Inflammation Research (2021) 70:1005–1009
https://doi.org/10.1007/s00011-021-01506-6

Inflammation Research

COMMENTARY

Adverse Ocular Events following COVID-19 Vaccination

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Received: 28 August 2021 / Revised: 28 August 2021 / Accepted: 13 September 2021 / Published online: 24 September 2021

Keywords Corona virus · COVID · Vaccine · Optic neuropathy · Uveitis

To the Editor,

We read with interest the article "Acute reduction of visual acuity and visual field after Pfizer-BioNTech COVID-19 vaccine 2nd dose" by Santovito and Pinna [1]. The timeline of events beginning after the vaccination supports that the exposure caused the patient's symptoms. However, little insight can be gained without a corroborative neuro-ophthalmic examination within the window that the patient exhibited symptoms.

The neurologic and ophthalmic manifestations of SARS-CoV-2 (COVID-19) are well established. In one study, COVID-19 infection resulted in ocular manifestations in 1.4% of patients; a review of the literature indicates that these manifestations most frequently result in reactive inflammation of the eyelids, follicular conjunctivitis, eye redness, foreign body sensation, and eye discharge [2–7]. Regarding neuro-ophthalmologic manifestations, optic neuritis has been reported in several reports at various stages of COVID-19 infection [8–13]. Several case reports have reported on cranial nerve palsies, particularly oculomotor (third cranial) nerve and abducens (sixth cranial) nerve palsies presenting with diplopia and/or ophthalmoplegia [14–20]. However, these ophthalmologic and neuro-ophthalmologic manifestations are non-specific, so definitive attribution to a particular exposure is generally difficult. In the current case, the onset, course, and duration of the reported symptoms narrow the field of etiological possibilities to the inflammatory and vascular categories.

Optic neuritis may manifest with reduction of visual acuity and darkening of the visual field, accompanied by pain exacerbated with ocular movement. In a review of adverse ocular events from 2010 to 2020, optic neuritis was found to be the most common event associated with nine different vaccines with a mean onset of 10.8 days (range: 1 day–1 month) post-injection [21]. The mechanism underlying optic neuritis in the setting of vaccination is not well understood; previous studies have suggested molecular mimicry between myelin basic protein and viral proteins, epitope spreading, bystander activation, and superantigen activation as potential mechanisms [22–26]. Visual prognosis is generally favorable, but ideal management remains elusive [21, 27].

Regarding the case presented by Santovito and Pinna, the likelihood the patient had an optic neuropathy is low given the brief duration (hours) of symptoms. Transient visual obscurations associated with optic disc edema (even that secondary to increased intracranial pressure, i.e., papilledema) are another consideration, but these events tend to manifest on the order of seconds and are elicited by transient increases in intrathoracic/central venous pressure.

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Table 1 Summary of reports demonstrating adverse ocular events after COVID-19 vaccination

Reports	Age (years)	Sex	Vaccine	Days after vaccine	Manifestations
Crnej et al. (2021) [38]	71	M	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	7	Acute unilateral endothelial graft rejection after Descemet membrane endothelial keratoplasty, 5 months post-operatively
Phylactou et al. (2021) [37]	66	F	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	7	Acute unilateral endothelial graft rejection after Descemet membrane endothelial keratoplasty, 21 days post-operatively
Phylactou et al. (2021) [37]	83	F	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #2	21	Acute bilateral endothelial graft rejection after Descemet membrane endothelial keratoplasty, 3 and 6 years post-operatively
Rallis et al. (2021) [36]	68	F	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	7	Acute unilateral endothelial graft rejection after Descemet membrane endothelial keratoplasty, 4 months post-operatively
Ravichandran and Natarajan (2021) [35]	62	M	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	21	Acute unilateral endothelial graft rejection after Descemet membrane endothelial keratoplasty, 2 years post-operatively
Wasser et al. (2021) [34]	73	M	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	13	Acute unilateral endothelial graft rejection 2 years after re-graft for penetrating keratoplasty originally performed 44 years earlier
Wasser et al. (2021) [34]	56	M	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	14	Acute unilateral endothelial graft rejection 10 months after repeat penetrating keratoplasty originally performed 25 years earlier
Book et al. (2021) [39]	21	F	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	3	Bilateral acute macular neuroretinopathy, bilateral paracentral scotomas with underlying bilateral circumscribed paracentral dark lesions on ophthalmoscopy, optical coherence tomography with outer plexiform layer thickening and discontinuity
Bohler et al. (2021) [40]	27	F	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	2	Unilateral acute macular neuroretinopathy, paracentral scotoma with a teardrop-shaped macular lesion nasal to the fovea on ophthalmoscopy
Mambretti et al. (2021) [40]	22	F	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	2	Unilateral acute macular neuroretinopathy, paracentral scotoma
Mambretti et al. (2021) [40]	28	F	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	2	Unilateral acute macular neuroretinopathy, paracentral scotoma
Goyal et al. 2021[43]	34	M	AZD1222 ChAdO×1 nCoV-19 (AstraZeneca), #1	7	Bilateral multifocal choroiditis with large unilateral serous macular detachment and severe choroidal thickening bilaterally
Mudie et al. (2021) [32]	43	F	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #2	3	Panuveitis with significant choroidal thickening and inflammation of the anterior chamber and vitreous
ElSheikh et al. (2021) [31]	18	F	Sinopharm COVID-19, #2	5	Bilateral acute uveitis with blurred vision and photophobia
Fowler et al. (2021) [33]	33	M	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #1	3	Central serous retinopathy with unilateral blurry vision and metamorphopsia
Renisi et al. (2021) [45]	23	M	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #2	14	Acute uveitis with pain, photophobia, conjunctival hyperemia, and posterior synechiae

Table 1 (continued)

Reports	Age (years)	Sex	Vaccine	Days after vaccine	Manifestations
Maleki et al. (2021) [46]	79	F	BNT162b2 mRNA SARS-CoV-2 (BioNTech/Pfizer), #2	2	Bilateral arteritic anterior ischemic optic neuropathy (AAION) with sudden loss of vision bilaterally, right eye significantly worse than left eye
Maleki et al. (2021) [46]	33	F	Moderna COVID-19 Vaccine (ModernaTX, Inc.)	10	Bilateral acute zonal occult outer retinopathy (AZOOR) with progressive unilateral nasal defect and bilateral flashes

M male, *F* female, *#1* first dose, *#2* second dose

We cannot know if the patient had optic neuritis or optic disc edema that was present for longer than his symptoms without an examination.

Presumed inflammatory cranial neuropathies in general are common among patients after vaccines. We recently encountered a 46-year-old male patient who developed torsional, binocular diplopia 3 days after the second dose of Oxford–AstraZeneca ChAdOx1 nCoV-19 (AZD1222). Examination revealed a pattern of strabismus fitting that of a right 4th cranial nerve palsy. Paretic ophthalmoplegia has also been reported with active COVID-19 infection. Falcone et al. reported a case of abducens cranial nerve palsy underlying binocular, horizonal diplopia in an otherwise healthy 32-year-old man 3 days after developing upper respiratory symptoms later confirmed to be COVID-19 infection [16]. Magnetic resonance imaging confirmed lateral rectus atrophy in the patient. Faucher et al. reported a case of oculomotor nerve palsy in an otherwise healthy 21-year-old man 2 weeks after COVID-19 infection manifesting after hospital discharge [28].

Intraocular inflammation is another possible mechanism by which the reported patient may have experienced his visual symptoms. Since February 2021, 46 reports of ocular side effects linked to the COVID-19 vaccine have been reported to the Vaccine Adverse Event Reporting System (VAERS) [21, 29]. The majority (74%) involve the eyelid or conjunctiva [29, 30]. Inflammation of the optic nerve, retina, uveal tract, and anterior segment, combined to account for 9% of VAERS [30]. We recently reported a case of acute juvenile idiopathic arthritis-associated uveitis 5 days after the 2nd dose of Sinopharm COVID-19 vaccine in an 18-year-old girl [31]. Panuveitis[32] and central serous retinopathy [33] have also been reported.

Despite the above-mentioned associations, the rapid resolution of visual symptoms over the course of hours argues against a uveitic process. It would be highly unusual for ocular inflammation to manifest and then self-resolve within hours. Photophobia, a hallmark symptomatic feature of uveitis, was not reported by the patient.

Table 1 summarizes our review of literature from 16 publications reporting on 20 patients with ocular complications following COVID-19 vaccinations. In brief, these included graft rejections [34–3831], macular neuroretinopathy [39–41], multifocal choroiditis [42, 43], acute uveitis [, 32, 44, 45], central serous retinopathy [33], arteritic anterior ischemic optic neuropathy [46], and acute zonal occult outer retinopathy [46].

In our opinion, the most likely explanation is that the patient suffered visual symptoms related to the central, systemic illness triggered by the vaccine. The presence of systemic symptoms (headache, dizziness and fatigue, and nausea) that accompanied and resolved with his visual symptoms reflect and support this hypothesis. Hypoperfusion

of the retina might account for the peripheral visual loss, which self-corrected rapidly. Reduction of central acuity is less straight forward to explain, but can result from transient hypoperfusion of the retina, optic nerves, or any part of the visual pathways extending to the visual cortices. If this were the case, then we might not expect that any findings would have been apparent on even a complete dilated ophthalmic examination.

Ultimately, reporting of this patient's vaccine triggered very transient visual symptoms as described is of little value without a corroborating examination or objective evidence of ophthalmic pathology. The relevance of optic neuritis, inflammatory cranial neuropathies, and ocular inflammation and uveitis to this case is suspect for the same reason. No doubt there is a miriad of ways in which vaccines, particularly second doses or first doses in previous infected individuals, can affect the eyes and visual pathways to produce visual symptoms. Reporting of these symptoms as in the case of Santovito and Pinna is very commanded. However, reports of these adverse events should always be verified and supported by objective data from clinical examination and ancillary testing if a causal relationship is to be asserted.

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