D, need of longer follow up in corneal graft rejection cases, and risk-benefit ratio and timing of second dose of vaccination. Authors proposed preventive check and integration of vitamin D before the vaccine administration.

A 62-year-old man complained of congestion and reduced vision in his right eye for 5 days. He had taken his first dose of ChAdO×1, COVID-19 vector vaccine, 3 weeks ago. He had a history of childhood corneal scar in his right. Penetrating keratoplasty surgery was done for the same 2 years ago. He had no other local ocular factors for precipitating a graft rejection. After establishing a diagnosis of corneal graft rejection, he was put on standard regimen for the same [15].

It has been proposed to increase dosage of topical steroids in cases with corneal grafts before they opt for any type of COVID-19 vaccination [16].

A 71-year-old male patient had a DMEK procedure of the right eye for endothelial decompensation post phacoemulsification surgery. He had history of coronary artery disease, high blood pressure and smoking. He had no complaints for five months post-surgery. Afterwards, he got his first shot of the BNT162b2 mRNA vaccine. After 7 days, he suddenly developed painless diminution of vision in his right eye. Acute endothelial graft rejection was diagnosed. He was put on topical steroid, dexamethasone, 2 hourly and oral antiviral, valacyclovir 1000 mg TID [17].

A 68-year-old lady underwent bilateral lamellar Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) procedure. He was earlier diagnosed with Fuchs' corneal endothelial dystrophy. Repeat penetrating keratoplasty (PKP) for failed DSAEK was done in October 2020 in left eye. She presented with pain, redness and rapid deterioration of vision in left eye for one day after receiving first dose of mRNA based BNT162b2 COVID-19 vaccine four days ago. Treatment for acute corneal graft rejection was started. Interestingly, corneal graft rejection was seen only in the left eye though she had bilateral corneal transplant history. Authors attributed this to the more recent and re-do surgery in left eye. In view of association between COVID-19 vaccination and graft rejection, a time gap of 3 - 6 months between 2nd dose and elective corneal transplant was suggested [18].

Two more patients with history of penetrating keratoplasty for keratoconus were noted to have acute corneal graft rejection 2 weeks after receiving a first dose of the BNT162b2 mRNA vaccine. Both patients responded to hourly dexamethasone 0.1% and oral prednisolone 60 mg per day. Both patients had undergone repeat PKP for previous graft failure in affected eye [19].

Uveal tissue inflammation

The following are the proposed pathways of pathomechanism of uveal tissue inflammation post SARS-CoV-2 vaccination: (1) uveal peptides and vaccine peptide fragments similarities leading to molecular mimicry (2) antigen-specific cell and antibody-mediated hypersensitivity reactions, (3) adjuvants in the vaccines causes inflammatory damage which stimulates innate immunity through endosolic or cytoplasmic nucleic acid receptors [22-26].

Reactivation of VKH

A 43- year-old woman had an episode of severe initial-onset VKH (Vogt Koyanagi Harada) disease. Steroids and non-steroidal immunosuppressants (mycophenolic acid and cyclosporine) were used to control the disease process. Additional infliximab infusions were also

used as ICGA showed the persistence of subclinical choroiditis. There was no inflammation, no subclinical disease and absence of sunset glow fundus under infliximab therapy alone for last 6 years. However, the second dose of Pfizer anti-SARS-CoV-2 vaccination led to severe resurgence after 6 weeks with exudative retinal detachments. Oral prednisone (1 mg/kg) and a new loading scheme of infliximab therapy were started to control the disease process [20].

70 patients, at 40 multinational centers over a duration of 3 months, complained of ocular inflammatory events within 14 days after COVID-19 vaccination. 41 cases of anterior uveitis, 9 cases of posterior uveitis and 7 cases of scleritis were noted. The mean time between onset of inflammation and 1st dose of vaccination was 5 days while it was 6 days in case of 2nd dose. Previous episodes of ocular inflammatory events were seen in 36 patients. Topical corticosteroids were used in most of the patients. 65 patients had unaffected final vision whereas 5 patients had reduced visual acuity. Nummular corneal lesion in one patient, cystoid macular oedema in two patients and macular scarring in two patients were seen. Although the causality is not proved, a temporal association is suggested between vaccination and ocular events. Most of the inflammatory episodes were mild and visual outcome was good. The most common ocular inflammatory event observed after COVID-19 vaccination was anterior uveitis. More than 50% of these patients had similar episodes in past. The Pfizer vaccine was most commonly associated with these inflammatory events. This association was probably related to the number of the administered doses [21].

Bilateral posterior uveitis (Choroiditis)

A 50-year-old woman presented with bilateral blurred vision and visual distortion 5 days after vaccination with the inactivated COVID-19 vaccine. She was diagnosed with bilateral posterior uveitis(choroiditis). Upon administration of local and systemic steroids, the symptoms improved markedly 5 weeks later [27].

Reactivation of prior infection/inflammation

At an ocular immunology unit in Italy, episodes of ocular inflammation and reactivation in patients after COVID-19 vaccination between January 2021 and October 2021 were analyzed. 3 herpetic keratitis, 2 anterior scleritis, 5 anterior uveitis (AU), 2 pars planitis, 3 multiple evanescent white dot syndromes (MEWDS), 2 Vogt-Koyanagi Harada (VKH) disease reactivations, 3 toxoplasma retinochoroiditis, 2 retinal vasculitis, 1 bilateral panuveitis in new-onset Behçet's disease, 1 acute macular neuroretinopathy (AMN), 5 retinal vein occlusions (RVO), 3 activations of quiescent choroidal neovascularization (CNV) secondary to myopia or uveitis, 1 central serous chorioretinopathy (CSCR), and 1 non-arteritic ischemic optic neuropathy (NAION) were recorded. Mean duration between vaccination and onset of ocular complication was 9.4 days (range 1 - 30 days). 23 cases post BNT162b2 mRNA vaccination, 7 post ChAdOx1 nCoV-19 vaccination, 3 post mRNA-1273 vaccination, and 1 post Ad26.COV2 vaccination were noted. Most of the patients developed ocular complications after the second dose of the vaccine [28].

Reactivation of herpetic kerato-uveitis

Patients with previous herpetic keratitis or kerato-uveitis can have reactivation of the disease following COVID-19 vaccination. It is proposed that herpes reactivation is due to alteration in the immune status. Lymphocyte exhaustion is a type of altered immunological profile. Here comes the role of prophylactic antiviral therapy with oral valacyclovir in high-risk patients with several previous episodes of herpetic uveitis [29].

AZOOR and AAION

An association between the mRNA COVID-19 vaccination and ocular inflammatory disease of autoimmune etiology was highlighted by following two cases.

A 79-year-old female complained of sudden loss of vision in both eyes. She received the second shot of recombinant mRNA vaccine (Pfizer) 2 days ago before loss of vision. A diagnosis of bilateral AAION was established after temporal artery biopsy. She was put on subcutaneous tocilizumab 162 mg weekly. Her ESR, CRP, and IL-6 was monitored regularly. A 33-year-old healthy female, after receiving the second shot of recombinant mRNA vaccine (Moderna) 10 days ago, turned up with a progressive nasal field defect in left eye, and flashes in both eyes. High ESR (25) and CRP (19) levels were recorded on laboratory investigation. A diagnosis of unilateral Acute zonal occult outer retinopathy (AZOOR) in her left eye was established. An intravitreal dexamethasone was implanted in the left eye [30]. Several pro-inflammatory pathways can be activated by mRNA vaccines before translation. Type I interferon, nuclear translation of the transcription factor and nuclear factor (NF)- kB are included in this activated pathways [31]. The basis of immune-mediated diseases is the activation of these pathways, more so in genetically predisposed patients such as young females [32,33].

Anterior uveitis

A 23-year-old male presented with red eye, pain and photophobia and diminution of vision in left eye after receiving his second dose of BNT162b2 COVID-19 vaccine 14 days ago. The ocular inflammatory signs disappeared and vision was completely restored after a 10 day treatment course of topical steroids and cycloplegic eye drops [34].

Molecular mimicry, inflammatory damage induced by adjuvants such as aluminium salts, direct viral infection (applicable to live and attenuated vaccines) are different mechanisms hypothesized for aforementioned events [35].

Retinopathy

AMN

A 27-year-old female complained of disturbances in vision in her left eye. She had flu-like symptoms on the day of vaccination with the first shot of the AstraZeneca vaccine. Resolution of symptoms happened 2 days later. It was followed by appearance of a left paracentral scotoma. Her best-corrected visual acuity was 20/20. She was on oral contraceptive (combined ethinylestradiol and desogestrel). A paracentral scotoma in the upper temporal quadrant of left eye was noted on threshold perimetry. Fundus examination of the left eye showed a teardrop-shaped macular lesion nasal to the fovea. It was better depicted on OCT. A diagnosis of acute macular neuroretinopathy (AMN) was established [36]. Ischemia in the deep retinal capillary plexus or choriocapillaris is the potential pathophysiological mechanism although the exact cause is unknown [37]. Recent infection, febrile illness and use of oral contraceptives are dominant associated factors.

PAMM and AMN

A 35-year-old male patient complained of blurred vision and black spots in visual field. He had the second dose of Covishield vaccine 1 month ago. His vision was 6/6 in both eyes. On examination, normal findings were seen in both anterior and posterior segments. Optical coherence tomogram depicted multiple hyperreflective lesions in the nerve fiber layer with back shadowing. OCT further showed hyperreflective spots in the ganglion cell layer and an intact inner segment/outer segment junction and outer plexiform layer with focal loss of external limiting membrane. A diagnosis of paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN) was established. He was put under observation [38]. It was hypothesized that the development of PAMM and AMN was due to vasculitic changes leading to ischemia of deep capillary plexus.

Disc edema and CSCR

A 41-year-old female complained of blurred vision in the right eye and a defect in inferior visual field in the left eye. She had her first COVID-19 vaccine (Vaxzevria) 2 days ago. She had no systemic disease. Vision was 20/20 and 20/30 in right and left eye respectively.

Disc edema in right eye and a dome-shape serous detachment over the upper arcade in the left eye were detected on fundus examination and FFA. With a diagnosis of idiopathic optic disc edema in right eye and central serous chorioretinopathy in left eye, she was put under regular follow-up without any invasive treatment. A complete resolution was seen in both eyes at 3 months follow-up [39].

Retinal vascular events

6 patients reported different retinal vascular events after receiving vaccination with the mRNA vaccine Comirnaty® (BioNTech®), the mRNA vaccine Spikevax® (Moderna®) and the adenoviral-vectored vaccine ChAdOx1 nCoV-19 (AstraZeneca®).

A 38-year-old healthy male patient was diagnosed with branch retinal arterial occlusion 4 days after receiving his shot of Comirnaty®.

An 81 year old female patient presented with combined arterial and venous occlusion in her right eye 12 days after the second shot of Comirnaty®.

A 40-year-old male patient presented with venous stasis retinopathy in his left eye 5 days after his first shot of Comirnaty®.

A 67-year-old male presented with non-arteritic anterior ischemic optic neuropathy in his right eye 4 days after getting the first shot of Vaxzevria®.

A 32-year-old man was diagnosed with circumscribed nerve fiber infarction 2 days after receiving the second shot of Spikevax®.

A 21-year-old female patient presented with bilateral acute macular neuroretinopathy 3 days after getting the first shot of Vaxzevria® [41].

A tertiary referral center from Abu Dhabi reported ocular complications within 15 days following administration of first of 2 doses of inactivated COVID-19 vaccine [Sinopharm]. One episcleritis, two anterior scleritis, one paracentral acute middle maculopathy, two acute macular neuroretinopathy and one subretinal fluid (forme fruste of central serous chorioretinopathy) were recorded post vaccination [42].

Neuropathy

Bell's palsy

A healthy 37-year-old white Caucasian male received the first injection of the mRNA Vaccine BNT162b2 on 8th January 2021. From the 11th, he started complaining of left-sided latero- cervical pain irradiating ipsilaterally to the mastoid, ear, and retro-maxillary region. On 13th January, he presented with a left-sided facial droop accompanied by reduced mobility (paresis). On examination, flattening of forehead's skin and marionette line (labial-buccal sulcus) ipsilaterally, mild fattening of the nasolabial fold, lagophthalmos and mild labial hypomobility were recorded. This was accompanied by a moderate Bell's sign. It was clinically diagnosed as Bell's palsy. The timing and mode of onset of the palsy strongly suggests that it was associated with BNT162b2 vaccine injection though a causal relationship cannot be established [43].

Using the database of largest healthcare in Israel, a retrospective cohort study with nonconcurrent historic comparative group was performed. A comparison between observed cases of Bell's palsy appearing after vaccination and the expected cases of Bell's palsy as estimated based on the experience of the Clalit Health Services population in 2019 prior to COVID-19 epidemic and introduction of vaccine was done. It suggested the association of BNT162b2 mRNA COVID-19 vaccine and increased risk of Bell's palsy. Although numbers were small, the most marked association was observed among women ≥ 65 years within a time interval of 21 days after receipt of the first vaccine dose. The association appeared more pronounced after the second dose of vaccine in patients with a previous history of Bell's palsy [44].

Abducen's nerve palsy

A healthy 23-year-old male suddenly developed double vision along with severe headache. He had received his first shot of COVID-19 vaccine (Covishield) 1 week ago. His best corrected visual acuity remained unaffected. On cover test, a 40 PD left esotropia was noted along with limited abduction of the left eye. 2 similar episodes had happened in the past. The first episode of left eye sixth nerve palsy occurred 5 years ago following fever. Complete resolution took place in 2 months after botox injection in medial rectus of left eye. After 2 years of this episode, 2nd episode in left eye happened after chickenpox infection. This time resolution period was of 3 months [45].

Ambiguity persists about the site of cellular injury and pathophysiological mechanism in sixth nerve palsy. Although there is temporal association between immunization and abducens nerve palsy. It is proposed that a neurotropic effect of the infectious agent, demyelination of parainfectious etiology, sectarian arteritis or microinfarction, and an immune-mediated reaction are the possible etiologies of the abducens nerve palsy post vaccination.

Optic neuritis

A 19-year-old female developed optic neuritis after single dose of Ad26.COV2.S vaccine 1 week ago. It responded to steroid therapy. On evaluation, left amaurosis, afferent pupillary defect and papillitis on fundoscopy of the left eye was noted. It was diagnosed as inflammatory optic neuritis clinically [46].

Optic neuritis is the most common demyelinating condition associated with vaccination. It includes hepatitis A and B, influenza, pneumococcal vaccine, measles, rabies, human papilloma virus and BCG [47,48].

Proposed hypothesis says that a dysregulated immunological reaction could be triggered by the active component of the Ad26.COV2.S vaccine (adenovirus type 26 vector containing the DNA of spike) and the specific B cell response targeting the vector-based vaccine. This leads to the adverse reactions. This cross reactivity is related to several genetic and environmental factors, such as aberrant major histocompatibility complex (MHC) class II antigen presentation to autoreactive T cells [49].

Nonarteritic anterior ischemic optic neuropathy

A 55-year-old woman complained of disturbance in the inferior visual field of the right eye for 4 days. She had the first shot of Pfizer-BioNTech COVID-19 vaccine 7 days ago. A diffuse swelling, more prominent above, of the optic disc, was seen in the right eye on fundus examination. An inferior altitudinal visual field defect with I/2 isopter was noted on Goldmann visual field testing in the right eye. NA-AION was diagnosed despite of the absence of a typical complete inferior visual field defect. The ambiguity about consequential or coincidental development of NA-AION after COVID-19 vaccination persists. Though the temporal relationship between the two points towards vasculopathy on the microvascular network of optic nerve head and inflammatory or immune mediated component behind the onset of NA-AION [50].

Superior ophthalmic vein thrombosis

A 55-year-old woman got admitted with conjunctival congestion, double vision, and retro- orbital pain after receiving her first shot of vaccine, ChAdOx1 nCoV-19 ten days ago. She had flu-like symptoms and fever on the night after vaccination. She had similar symptoms 7 days later. On examination, binocular diplopia was noted at vertical and right lateral gaze. Bilateral visual acuity was 0.85. No contrast filling, bilateral high T2 signal intensity of the superior ophthalmic vein was detected on MRI leading to a diagnosis of Superior ophthalmic vein thrombosis [51].

Secondary immune thrombocytopenia (ITP) was confirmed on laboratory investigations. She was on heparin, still she developed ischaemic stroke with complaints of a transient, mild, right-sided hemiparesis, and aphasia. MRI findings were consistent with the diagnosis.

Thus 8, 10, and 18 days after the ChAdOx1 nCoV-19 vaccination, the previously healthy patient developed marked flu-like symptoms, two rare disorders-bilateral SOVT and ITP, and an ischaemic stroke. A causal relationship was indicated. The thrombotic events like bilateral SOVT may occur in the context of thrombocytopenia.

Grave's disease

A 40-year-old Chinese woman had 8-year old history of hypothyroidism. She was on thyroxine replacement therapy. She remained euthyroid clinically. She developed thyrotoxicosis 5 weeks after the 2nd shot of BNT162b2 mRNA vaccine. A diagnosis of Graves' disease was established. Her thyroid stimulating immunoglobulin level was positive. Thyroid ultrasonography showed diffuse goiter with hypervascularity. Technetium thyroid scan revealed diffusely increased thyroid uptake. Her anti-thyroglobulin antibodies and anti-thyroid peroxidase turned positive from negative. She was put on carbimazole. Author specifically mentioned that none of the five cases of Graves' disease in literature post SARSCoV-2 vaccination, had associated Graves' orbitopathy till the time of reporting [52].

In genetically susceptible individuals, it is believed that an external factor, such as infection, triggers switch from hypothyroid to hyperthyroid [53].

The functional receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). Many endocrine organs like thyroid express this receptor [54]. This explains the new onset of autoimmune thyroid disorders after SARS-CoV-2 vaccination. Molecular mimicry is behind thyroid dysfunction. This fact is all the more important as first mRNA vaccine to be used clinically in humans is SARS-CoV2 mRNA vaccine.

Discussion

Adverse effects of approved COVID-19 vaccines on eye as reported are quite infrequent, transient and treatable if diagnosed early and prompt treatment instituted. Serious adverse effects related to retinal vascular occlusions, corneal graft rejections call for further multicentric studies, prompt reporting and formulation of a protocol for proper management of these cases. Decisions on timing of vaccination in such cases and also delay in interventional elective surgeries like penetrating keratoplasty should be emphasized.

Both general physicians and ophthalmologists should make themselves aware of possibilities of adverse effects of COVID -19 vaccination on eye. Their role in educating general populations about this is of great value so that patients seek timely consultation and intervention as and when required.

To contain unprecedented COVID-19 pandemic, vaccines are a boon. These fewer infrequent adverse should not deter the mass vaccination programme globally though a vigilant approach to diagnose and treat them is also a must.

Conclusion

With emergence of newer mutated strains of corona virus and third wave of pandemic worldwide, mass campaign to vaccinate the world population is the need of hour.

COVID-19 vaccines are a boon in our armamentarium to restore normalcy globally.

Though the reports of ophthalmic adverse events of COVID-19 vaccination are being reported world-wide, its incidence rate is less than the prevalence rate of ophthalmic manifestations of COVID -19 [40].

With newer vaccines in pipeline and probable endemicity of COVID-19 infection, large multicentric and longitudinal studies are required in future to establish definite association of vaccines to ocular adverse events. This would help in management protocols to combat

COVID-19 vaccination induced ocular adverse effects.

Conflict of Interest

None.

Bibliography

1. Different COVID-19 Vaccines.
2. COVID-19 vaccine tracker and landscape.
3. https://www.mohfw.gov.in/covid_vaccination/vaccination/faqs.html#about-the-vaccine
4. Quillan M Austria., *et al*. "Transient Eyelid Edema Following COVID-19 Vaccination". *Ophthalmic Plastic and Reconstructive Surgery* 37.5 (2021): 501-502.
5. C Mazzatenta., *et al*. "Purpuric lesions on the eyelids developed after BNT162b2 mRNA COVID-19 vaccine: another piece of SARS-CoV-2 skin puzzle?" *Journal of European Academy of Dermatology and Venereology* (2021).
6. Lee EJ., *et al*. "Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination". *The American Journal of Hematology* 96 (2021): 534-537.
7. Greinacher A., *et al*. "Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination". *The New England Journal of Medicine* (2021).
8. Obaidur Rehman., *et al*. "Herpes Zoster Ophthalmicus After COVID- 19 Vaccination: Chance Occurrence or More Than That?" *Cornea* (2021): 1-3.
9. Furer V., *et al*. "Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series". *Rheumatology* (2021): keab345.
10. Parmar DP., *et al*. "Acute graft rejection in a high-risk corneal transplant following COVID -19 vaccination: A case report". *Indian Journal of Ophthalmology* 69 (2021): 3757-3758.
11. Wertheim MS., *et al*. "Corneal transplant rejection following influenza vaccination". *British Journal of Ophthalmology* 90 (2006): 925.
12. Steinemann TL., *et al*. "Corneal allograftrejection following immunization". *American Journal of Ophthalmology* 106 (1988): 575-578.
13. Solomon A and Frucht-Pery J. "Bilateral simultaneous corneal graft rejection after influenza vaccination". *American Journal of Ophthalmology* 121 (1996): 708-709.
14. Matteo Nioi., *et al*. "Dual Corneal-Graft Rejection after mRNA Vaccine (BNT162b2) for COVID-19 during the First Six Months of Follow-Up: Case Report, State of the Art and Ethical Concern". *Vaccines* 9 (2021): 1274.
15. Ravichandran S and Natarajan R. "Corneal graft rejection after COVID-19 vaccination". *Indian Journal of Ophthalmology* 69 (2021): 1953-1954.
16. Lockington D., *et al*. "Survey of Corneal Surgeons' Attitudes Regarding Keratoplasty Rejection Risk Associated With Vaccinations". *Cornea* (2021).
17. A Crnej., *et al*. "Acute corneal endothelial graft rejection following COVID-19 Vaccination". *Journal Françaisd'Ophtalmologie* 44 (2021): e445-e447.

18. Konstantinos I Rallis., *et al*. "Corneal graft rejection following COVID-19 vaccine". *Eye* (2021).

19. Lauren M Wasser., *et al*. "Keratoplasty Rejection After the BNT162b2 messenger RNA Vaccine". *Cornea* 40 (2021): 1070-1072.

20. Oannis Papasavvas and Carl P Herbort Jr. "Reactivation of Vogt-Koyanagi-Harada disease under control for more than 6 years, following anti-SARS-CoV-2vaccination". *Papasavvas and Herbort Journal of Ophthalmic Inflammation and Infection* 11 (2021): 21.

21. Ilaria Testi., *et al*. "Ocular inflammatory events following COVID-19 vaccination: a multinational caseseries". *Journal of Ophthalmic Inflammation and Infection* 12 (2022): 4.

22. Cunningham ET Jr., *et al*. "Vaccineassociated uveitis". *Ocular Immunology and Inflammation* 27.4 (2019): 517-520.

23. Watad A., *et al*. "Immune-Mediated Disease Flares or New- Onset Disease in 27 Subjects Following mRNA/DNA SARSCoV-2 Vaccination". *Vaccines* 9.5 (2021): 435.

24. Teijaro JR and Farber DL. "COVID-19 vaccines: modes of immune activation and future challenges". *Nature Reviews Immunology* 21.4 (2021): 195-197.

25. Rodero MP and Crow YJ. "Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview". *Journal of Experimental Medicine* 213.12 (2016): 2527-2538.

26. Cunningham ET Jr and Moorthy RS. "Vaccine-associated posterior uveitis". *Retina* 40.4 (2020): 595-598.

27. Lijie Pan., *et al*. "Bilateral uveitis after inoculation with COVID-19 vaccine: A case report". *International Journal of Infectious Diseases* 113 (2021): 116-118.

28. Elena Bolletta., *et al*. "Uveitis and Other Ocular Complications Following COVID-19 Vaccination". *Journal of Clinical Medicine* 10 (2021): 5960.

29. Triantafyllidis KK., *et al*. "Varicella zoster virus reactivation following COVID-19 vaccination: A systematic review of case reports". *Vaccines* 9 (2021): 1013.

30. Arash Maleki., *et al*. "COVID-19 Recombinant mRNA Vaccines and Serious Ocular Inflammatory Side Effects: Real or Coincidence?" *Journal of Ophthalmic and Vision Research* 16.3 (2021): 490-501.

31. Reikine S., *et al*. "Pattern recognition and signaling mechanisms of RIG-I and MDA5". *Frontiers in Immunology* 5 (2014): 342.

32. Pelka K., *et al*. "Nucleic acid-sensing TLRs and autoimmunity: novel insights from structural and cell biology". *Reviews Immunology* 269 (2016): 60-75.

33. Schurz H., *et al*. "The X chromosome and sex-specific effects in infectious disease susceptibility". *Human Genomics* 13 (2019): 2.

34. Giulia Renisi., *et al*. "Anterior uveitis onset after bnt162b2 vaccination: is this just a coincidence?" *International Journal of Infectious Diseases* 110 (2021): 95-97.

35. Cunningham ET., *et al*. "Vaccine-Associated Uveitis". *Ocular Immunology and Inflammation* (2019).

36. Anders DjupeslandBøhler., *et al*. "Acute macular neuroretinopathy following COVID-19 vaccination". *Eye* (2021).

37. Bhavsar KV., *et al*. "Acute macular neuroretinopathy: a comprehensive review of the literature". *Survey of Ophthalmology* 61 (2016): 538-565.

38. Vinzamuri S., *et al*. "Bilateral paracentral acute middle maculopathy and acute macular neuroretinopathy following COVID-19 vaccination". *Indian Journal of Ophthalmology* 69 (2021): 2862-2864.

39. Daniel Yu Lee., *et al.* "Disc edema in one eye and central serous chorioretinopathy in the other eye shortly after AstraZeneca COVID-19 vaccination". *The Kaohsiung Journal of Medical Sciences* (2021): 1-3.

40. Sopp NM and Sharda V. "An Eye on COVID-19: A Meta-analysis of Positive Conjunctival Reverse Transcriptase-Polymerase Chain Reaction and SARS-CoV-2 Conjunctivitis Prevalence". *Optometry and Vision Science* 98 (2021): 429-436.

41. Christian Girbardt., *et al*. "Retinal Vascular Events after mRNA and Adenoviral-Vectored COVID-19 Vaccines-A Case Series". *Vaccines* 9 (2021): 1349.

42. Francesco Pichi., *et al*. "Association of Ocular Adverse Events With Inactivated COVID-19 Vaccination in Patients in Abu Dhabi". *JAMA Ophthalmology* 139.10 (2021): 1131-1135.

43. Giuseppe Colella., *et al*. "Bell's palsy following COVID-19 vaccination". *Journal of Neurology* (2021).

44. Rana Shibli., *et al*. "Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and Bell's palsy: a population-based study". *The Lancet Regional Health - Europe* 11 (2021): 100236.

45. Pawar N., *et al*. "Acute abducens nerve palsy after COVID-19 vaccination in a young adult". *Indian Journal of Ophthalmology* 69 (2021): 3764-3766.

46. Christian García-Estrada., *et al*. "Optic neuritis after COVID-19 vaccine application". *Clinical and Experimental Neuroimmunology* (2021): 1-3.

47. Cheng JY and Margo CE. "Ocular adverse events following vaccination: overview and update". *Survey of Ophthalmology* 21 (2021): S0039-6257.

48. Karussis D and Petrou P. "The spectrum of post-vaccination inflammatory CNS demyelinating syndromes". *Autoimmunity Reviews* 13.3 (2014): 215-224.

49. Segal Y and Shoenfeld Y. "Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction". *Cellular and Molecular Immunology* 15.6 (2018): 586-594.

50. Rika Tsukii., *et al*. "Nonarteritic Anterior Ischemic Optic Neuropathy following COVID-19 Vaccination: Consequence or Coincidence". *Case Reports in Ophthalmological Medicine Volume* (2021): 4.

51. Antonios Bayas., *et al*. "Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination". *Lancet* 397 (2021): e11.

52. David Tak Wai Lui., *et al*. "Development of Grave's Disease after SARS-CoV-2 m RNA Vaccination: A Case Report and Literature Review". *Frontiers in Public Health* 9 (2021): 778964.

53. Ahmad E., *et al*. "Hypothyroidism conversion to hyperthyroidism: it's never too late". *Endocrinology, Diabetes and Metabolism Case Reports* (2018): 18-47.

54. Pal R and Banerjee M. "COVID-19 and the endocrine system: exploring the unexplored". *Journal of Endocrinological Investigation* 43 (2020): 1027-1031.

Volume 13 Issue 3 March 2022