Ocular inflammatory events following COVID-19 vaccination in the paediatric population: a multinational case series

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Abstract

Background: Ocular inflammatory events following COVID-19 vaccination have been reported in the adult population.

Methods: Multinational case series of patients under the age of 18 diagnosed with ocular inflammatory events within 28 days of COVID-19 vaccination.

Results: Twenty individuals were included. The most common event was anterior uveitis (n=8, 40.0%), followed by intermediate uveitis (7 patients, 35%), panuveitis (4 patients, 20%), and posterior uveitis (1 patient, 5%). The event was noticed in the first week after vaccination in 11 patients (55.0%). Twelve patients (60.0%) had a previous history of intraocular inflammatory event. Patients were managed with topical corticosteroids (n=19, 95.0%), oral corticosteroids (n=10, 50.0%), or increased dose of immunosuppressive treatment (n=6, 30.0%). Thirteen patients (65.0%) had a complete resolution of the ocular event without complications. All patients had a final visual acuity unaffected or less than three lines of loss.

Conclusion: Ocular inflammatory events may happen in the paediatric population following COVID-19 vaccination. Such events are uncommon. Most events were successfully treated, and all showed a good visual outcome.

Keywords: Paediatric; Uveitis; Ocular inflammation; Coronavirus; COVID-19; SARS-CoV-2; Vaccination.

In December 2020, the United States (UN) Food and Drug Administration (FDA) released the emergency use authorisation for the first vaccines for the prevention of coronavirus disease 2019 (COVID-19), namely BNT162b2 (Pfizer Inc/BioNTech SE) and mRNA-1273 (Moderna Therapeutics Inc). ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine was authorised by the European Medicines Agency (EMA) soon after in January 2021. Since then, massive progress has been made in the vaccination campaign effort, with 68.4% of the world population having received at least one dose of COVID-19 vaccine, with over 12 billion doses administered wordwide.[1]

COVID-19 has been shown to cause more severe illness in adults compared to children and adolescents, with a greater burden in terms of disease outcome and death amongst older adults or those with comorbidities.[2,3] However, cases of severe disease have been recorded in neonates and paediatric patients, including the paediatric inflammatory multisystem syndrome associated with COVID-19, and children have developed prolonged clinical symptoms following infection (long COVID).[3] In addition to being susceptible to the infection, children and young adults can transmit the virus to other individuals, contributing to the spread of disease, and societal disruption. In June 2022, the US FDA authorized the emergency use of the Moderna and Pfizer-BioNTech COVID-19 vaccine in children down to 6 months of age. As of November 2022, the Centres for Disease Control and Prevention reported that 1.7 million US children ages 6 months-4 years, 10.9 million US children ages 5-11 and 17.7 million US children and adolescents ages 12-17 had received at least one dose of COVID-19 vaccine, representing respectively 10%, 38%, and 68% of the US age group to which they belong.[4] This expanding COVID-19 vaccine uptake for pediatric populations has been replicated globally, with more than 20 million children and young adults aged less than 18 receiving at least one dose of COVID-19 vaccine in Europe.[5-8] *As of April 2023, median cumulative vaccine uptake in EU/EEA countries by age groups indicates an uptake of the primary vaccination course of 24.5% in < 18 year old population, with at least one dose in 27.4%.*

Ocular inflammatory events are uncommon in the paediatric population but associated with significant morbidity.[9] There have been reports of an association between administration of COVID-19 vaccines and new ocular inflammatory events.[10-13] The objective of this study is to describe the spectrum and outcome of ocular inflammatory events following the

administration of COVID-19 vaccination in an internationally representative paediatric population.

Methods

Case series of individuals under 18 years old diagnosed with an ocular inflammatory event following COVID-19 vaccination collected from across an international collaborative network (seven centres) from January 2022 to June 2022. The study was conducted with ethics approval obtained by the central research team (ref 22/WS/0072) alongside any necessary international institutional research board approvals. Patients who satisfied the following specific criteria were eligible for inclusion in the series: children diagnosed with ocular inflammatory events within 28 days following COVID-19 vaccination manifesting their first episode of uveitis or recurrence of disease activity in an eye previously quiescent (< 0.5+ SUN ACC or < 1+ SUN vitreous haze and absence of active posterior segment disease, for more than 12 months, or, according to SUN criteria, two-step increase in the level of ocular inflammation); age less than 18 years. The eligibility period ran from 1st Jan 2022 to 30th June 2022.

The invitation to participate in the study was sent to all members of the International Ocular Inflammation Society (IOIS) and the International Uveitis Study Group (IUSG). A form for data collection was then sent to the members who observed an ocular inflammatory event satisfying the criteria The following information was required: type of COVID-19 vaccine; timing of the events, including date of vaccination and date of onset of intraocular inflammation; past ocular history; type of ocular inflammatory event, including episcleritis, scleritis, uveitis and optic neuritis; treatment details and outcome.

Data collection

A purpose-built REDCap data entry form was created to collect the ocular inflammatory events following COVID-19 vaccination in the paediatric population. Statistical analysis was done using the software R v 4.1.1 [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria]. All variables were binary and described as number (%).

Results

Twenty patients from seven centres were included in the study. The characteristics of the patients, including gender, age group, ethnicity, COVID infection history, past ocular history, and treatment history, are described in **Table 1**. Countries from where the cases were reported included Colombia, Mexico, India, Turkey, Slovenia, Palestine and Spain.

Nineteen patients (95%) received the Pfizer vaccine and 1 (5%) received the Corbevax vaccine. The first event occurred after the first dose in 10 patients (50%), after the second dose in nine patients (45%), and after the third dose in one patient (5%). The event was noticed in the first week after vaccination in 11 patients (55%), in the second week after vaccination in six patients (30%), in the third week after vaccination in two patients (10%), and in the fourth week after vaccination in one patient (5%).

Eleven (55%) events were bilateral. The most common event was anterior uveitis (8 patients, 40%), followed by intermediate uveitis (7 patients, 35%), panuveitis (4 patients, 20%), and posterior uveitis (1 patient, 5%). Three patients (15%) also presented extra-ocular or non-ocular inflammation during the event: two patients presented extraocular signs of Behçet's disease (although the diagnosis of Behçet's was only made after the post-vaccination ocular event, both patients reported a history of pre-vaccination non-ocular symptoms suggestive of the disease), and one patient with diagnosis of juvenile idiopathic arthritis (JIA) presented with knee arthritis. Eleven out of twelve patients (91.7%) with previous history of uveitis had an event like their previous ones. One patient with diagnosis of pars planitis presented with novel anterior uveitis after the vaccination.

An additional dose of the COVID-19 vaccine was given to ten patients (50%) who had ocular inflammation after the first dose. Among those, seven patients (70%) had no uveitis recurrence after the subsequent dose. The three patients (30%) who had recurrences of ocular inflammation after the additional dose had history of previous uveitis: two had JIA-related uveitis and one of pars planitis.

Steroid treatment was purely topical for seven patients (35%), a further seven patients (35%) received topical and oral corticosteroids, three patients (15%) received topical corticosteroids along with immunosuppressive treatment at increased dosage, two patients (10%) received topical and oral corticosteroids along with immunosuppressive treatment at increased dosage,

and one patient (5%) received oral corticosteroids along with immunosuppressive treatment at increased dosage.

Thirteen patients (65%) had a complete resolution of the ocular event, without complications. For six patients (30.0%), the resolution was only partial. All 8 patients with a new diagnosis of uveitis recovered completely, and were able to discontinue all medications. All 6 patients that increased the dose of immunotherapy continued the systemic treatment at the increased dose. Two patients with panuveitis in Behçet's disease developed complications including both posterior synechiae and peripheral retinal atrophy. One patient (5.0%) with JIA had no response to therapy and presented a chronic persistent anterior uveitis complicated by serous retinal detachment. All cohort patients had a final visual acuity unaffected or with less than 3 logMAR lines of loss. Among the three patients with a final visual acuity of 1-3 logMAR lines of loss, one was the patient with panuveitis in Behçet's disease experiencing chronic serous retinal detachment.

Aggregated description of the study cases is provided in **Table 2.**

Discussion

We present a multinational case series of ocular inflammatory events following COVID-19 vaccination in the pediatric population. A search of Medline, using Google Scholar and PubMed, performed in November 2022, using the following keywords: 'uveitis', 'paediatric', 'children', 'adolescence', 'vaccination', 'COVID- 19', including the 18-year-old age group, revealed three case reports describing presumed COVID-19 vaccine-related uveitis, including a bilateral multifocal choroiditis with disc edema in a 15-year-old girl, a unilateral acute posterior multifocal placoid pigment epitheliopathy in a 17-year-old boy, and a bilateral juvenile idiopathic arthritis-associated anterior uveitis in 18-year-old girl; one case series reporting one case of pars planitis and one case of multiple evanescent white dot syndrome, both in 18-year-old females.[10-13] Recently, Singh et al conducted a retrospective study using the data from the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System from December 2020 to May 2022.[14] Among the 1094 cases of vaccine-associated uveitis, they reported 12 (1.10%) and 38 (3.47%) cases in the 5-12 and 13-18 age group, respectively. In our series, 85% of the patients developed the episode within 14 days.

Similarly, Singh et al reported a mean onset interval of 10.11±16.62 days in the 5-12 age group and 15.96±22.82 days in the 13-18 age group.

In our case series, the most common event was anterior uveitis, detected in 40% of the patients. Among the 1094 patients included in the analysis by Singh et al, 491 (44.88%) were diagnosed with anterior uveitis.[14] However, no sub-analysis of paediatric phenotypes was provided. Similarly, anterior uveitis (n=41, 58.6%) was found to be the most common event in the multinational case series of 70 adults diagnosed with an ocular inflammatory event post COVID-19 vaccination, as reported last year.[15] Contrary to the adult series, where most of the inflammatory episodes were not severe and 70% (n=49 patients) were mainly managed with topical corticosteroids or observation only, in our paediatric series 65% required additional systemic treatment, including oral corticosteroids and/or immunosuppressive treatment at increased dosage. From our paediatric study, it emerged that all patients had a final visual acuity unaffected or with less than three lines of loss, and very few patients developed ocular complications, which did not result in permanent visual loss. Whilst these post vaccination ocular inflammatory events are rare, our findings suggest that children are at risk of more severe inflammatory response compared to adults.[15] Therefore, an intensive anti-inflammatory therapeutic regimen is often required to avoid intraocular complications and achieve a positive treatment and functional outcome.

Onset of ocular inflammatory events has been reported following the administration of different vaccines, including against hepatitis A and B virus, influenza virus, human papillomavirus, measles- mumps-rubella, varicella virus, bacillus Calmette-Guerin, Neisseria meningitides and yellow fever.[16-27] The similarity between these events and ocular inflammatory events following COVID-19 vaccination supports one of the Bradford-Hill criteria, namely ‘analogy’.[28] Bradford-Hill criteria are used to infer causality between events.[28] Other criteria include ‘temporality’, meaning that the event occurs after the cause, and this is satisfied by the 28 day interval between the date of vaccination and onset of uveitis; ‘consistency’ (reproducibility), which is guaranteed by the fact that similar inflammatory events have been observed in different places of the world by different specialists, and that we reported three individuals who developed an event of uveitis after the first dose manifesting a recurrence of the event after the second dose; ‘plausibility’, meaning that there is a plausible underlying mechanism to explain the cause and the effect. Different

hypotheses have been formulated to support plausibility, including a mechanism of molecular mimicry between the foreign peptides, namely vaccine peptide fragments, and the uveal self-peptides; an immune reaction to vaccine adjuvants inducing inflammatory damage; and an antigen-specific cell and antibody-mediated hypersensitivity reaction leading to immune complex deposition.[29-32] The Bradford-Hill criteria of specificity, biological gradient, coherence and experiment are not met; however, as (respectively) uveitis onset or disease flare occurs in the absence of vaccination, we lack evidence on any relationship between dose and post vaccination events, we lack the full details of co-existent laboratory findings for the observed events, and the existing randomised controlled trials are not sufficiently powered to examine rare events such as ocular inflammation.[33]

The absence of these supporting criteria does not negate the association. Paediatric non-infectious uveitis is typically 'idiopathic', a collection of disorders with complex multi-factorial aetiology, within which post viral exposure immunogenetic disease mechanisms have long been postulated to play a role.[34]

Potential mechanisms involved in the development of inflammatory events after COVID-19 vaccination include molecular mimicry due to resemblance between uveal peptides and vaccine peptide fragments; antibody-mediated and antigen-specific cell hypersensitivity reactions; and inflammatory damage caused by vaccine adjuvants producing innate immunity through cytoplasmic or endosolic nucleic acid receptors.[15] The molecular and cellular basis of mRNA vaccine, consisting of a mRNA encoding the spike (S) protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles (LNPs), must be taken into consideration.[35] The proinflammatory action of the LNPs used, and the proinflammatory effects of the antigens that are produced in human tissues, including S protein and its peptide fragments, can potentially play role in the cascade leading to the development of inflammatory events.[35]

Study limitations, other than the challenges in inferring a causal relationship, include the inability of a case series such as this to clarify issues related to incidence or relative risk rates, which would be valuable population health data. There may have been under ascertainment of cases due to the absence of active surveillance. Also, suboptimal registration of vaccination history may have resulted in under ascertainment, and the data collection form may have led to a biased dataset and sample which is not representative of events in all populations, although this is potentially mitigated by the use of a multicentre study approach.

The paucity of national uveitis registries, and the absence of an international disease registry, prevent robust comparison of uveitis incidence pre and post pandemic or pre and post introduction of the COVID19 vaccine. However, our evidence and findings from other investigators suggests that childhood ocular inflammation is a rare adverse event following vaccination.[14] By June 2022 (when the ascertainment window for this study closed) approximately 30 million children in the US, and more than 27 million in the U/EAA had received at least one COVID 19 vaccine, with positive evidence on the safety profile of this important intervention.

In conclusion, we report a case series of ocular inflammatory events occurred following COVID- 19 vaccination in the paediatric population observed in seven different centres worldwide. The hypothesis suggesting a causal relationship is based on a temporal association and global reproducibility. Most events were successfully managed by topical and/or systemic anti-inflammatory treatment, and all had preserved visual function.

Declarations

Competing interests - The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 1 – Pre-vaccination characteristics

VARIABLE	LEVEL – TOTAL (%)
Sex	FEMALE: 17 (85.0)
	MALE: 3 (15.0)
Age group	06-07 YEARS: 3 (15.0)
	08-09 YEARS: 3 (15.0)
	10-11 YEARS: 1 (5.0)
	12-13 YEARS: 3 (15.0)
	14-15 YEARS: 6 (30.0)
	16-17 YEARS: 2 (10.0)
Child's ethnicity	ARAB: 4 (20.0)
	HISPANIC: 4 (20.0)
	LATIN AMERICAN: 2 (10.0)
	SOUTH INDIAN: 1 (5.0)
	TURKISH: 4 (20.0)
	WHITE EUROPEAN: 5 (25.0)
Previous COVID	NO: 17 (85.0)
	YES: 3 (15.0)
Time since COVID infection	03-06 MONTHS: 1 (33.3)
	06-12 MONTHS: 2 (66.6)
Previous uveitis diagnosis	FAMILIAL MEDITERRANEAN FEVER: 1 (5.0)
	IDIOPATHIC ANTERIOR UVEITIS: 2 (10.0)
	JUVENILE IDIOPATHIC ARTHRITIS (JIA): 4 (20.0)
	NONE: 8 (40.0)
	PARS PLANITIS: 5 (25.0)
Uveitis treatment for those with pre-existing disease	NONE: 2 (10.0)
	SYSTEMIC: 8 (40.0)
	TOPICAL AND SYSTEMIC: 2 (10.0)

Table 2 – Aggregated description of the study cases

Demographics	Vaccine	Laterality	Management of ocular event	Outcome	Final VA	Comments
Within 1 week of first dose, n=6						
Female 6/6, age range 6 – 17 years	Pfizer 6/6	Bilateral anterior 1/6, Bilateral intermediate 2/6, Unilateral anterior 2/6, Unilateral intermediate 1/6	Topical corticosteroids 3/6 Topical corticosteroids, immunotherapy in increased dose 2/6, Oral corticosteroids, immunotherapy in increased dose 1/6	Complete resolution, no complications 4/6 Partial resolution, no complications 2/6	Unaffected 5/6 < 3 lines loss 1/6	2 recurrences in subsequent dose In 1 patient with previous intermediate uveitis. event post covid-19 vaccination was anterior uveitis.
Within 1 week of subsequent dose (2nd dose n=4, 3rd dose n=1)						
Female 4/5, age range 10 – 15 years	Pfizer 5/5	Bilateral anterior 1/5, Bilateral intermediate 1/5, Bilateral panuveitis 1/5, Unilateral anterior 1/5, Unilateral panuveitis 1/5	Topical corticosteroids 2/5 Topical and oral corticosteroids 3/5	Complete resolution, no complications 3/5 Partial resolution, no complications 2/5	Unaffected 5/5	
During week 2 post 1st dose, n=2,						
Female 2/2, age range 14-15 years	Corbevax 1/2 Pfizer 1/2	Bilateral intermediate 2/2	Topical corticosteroids 1/2 Topical and oral corticosteroids, 1/2	Complete resolution, no complications 1/2 Partial resolution, no complications 1/2	Unaffected 2/2	
During week 2 post subsequent dose, n=4 (all 2nd dose)						
Female 3/4, age range 6 -13 years	Pfizer 4/4	Bilateral anterior 1/4, Bilateral panuveitis 1/4, Unilateral anterior 1/4, Unilateral posterior 1/4	Topical and oral corticosteroids 3/4 Topical corticosteroids, immunotherapy in increased dose 1/4	Complete resolution, no complications 3/4 Partial resolution, no complications 1/4	Unaffected 3/4 < 3 lines loss 1/4	
During week 3 -4 post dose, n=3 (1st dose n=2, 2nd dose n=1)						
Female 3/4, age range 6 - 15 years	Pfizer 3/3	Bilateral panuveitis 1/3, Unilateral anterior 1/3, Unilateral intermediate 1/3	Topical and oral corticosteroids 1/3 Topical corticosteroids, immunotherapy in increased dose 2/3	Complete resolution, no complications 2/3 Partial resolution, no complications 1/3	Unaffected 1/3 < 3 lines loss 1/3	In 1 case: persistent inflammation with loss of 2 lines of vision and small macular serous neuroretinal detachment In 1 case: Recurrence in subsequent dose