

After the Storm: Ophthalmic Manifestations of COVID-19 Vaccines

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Several COVID-19 vaccines have been developed and approved for use around the world from December 2020, to combat the pandemic caused by the novel SARS-CoV-2 virus. Several ophthalmic manifestations of the COVID-19 vaccines have been reported by ophthalmologists. This review was undertaken to recognize, encourage active reporting and determine the pathogenesis and time of appearance for better awareness and understanding of the ophthalmic manifestations of COVID-19 vaccines. A literature search was performed for publications on the ophthalmic manifestations of COVID-19 vaccines between January 1, 2021 and November 7, 2021. 23 case reports, 17 letters to editors, 3 ophthalmic images, 4 brief communications, 4 retrospective cohort studies and 2 case control studies were included. Posterior segment, including the uvea, choroid and retinal vasculature, was most commonly affected and the reported clinical features developed at a median of four days from the time of vaccination. The possible mechanisms include molecular mimicry of the vaccine components with host ocular tissues, antigen-specific cell and antibody-mediated hypersensitivity reactions to viral antigens and adjuvants present in the vaccines. The causal relationship of the ocular signs and symptoms and COVID-19 vaccines has not been established and requires long-term and large multicentre data. Most of the reported manifestations are mild, transient and adequately treated when diagnosed and managed early. The benefits of COVID-19 vaccination outweighs the reported rare adverse events and should not be a deterrent to vaccination.

Key words: Corneal graft rejection, COVID-19 vaccine, COVID-19, inactivated vaccine, mRNA vaccine, ophthalmic manifestations, SARS-CoV-2, vascular occlusion, vector based vaccine

The year 2020 was unlike any other, a year of uncertainty, distancing, and loss. Man has always found his way through obstacles and challenges; David must come to fell Goliath. The best minds around the world worked at an unprecedented pace to develop vaccines against the novel SARS-CoV-2 virus. By December 2020, vaccines against COVID-19 were authorized for emergency use through expedited clinical trials. Like any change, any revolution, it too faced trials and tribulations, hype and hysteria, media and political might. As we enter the last quarter of 2021, it may be safe to say that the vaccines have “lived and let live.” A large population has been vaccinated, 7,027,377,238 vaccine doses, to be exact, as of November 7, 2021, have been administered, lockdowns are being lifted and gradually life seems to be returning to normal, albeit a new one.^[1]

The main vaccines approved for use around the world are the nucleoside-modified RNA vaccine (BNT162b2) by Pfizer-BioNTech, the recombinant adenoviral vector encoding SARS-CoV-2 spike (S) glycoprotein (ChAdOx1 nCoV-19 Coronavirus vaccine Recombinant COVISHIELD by Serum Institute of India based on the Oxford AstraZeneca Chimpanzee Adenovirus Vected Vaccine (AZD1222)), and the inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Sinopharm). Additionally, there are other vaccines including Sputnik

V, Russia, mRNA-1273 Moderna, Janssen, Johnson and Johnson COVAXIN by Bharat Biotech, India, and CoronaVac from China. The vaccines have been found to be 94%–95% effective.^[2-4] The common side effects of these vaccines are mild to moderate pain, swelling, and erythema at the injection site, chills, fatigue, malaise, headache, and fever. Diarrhea, nausea, vomiting, and dermatitis are less frequent side effects documented. These usually start within 24–48 hours of the inoculation and last for 1–2 days. Table 1 shows the vaccines, their mechanism of action, and doses recommended.^[2-5]

Still, in infancy, there is a paucity of data on the ocular manifestations following COVID-19 vaccines. At the beginning of this year, we reviewed the ophthalmic manifestations of the SARS-CoV-2 virus.^[6] In this article, we decided to review the ophthalmic manifestations of the vaccines against COVID-19.

Methods

A literature search was performed on PubMed with search words, COVID-19 vaccine, ophthalmology, eye, adverse effects, SARS-CoV-2, ocular manifestations, graft rejection, retina, vitreous, orbit, facial palsy, uveitis, nerve palsies, choroiditis, retinal vascular occlusion, mRNA vaccine, adenovirus vector vaccine, and inactivated vaccine. The articles included in this

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Table 1: COVID-19 vaccines approved for use around the world

Vaccine	Manufacturer	Type	Details	Dosage	Safety data from clinical trials: serious adverse events
BNT162b2	Pfizer, Inc. and BioNTech (COMIRNATY)	mRNA	Lipid nanoparticle formulated nucleoside- modified mRNA vaccine encoding prefusion stabilized, membrane-anchored full length SARS-CoV-2 spike (S) glycoprotein	12 years or older 2 doses 21 days apart Additional dose- recommended for moderate to severely immunocompromised people- 4 weeks after the 2 nd dose Booster- Some groups of people are recommended to get a booster shot at least 6 months after getting their second shot	Myocarditis or pericarditis: rare, 12.6/100000 adolescents and young adults
mRNA-1273	ModernaTX, Inc	mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	18 years or older 2 doses, 28 days apart Additional dose- recommended for moderate to severely immunocompromised people- 4 weeks after the 2 nd dose	Myocarditis or pericarditis: rare, 12.6/100000 adolescents and young adults
ChAdOx1 nCoV-19 Corona Virus Vaccine AZD1222	Serum Institute of India- Covishield AstraZeneca- Vaxzevria	Viral vector-based	Recombinant vaccine from the genetically modified human embryonic kidney (HEK) 293 cells with replication- deficient chimpanzee adenovirus vector encoding SARS-CoV-2 Spike (S) glycoprotein. Induces binding and neutralizing antibodies and interferon-gamma enzyme-linked immunospot responses.	2 doses 12-16 weeks apart	Cerebral venous sinus thrombosis, thrombosis with thrombocytopenia
JNJ-78436735 Ad26COV2.S	Janssen Pharmaceuticals Companies of Johnson and Johnson	Viral vector-based	Recombinant, replication-incompetent Ad26 vector, encoding a stabilized variant of the SARS-CoV-2 DNA encoding Spike (S) protein	18 years or older 1 shot Additional doses- not recommended Booster- At least 2 months after receiving your vaccine. You can get any of the COVID-19 vaccines authorized in the United States for your booster shot	Thrombosis with thrombocytopenia syndrome: 7/100000 vaccinated women 18-49 years Guillain-Barré syndrome
Gam-COVID-Vac	Sputnik V Gamaleya National Research Centre	Viral vector-based	Heterologous recombinant adenovirus approach with adenovirus (Ad26) and adenovirus 5 (Ad5) as vectors for expression of SARS-CoV-2 spike protein	18 years or older Two doses, 21 days apart	
BBV152	COVAXIN Bharat Biotech	Inactivated coronavirus Vaccine	The whole virion inactivated Iridazoquinoline class molecule (TLR 7/8 agonist) adsorbed to alum	18 years or older 2 doses, 28 days apart	
BBIBP-CorV	Sinopharm	Inactivated coronavirus vaccine	An inactivated vaccine with aluminum-based adjuvant	2 doses 3-4 weeks apart	Inflammatory demyelination syndrome, acute disseminated encephalomyelitis
CoronaVac	Sinovac Biotech Ltd Beijing	Inactivated coronavirus vaccine	The whole virion inactivated vaccine. Aluminum hydroxide adjuvant	18 years or older 2 doses, 2-4 weeks apart Additional dose- recommended for moderate to severely immunocompromised people - 4 weeks after the 2 nd dose Booster - not recommended yet	

review are in English language, published between January 2021 and November 7, 2021. It is not an exhaustive review, but the authors have tried to include all the important reports with 23 case reports, 17 letters to editors, 3 image-based reports, 4 brief clinical communications, 4 retrospective cohort, and 2 casecontrol studies.

Eyelid, Ocular Surface and Anterior Segment Manifestations of COVID-19 Vaccine

The eyelid, ocular surface, and cornea are easily observable by patients and, therefore, present as soon as the symptoms develop. Eighteen cases of ocular adnexal and anterior segment manifestations have been reported [Table 2].^[7-16] The mean age of the patients was 57.5 ± 15.6 (median 62.5) years, and there were 9 females and 6 males (3 gender unspecified). The Pfizer-BioNTech mRNA vaccine was the most common vaccine, used in 13 patients, two had received the viral vector-based Covishield, and three had received the inactivated Sinopharm vaccine. The majority of the symptoms were after the first dose,^[11] whereas four patients presented after the second dose. The median interval from vaccination to development of symptoms was 7 (mean 9.8 ± 8) days.

Eyelid

The eyelid involvement was transient in all cases limited to unilateral erythematous edema and bilateral purpuric rash. All cases were after the Pfizer-BioNTech mRNA vaccine. The three cases of acute onset eyelid edema reported by Austria *et al.*^[7] resolved with observation, antihistamine, and oral corticosteroids, respectively, within 1–2 days. The purpuric rash observed in three patients developed at a median of 18 days and resolved spontaneously within 10–15 days. The coagulation profile was normal in all three.^[8] [Fig. 1] Eyelid edema can be a part of an anaphylactic reaction, but none of the patients reported any systemic adverse effects. Periorbital swelling is seen in ocular vaccinia after the smallpox vaccine, and ocular



Figure 1: Purpuric lesions on the upper eyelids in patient 2 (a and b) and patient 1 (c and d). (Reproduced with permission from Mazzatenta C, Piccolo V, Pace G, Romano I, Argenziano G, Bassi A. Purpuric lesions on the eyelids developed after BNT162b2 mRNA COVID-19 vaccine: another piece of SARS-CoV-2 skin puzzle?. *Journal of the European Academy of Dermatology and Venereology*. 2021 May 28.)

respiratory syndrome is reported with the influenza vaccine.^[8] The mechanisms proposed after COVID-19 vaccination include complement-induced reaction and molecular mimicry with an autoimmune response.

Cornea

Corneal graft rejection was the most common anterior segment manifestation of the COVID-19 vaccine. Seven of the nine cases were following the Pfizer-BioNTech mRNA vaccine at a median duration of 7 (mean 10.3 ± 7.2) days. The remaining two received the viral vector-based Covishield vaccine. Four patients had undergone penetrating keratoplasty, whereas the rest had undergone lamellar keratoplasty. Five of eight patients were on topical corticosteroids at the time of vaccination. In the case reported by Phylactou *et al.*, the patient also had a retroviral infection and was on treatment for the same.^[11] Three patients had bilateral corneal transplants and of these, one patient developed rejection in only one eye. Five eyes had undergone repeat transplants following prior failures. Only one patient developed systemic symptoms, moderate chills, and myalgia following the vaccination.^[9] The symptoms and signs were typical of endothelial graft rejection with acute onset of diminution of vision, redness, photophobia with or without pain, graft edema, Descemet's folds, and anterior chamber (AC) reaction. [Figs. 2 and 3] Treatment was with frequent (1–2 hourly) administration of topical corticosteroids with or without oral steroids. Acyclovir/Valacyclovir was started in two patients to counter a possible viral infection.^[9,14] All the patients recovered within 1–4 weeks.

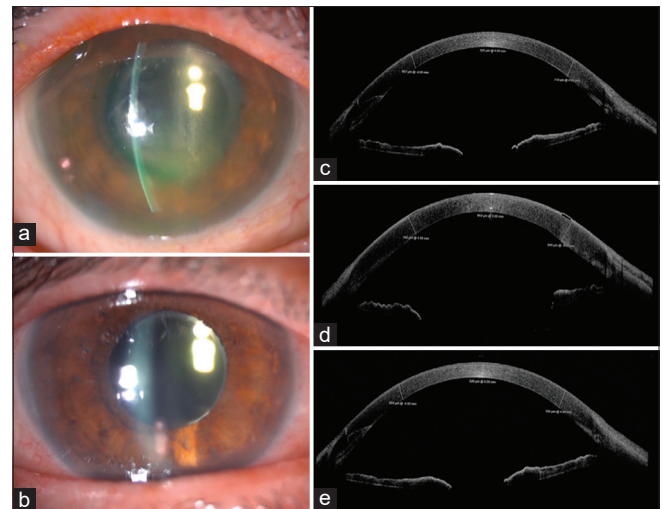


Figure 2: Early acute endothelial rejection post-DMEK following vaccination. Slit-lamp image at presentation on day 7 postvaccination with rejection and corneal edema (a), and on day 14 postvaccination and intensive treatment with topical dexamethasone showing improved stromal transparency (b). Anterior segment OCT on day 7 post-DMEK, indicating full graft attachment and CCT of $525 \mu\text{m}$ (c), on day 21 post-DMEK (day 7 postvaccination) at presentation with rejection and CCT of $652 \mu\text{m}$ corresponding to observed stromal edema and inflammation (d), and on day 28 post-DMEK (day 14 post-vaccination), following increased frequency of topical steroids and CCT of $526 \mu\text{m}$ (e). (Reproduced with permission from Phylactou M, Li JP, Larkin DF. Characteristics of endothelial corneal transplant rejection following immunization with SARS-CoV-2 messenger RNA vaccine. *British Journal of Ophthalmology*. 2021 Jul 1;105(7):893-6.)

Table 2: Review of literature of eyelid, ocular surface, and corneal manifestations of COVID-19 vaccines

Author	Type	Location	Sample	Age	Sex	Systemic/ocular illness	Vaccine	Dose	Duration between vaccine and symptoms (days)	Systemic adverse reaction
Austria <i>et al.</i> ^[7]	Letter to editor	New York	3	Mean 39.3	F	-	BNT162b2 mRNA	-	1-2	-
					F	-	BNT162b2 mRNA	-	1-2	-
					F	-	BNT162b2 mRNA	-	1-2	-
Mazzatenta <i>et al.</i> ^[8]	Letter to editor	Italy	3	44	F	-	BNT162b2 mRNA	2	21-25	-
					M	-	BNT162b2 mRNA	2	21	-
					F	-	BNT162b2 mRNA	1	10	-
Rallis <i>et al.</i> ^[9]	Brief communication	UK	1	68	F	OU lamellar DSAEK for Fuchs' corneal endothelial dystrophy and a OS re-do PK for failed DSAEK in October 2020. On topical prednisolone OS and dexamethasone OD	BNT162b2 mRNA	1	4	moderate-chills, myalgia, tiredness
Abouy <i>et al.</i> ^[10]	Case report	USA	1	73	F	Fuchs'- OU DSEK- 8 years	BNT162b2 mRNA	2	4	-
Phylactou <i>et al.</i> ^[11]	Case report	UK	2	66	F	Fuchs'- OD DMEK 14 days before vaccination. Patient on dexamethasone. HIV+: undetectable viral load, CD4>600 on antiviral therapy	BNT162b2 mRNA	1	7	-
					F	Fuchs'- OU DMEK- 3 and 6 years ago (OD DSEK → DMEK).	BNT162b2 mRNA	2	21	-
Wasser <i>et al.</i> ^[12]	Case report	Jerusalem	2	73	M	PK- keratoconus and re-graft for late endothelial failure. On dexamethasone 0.1% once daily	BNT162b2 mRNA	1	13	-
					M	OU PK- keratoconus. Repeat PK in OD due to late endothelial failure.	BNT162b2 mRNA	1	14	-
Ravichandran <i>et al.</i> ^[13]	Photo essay	India	1	62	M	PK- corneal scar OD, 2 years ago. Eye aphakic and amblyopic. On topical corticosteroids	ChAdOx1 nCoV-19 viral vector based	1	21	-
Crneji <i>et al.</i> ^[14]	Letter to editor	Lebanon	1	71	M	DMEK OD for endothelial decompensation following cataract surgery. HTN, smoking, CAD	BNT162b2 mRNA	1	7	-
Parmar <i>et al.</i> ^[15]	Case report	India	1	35	M	Therapeutic PK 3 years ago. Re-PK for graft failure 6 months ago; on topical corticosteroids	ChAdOx1 nCoV-19 viral vector based	1	2	-
Pichi <i>et al.</i> ^[16]	Case series	Abu Dhabi	3 (7)	Mean 41.4	-	-	BB1Bp-CorV inactivated	1	Mean 5.2	-
					-	RA on sulfasalazine	BB1Bp-CorV inactivated	1	-	-
					-	-	BB1Bp-CorV inactivated	1	-	-

Contd...

Table 2: Contd...

Author	Laterality	Clinical features	Diagnosis	Management	Outcome
Austria et al. ^[7]	Unilateral unilateral	UL>LL erythema and edema UL>LL erythema and edema	Transient eyelid edema Transient eyelid edema	Observation Antihistamines	Resolved 1-2 days Resolved 1-2 days
Mazzatenta et al. ^[8]	OU	UL>LL erythema and edema purpuric lesions on OU UL.	Transient eyelid edema Transient purpuric lesions on eyelid	Oral corticosteroids Observation	Resolved 1-2 days Spontaneously resolved 10 days
	OU	purpuric lesions on OU UL	Transient purpuric lesions on eyelid	Observation	Spontaneously resolved 15 days
	OU	echymotic lesions- moderately itchy	Transient purpuric lesions on eyelid	Observation	Spontaneously resolved 12 days
Rallis et al. ^[9]	OS	Pain, redness. Diffuse punctate corneal staining, graft edema, Descemet's folds, KPs, AC activity	Acute corneal endothelial graft rejection	Hourly topical dexamethasone 0.1% and a week of oral acyclovir 400 mg 5x/day	Resolved, 3 weeks
Abousy et al. ^[10]	OU	Va OD 20/200, Os 20/40, ocular pain, and photophobia, corneal edema, AC cells. Increased CCT	Acute corneal endothelial graft rejection	Prednisolone acetate 1% every 1 to 2 hours with Muro ointment at bedtime. Then tapered to qid	Improved.
Phylactou et al. ^[11]	OD	Acute onset blurred vision, redness, photophobia, OD 6/36, diffuse corneal edema, KPs, AC 1+cells	Acute corneal endothelial graft rejection	Topical corticosteroids- 1 hourly	Improved by day 7. Irreversible endothelial loss
	OU	OD 6/24, OS 6/12 photophobia, redness, circumcorneal congestion, KPs, AC cells	Acute endothelial graft rejection	Topical corticosteroids- 1 hourly	Improved by day 7
Wasser et al. ^[12]	OS	20/200, ciliary injection, corneal edema, descemet's folds, KPs	Graft rejection	Topical hourly corticosteroids, oral prednisone 60 mg per day	Resolved 1 week
	OD	Diffuse corneal edema, KPs, AC	Graft rejection	Topical hourly corticosteroids, oral prednisone 60 mg per day	Resolved 4 weeks
Ravichandran et al. ^[13]	OD	Congestion, diminution of vision, advancing Khodadoust rejection line, graft edema, AC reaction	Acute corneal Graft rejection	Appropriate	-
Crnej et al. ^[14]	OD	Sudden painless vision loss, 20/125, diffuse corneal edema, increasing CCT	Acute corneal endothelial graft rejection	Topical dexamethasone 2 hourly, oral valacyclovir 1000 mg TID	Resolved 1 week
Parmar et al. ^[15]	OS	Acute vision loss, epithelial and stromal edema, KPs	Acute corneal endothelial graft rejection	Hourly prednisolone, atropine TID, IVMP 1000 mg for 3 days- oral prednisolone. Considering immunologist opinion for NSAID before second dose of vaccine.	Resolved 3 weeks
Pichi et al. ^[16]	OU	Pain, redness, diffuse scleral hyperaemia, positive phenylephrine test	Episcleritis Anterior scleritis	Topical corticosteroids Topical corticosteroids	Resolved Resolved, 7 days
			Anterior scleritis	Topical corticosteroids	Resolved

AC: Anterior chamber, CAD: Coronary artery disease, CCT: Central corneal thickness, DMEK: Descemet membrane endothelial keratoplasty, DSAEK: Descemet stripping automated endothelial keratoplasty, DSEK: Descemet stripping endothelial keratoplasty, F: Female, HIV: Human immunodeficiency virus, HTN: Hypertension, IVMP: Intravenous methylprednisolone, KP: Keratic precipitates, LL: Lower eyelid, M: Male, NSAID: Non-steroidal anti-inflammatory drug, OD: Right eye, OS: Left eye, OU: Both eyes, PK: Penetrating keratoplasty, RA: Rheumatoid arthritis, TID: Three times a day, UL: Upper eyelid

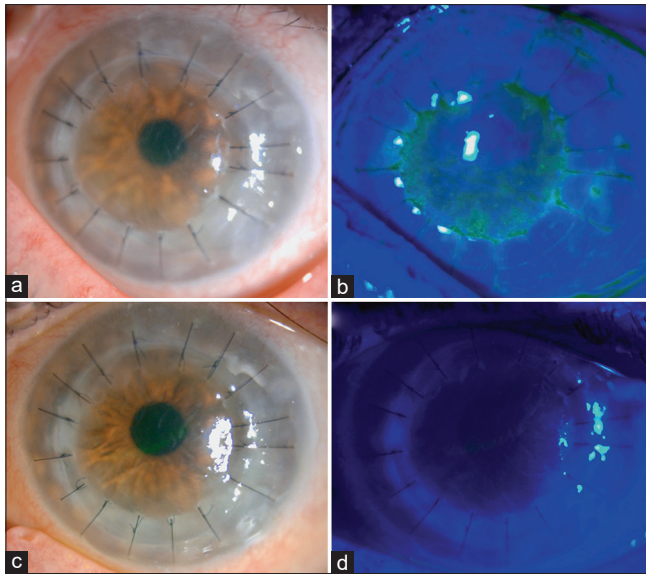


Figure 3: A case of acute corneal endothelial graft rejection after COVID-19 vaccine. A, B Slit-lamp photography demonstrating conjunctival hyperemia, corneal graft haze, diffuse corneal epithelial, and stromal edema (within the graft), Descemet's folds, scattered keratic precipitates (KPs), and 1+ cells in the anterior chamber. An unusual distribution of fluorescein staining with coarse punctate epitheliopathy over the corneal graft was observed. The central corneal thickness (CCT) was 730 μm . C, D At 3-week post-treatment, the corneal graft rejection was successfully treated with considerable improvement in the graft transparency, reduction in epithelial and stromal edema, and resolution of epitheliopathy and anterior chamber inflammation. The best-corrected visual acuity improved to 6/12, with a CCT of 609 μm (Reproduced with permission from Rallis KI, Ting DS, Said DG, Dua HS. Corneal graft rejection following COVID-19 vaccine. *Eye*. 2021 Aug 23:1-2.)

The cornea is an immunoprivileged organ, and corneal transplantation has the highest rate of success. Lamellar keratoplasty has ensured further protection of the graft. Graft rejection can follow the breakdown of the blood-ocular barrier following intraocular inflammation or recurrent viral infection.^[11] Corneal graft rejection after immunization has been reported with influenza, hepatitis B, tetanus, and yellow fever vaccines.^[10,11] Bilateral graft failure in two of three patients with transplants in both eyes, and the temporal sequence of events points towards the role of the COVID-19 vaccine. The suggested mechanisms of graft failure are the vaccine-induced immune enhancement and cross-reactivity of virus antigen-specific T-cells with HLA antigen-disparate corneal allograft endothelial cells, increased vascular permeability after the vaccination, and presence of mRNA in the aqueous following a prior COVID-19 infection.^[14] The COVID-19 vaccine induces a strong antibody response with CD4 + Th1 cells, which are also mediators of corneal graft rejection.^[10] Systemic reactivity would be more likely after the second dose of vaccination than the first one, but seven of the nine patients developed rejection after the first dose itself. Also, none of the patients were reported to have had prior COVID-19 infection, but one cannot rule out mild, asymptomatic infection. Nevertheless, the possibility of graft rejection following immunization necessitates considering deferral of elective corneal transplants by 3–6 months after the final dose of COVID-19 vaccine and initiating corneal transplant patients on topical corticosteroids before the first

dose of vaccine and continuing for a month after the second dose.^[10] Patients with repeat grafts and immunocompromised state are at a higher risk of rejection and should be forewarned. While all patients recovered, it must be borne in mind that endothelial cell loss following graft rejection is irreplaceable.

Ocular Surface and Sclera

Pichi *et al.* reported a case series of seven patients with a mean age of 41.4 years who developed ocular complaints following the first dose of the inactivated Sinopharm vaccine.^[16] Four eyes of three patients developed episcleritis and scleritis at a mean of 5.2 days. One patient had a history of rheumatoid arthritis, was on sulfasalazine and presented with scleritis. Tapering doses of topical corticosteroid were prescribed, and the inflammation resolved in all the cases. Scleritis and episcleritis have been reported after the administration of live attenuated vaccines as well as post-COVID-19 infection.^[6,17]

Posterior Segment Manifestations of COVID-19 Vaccine

The retina and the uvea are the most commonly involved ocular structures following COVID-19 vaccination with 50 cases reported in the literature, 21 being contributed by a retrospective study from Israel [Table 3].^[16,18-42] The mean age was 43.6 ± 17.2 (median 40) years with 23 males and 23 females (unspecified in 4). The symptoms developed at a median interval of 4 (mean 7.4 ± 8.5) days from the time of vaccination. None of the patients had a prior history of COVID-19 although one patient with panuveitis tested positive for COVID-19 post-vaccination.^[27] Thirty patients had received the Pfizer-BNT mRNA vaccine, the adenoviral vector-based vaccines by AstraZeneca and Serum Institute of India were given to 11 patients, whereas the vector-based vaccine by Johnson and Johnson had been used in one patient. One patient had received the Sputnik V vaccine, one had received Moderna mRNA vaccine, and six had received inactivated vaccine. The symptoms developed after the first dose in 25 patients and after the second dose in 21 patients. Two patients developed adverse effects after both the first and the second dose. Systemic side effects of the vaccine were seen in 12 patients, the majority being mild cases of headache, myalgia, and fever. Valenzuela reported a case of acute macular neuroretinopathy in a patient who developed cervical and supraclavicular lymphadenopathy and difficulty in swallowing, which required treatment with prednisolone and diphenhydramine.^[37]

Uvea

Vogt-Koyanagi-Harada Syndrome (VKH)

The three cases of VKH following COVID-19 vaccination were characterized by the typical acute onset of bilateral painless loss of vision, anterior chamber granulomatous inflammation, and exudative retinal detachment [Fig. 4]. Pappasavvas reported a case of a 43-year-old female who had a past history of VKH, on infliximab and without inflammation for 6 years. There was a reactivation 42 days after the second dose of the mRNA vaccine.^[20] Two of the three cases were following the mRNA Pfizer-BioNTech vaccine. All the cases were treated with systemic corticosteroids and resolved.

VKH is a T-cell-mediated multisystem autoimmune disease against melanocytes with ocular, neurological, audiovestibular, and dermatological manifestations. Viral infections have been

known to trigger VKH with cytomegalovirus (CMV), influenza A, hepatitis C being implicated.^[18] Antigenic cross-reactivity, HLA-DR4 status of patient (with influenza A), and interferon have been the mechanisms suggested in relation to viral infections causing VKH. Bacillus Calmette-Guerin (BCG) vaccine, influenza, hepatitis B, and yellow fever vaccinations have all been reported to cause cases of VKH, the onset ranging from 3 days to 4 weeks.^[18] VKH after COVID-19 vaccination may be a result of T- and B-cell-induced hypersensitivity reaction, an inflammatory reaction to adjuvants in a vaccine, or sensitization to melanocytic antigens by viral antigens. mRNA-based vaccines do not have any viral antigens or adjuvants but induce humoral immunity, T helper (CD4+ cells) and cytotoxic T cell response which could potentially trigger the inflammatory response.^[19]

Uveitis

Renisi *et al.* reported one of the earliest cases of anterior uveitis following both the first and second doses of the mRNA vaccine. The first episode was within a few hours of the first dose of the vaccine, whereas the second episode was delayed by 14 days from the date of vaccination. Systemic work-up for autoimmune diseases and serology for infections were negative, and it responded to topical corticosteroids and cycloplegics.^[23] The second case reported by ElSheikh *et al.*, triggered bilateral anterior uveitis in a patient with juvenile idiopathic arthritis (JIA) without any prior history of uveitis. This was after the second dose of the inactivated Sinopharm vaccine.^[21] Jain *et al.* reported another case of JIA-associated uveitis in a 27-year-old male with HLAB27, 2 days after the Covishield vaccine.^[22] A multicentric, retrospective study in Israel by Rabinovitch *et al.* reported 19 cases of anterior uveitis following vaccination by the BNT162b2 mRNA vaccine.^[24] All the cases were classified as possible or probable consistent with the other articles where a definitive causal relationship with the vaccine could not be established. Two cases of panuveitis have also been reported.^[25,26] One of the patients had Behcet's disease and required azathioprine in addition to topical and oral corticosteroids for control of inflammation.^[25] Thus, all three types of vaccines have been associated with uveitis.

Vaccine-induced uveitis is more common in females and is often seen when two or more vaccines are administered simultaneously. It has been seen most frequently after hepatitis B (40.5%) and human papillomavirus (15.6%) vaccines.^[26] More than 200 cases of uveitis after the mRNA or vector-borne vaccines have been reported as per the US Food and Drug Administration Vaccine Adverse Event Reporting System.^[28] In the review of published literature, a definite predilection for females was not observed. Only three patients had any known pre-existing autoimmune disease. In addition to the concept of molecular mimicry between the vaccine peptide fragments and uveal self-peptides, delayed hypersensitivity and immune complex deposition as triggers for the inflammation have also been suggested.^[21] The role of vaccine-induced type 1 interferon secretion driving autoimmune phenotypes in the background of autoimmunity is another concept that may explain the high frequency of anterior uveitis after mRNA vaccines. The uveitis, however, is mild and easily controlled with topical corticosteroids and cycloplegics.

Multiple evanescent white dot syndrome

Two cases of multiple evanescent white dot syndrome (MEWDS) were reported by Rabinovitch *et al.*²⁴ Both presented shortly after the second dose and improved without any treatment.



Figure 4: (a) Fundoscopy, (b) autofluorescence, and (c) fluorescein angiography of both eyes showing serous retinal detachment, optic disc hyperemia, and choroidal inflammation in a patient with Vogt-Koyanagi-Harada syndrome after COVID-19 vaccination. (Reproduced with permission from Saraceno JJ, Souza GM, dos Santos Finamor LP, Nascimento HM, Belfort R. Vogt-Koyanagi-Harada Syndrome following COVID-19 and ChAdOx1 nCoV-19 (AZD1222) vaccine. *International Journal of Retina and Vitreous*. 2021 Dec;7(1):1-7.)

Choroid

Choroiditis

In multifocal choroiditis, the pathological process lies in the retinal pigment epithelium (RPE). Two cases of bilateral choroiditis presenting 4–5 days after vaccination have been published. The case from India was in a healthy male who developed symptoms after the second dose of the viralvector-based vaccine, Covishield. The patient had systemic symptoms of headache, ocular pain, and pain at the injection site for 2 days after both doses of the vaccine.^[27] The second case from China was following the first dose of the inactivated vaccine.^[28] Both patients responded to corticosteroids.

Central serous chorioretinopathy (CSCR)

In January 2021, Fowler *et al.* reported the only case of central serous chorioretinopathy in a 33-year-old healthy male after 3 days of the first dose of the mRNA vaccine.^[29] The OCT and fluorescein angiography (FA) showed the typical features of CSCR. [Fig. 5] The patient was initiated on spironolactone, and it resolved in 3 months. In the absence of any other risk factor for CSCR, (space)like the use of corticosteroids or type A personality, the authors attributed it to the vaccine.^[29] A second case of forme fruste CSCR has been reported by Pichi *et al.* after the Sinopharm inactivated COVID-19 vaccine.^[16] Rare cases of CSCR after influenza, yellow fever, anthrax, and small pox

Table 3: Review of literature of posterior segment manifestations of COVID-19 vaccines

Author	Type	Location	Sample	Age	Sex	Systemic/ocular illness	Vaccine	Dose
Saraceno <i>et al.</i> ^[18]	Letter to editor	Brazil	1	62	F	-	ChAdOx1 nCoV-19 AZD1222 viral vector based	-
Koong <i>et al.</i> ^[19]	Letter to editor	Singapore	1	54	M	DM, hyperlipidemia	BNT162b2 mRNA	1
Papasavas <i>et al.</i> ^[20]	Case report	Switzerland	1	43	F	VKH treated with corticosteroids, infliximab. In remission for 6 years	BNT162b2 mRNA	2
ElSheikh <i>et al.</i> ^[21]	Letter to editor	USA	1	18	F	JIA, ANA positive, no prior history of uveitis	BB1Pp-CorV inactivated	2
Jain <i>et al.</i> ^[22]	Letter to editor	India	1	27	M	JIA with HLAB27 on adalimumab for 3 years, discontinued.	ChAdOx1 nCoV-19 viral vector based	1
Renisi <i>et al.</i> ^[23]	Case report	Italy	1	23	M	Recurrent panic attacks on benzodiazepines	BNT162b2 mRNA	(1), 2
Rabinovitch <i>et al.</i> ^[24]	Retrospective study	Israel	21				BNT162b2 mRNA	
				43	F	OU anterior uveitis		1
				34	M	Ankylosing spondylitis, OU anterior uveitis		1
				34	F	Mild psoriasis, OS anterior uveitis		1
				78	M	-		2
				53	M	Crohn's		1
				64	M	-		1
				68	M	-		1
				61	F	OU anterior uveitis		1
				59	M	-		2
				72	M	Ankylosing spondylitis		2
				51	M	Ankylosing spondylitis		2
				42	F	OU anterior uveitis		2
				74	M	-		2
				39	M	-		2
				64	F	Herpes zoster ophthalmicus, OD keratouveitis		2
				50	F	OU anterior uveitis		2
				23	F	-		2
				65	F	-		2
				36	M	OS anterior uveitis		2
				41	M	-		1
				28	F	-		2
				28	M	Behcet's disease, on colchicine	BNT162b2 mRNA	1
Ishay <i>et al.</i> ^[25]	Case series	Israel	1 (8)				BNT162b2 mRNA	2
Mudie <i>et al.</i> ^[26]	Case report	USA	1	43	F	-	ChAdOx1 nCoV-19 viral vector based	2
Goyal <i>et al.</i> ^[27]	Letter to editor	India	1	34	M	-		2
Pan <i>et al.</i> ^[28]	Case report	China	1	50	F	-	Inactivated vaccine	1
Fowler <i>et al.</i> ^[29]	Case report	USA	1	33	M	-	BNT162b2 mRNA	1
Pichi <i>et al.</i> ^[16]	Case series	Abu Dhabi	1 (7)				BB1Pp-CorV inactivated	1
Bialasiewicz <i>et al.</i> ^[30]	Letter to editor	Qatar	1	50	M	Atopic dermatitis on topical treatment	BNT162b2 mRNA	2

Contd...

Table 3: Contd...

Author	Type	Location	Sample	Age	Sex	Systemic/ocular illness	Vaccine	Dose
Endo <i>et al.</i> ^[31]	Case report	Colombia	1	52	M	-	BNT162b2 mRNA	1
Goyal <i>et al.</i> ^[32]	Letter to editor	India	1	28	M	-	Gam-COVID-Vac viral vector based	2
Mambretti <i>et al.</i> ^[33]	Letter to editor	Italy, Austria	2	22	F	OCP	ChAdOx1 nCoV-19 AZD1222 viral vector based	1
Patel <i>et al.</i> ^[34]	Case report	USA	1	26	F	OCP	ChAdOx1 nCoV-19 AZD1222 viral vector based	1
Vinzamuri <i>et al.</i> ^[35]	Case report	India	1	35	M	-	JNJ-78436735 viral vector based	1
Book <i>et al.</i> ^[36]	Images	Germany	1	21	F	OCP	ChAdOx1 nCoV-19 AZD1222 viral vector based	1
Valenzuela ^[37]	Case report	USA	1	20	F	Vaginal ring with ethinyl estradiol	BNT162b2 mRNA	2
Drüke <i>et al.</i> ^[38]	Case report	Germany	1	23	F	JIA associated iritis, OCP	ChAdOx1 nCoV-19 AZD1222 viral vector based	-
Böhler <i>et al.</i> ^[39]	Brief communication	Norway	1	27	F	OCP	ChAdOx1 nCoV-19 AZD1222 viral vector based	1
Pichi <i>et al.</i> ^[16]	Case series	Abu Dhabi	3 (7)*			OU CSCR with chronic serous PED in OS	BB1BP-CorV inactivated	1
Michel <i>et al.</i> ^[40]	Case report		1	21	F	OCP	BB1BP-CorV inactivated	1
Mishra <i>et al.</i> ^[41]	Case report	India	1	71	M	Chickenpox 25 years ago, DM, HTN	ChAdOx1 nCoV-19 AZD1222 viral vector based	1
Maleki <i>et al.</i> ^[42]	Case report	USA	1	33	F	Preeclampsia, unexplained miscarriage	mRNA-1273 mRNA	2

Author	Duration between vaccine and symptoms (days)	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
Saraceno <i>et al.</i> ^[18]	4	Headache, tinnitus	OU	Acute vision loss, AC and vitreous cells, serous RD	VKH	Oral prednisolone 1.5 mg/kg/day	Resolved, 3 weeks
Koong <i>et al.</i> ^[19]	1	-	OU	Bilateral serous RD, disc staining in late stages of FA	VKH	IVMP, oral corticosteroids	Improved, on follow up
Papasavvas <i>et al.</i> ^[20]	42	-	OU	AC inflammation, mutton fat KPs, subretinal fluid, increasing choroidal thickness on EDI OCT	Reactivation of VKH	Oral corticosteroids, infliximab	Resolved
EISheikh <i>et al.</i> ^[21]	5	-	OU	Anterior uveitis	JIA associated uveitis	Topical corticosteroids and cycloplegics	Resolved, 6 weeks
Jain <i>et al.</i> ^[22]	2	-	OS	Pain, redness, AC cells 2+, non granulomatous KPs	Uveitis	Topical corticosteroids, cycloplegics	-
Renisi <i>et al.</i> ^[23]	14	-	OS	Pain, photophobia, post synechiae, AC cells, KPs	Acute anterior uveitis	Topical corticosteroids, cycloplegics	Resolved 6 weeks

Contd...

Table 3: Contd...

Author	Duration between vaccine and symptoms (days)	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
Rabinovitch <i>et al.</i> ^[24]	2	Fatigue	OD	Redness, pain, blurred vision, C+3, F+1, fibrin	Anterior uveitis	PF q1hwa, Dex-oint nocte, Cyclo x3/d	Complete resolution
	4		OD	Redness, pain C+1, nongranulomatous KPs	Anterior uveitis	Dex-SP q3hwa, Tropi x1/d	Complete resolution
	1	Pain, fatigue	OS	Redness, pain, photophobia C+2, nongranulomatous KPs	Anterior uveitis	Dex-SP q2hwa, Dex-oint nocte, Tropi x3/d	Complete resolution
	3		OS	Redness, pain, blurred vision C+2, F+2, posterior synechiae	Anterior uveitis	PF q2hwa, Dex-oint nocte, Cyclo x3/d,	Complete resolution
	13	Pain, headache	OS	Pain C+0.5	Anterior uveitis	Dex-SP x4/d, Tropi x1/d	Complete resolution
	14	-	OS	Pain, redness, photophobia, C+0.5	Anterior uveitis	Dex-SP x4/d, Tropi x1/d	Complete resolution
	5	Nausea	OD	Redness, pain, C+1	Anterior uveitis	PF q3hwa, Cyclo x1/d	Complete resolution
	12	-	OD	Pain, photophobia, C+2	Anterior uveitis	PF q2hwa, Dex-oint nocte Cyclo x3/d,	Complete resolution
	8	Fatigue	OS	Pain, photophobia, blurred vision C+2	Anterior uveitis	PF q2hwa, Cyclo x3/d, Dex-oint nocte	Complete resolution
	16	-	OD	Redness C+1	Anterior uveitis	Dex-SP q3hwa, Tropi x1/d	Complete resolution
	2	-	OS	Redness, pain C+2	Anterior uveitis	Dex-SP q2hwa, Dex-oint nocte, Tropi x3/d	Complete resolution
	20	-	OU	Pain, blurred vision C+2	Anterior uveitis	Dex-SP q2hwa, Tropi x3/d, Dex-oint nocte,	Complete resolution
	7	-	OS	Pain C+1, F+2	Anterior uveitis	PF q3hwa, Cyclo x3/d	Complete resolution
	5	-	OS	Blurred vision, visual field defect, photopsia Outer retinal changes	MEWDS	No treatment	Significant improvement
	6	-	OD	photophobia C+1	Anterior uveitis	po Valacy 1g x3/d, Dex-SP q3hwa, Tropi x1/day	Complete resolution
	2	Pain	OS	Pain C+1	Anterior uveitis	Dex-SP q3hwa, Tropi x1/d	Complete resolution
	2	Pain, fatigue	OU	Redness, blurred vision, photophobia C+1, F+1	Anterior uveitis	PF q3hwa, Tropi x2/d	Complete resolution
	3	Pain	OD	Redness, pain, photophobia, blurred vision C+2, F+2	Anterior uveitis	PF q2hwa, Dex-oint nocte, Cyclo x3/d	Complete resolution

Contd...

Table 3: Contd...

Author	Duration between vaccine and symptoms (days)	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
	1	Pain, flu like, fatigue	OS	Redness, photophobia, blurred vision, C+3, F+3, granulomatous KPs	Anterior uveitis	PF q1hwa, Dex-oint nocte, Cyclo x3/d	Complete resolution
	2	Pain	OD	Redness, photophobia, blurred vision, C+2, F+2	Anterior uveitis	PF q2hwa, Dex-oint nocte, Cyclo x3/d	Complete resolution
	30	Fever	OS	Blurred vision, visual field defect, photopsia, outer retinal changes	MEWDS	No treatment	Significant improvement
Ishay <i>et al.</i> ^[26]	10		OS	Pain, redness, photophobia, leukocytosis, elevated ESR, CRP	Panuveitis	IVMP, topical prednisolone, oral corticosteroids, azathioprine	Improvement
Mudie <i>et al.</i> ^[26]	3	Asymptomatic COVID-19 after vaccination	OU	AC and vitreous cells, OCT- choroidal thickening, FA- peripheral vascular leakage	Panuveitis	Oral and topical corticosteroids	Recurrence after 3 weeks, on extended tapering of corticosteroids
Goyal <i>et al.</i> ^[27]	4	Headache, ocular pain, myalgia, injection site pain	OU	6/36, large serous RD, nilateral yelloweye oval lesions in choroid from macula to mid periphery	Bilateral multifocal choroiditis	Oral corticosteroids	Improved, 2 weeks
Pan <i>et al.</i> ^[28]	5		OU	Bilateral posterior uveitis, FA	Bilateral choroiditis	Periocular, oral corticosteroids	Improved, 5 weeks
Fowler <i>et al.</i> ^[29]	3	Fatigue, soreness at injection site	OD	Metamorphopsia, serous detachemnt of neurosensory retina	CSCR	Spironolactone 50 mg/ day	Resolved, 3 months
Pichi <i>et al.</i> ^[16]			OU	SRF, hypertrophy of photoreceptor layer	SRF, forme fruste CSCR		
Bialasiewicz <i>et al.</i> ^[30]	15 mins	-	OS	Retrolubar pain, redness, diminution of vision	Hemorrhagic CRVO	Low dose acetylsalicylic acid, monthly aflibercept	Resolved CME, on follow up
Endo <i>et al.</i> ^[31]	15	-	OS	Sudden blurring of vision, retinal venous dilatation, tortuosity, dot hemrrhage, exudates	Non ischemic CRVO	Intravitreal dexamethasone, bevacizumab, oral apixaban	Visual acuity improved
Goyal <i>et al.</i> ^[32]	11	-	OD	Visual deterioration, CME	Superior HRVO	Oral prednisolone 40 mg, apixaban 2.5 mg	Improving, 10 days, on follow up
Mambretti <i>et al.</i> ^[33]	2	Fever 24 hrs	OD	Acute paracentral scotoma, barely visible parafoveal lesions	AMN	-	-
Patel <i>et al.</i> ^[34]	2	Fever 24 hrs	OD	Acute paracentral scotoma.	AMN	-	-
	2	-	OU	Paracentral scotoma. OCT parafoveal hyperreflective bands in outer retina	AMN		

Contd...

Table 3: Contd...

Author	Duration between vaccine and symptoms (days)	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
Vinzamuri <i>et al.</i> ^[95]	28	-	OU	1st dose- mild blurring of vision. 2nd dose- blurry vision, AS Ps normal, reduced brightness sensitivity	AMN, PAMM	Observation	Better 3 weeks
Book <i>et al.</i> ^[96]	3	-	OU	Paracentral scotoma, circumscribed paracentral dark areas	AMN	Observation	
Valenzuela ^[37]	2	Myalgia, headache and bilateral anterior cervical and supraclavicular lymphadenopathy, difficulty in swallowing- treated with oral prednisolone and diphenhydramine	OU	Photopsia, paracentral scotomata on VF, OCT	AMN	obs	Resolved 14 days
Drüke <i>et al.</i> ^[98]	1	Headache, cervical pain	OU	Paracentral scotoma, subtle brownish rimmed parafoveal lesion, IR, disruption of EZ and IZ	AMN	40 mg prednisolone x 1 week	Improved, 15 weeks
Bohler <i>et al.</i> ^[99]	2	Flu like symptoms	OS	Paracentral scotoma, tear drop shaped lesion nasal to fovea, perimetry, SS OCT	AMN	-	-
Pichi <i>et al.</i> ^[16]			OS	Acute vision loss, SDOCT findings	AMN	Observation	Resolved, 2 months
Michel <i>et al.</i> ^[40]	2	Persistent tachycardia, SBP 210 mmHg	OS	Blurry vision, headache, inferior scotoma, OCT and OCT-A characteristic	AMN PAMM		
Mishra <i>et al.</i> ^[41]	3	Fever and chills	OS	Central scotomas, 20/20, IR well demarcated dark lesion near fovea, SDOCT findings; high ESR, CRP	AMN	Observation	Improvement, on follow up
		Fever, myalgia	OD	FC1m, panuveitis, vitritis, disc hyperemia, large areas of yellow white retinal opacification	Reactivation of VZV ARN	valacyclovir 1 g TID + topical corticosteroids, cycloplegic, gancyclovir- ntravitreal, oral corticosteroids	Resolved
Maleki <i>et al.</i> ^[42]	10		OU	OCT- disruption of outer retinal layers, nasal visual field defect, multifocal ERG defect. High ESR, CRP	AZOOOR	OS intravitreal dexamethasone implant	

*Case series with 7 patients, 3 developed AMN/PAMM. AC: anterior chamber, AMN: acute macular neuroretinopathy, ANA: anti-nuclear antibody, AZOOOR: acute zonal occult outer retinopathy, C: cells, CME: cystoid macular edema, CRP: C-reactive protein, CRVO: central retinal vein occlusion, CSCR: central serous chorioretinopathy, Cyclo, cyclopentolate 1%, Dex-oint, ointment containing dexamethasone 1mg, neomycin sulphate 3500 I.U., Polymyxin B sulphate 6000 I.U; Dex-Sp, dexamethasone sodium phosphate 0.1%, DM: diabetes mellitus, EDI: enhanced depth imaging, ERH: electroretinography, ESR: erythrocyte sedimentation rate, F: female, F+: flare, FA: fluorescein angiography, FC: finger counting, IVMP: intravenous methylprednisolone, JJA: juvenile idiopathic arthritis, HRVO: hemiretinal vein occlusion, HTN: hypertension, KP: keratic precipitates, M: male, MEWDS: multiple evanescent white dot syndrome, OCP: oral contraceptive pill, OCT: optical coherence tomography, OD: right eye, OS: left eye, OU: both eyes, PAMM: paracentral acute middle maculopathy, PED: pigment epithelial detachment, PF, prednisolone acetate 1%; po, peroral; q-hwa, every - hours while awake, RD: retinal detachment, SBP: systolic blood pressure, SD: spectral domain, SRF: subretinal fluid, SS: swept source, Tropi, tropicamide 0.5%; Valacy, Valacyclovir hydrochloride VF: visual field, VKH: Vogt-Koyanagi-Harada disease, VZV: varicella zoster virus

vaccines have been described. mRNA-induced endogenous glucocorticoid release and increased permeability of endothelial cells and leaky choriocapillaris on exposure to extracellular naked RNA are the possible pathological mechanisms for the development of CSCR after COVID-19 vaccination.^[29]

Retinal vascular occlusions

Central and hemi- retinal vein occlusion

Bialasiewicz *et al.* and Endo *et al.* reported a case of central retinal vein occlusion (CRVO) each from Qatar and Colombia, respectively.^[30,31] [Fig. 6] Systemic vascular events have been reported following the adenoviral vector-based vaccines, but these are rare with mRNA vaccines with isolated cases being reported of deep vein thrombosis and thrombocytopenia.^[43,44] In the eye, both were following the Pfizer-BNT mRNA vaccine. One patient, with atopic dermatitis developed acute onset of pain, redness, and reduction of vision within a few minutes of administration of the second dose of the vaccine. Fundus examination showed a hemorrhagic CRVO and was treated with monthly intravitreal aflibercept injections and low dose acetylsalicylic acid as an antithrombotic measure. The retinal findings improved, and the patient is still under active treatment.^[30] The second case was of a healthy 52-year-old male who developed nonischemic CRVO after 15 days of the first dose of the vaccine. He was treated with intravitreal corticosteroid injection initially, and intravitreal bevacizumab was added later along with oral apixaban.^[31] This issue of Indian Journal of Ophthalmology (IJO) has a case of hemiretinal vein occlusion (HRVO) reported in a young healthy male following the second dose of Sputnik V vaccine.^[32] The patient's blood work-up, inflammatory markers, and coagulation profile were unremarkable as was the history for any systemic diseases increasing the risk of vascular occlusive events. The patient had strongly positive antibodies IgG to the vaccine and may represent an unusually enhanced immune and possible inflammatory response to the vaccine.^[32] The development of retinal vascular

occlusions in patients with no other systemic risk factors suggests a possible association of the vaccine to the event.

Acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM)

AMN typically affects young women with changes observed in the optical coherence tomography (OCT) and subtle reddish wedge-shaped lesion directed towards the fovea on fundus evaluation with an ischemic origin in the deep capillary plexus or choriocapillaris. PAMM shows hyperreflective band-like lesions in the outer plexiform layer (OPL)/inner nuclear layer (INL) junction on OCT.^[35] Thirteen cases of AMN following COVID-19 vaccine have been published to date. There was a definite female predilection (8 of 9 patients), and all of them gave a history of using contraceptives – oral or vaginal ring with ethinyl estradiol.^[33,34,36,37,39] Oral contraceptives (OCPs) are a known risk factor for AMN and the vaccine-related inflammation may aggravate a pre-existing thrombophilic state in patients on OCPs.^[34] The only male patient with the reported complication had simultaneous PAMM and had ocular manifestations after both doses of the vaccine. This case was also unique in that the ocular symptoms developed almost 4 weeks after the second dose of the vaccine.^[35] The remaining five presented with the mild blurring of vision, paracentral scotomas, photopsia, and floaters within 3 days of the vaccination. Drüke *et al.*^[38] reported a case of AMN in a 23-year-old female with JIA-associated iritis treated with methotrexate, sulfasalazine, and topical corticosteroids. This was the only patient who was treated with oral corticosteroid for the AMN, all others were observed with spontaneous resolution of the OCT findings. Eight patients received the viral vector-based vaccine (Janssen, Covishield, AstraZeneca). In the retrospective case series from Abu Dhabi by Pichi *et al.*, there are reports of three more patients who developed AMN and PAMM after the first dose of the inactivated Sinopharm vaccine.^[16] Viral febrile illness (influenza, dengue, CMV, SARS-CoV-2), vasoconstrictors,



Figure 5: Clinical evaluation of a patient with unilateral central serous retinopathy. The right eye (left column) and left eye (right column) are shown. Fundus photography of the posterior pole (a) of the right eye shows an inferotemporal parafoveal depigmented lesion. The left eye fundus was normal. Optical coherence tomography (b) of the right eye shows a serous detachment of the neurosensory retina in the central macula. (Reproduced with permission from Fowler N, Martinez NR, Pallares BV, Maldonado RS. Acute-onset central serous retinopathy after immunization with COVID-19 mRNA vaccine. *American Journal of Ophthalmology Case Reports.* 2021 Sep 1;23:101136.)

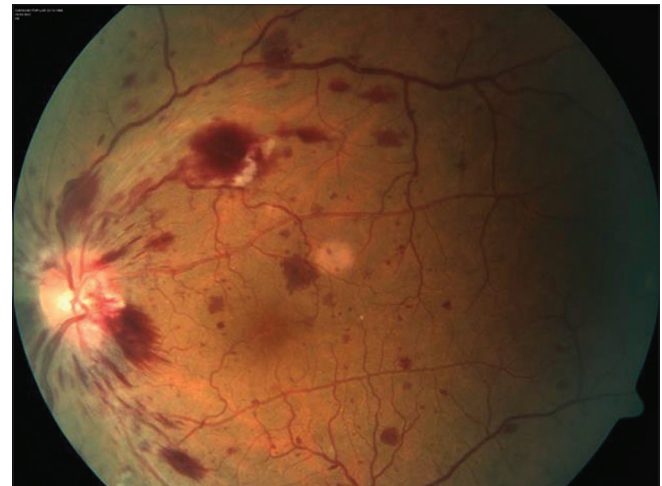


Figure 6: Color fundus photograph of the left eye of a patient with central retinal vein occlusion following COVID-19 vaccination showing dot-blot and flame-shaped hemorrhages, dilated tortuous veins, and blurred margins in the disc, especially in the temporal quadrant (Reproduced with permission from Endo B, Bahamon S, Martínez-Pulgarín DF. Central retinal vein occlusion after mRNA SARS-CoV-2 vaccination: A case report. *Indian Journal of Ophthalmology.* 2021 Oct 1;69 (10):2865-6.)

hypovolemic shock, anemia, thrombocytopenia, and hyperviscosity are other risk factors for AMN. The development of AMN in a male patient, patients with JIA, response to immunosuppressants, and delayed manifestation indicate an inflammatory, vasculitic mechanism at play rather than a direct result of vaccination. The case following the second dose of mRNA vaccination reported by Valenzuela *et al.* suggests the role of immune-mediated development of AMN and PAMM.^[37] AMN has also been reported following influenza vaccination.^[45,46] Five patients had bilateral disease and normal anterior segment findings. The fundus is often normal, and the lesion is best appreciated in infrared reflectance. It is possible that many cases of AMN and PAMM are not diagnosed due to the lack of obvious ocular findings. Awareness of the disease and its association with vaccination, and a high degree of suspicion are essential for the diagnosis.

Retina

Acute retinal necrosis (ARN)

Mishra *et al.* reported the only case of ARN following the viral vector-based vaccine, Covishield, with reactivation of varicella-zoster infection in an immunocompetent male with a history of chickenpox 25 years ago. It was preceded by fever and myalgia after the vaccination.^[41] ARN has been reported after the influenza vaccine and SARS-CoV-2 infection. A case series of seven adults developing varicella zoster virus (VZV) reactivation after COVID-19 vaccination has been published and involves a T-cell-mediated immune mechanism.^[47] ARN may resolve spontaneously in immunocompetent patients. In the case of ARN reported, the anti-SARS-CoV-2 spike protein antibodies following vaccination were inadequate, and he was treated with valacyclovir, topical corticosteroids, cycloplegic, intravitreal ganciclovir, and oral corticosteroids. Firstly, it could be immunosenescence, and reduced thymic production of T-cells, which after vaccination caused a relative paucity of T-cell-mediated immunity at the site of VZV infection and its intraocular spread via long ciliary nerves. Secondly, an exhaustion of T-cells following vaccination could lead to a reactivation of VZV, leading to acute retinal necrosis. The third possibility could be a cross-reaction between COVID-19 anti-spike antibodies with varicella zoster spike glycoprotein amino acids amounting to anergy of T-cell-mediated immunity and subsequent reactivation of VZV.^[41]

Acute zonal occult outer retinopathy (AZOOR)

A single case of bilateral AZOOR was documented by Maleki *et al.* in a healthy woman 10 days after vaccination with the Moderna mRNA-1273 vaccine.^[42] There was a nasal visual field defect in the left eye, and multifocal electroretinography (ERG) showed defective areas in inferotemporal macula in the right eye and temporal macula in the left eye. OCT showed characteristic disruption of the outer retinal layers. The patient was treated with an intravitreal dexamethasone implant in the left eye. Elevated erythrocyte sedimentation rate (ESR) indicated the inflammatory nature of the pathology. T helper cells and cross-reacting antibodies against the outer retinal layers and retinal pigment epithelial cells were most likely involved in the pathogenesis.

Several posterior segment ophthalmic features of the COVID-19 infection have been reported and are associated with the procoagulant/prothrombotic state created by the cytokines released in response to the virus. The immune dysregulation

induced by the virus can also lead to many of the ocular diseases described. The association of the vaccine with the rare retinal and uveal manifestations may be coincidental given the large scale of vaccination drive. However, the adenoviral vector vaccines have been associated with potentially life-threatening cerebral venous sinus thrombosis.^[48] The pathogenesis is similar to the autoimmune heparin-mediated thrombocytopenia involving the activation of the coagulation cascade by the platelet-activating autoantibodies against platelet factor 4. The adverse event, vaccine-induced immune thrombotic thrombocytopenia (VITT) has been noted most frequently in young women within the first 3 weeks. The reported rate is close to five cases per million vaccinated adults (April 2021) for the AstraZeneca vaccine that contains chimpanzee replication-incompetent adenovirus without modification to mitigate the shedding of the expressed S protein. The S protein in the circulation can induce a proinflammatory/procoagulant response.^[49] The rate is 0.87 cases per million for the Johnson and Johnson vaccine (April 2021) with human replication-incompetent adenovirus. The complication has not been reported with the mRNA-based vaccines.

Vaccine-related uveitis is not uncommon, both mild, transient anterior uveitis and more severe posterior and panuveitis have been reported. Stimulation of cytokine production, modification of surface antigens, and induction of new antigens with molecular mimicry to host tissue antigens, polyclonal B-cell activation, epitope spreading, bystander activation, and reaction to adjuvants are all the suggested mechanisms.^[27]

It was difficult to identify any specific trend other than the female gender and OCPs being used by the majority of the cases who developed AMN and association of the Pfizer mRNA vaccine with mild anterior uveitis. There may be multiple mechanisms at play simultaneously. Patients with a history of autoimmune diseases or JIA should be educated about the symptoms of floaters, scotoma, decreased contrast sensitivity, photopsia, and blurring of vision after vaccination and advised to seek medical attention at the earliest.

Neuro-ophthalmic Manifestations of COVID-19 Vaccine

The COVID-19 vaccines have been observed to produce several neuro-ophthalmic manifestations. While most are transient, self-resolving, and mild, there are some that leave a residual effect. At present, there are 22 cases with neuro-ophthalmic adverse effects [Table 4].^[39,50-59] These aside, Shemer *et al.* have reported 21 cases of patients with acute facial palsy following COVID-19 vaccination in a retrospective case-control study.^[60] These cases have not been included in the Table 4 as all the details of the individual cases were not available. The mean age of the patients was 58.3 ± 20.6 (median 61.5) years with 11 males and 11 females. Thirteen patients had received the Pfizer mRNA vaccine, 4 had received Covishield, 3 inactivated CoronaVac from Sinovac, 1 Moderna mRNA vaccine, and 1 Covaxin. The events were equally distributed between the first (9) and second (8) doses, 1 patient developed facial palsy after both the first and second doses, and the dose status was not specified in 4 cases. The median interval of development of symptoms from the vaccination was 4 (mean 7.8 ± 8.1) days.

Optic nerve

Arteritic anterior ischemic optic neuropathy (AAION)

In the only reported case of AAION, a 79-year-old presented with bilateral loss of vision and optic disc pallor on examination 2 days after the second dose of the Pfizer-mRNA vaccine. The diagnosis was confirmed with elevated ESR and CRP and temporal artery biopsy. The authors attributed it to be an immune-mediated inflammation involving cross-reacting antibodies produced against the SARS-CoV-2 spike protein and helper T cells cross-reacting with proteins and antigens of large arteries. The patient was treated with high-dose intravenous methylprednisolone for 3 days followed by oral corticosteroids.^[42]

Optic neuritis

Acute optic neuritis is an idiopathic disease presenting with painless vision loss and is usually unilateral and inflammatory. Leber *et al.* reported a case of bilateral optic neuritis with symptoms developing within 12 hours of vaccination with the second dose of inactivated CoronaVac vaccine.^[50] The patient's infectious and inflammatory workup was unremarkable barring the detection of reactive MOG-IgG and elevated thyroid-stimulating hormone, antithyroglobulin, and antithyroid peroxidase.^[50] The optic neuritis in this patient may be the initial manifestation of a demyelinating disorder associated with MOG-IgG, and the patient needs to be followed up for evaluation. She also had subacute thyroiditis which responded to the corticosteroid therapy. The second case of optic neuritis was in a healthy 28-year-old female after the first dose of vector-based Covishield vaccine.^[53] Immune-mediated optic neuritis has been documented with BCG, hepatitis B, and tetanus vaccines.

Acute vision loss

Two separate cases of acute, unspecified, transient episodes of visual loss have been reported in middle-aged, relatively healthy males. The case reported by Santovito *et al.* was following the second dose of the Pfizer mRNA vaccine.^[51] The patient had a prior history of COVID-19 infection. He developed fever with chills after the vaccination. The case description was subjective as no formal evaluation was done, and the patient presented after the spontaneous resolution the same day. There was sudden onset darkening of the visual field and visual distortion associated with nausea, light confusion, and asthenia. The second case was interesting because it was the self-observed report by an ophthalmologist who described the sudden onset of bilateral blurring of vision within an hour of the second dose of the CoronaVac vaccine. Computerized automated perimetry showed left congruous hemianopia respecting the vertical midline. The eye examination, OCT, neurological evaluation, blood investigations including lipid and coagulation profile, magnetic resonance imaging (MRI) were unremarkable. Only the blood pressure of the patient was elevated from the baseline to 150/90 mmHg. There was a spontaneous resolution, though the patient was admitted for observation, intravenous fluids, and oral aspirin. The author gives a logical and acceptable explanation – acute arterial vasospasm in the postchiasmatic visual pathway, most likely the right occipital lobe with macular sparing, with reperfusion to produce complete recovery.^[52]

Cranial nerve palsies

Abducens nerve palsy

Reyes-Capo *et al.* reported one case of acute abducens nerve palsy in a 59-year-old female, 2 days after vaccination with

Pfizer mRNA vaccine. She developed sudden onset diplopia and right esotropia. Although the ESR and CRP were mildly elevated, her MRI was normal.^[54] Two cases have been reported from India after the vector-based Covishield vaccine.^[53] Abducens nerve palsy has been described following immunization with diphtheria-pertussis-tetanus (DPT), measles-mumps-rubella (MMR), hepatitis B, and influenza vaccine and can occur any time between 2 days and 3 weeks with spontaneous, slow resolution. An immune-mediated vasculitis, thrombosis, or demyelination have been proposed as possible mechanisms for the vaccine-associated nerve palsy.

Oculomotor nerve palsy

Pappaterra *et al.* reported a case of partial, pupil sparing oculomotor nerve palsy in an 81-year-old male with hypertension, diabetes, and hypercholesterolemia, 4 days after the first dose of Moderna mRNA-1273 vaccine.^[55] An MRI and MR angiography were done to rule out ischemic or aneurysmal compression. The patient gave a history of COVID-19 infection in the past, and the authors suggest reactivation of the COVID-19-associated immune phenomena with molecular mimicry. In an older individual with known risk factors, a microvascular ischemic event causing pupil sparing 3rd nerve palsy is highly plausible. But the quick recovery and temporal association led the authors to consider the role of the vaccine.^[55]

Facial nerve palsy: Bell's palsy and Ramsay-Hunt syndrome

Cases of facial palsy have been included in this review because of the ocular implications due to lagophthalmos [Fig. 7]. Shemer *et al.* reported the largest series (9 cases) of facial nerve palsy after vaccination with Pfizer mRNA vaccine in Israel.^[56] Bell's palsy is an acute, idiopathic, unilateral facial palsy often related to a preceding viral infection. The clinical features were typical, and cases of Bell's palsy responded well to prompt initiation of systemic corticosteroids. The ocular surface must be protected with liberal use of lubricants and night-time taping. Yu *et al.* reported the first case of Bell's palsy, following an inactivated vaccine in a patient who had a history of Bell's palsy in the past.^[58] COVID-19 vaccine trials have documented cases of facial palsy, four with Pfizer-BioNTech and three with the Moderna mRNA vaccine compared to a single case in the placebo arm of the trial.^[61,62] Ozonoff *et al.* reviewed the vaccines trials and concluded that the observed incidence of Bell's palsy following mRNA vaccines was 3.5–7 times higher than the expected incidence in the general population (15–30/100000/year).^[63] The risk is also higher after the second dose. In a retrospective case-control study, Shemer *et al.* found no association between vaccination with BNT162b2 mRNA vaccine and development of new-onset facial palsy after adjustment for pre-existing immune or inflammatory diseases, diabetes, and previous episode of peripheral nerve palsy.^[60] Like the other ophthalmic manifestations, Bell's palsy is not unique to the COVID-19 vaccine and has been described post influenza, hepatitis B, polio, DPT, and MMR vaccines. Conflicting and limited available data make definitive conclusions about a causal relation difficult. The autoimmune process with host cell mimicry, bystander activation of dormant autoreactive T-cells, or induction of innate immunity and interferon production by the combined effect of mRNA and lipids, could be responsible for the resultant facial nerve palsy.

Ramsay-Hunt syndrome is caused by reactivation of latent VZV in the geniculate ganglion and is characterized by a

Table 4: Review of literature of neuro-ophthalmic manifestations of COVID-19 vaccines

Author	Type	Location	Sample	Age	Sex	Systemic/ocular illness	Vaccine	Dose	Duration between vaccine and symptoms (days)
Maleki <i>et al.</i> ^[42]	Case report	USA	1	79	F	Osteoporosis, osteoarthritis	BNT162b2 mRNA	2	2
Leber <i>et al.</i> ^[50]	Letter to editor	Brazil	1	32	F	Subacute thyroiditis	CoronaVac inactivated	2	12hours
Santovito <i>et al.</i> ^[51]	Letter to editor	USA	1	Middle aged	M	Dyslipidemia	BNT162b2 mRNA	2	3
Jumroendarasame <i>et al.</i> ^[52]	Case report	Thailand	1	42	M		CoronaVac inactivated	2	1 hour
Pawar <i>et al.</i> ^[53]	Letter to editor	India	4	28	F		ChAdOx1 nCoV-19 viral vector based	1	21
				24	F	Polio in childhood		1	21
				44	M	Chickenpox, recurrent 6 th nerve palsy			28
				Young adult	M				6
Reyes-Capo <i>et al.</i> ^[54]	Case report	USA	1	59	F	-	BNT162b2 mRNA	-	2
Pappaterra <i>et al.</i> ^[55]	Clinical correspondence	Puerto Rico	1	81	M	HTN, hypercholesterolemia, uncontrolled DM	mRNA-1273 mRNA	1	4
Shemer <i>et al.</i> ^[56]	Case report	Israel	9	86	F		BNT162b2 mRNA	1	14
				78	F			2	5
				79	M			1 and 2	4,2
				69	F			1	3
				73	F			1	12
				77	M			2	1
				64	M			1	7
				51	M			2	9
				35	M			1	4
Ish <i>et al.</i> ^[57]	Letter to editor	India	1	50	M		Covaxin	2	21
Yu <i>et al.</i> ^[58]	Case report	China	1	36	F		Sinovac inactivated	1	2
Rodríguez-Martín <i>et al.</i> ^[59]	Letter to editor	Spain	1	78	F	Childhood poliomyelitis, HTN	BNT162b2	-	3

Author	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
Maleki <i>et al.</i> ^[42]		OU	OU ON pallor. Temporal artery biopsy, high ESR, CRP	AAION	IVMP, oral corticosteroids	On follow up
Leber <i>et al.</i> ^[50]		OU	Decreased visual acuity, pain with ocular movements, headache. MRI normal. Subacute thyroiditis	Optic neuritis	IVMP, oral corticosteroids	Improved
Santovito <i>et al.</i> ^[51]	Fever chills. unilateral oppressive headache in parietal to frontal lobe		Sudden onset darkening of VF and subjective reduction of visual acuity. Associated with confusion, asthenia and nausea	Acute transient reduction of visual acuity	-	Spontaneously resolved

Contid...

Table 4: Contd...

Author	Systemic adverse reaction	Laterality	Clinical features	Diagnosis	Management	Outcome
Jumroendarasame <i>et al.</i> ^[52]	-	OU	Blurred vision starting centrally, 20/20, left congruous hemianopia respecting vertical midline. BP 150/90	Transient VF defect	IV fluids, oral aspirin	Spontaneously resolved
Pawar <i>et al.</i> ^[53]		OS	Sudden decrease in vision, blurred disc margins, MRI normal	Optic neuritis	IVMP	Resolved
		OU	Diplopia, restricted elevation, MRI normal	OU vertical gaze palsy	Systemic corticosteroids	Resolved
		OS	Diplopia	6 th nerve palsy	OS botox to MR	Minimal residual
		OS	Headache, esotropia	6 th nerve palsy		Resolved
Reyes-Capo <i>et al.</i> ^[54]	fever	OD	Acute binocular diplopia, right esotropia, abduction deficit. ESR, CRP mildly elevated	Abducens nerve palsy	Observation	Resolved
Pappaterra <i>et al.</i> ^[55]	-	OS	Binocular diplopia, ptosis, limited adduction, infraduction, no RAPD. Elevated CRP, normal ESR	Partial oculomotor nerve palsy	Observation	Spontaneously Resolved
Shemer <i>et al.</i> ^[56]		OS	Facial asymmetry, lagophthalmos, corneal punctate erosions	Facial palsy	oral glucocorticoids, artificial tears, temporary closure of eyelids at night	
		OS	Tinnitus, periauricular rash, bilateral SNHL, complete left sided facial palsy	Facial palsy	admitted, antimicrobial treatment, conventional treatment	
		OD	Facial asymmetry	Facial palsy	oral corticosteroids	
		OD	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
		OS	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
		OS	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
		OS	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
		OD	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
		OS	Facial asymmetry	Facial palsy	oral corticosteroids, AT	
Ish <i>et al.</i> ^[57]		OD	Lagophthalmos, LL temporal ectropion, right sided LMN facial palsy	Facial palsy	oral corticosteroids, AT	
					topical antibiotics and AT for eye, taping of the eye.	Improved, day 10, on follow up
Yu <i>et al.</i> ^[58]		OD	Bilateral keratoconjunctivitis, right sided facial weakness	Facial palsy	Oral prednisolone 1mg/kg for 2 weeks	
					Prednisolone x 1 week, AT, fluoromethalone eye drops, acupuncture	Resolved, 54 days
Rodríguez-Martin <i>et al.</i> ^[59]	instability, malaise, nausea, severe pain in ext aud canal	OD	Right sided facial palsy, left horizontal nystagmus, gait instability, bilateral snhl, vesicles and crusted lesions on concha	Ramsay Hunt syndrome		Persistent instability and SNHL. Facial palsy improved 2 weeks

AAION: arteritic anterior ischemic neuropathy, AT: artificial tears, BP: blood pressure, CRP: C reactive protein, DM: diabetes mellitus, ESR: erythrocyte sedimentation rate, F: female, HTN: hypertension, IV: intravenous, IVMP: intravenous methylprednisolone, LL: lower eyelid, LMN: lower motor neuron, M: male, MR: medial rectus, MRI: magnetic resonance imaging, OD: right eye, ON: optic nerve, OS: left eye, OU: both eyes, RAPD: relative afferent pupillary defect, SNHL: sensory neural hearing loss, VF: visual fields

vesicular rash on the concha of the ear and external auditory canal and peripheral facial nerve palsy. Influenza, and hepatitis B vaccines have been associated with Ramsay-Hunt syndrome, and the COVID-19 vaccines can be added to the list of vaccines implicated.^[59]

In addition to the cases elaborated in the table, Thunstedt et al reported a case of raised intracranial pressure in a healthy 23-year old male a week after receiving the AstraZeneca ChAdOx1 vaccine. Despite bilateral papilloedema, the patient had normal vision. Headache is a common side effect after the COVID-19 vaccines. However, persistent and pulsatile headache demands complete evaluation to rule out cerebral venous thrombosis, meningitis and drug related raised intracranial tension with CSF analysis and neuroimaging. Patient was successfully treated with acetazolamide and torsemide.^[64]

Orbital Manifestations of COVID-19 Vaccine

Orbital complications are uncommon, and there are four published reports to date. [Table 5]^[65-68] The mean age affected was 44.6 ± 11.3 (median 47.5) years with 3 females. There was one case each following the two mRNA vaccines from Pfizer and Moderna. Both cases of superior orbital vein thrombosis (SOVT) were following vaccination with ChAdOx1 nCoV-19 vaccine.^[67,68] Information about the vaccine dose was available for three patients, two of them were following the first dose and one after the second dose. The onset of symptoms was at a median of 6 (mean 6.3 ± 3) days from the time of vaccination.

Thyroid eye disease

Rubinstein et al. reported a case of thyroid eye disease in a patient with a history of Graves' disease for 11 years but without any ophthalmic involvement.^[65] The onset of eyelid edema, proptosis, ptosis, and diplopia were



Figure 7: IL of facial symmetry, incomplete right eye closure, loss of nasolabial fold, and drooping of the angle of the mouth of the right side suggestive of right-sided Bell's palsy (Reproduced with permission from Ish S, Ish P. Facial nerve palsy after COVID19 vaccination – A rare association or a coincidence. Indian J Ophthalmol 2021;69:2550-2.)

within 3 days of the second dose of vaccine. Thyroid ophthalmopathy was confirmed on clinical examination (CAS 5), computed tomography (CT) scan, and elevated serum thyroid-stimulating immunoglobulin. The patient responded to teprotumumab.

Tolosa-Hunt syndrome

Chuang et al. reported a case of Tolosa-Hunt syndrome following vaccination.^[66] [Fig. 8] A granulomatous inflammatory process involving the cavernous sinus remains a diagnosis of exclusion and responds to corticosteroids. Spontaneous remission has been reported.

Superior orbital vein thrombosis

Patients with SOVT present with headache, proptosis, ophthalmoplegia, diplopia, and diminished vision and filling defect on CEMRI with a dilated SOV confirms the diagnosis. Two cases of superior orbital vein thrombosis after the viral vector-based vaccine ChAdOx1 nCoV-19 vaccine have been published. In the report by Panovska-Stavridis et al., the patient had thrombocytopenia, high D-dimer levels, and platelet factor 4 antibodies.^[68] She was treated with intravenous immunoglobulin (IVIG) and tapering doses of oral corticosteroids. The second patient was an older female, fifty-five-year-old with features suggestive of secondary immune thrombocytopenia. She was treated with heparin but developed ischemic stroke.^[67]

As discussed in the previous section, cases of CSVT after the adenoviral vector vaccines have been described and are amongst the most serious adverse effects. Thrombotic

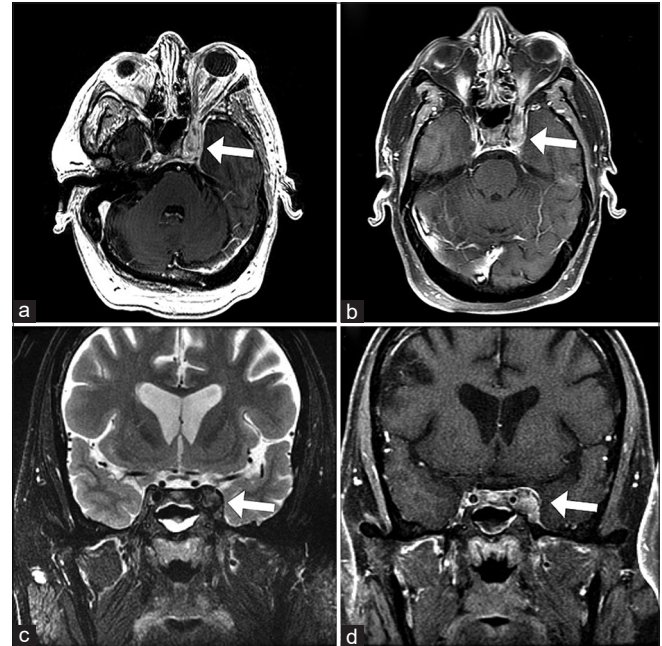


Figure 8: MRI of an inflammatory left cavernous sinus process consistent with Tolosa-Hunt syndrome T2 axial FLAIR (a) and FSE coronal (c) images showing bulky perineural tissue extending into the left cavernous sinus. The perineural tissue has heterogeneous postcontrast enhancement and slightly decreased enhancement centrally consistent with a component of thrombosis on postcontrast T1 axial (b) and coronal (d) images (Reproduced with permission from Chuang TY, Burda K, Teklemariam E, Athar K. Tolosa-Hunt Syndrome Presenting After COVID-19 Vaccination. Cureus. 2021 Jul; 13 (7).)

Table 5: Review of literature of orbital manifestations of COVID-19 vaccines

Author	Type	Location	Sample	Age	Sex	Systemic/ocular illness	Vaccine	Dose	Duration between vaccine and symptoms (days)	Systemic adverse reaction
Rubinstein ^[65]	Case report	USA	1	50	F	Graves' disease without ophthalmopathy since 11 years treated with radioactive iodine, hypertension, anxiety, hypothyroidism treated with levothyroxine	mRNA	2	3	
Chuang et al. ^[66]	Case report	USA	1	45	M	-	BNT162b2 mRNA	-	5	
Bayas et al. ^[67]	Clinical picture	Germany	1	55	F	-	ChAdOx1 nCoV-19 viral vector based	1	7	fever
Panovska-Stavridis ^[68]	Letter to editor	Republic of North Macedonia	1	29	F	-	ChAdOx1 nCoV-19 viral vector based	1	10	fever

Author	Laterality	Clinical features	Diagnosis	Management	Outcome
Rubinstein ^[65]	OU	Irritation, tearing, orbital pain, abduction limitation, proptosis, normal thyroid functions, normal inflammatory markers. CT- OS>OD enlarged IR, MR without tendon involvement or sinus disease.	Thyroid eye disease	IV teprotumumab	Improvement in congestion and proptosis
Chuang et al. ^[66]	OS	Severe left sided headache, progressive ptosis, decreased vision, RAPD, complete ophthalmoplegia. Inflammation and infection markers normal. Elevated CRP. CT and MRI	Tolosa Hunt syndrome	Initially antibiotics- discontinued after results of blood and CSF. IV methylprednisolone 1 g x 3 days- oral	Pain decreased. Improvement in cranial nerve deficit over 2 months- partial recover, on follow up
Bayas et al. ^[67]	OU	Conjunctival congestion, retro-orbital pain and diplopia. MRI- SOVT. Thrombocytopenia, antiplatelet IgG Ab positive	SOVT	Heparin, IV dexamethasone	Ischemic stroke
Panovska-Stavridis ^[68]		Severe headache, left proptosis, blurred vision. Thrombocytopenia, high D-dimer. MRI SOVT, PF4 Ab	SOVT	IVIG 1 g/kg x 2 days, Rivaroxaban, oral prednisolone	Improved, on follow up

Ab: antibody, CRP: C reactive protein, CSF: cerebrospinal fluid, CT: computed tomography, F: female, IR: inferior rectus, IV: intravenous, IVIG: intravenous immunoglobulin, M: male, MR: medial rectus, MRI: magnetic resonance imaging, OS: left eye, OU: both eyes, PF: platelet factor, RAPD: relative afferent pupillary defect, SOVT: superior ophthalmic vein thrombosis

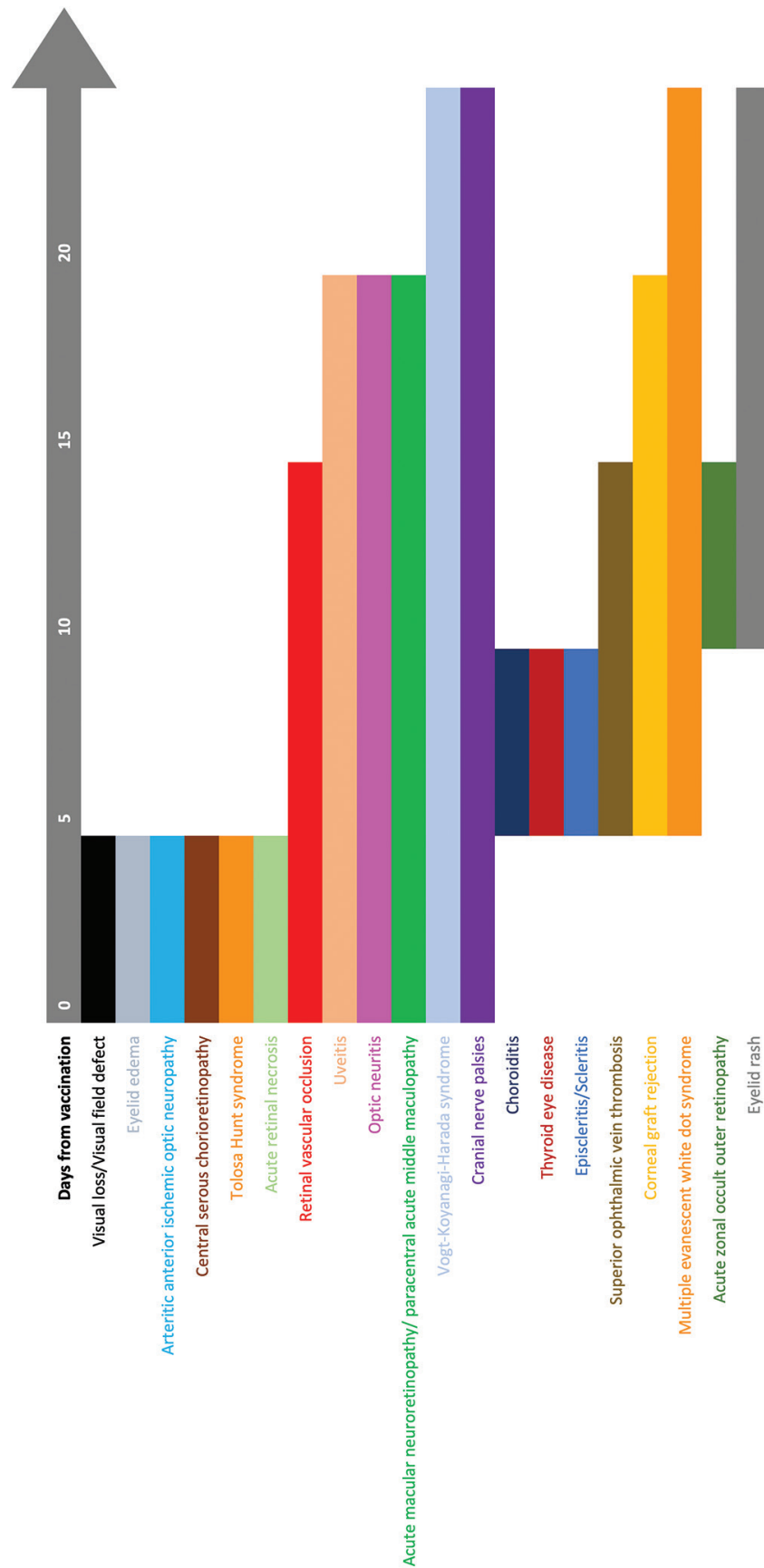


Figure 9: Timeline showing the onset of signs and symptoms from the time of COVID-19 vaccination (Day 0)

thrombocytopenia is an immune-mediated post-vaccination complication. A multicentric cohort study by Perry et al found that patients with VITT related CSVT were more likely to have received the ChAdOx1 vaccine, younger, without systemic risk factors, had more extensive venous thrombosis, intracranial hemorrhage and more concurrent extracranial and arterial thrombosis with worse outcome as compared to patients without VITT associated CSVT. The outcome improved with use of IVIG and non-heparin anticoagulants.^[69] Ophthalmologists should be aware of the occurrence of such thrombotic events. Frequently, they may be the ones to diagnose the condition which may pre-empt fatal cerebral ischemia.

Patients with underlying thyroid disease should undergo a baseline ophthalmic examination before vaccination and be informed about the possibility of thyroid eye disease flaring.

Discussion

Ocular manifestations of the COVID-19 vaccine are not uncommon but relatively mild and transient except for cases of retinal and ophthalmic vascular occlusions and graft rejections. In a cross-sectional study based on an online survey questionnaire, Kadali et al. found that of the 803 healthcare workers who received the BNT162b2 mRNA vaccine, very few had non-specific ocular symptoms of blurred vision (4/803, 0.5%), eye pain (7/803, 0.87%), and flashes (2/803, 0.25%).^[70] A similar study on 432 healthcare workers who received the mRNA-1273 vaccine showed that frequency of ophthalmic side effects was rare (eye pain: 15/432, 3.47%), to extremely rare (blurring of vision: 4/432, 0.93%; flashing lights: 3/432, 0.69%).^[71] The posterior segment, the retinal vasculature, and the uvea are most frequently affected. Comparison by age shows that patients with posterior segment manifestation were relatively younger (mean age 43.6 years) as compared to patients with neuro-ophthalmic lesions (mean age 58.3 years) and corneal graft rejections (mean 65 years). The median time for the development of ocular signs and symptoms was 7 days for eyelid, ocular surface, and anterior segment, 6 days for orbit and 4 days for the posterior segment and neuro-ophthalmological cases. These details are important to follow up high-risk patients in the ophthalmic clinic. [Fig. 9] Patients with corneal grafts should be followed within a week, whereas those with JIA or prior history of uveitis need to be called in earlier.

The vaccines have been found to be safe before receiving approval from the appropriate authority. Adverse effects following vaccination are infrequent, benign, transient, and treatable. Serious adverse effects including anaphylaxis and thrombocytopenia are rare. The ocular manifestations have been attributed to molecular mimicry (similarities in the structure of SARS-CoV-2, human or chimpanzee adenoviral components), antigen-specific cell, and antibody-mediated hypersensitivity reactions to spike antigen, or other viral antigens and adjuvants present in the vaccines that enhance immunogenic activity. The mechanisms are similar to those seen with various other vaccines that have been used for several years including influenza, MMR, hepatitis A and B, yellow-fever, BCG, DPT, and HPV. Almost all the manifestations have been managed conservatively or with steroidal and nonsteroidal immunosuppressants.

That being said, it is important to report all manifestations to improve the knowledge base of physicians and patients. For ophthalmologists, this awareness is necessary to be able to counsel patients for vaccination, informing them of the possible symptoms for early presentation, diagnosis, and initiation of treatment. Patients with corneal grafts can be started on frequent topical corticosteroids a week before vaccination, and this can be tapered slowly after the second dose. Those who require non-urgent corneal transplantation may be scheduled after 4–6 months of the completion of all doses of vaccination. Patients with a history of inflammatory eye diseases should be warned of possible reactivation or recurrence and educated about early symptoms. Knowledge about the adverse effects is also important to encourage patients for vaccination and counter false information.

It is encouraging to note that all the authors have reported with great maturity, highlighting rightly that the causal relationship of all the manifestations to the COVID-19 vaccine are only possibilities and not established with certainty because of the lack of large-scale real-world studies. They have also vehemently supported the need for every individual to get vaccinated as the benefits far outweigh the risks. Responsible reporting is the need of the hour.

Future Directions and Conclusion

As further information is acquired and shared, the long-term implications of the vaccines will become more clear. Patients who developed the signs after the first dose need to be followed up after the second dose to document if they had a similar reaction or not. This will throw further light on the true association of the vaccines with the ocular events as well as the risk factors for the same. It may also be prudent to classify the associations as possible, probable, definite, or unrelated as more cases come to light. Corneal graft rejection after the first dose raises the question of the timing of the second dose. The permanent or residual effects of the manifestations are also to be determined.

From the review of cases, it is evident that a maladaptive immune system at work in response to the vaccine may reactivate some autoimmune diseases in the patients like uveitis, thyroid ophthalmopathy, and thrombocytopenic thrombosis. New-onset uveitis may be the first sign of an underlying autoimmune disease. This raises the question of the need for complete systemic evaluation of a patient with uveitis following vaccination. COVID-19 vaccines do not have any live virus and therefore, individuals on immunomodulators can have the vaccine safely, but the efficacy in them may be questionable.^[4] The currently available studies have not demonstrated an increased risk of reactivation following vaccination with COVID-19 including in patients with multiple sclerosis.^[72]

New vaccines are on the horizon, booster doses are definite in the near future, and children are soon to be vaccinated, creating a platform for a plethora of new and exciting information. As of October 29, 2021, there are 128 vaccines in clinical development and 194 vaccines in the preclinical development stage.^[3] Many of the adverse events are treated with immunosuppressants, and one is curious to see if the vaccine efficacy is affected by drugs used for the reactions like corticosteroids, and teprotumumab. With travel also returning

to the forefront, the mixing of vaccines may also bring about more information.

COVID-19 vaccines are a boon that needs to be studied, improved, and harnessed to their full potential for safety as well as returning to as normal a life as possible. As ophthalmologists, we need to be aware of the emerging manifestations and complications pertaining to the eye following the vaccination with different vaccines, to be better prepared to diagnose, manage, and give correct information to patients.

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Conflicts of interest

There are no conflicts of interest.

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