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Features of the course of corneal and choroidal inflammation in children infected with SARS-CoV-2

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Purpose: *To examine the course of corneal and choroid inflammation in children infected with COVID-19 who were treated at the Department of Pediatric Eye Pathology, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", in 2021-2023.*

Material and Methods: *The study sample included 62 children (94 eyes) with corneal and choroidal inflammation who were treated at the Department of Pediatric Eye Pathology, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", in 2021-2023. SARS-CoV-2 infection was confirmed by laboratory testing in all children. The age of children ranged from 6 months to 17 years (mean age, 10.67 ± 2.95 years). Enzyme-linked immunosorbent assay (ELISA) was used to detect SARS-CoV-2- immunoglobulin (Ig)M antibodies in children suspected for past COVID-19 infection.*

Results: *The detection of immunoglobulin IgM antibodies indicated a recent past SARS-CoV-2 infection, whereas positive COVID-IgG indicated a prior past infection. Uveitis was the most common ocular finding (48/62 children (77.4%), 78 eyes); 77% of uveitis cases were bilateral. Acute uveitis, acute exacerbation of chronic uveitis and sequelae of chronic uveitis were observed in 33.3%, 53.9%, and 12.8%, respectively, of study eyes. Panuveitis with severe complications (seclusio and occlusio papillae, uveal cataract, secondary glaucoma, retinal detachment, subretinal neovascular membranes, vitreous hemorrhage, vitreous fibrosis and phthisis bulbi) was diagnosed in 57.7% of study eyes, mostly in eyes with bilateral uveitis. Post-COVID-19 keratitis was found in 14 children (16 eyes; 12.4%) and was unilateral in 85.7% and acute in 62.5% of cases.*

Conclusion: *Past SARS-CoV-2 infection may cause an acute ocular inflammatory disease or recurrent chronic inflammatory process in children. Uveitis with lesions in all uveal tract compartments and severe complications was the most common finding. Family doctors should be encouraged to refer all children with a past COVID-19 infection to an ophthalmologist. Pediatric ophthalmologists should be aware of possible post-COVID-19 ocular complications.*

Key words:

COVID-19, ocular symptoms, uveitis, keratitis, children

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemics began in early 2020, but its consequences are still unfolding. The infection can range from asymptomatic, mild to life threatening respiratory distress, and can affect almost every organ of the body [1]. Various ocular symptoms of SARS-CoV-2 infection have been reported. Most studies pay attention to the ocular symptoms in acute COVID-19 illness phase in the form of conjunctivitis of various severities, which can be even the initial symptom in the affected people [2-6]. Children are less susceptible to SARS-CoV-2 infection and typically have milder symptoms than adults [7, 8]. A meta-analysis [9] reported that, of the children with SARS-CoV-2 infection, approximately 23% were asymptomatic whereas 10% were severe or critical cases most commonly exhibiting clinical features of Kawasaki disease-like condition known as multisystem inflammatory syndrome in children (MIS-C) [10, 11]. Conjunctivitis was found to be a common ocular symptom in acute COVID-19 patients (not only in adults, but also in children even in newborns) [12, 13]. A relationship between conjunctivitis and an unfavorable course of COVID-19 was, however, found for adults but not for children [14, 15]. Only isolated reports on pediatric ocular pathology secondary to past COVID-19 infection are available [13, 16, 17].

The purpose of this study was to examine the course of inflammation in the cornea and choroid in children with COVID-19 who were treated at the Department of Pediatric Eye Pathology, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", in 2021-2023.

Material and Methods

The study sample included 62 children (94 eyes) with corneal and choroidal inflammation who were treated at the Department of Pediatric Eye Pathology, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", in 2021-2023. SARS-CoV-2 infection was confirmed in all these children. At admission, in all children, a SARS-CoV-2 polymerase chain reaction (PCR) test or nucleocapsid antigen-based SARS-CoV-2 test using a nasopharyngeal or oropharingeal swab was performed, or enzyme-linked immunosorbent assay (ELISA) was used to detect SARS-CoV-2-specific IgM antibodies. A positive test for SARS-CoV-2-specific IgM antibodies was a contraindication for admission. The age of children ranged from 6 months to 17 years (mean age, 10.67 ± 2.95 years). Of the 62 children, 30 were boys and 32 were girls. A detailed history (with a focus on possible past COVID-19 infection confirmed by laboratory tests) was collected in children suspected of past COVID-19 infection. In the absence of this data during the in-patient stay a suspect, ELISA was used to detect SARS-CoV-2-specific IgM and IgG antibodies.

Informed consent was obtained from parents of all children. The study was approved by the local bioethics committee and adhered to the tenets of the Declaration of Helsinki.

A Student t-test was used to compare quantitative normally distributed variables. Mean age and standard deviation (SD) were calculated.

Results

The detection of IgM antibodies indicated a recent past (less than 1-month, rarely less than 3-months) SARS-CoV-2 infection, whereas a positive COVID- IgG indicated a prior past infection, because IgG antibodies can be detected in most recovered patients at 3-4 months after infection and can persist for long periods of time. This allows for assessing the immune protection against repeat COVID-19 infection. Of note, in most (85%) cases, neither a child, nor his/her parents suspected that he/she had had COVID-19 infection, because the infection was asymptomatic or runny nose was the only symptom. Consequently, prior COVID-19 infection was diagnosed exclusively by IgM or IgG positivity by ELISA. Only in 15% of pediatric patients, either adolescents or parents of younger children recalled a recent serologically confirmed COVID-19 infection during history collection.

Choroidal inflammation (uveitis) was the most common ocular finding (48/62 children (77.4%), 78 eyes) in children with prior COVID-19 infection. Uveitic lesions were found in children of age ranging from 6 months to 16 years (mean age, 10.65 ± 3.41 years), and the proportion of this finding in boys (23/30) was similar to girls (25/32). Data on uveitis secondary to COVID-19 infection in study children are summarized in table 1. Bilateral uveitis secondary to current or past COVID-19 infection was found in 30 children (60 eyes; 62.5%), and unilateral uveitis, in 18 children (18 eyes; 37.5%). Acute uveitis, acute exacerbation of chronic uveitis and sequelae of chronic uveitis were observed in 26/78 eyes (33.3%), 42/78 eyes (53.9%), and 10/78 eyes (12.8%), respectively. Viral etiology of recurrent uveitis secondary to COVID-19 infection was the most common (28 eyes), followed by autoimmune etiology (juvenile idiopathic arthritis (JIA)-associated uveitis, 9 eyes) and parasitic etiology (toxoplasmosis and toxocarosis, 2 eyes each). A child with acute posterior uveitis was found to be positive for anti-SARS-CoV-2 IgM antibodies, which was indicative of a recent infection, although the parents did not note any specific symptoms of the disease. SARS-Cov-2 IgG antibodies titers ranged from 80 to 8288 Au/mL (particularly, the titers were less than 100 Au/mL in 5 children, ranged from 100 to 500 Au/mL in 7 children, from 500 to 1000 Au/mL in 9 children, from 1000 to 2000 Au/mL in 12 children, and exceeded 2000 Au/mL in 8 children). Of the

Table 1. Summary data on children with uveitis secondary to COVID-19 infection

Characteristic	Number
Boys Girls	23 25
Bilateral uveitis Unilateral uveitis	30 children (60 eyes) 18 children (18 eyes)
Acute uveitis Exacerbation of chronic uveitis Uveitis sequelae	26 eyes 42 eyes 10 eyes
Etiology of chronic uveitis - viral - autoimmune (JIA) - toxoplasmosis - toxocarosis	 28 eyes 9 eyes 2 eyes 2 eyes
IgM for SARS-CoV-2 IgG for SARS-CoV-2	1 child 47 children
Anterior uveitis Intermediate uveitis Posterior uveitis Panuveitis	9 eyes 12 eyes 10 eyes 45 eyes
Complications: - uveal cataract - secondary glaucoma - retinal detachment - vitreous fibrosis - vitreous hemorrhage - SNM - phthisis bulbi	 28 eyes 8 eyes 4 eyes 3 eyes 2 eyes 2 eyes 2 eyes
Visual acuity - «0» - Light perception - 0.01-0.04 - 0.05-0.12 - 0.16-0.3 - 0.3-1.0	 2 eyes 4 eyes 10 eyes 14 eyes 16 eyes 32 eyes

Note: JIA, juvenile idiopathic arthritis; SNM, subretinal neovascular membrane toxoplasmosis and toxocarosis

Table 2. Summary data on children with corneal pathology secondary to COVID-19 infection

Characteristic	Number
Boys Girls	7 7
Unilateral lesion Bilateral lesion	12 children (12 eyes) 2 children (4 eyes)
Acute keratitis Exacerbation of chronic keratitis	10 eyes 6 eyes
Type of keratitis: - keratoconjunctivitis - corneal erosion - subepithelial keratitis - stromal keratitis	 5 eyes 2 eyes 4 eyes 5 eyes
Visual acuity: - light perception - 0.01 – 0.04 - 0.05 – 0.12 - 0.16 – 0.3 - 0.3 – 1.0	 2 eyes – – 1 eye 13 eyes

48 children, 36 exhibited a high level of antibodies (> 500 Au/mL), which was indicative of immunity stress caused by recent SARS-CoV-2 infection.

Panuveitis with lesions in all uveal tract compartments was diagnosed in the majority of eyes (45/78 or 57.7%), especially in eyes with bilateral uveitis (Fig. 1). Intermediate, posterior and anterior uveitis were observed in 12 eyes (15.4 %), 10 eyes (12.8 %) and 9 eyes (11.5 %), respectively (Fig. 2). Inflammation severity was manifested by complications like seclusio and occlusio pupillae with the formation of uveal cataract in 28 eyes (Fig. 3) and secondary glaucoma in 8 eyes (Fig. 4), which was most common in panuveitis and less common in intermediate uveitis. Of the eyes with severe uveitis, four showed retinal detachment, two showed subretinal neovascular membranes (Fig. 5), two showed vitreous hemorrhages, three showed vitreous fibrosis, and two showed phthisis bulbi. Vitreous opacification of varying severity and retinal edema were typical of posterior uveitis. Anterior uveitis was always acute with no complications.

Visual acuity was zero in two eyes with phthisis bulbi, light perception only in 4 eyes, 0.01 – 0.04 in 10 eyes, 0.05 – 0.12 in 14 eyes, 0.16 – 0.3 in 16 eyes and 0.3 – 1.0 in 32 eyes.

Corneal lesions secondary to SARS-CoV-2 were documented in 14 children (16 eyes) aged 4 to 15 years of age (mean age, 10.7 ± 2.5 years). The proportion of this finding in boys (7/30) was similar to girls (7/32) (Table 2). Of the 14 children, 12 (85.7%) had a unilateral lesion, as 2 had a bilateral lesion. Of the 16 eyes with corneal inflammatory lesions, 5 had keratoconjunctivitis, 2 had corneal erosion, 4 had subepithelial keratitis, and 5 had stromal keratitis (Fig. 6). A mixed viral (herpetic plus SARS-CoV-2) etiology of keratitis was found in 11 eyes, and a bacterial-viral etiology of keratitis was found in 5 eyes.

Visual acuity ranged from light perception (2 eyes with severe stromal keratitis with stromal opacity) to 0.3 – 1.0 (13 eyes) in eyes with mild peripheral corneal changes. In one eye, visual acuity was 0.16 – 0.3.

Increased SARS-Cov-2 IgG antibody titers were found in all children with corneal lesions. Particularly, the titers were less than 100 Au/mL in 2 children, ranged from 100 to 500 Au/mL in 6 children, from 500 to 2000 Au/mL in 3 children, and exceeded 2000 Au/mL in 3 children (the maximum IgG antibody titer was 4320 Au/mL)). The majority of the children (24 of 35) exhibited a high level of antibodies (> 500 Au/mL), which was indicative of immunity stress caused by recent SARS-CoV-2 infection.

Discussion

Ocular surface cells (especially conjunctival cells) are known to be potentially susceptible to SARS-CoV-2 and a place of entry for transmission for the virus [4]. SARS-CoV-2 binds to angiotensin converting enzyme-2 (ACE2) to facilitate infection in humans. Transmembrane protease, serine 2 (TMPRSS2) has been identified as key host cell factor for viral entry and pathogenesis of SARS-CoV-2. There is some evidence for ACE2 and TMPRSS2 expression on post-mortem and surgical eye samples (involving conjunctival, limbal, corneal, and inner epithelial layer cells, especially fibroblasts and dendritic cells) [4, 18]. ACE2 receptors are widely expressed on various organs (particularly, the retina) and is involved in the pathogenesis of systemic vascular disorders that have ocular manifestations [1, 19]. Immunohistochemistry of the human eye has demonstrated a high level of ACE2 receptors in the ciliary body, choroid, and retinal pigment epithelium, which may explain a wide range of potential ocular manifestations of SARS-CoV-2 infection. These manifestations may vary from conjunctivitis to episcleritis, corneal transplant failure, orbital cellulitis, orbital inflammatory disease, dacryoadenitis, retinal vascular occlusion, retinopathy, maculopathy, endophthalmitis, cranial nerve paralysis, optic neuritis and uveitis with varying prognosis [1, 20, 21]. It is this that was observed, mostly in the form of inflammatory ocular pathology, in our pediatric patients.

Konjunctivitis and keratitis with severe corneal epitheliopathy are the most common ocular manifestations of SARS-CoV-2 infection both in children and adults. In the majority of children they are caused by a systemic inflammatory response, whereas in adults they are caused by direct viral infection [1, 20, 21]. Keratitis caused by SARS-CoV-2 was a significantly less common ocular finding than uveitis caused by SARS-CoV-2 in our pediatric patients (12.4% versus 42.5%).

Pediatric uveitis may be a manifestation of MIS-C or Kawasaki disease [22–25]. To our knowledge, there have been only isolated case reports of uveitis secondary to past SARS-CoV-2 [16, 17]. In our practice, we, however, observed initial manifestations of uveitis or exacerbations of chronic uveitis following SARS-CoV-2 in a large number of pediatric patients.

The mechanism by which SARS-CoV-2 may activate inflammatory response following infection has not been completely elucidated. It is believed that SARS-CoV-2 activates T-cells, with an increase in the levels of T-helper 1 (Th1) cells, inflammatory cytokines (interferon gamma [INFγ], C-X-C motif chemokine ligand 9, and C-X-C motif chemokine ligand 10) [25, 26]. This may explain a temporal association between SARS-CoV-2 and the development of uveitis in children, because a systemic immune response may affect various organs (e.g., the eye) and modulate an inflammatory response following acute infection. Additionally, the family history of autoimmunity may be indicative of the genetic predisposition to develop inflammatory disease, making some children more susceptible to post-infectious inflammatory sequelae. In such cases, COVID-19 acts as environmental trigger [17], and this is what we observed in children with exacerbated chronic JIA-associated uveitis secondary to past SARS-CoV-2 infection. Unfortunately, in the current study, the most common type of choroidal inflammation following SARS-CoV-2 was panuveitis, which was accompanied by the development of complications (seclusio and occlusio papillae, uveal cataract, secondary glaucoma, retinal detachment and vitreous fibrosis) that required not only active anti-inflammatory, resolution and dehydration therapy with the involvement of physiotherapeutic techniques, but also surgical intervention in the remission period.

Conclusion

Past or current infection with SARS-CoV-2 may cause an acute ocular inflammatory disease or provoke a recurrent chronic inflammatory process in children. The most common ocular complication of COVID-19 was uveitis (77.4 %), especially bilateral panuveitis with lesions in all uveal tract compartments (55.7% of all cases of choroidal inflammation), which was accompanied by severe complications (seclusio and occlusio papillae, uveal cataract. secondary glaucoma, retinal detachment and vitreous fibrosis). Corneal inflammatory disease was less common (22.6%), although it is this disease and conjunctivitis that have been commonly reported as major systemic inflammatory-response-induced ocular manifestations of COVID-19 both in children and adults. Only in 15% of pediatric patients, either children or their parents recalled a recent serologically confirmed COVID-19 infection. In the rest of cases, patients were referred by specialists of the Department of Pediatric Eye Pathology to have the ELISA test to detect SARS-CoV-2-specific IgM and IgG antibodies.

Practical recommendations

Family doctors should be encouraged to refer all children with a past COVID-19 infection to an ophthalmologist. Pediatric ophthalmologists should be aware of possible post-COVID-19 ocular manifestations, and even in the absence of history of COVID-19 infection, refer a suspected child for ELISA testing for the detection of titers of SARS-CoV-2-specific IgM and IgG antibodies, in an attempt to clarify the etiology of inflammation, and to determine treatment strategy and prognosis.

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Disclosures

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Author's contribution. *NFB: Conceptualization, Writing – review & editing; TAS: Methodology, Writing – original draft, Formal Analysis, Writing – review & editing; SAT: Writing – review & editing; TVR: Writing – review & editing; GMD: Writing – original draft, Formal Analysis, Writing – review & editing; OOS: Writing – original draft, Formal Analysis; AVS: Statistics; ODS: Writing – original draft, Formal Analysis; OMR: Writing – review & editing. All authors read and approved the final manuscript.*

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Study subjects*: Informed consent was obtained from parents of all children included in this study. The study was conducted in accordance with the standards expressed in the Helsinki Declaration and was approved by the Filatov Institute ethics committee. This study did not include animal experiments.*

Disclaimer. *The opinions presented in this article are those of the authors and do not necessarily represent those of their institution.*

Abbreviations: *Au/mL, arbitrary units per ml; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; IgM, immunoglobulin M; IOL, intraocular lens; JIA, juvenile idiopathic arthritis; MIS-C, multisystem inflammatory syndrome in children; SD, standard deviation; severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; Th1, T-helper 1 cells*

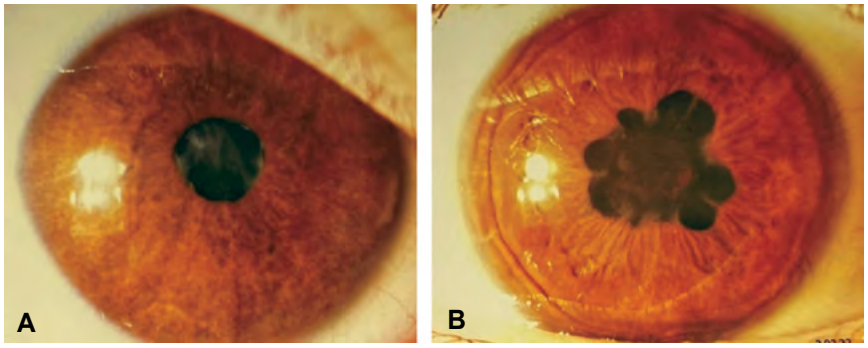

Fig. 1. Photographs of the right (A) and left (B) eyes of a child with panuveitis secondary to past COVID-19 infection

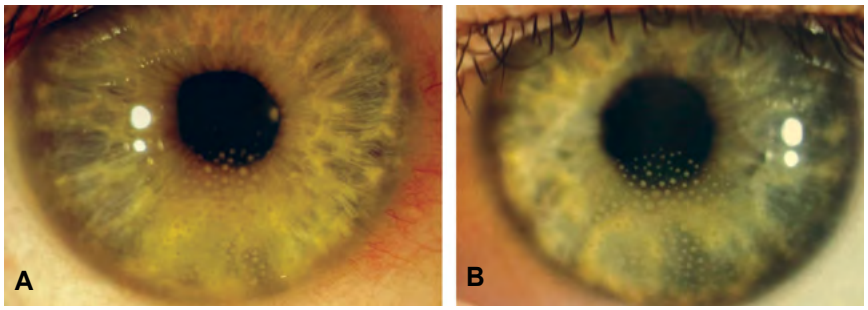

Fig. 2. Photographs of the right (A) and left (B) eyes of a child with acute anterior uveitis secondary to past COVID-19 infection.

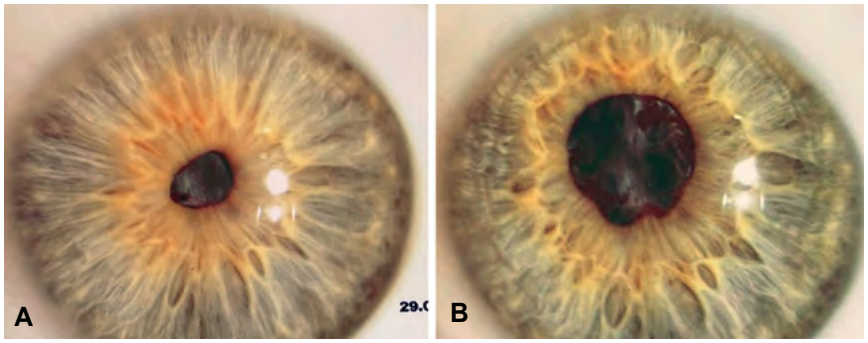

Fig. 3. Photographs of the right (A) and left (B) eyes of a child with exacerbation of intermediate uveitis (seclusio and occlusio papillae, prelenticular membrane and uveal cataract) secondary to past COVID-19 infection

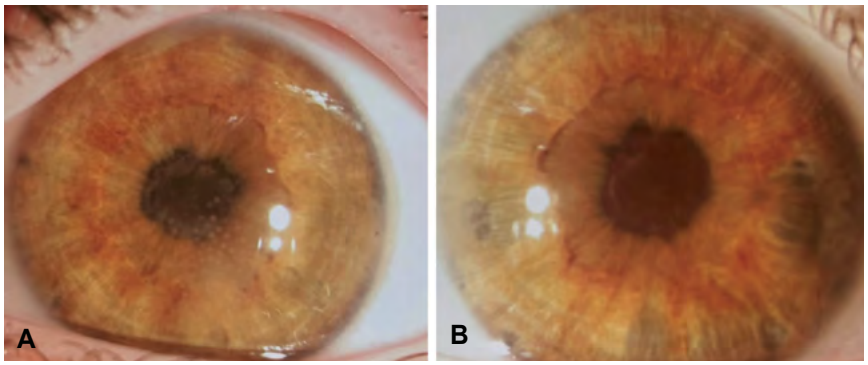

Fig. 4. Photographs of the right (A) and left (B) eyes of a child with exacerbation of autoimmune panuveitis, also known as Still's disease (corneal edema, peripheral corneal degeneration, seclusio and occlusio papillae, iris bombe, prelenticular membrane and complicated cataract) secondary to past COVID-19 infection. Note secondary glaucoma in the right eye, status post- laser iridectomy.

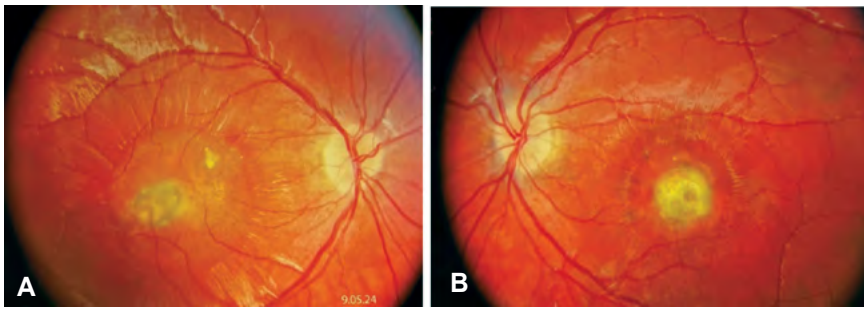

Fig. 5. Fundus photographs of the right (A) and left (B) eyes of a child with acute panuveitis sequelae (subretinal neovascular membranes and hemorrhage) secondary to past COVID-19 infection.

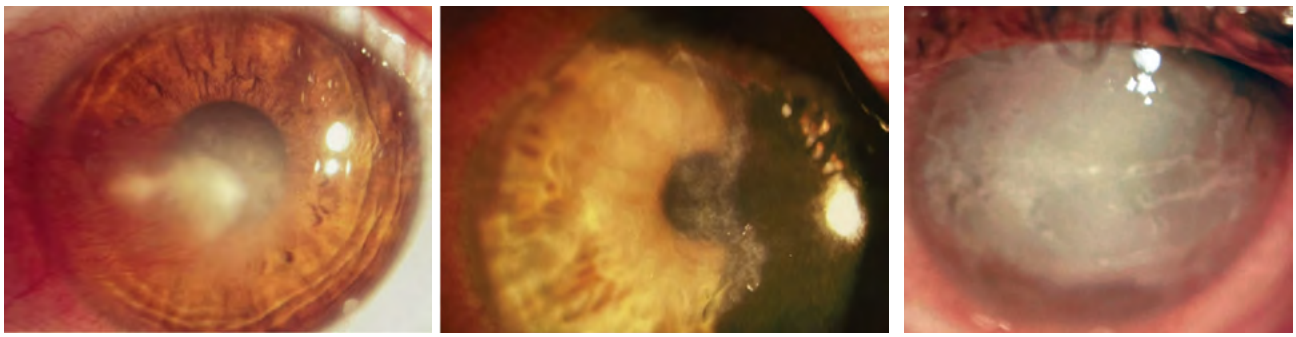

Fig. 6. Fotographs of the anterior eye of children with different type of keratitis secondary to past COVID-19 infection