

COVID-19 ocular findings in paediatric population

Celia Fernandez Alcalde (✉ celia.far93@gmail.com)

Hospital La Paz

Maria Granados Fernandez

Hospital La Paz

María Nieves Moreno

Hospital La Paz

Susana Noval Martin

Hospital La Paz

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Abstract

Purpose To investigate and describe ocular findings in COVID-19 paediatric patients.

Methods A total of 17 COVID-19 patients aged between 0 and 17 years old were recruited at the Paediatric Hospital of La Paz University Hospital (Madrid, Spain). A complete ophthalmological examination was performed in all patients.

Results Of 17 patients, 50% had a known COVID-19 previous exposure. PCR from nasopharyngeal swabs was positive in 35.29%, whereas IgM and/or IgG serology tests were positive in 81%. Clinical manifestations were: 6 COVID-19 associated Paediatric Inflammatory Multisystem Syndrome (PIMS), 7 pneumonias and 2 cutaneous purpura and/or chilblains. Ocular findings were ocular hyperaemia (5 patients), as bilateral acute conjunctivitis (3 patients) or unilateral episcleritis (2 patients). Mean best corrected visual acuity was 1/1 in all tested cases. Only one patient, presenting unilateral optic neuritis, had visual symptoms as unilateral inferior temporal quadrantanopsia. Retinal involvement was found in one patient, where ocular fundus exam showed unilateral retinal vasculitis.

Conclusion SARS-CoV-2 infection could produce ocular pathology in children, frequently presented weeks after the acute phase of the disease. We should take into account COVID-19 when performing differential diagnosis of children presenting with conjunctivitis, episcleritis, retinal vasculitis and/or optic neuritis, meanwhile this world-wide pandemic lasts.

Key Messages

1. COVID-19 most common ocular manifestation described so far is conjunctival congestion. Most studies have been performed in adult population, taking into account the under diagnosed COVID-19 infection in children. Very little literature explores COVID-19 ocular findings in paediatric population diagnosed at a tertiary hospital.
2. SARS-CoV-2 infection could produce ocular pathology in children, in form of: conjunctivitis, episcleritis, retinal vasculitis, optic neuritis...
3. Patients diagnosed with PIMS (Kawasaki like disease) showed mild follicular conjunctivitis, but no findings of anterior uveitis compared to Kawasaki disease.
4. Inflammatory ophthalmic complications could occur in a convalescent and non- infectious phase of the disease, as other more common viral infections

Introduction

Since December 2019 we are immersed in a declared public health emergency of international concern, caused by the Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2). Children have accounted for 1% of cases of COVID-19 in most published series, with significantly reduced risk of developing severe forms of disease or death (She et al. 2020; Ludvigsson 2020; Tagarro et al. 2020).

Since most of them presented with mild forms of acute respiratory infections, the focus was on children with underlying/comorbid disease who concentrated the rare fatalities (She et al. 2020; Climent et al. 2020).

In children with active COVID-19, the most common clinical manifestations were fever and cough, sometimes accompanied by fatigue, myalgia, rhinorrhoea, sneezing, sore throat, headache, dizziness, diarrhoea, vomiting, and abdominal pain (She et al. 2020; Ludvigsson 2020; Hong et al. 2020). Dyspnoea was more common in adults, described in more than 20% of patients, although lower respiratory tract infection may also develop in children (Li et al. 2020; De Ceano-Vivas et al. 2020).

The most common ocular manifestation described is conjunctival congestion, although it is rarely mentioned in non-ophthalmology-specific studies (Li et al. 2020). However, it was present in 1 to 5% of adults consistent with mild follicular conjunctivitis without pseudomembrane formation (Hu et al. 2020).

Concern with children began later, when they started to present from mild but unanticipated manifestations like chilblains, to a severe Paediatric Inflammatory Multisystem Syndrome (PIMS) mimicking Kawasaki disease (KD) (Whittaker et al. 2020; Pouletty et al. 2020; Toubiana et al. 2020).

Scarce literature has been published so far regarding ocular findings in COVID-19 paediatric population. A cross-sectional study performed in Wuhan (China) showed conjunctival discharge and conjunctival congestion as the most common manifestation, and a higher risk of developing ocular symptoms when systemic clinic was present (referencia 35). Therefore, we aim to share our experience with ocular involvement possibly related to COVID-19 paediatric infection in our media.

Materials And Methods

This is a prospective observational, study performed at the Paediatric Ophthalmology Department of La Paz University Hospital (Madrid, Spain) between the 1st of April and the 1st of June 2020. Informed consent was obtained from all parents and/or legal tutors of patients involved.

All patients diagnosed with COVID-19 and explored at the Paediatric Ophthalmology Department were included; admitted at the Paediatric and Infectious Diseases Department or the Paediatric Intensive Care Unit of La Paz University Hospital. The inclusion criteria were as follows: (1) children from 0 to 18 years of age; and (2) SARS-CoV-2 positive PCR (Polymerase chain reaction) from nasopharyngeal swabs (TaqMan 2019-nCoV Assay Kit v1 [ThermoFisher, MA, USA] and SARS-CoV-2 Realtime PCR Kit (Vircell).) and/or SARS-CoV-2 IgG/IgM positive serology test (Chemiluminescence immunoassay, Vircell/Abbott/Siemens). Presumed COVID-19 patients without a positive result of this tests were excluded.

Demographic, epidemiological and clinical data were collected from patient's electronic medical records. All patients underwent a complete ophthalmological examination and detailed anamnesis, that included: best corrected visual acuity (*Pigassou* or *Wecker* eye chart based on patient's cooperation), slit lamp

examination (Haag-Streit Diagnostics® or handle Keeler® model), ocular fundus exam and, in some cases, optical coherence tomography (OCT; Heidelberg Engineering SPECTRALIS®). When PCR was positive, appropriate safety equipment was used: filtering facepiece mask 2 (FFP2), protective goggles and personal protective equipment. In all cases, the examination room and the devices were disinfected every time a patient was examined, and monodose eye drops were used.

Results

A total of 17 patients aged between 4 and 17 years old were recruited, Table 1 shows demographic data. The mean age was 9.23 years, and the proportion of female patients was 18%. None of them had any relevant systemic or ocular disease previous to the pandemic. Half of patients had a positive epidemiological history for COVID-19, being parents the most frequent known contact. PCR from nasopharyngeal swabs was positive in 6 patients (35%), whereas 14 patients had positive IgG (82%), and 19% had both IgM and IgG positive serology tests. Systemic manifestations were the following: 35% had PIMS, 41% were diagnosed with pneumonia, 12% had chilblains and cutaneous purpura and 12% of them only had red eye. There was only one patient referring visual symptoms, as unilateral inferior temporal quadrantanopsia, who was later diagnosed with unilateral optic neuritis (Case 2).

Mean best corrected visual acuity was 1/1 in all patients. 29% of patients presented red eye and they were diagnosed by slit lamp examination of: mild acute bilateral conjunctivitis (3 patients) and unilateral episcleritis (2 patients) (Figure.1). Ocular fundus exam was normal in all patients, but in one of them, with unilateral retinal vasculitis, perivascular infiltrates and retinal exudates (Case 1) (12). OCT exam showed preserved macular and optic nerve head architecture in all patients, without any inflammatory signs.

Case 1 was the first child we explored. He was an 11-year-old patient who arrived at the Paediatric Emergency Department with a 2-weeks history of asymptomatic plaques on his toes, and he was diagnosed of chilblains with SARS-CoV-2 positive IgG antibodies. At that time, concern had raised about potential thromboembolic complications related to COVID-19, and the patient was referred to the Ophthalmology Department, despite being visually asymptomatic and not reporting any ocular complaint. Ocular fundus exam showed retinal vasculitis with perivascular infiltrate and retinal exudates on retinal equator of his left eye.(12) OCT did not show inflammation on macular area. A close follow-up was held, and after two weeks retinal exudates disappeared with no residual signs of atrophy. The patient did not receive any specific treatment for COVID-19.

Case 2 was a 13-year-old boy, with no previous medical records, who consulted first for red eye; he was diagnosed with unilateral episcleritis and treated with corticosteroid drops with good response. He returned to the Paediatric Emergency Department 10 days after, due to blurry vision on his right eye. Two members of his family referred possible COVID-19 infection during the previous 3 weeks, but he had remained asymptomatic up to that date. Visual acuity was 1/1 on both eyes and Ishihara test was 21/21 on both eyes. A relative afferent pupillary defect was found on his right eye. Slit lamp exam was normal, as well as ocular fundus and OCT exam (Figure.2). A computerized perimetry was performed, showing

defects on the inferior temporal quadrant with a Visual Field Index (VFI) of 75% and a Mean Defect (MD) of -9.64 Db (Figure.2). The magnetic resonance image of brain and orbits showed no optic nerve Gadolinium enhancement. A complete laboratory and serology test for bacterial and viral infections was performed (*Mycoplasma pneumoniae*, *Brucella* spp., *Toxoplasma gondii*, Rubella, Cytomegalovirus, Epstein-Barr Vi, SARS-CoV-2V2). They all turned out to be negative, but SARS-CoV-2 IgG which was positive. PCR from nasopharyngeal swabs was negative. Considering the epidemiological situation and the serology test results, the patient was diagnosed with a post-infectious right optic neuritis most likely caused by SARS-CoV-2. An extended oral Prednisone treatment was started. Visual symptoms disappeared within 3 weeks since the debut, with no recurrence thus far.

Discussion

Conjunctivitis was the most frequent finding, especially in patients with PIMS versus those with acute pneumonia. This is a common feature with KD, however and unlike it, no cases of anterior uveitis were diagnosed. Ocular findings were mainly detected in the convalescence phase of the disease, two children with episcleritis, one with chilblains and retinal vasculitis, and a teenager presenting with optic neuritis. Conjunctival congestion was the main ocular manifestation described in up to 5% of adults during active COVID-19 infection. SARS-CoV-2 has been associated with increased conjunctival secretion, ocular pain, photophobia, dry eye or tearing during a mean time of 6 days (Liu et al. 2018; Chen et al. 2020). Ocular exam findings were consistent with mild follicular conjunctivitis without pseudomembrane formation (8). We explored seven children admitted with pneumonia. Nor parents or children refer any ocular symptom or sign, and we did not find any case of red eye among them. Conjunctivitis in adults seemed to be more common in hospitalized patient with severe disease (Wu et al. 2020; Loffredo et al. 2020). This finding suggests that conjunctivitis during the acute phase is rare in children.

In April 2020, alarms were triggered among paediatricians since COVID-19 was linked with a KD-like disease (Deza et al. 2020). KD is a medium vessel vasculitis with predilection for coronary arteries of unknown aetiology that occurs mainly in infants and young children less than 5 years old (Singh et al. 2018; Choi et al. 2015; Fernandez-Cooke et al. 2019). PIMS is the termed used to denominate the initial KD-like disease (Deza et al. 2020). This entity involved systemic hyperinflammation, multiorgan involvement, abdominal pain, gastrointestinal symptoms, and very prominent cardiogenic shock with myocardial dysfunction (Shulman 2020). PIMS began to appear approximately 1 month after COVID-19's incidence peak, rather than contemporaneously, in the heavily impacted areas (Shulman 2020). This delay and the frequent SARS-CoV-2 PCR negativity suggest that COVID-19 infection would serve as a delayed trigger for PIMS, following a post-infectious inflammatory process (Shulman 2020). Bilateral conjunctival injection, without exudate and limbus sparing, is one of the main KD diagnostic criteria, together with persistent fever (Singh et al. 2018). It may be seen in up to 89% of patients. The second most common KD ocular manifestation is anterior uveitis, it is usually bilateral, mild and can present keratic precipitates; most frequently appears 1 week after fever onset and recovers within 2-8 weeks without any sequelae (Choi et al. 2015; Ohno et al. 1982). Less common ocular findings in KD have been: superficial punctate keratitis, vitreous opacity, papilledema and subconjunctival haemorrhage (Choi et al.

2015; Ohno et al. 1982). Therefore, ophthalmic examination is usually demanded in children with persistent fever and suspected KD. In this context of PIMS first cases emerging in Spain, we explored 6 children with the disease between 4 and 13 years of age. 3 of them showed bilateral non-purulent conjunctival injection, but no signs of anterior uveitis or posterior pole involvement were detected in any case. A Korean research group studied the incidence of anterior uveitis in KD, and found that it appeared in 37% of cases. An interesting finding, was that coronary artery dilatation was significantly higher in patients with uveitis (27%) compared to patients without it (1.4%) (Choi et al. 2015;). Authors even suggested, that detection of anterior uveitis could lead to earlier diagnosis and treatment of KD before coronary artery lesions were developed. None of our cases showed coronary artery dilatation.

Episcleritis is an uncommon inflammatory condition that is localized to the superficial layers of Tenon's capsule. Diagnosis is based on clinic, as a selective dilation of the superficial episcleral venous plexus in absence scleral involvement, without exudation and conjunctival inflammation. It is a benign, self-limited inflammatory process that usually responds to topical anti-inflammatory agents (Jabs et al. 2000; Read et al. 1999). In Jabs D. *et al* review, episcleritis was associated to systemic rheumatic disease in 30% of cases, such as rheumatoid arthritis, and in 5% to infections like Herpes Zoster *ophthalmicus* or Lyme disease (Jabs et al. 2000). Read R. *et all*, published the largest series of episcleritis in 12 children, 50% had a bilateral disease and 92% had simple episcleritis. 3 out of those 12 cases, were possibly related to a viral infection: one patient had a history of a previous febrile episode with skin rash, and two patients have had upper respiratory tract infections (Read et al. 1999). Ali Shah SA *et all* studied 6 children with recurrent episcleritis, 4 of them had a history of upper respiratory tract infection in the recent past (Syed et al. 2006). Ocular episcleritis is a rare disease in childhood, but 4 cases were diagnosed in our Emergency Department in a month (2 of them with negative serology test, despite positive COVID-19 family members).

Optic neuritis is an inflammatory condition of the optic nerve, that causes visual impairment and is associated to demyelinating inflammatory diseases in most non-idiopathic cases (Lock et al. 2019). Initial visual acuity of optic neuritis, varies from normal to no light perception, although it is usually poor in children. Bilateral involvement and optic disc oedema are more common in children, whereas pain and dyschromatopsia are more likely to be found in adults (Vieira et al. 2017; Good et al. 1992). Viral infections precede optic neuritis in up to two thirds of paediatric patients, even in the context of demyelinating diseases (Morales et al. 2000). This latter setting is designated as parainfectious optic neuritis. It seems to develop more often in prepubescent, teenagers and young adults (Rappoport et al. 2014). Interval from febrile illness to symptom onset ranges from days, in the youngest patients, to weeks in adults; what reinforce the theory that parainfectious optic neuritis is due to an immunologic-inflammatory reaction when doesn't happen simultaneously. Visual prognosis tends to be excellent and recurrences are rare (Rappoport et al. 2014).

In case 2, the most inconsistent finding was the absence of Gadolinium enhancement on the orbit MRI . The visual scotoma appeared a few days after an unilateral episcleritis, and weeks after his family had presented a mild form of COVID-19 infection, which made us suspect we were facing a case of

parainfectious optic neuritis. Coronaviruses can cause severe ocular disease in animals, including anterior uveitis, retinitis, vasculitis, and optic neuritis in feline and murine species. However, so far, ocular manifestations described in humans were mild and rare (Seah et al. 2020; Amesty et al. 2020).

Retinal vasculitis may occur as an isolated idiopathic condition, associated with a systemic inflammatory disease or as a complication of neoplastic disorders or infections. Diagnosis is made by ocular fundus exam, characterized by exudates around retinal vessels and sheathing or cuffing of the affected vessels. Leakage from the inflamed vessels, results in retinal swelling and exudation. Leakage of dye and staining of the blood vessels seen in fundus fluorescein angiography confirms the diagnosis (Abu et al. 2009). We decided not to perform the procedure in our patient, due to age, special pandemic circumstances and the absence of immediate visual threat. On the other hand, the patient was followed closely. The most frequent causes of viral retinal vasculitis or retinitis, come from the herpes virus family and usually affect immunosuppressed patients. Nevertheless, some viruses such as Dengue and Chikungunya are known to cause retinal vasculitis, usually after acute infection, as shown in our patient (Lee et al. 2017). Retinal vasculitis has also been reported in KD (12), but our patient didn't develop any other manifestation of PIMS, as none of the patients with PIMS in our study had retinal vasculitis.

Six out of 17 patients presented ocular manifestations, as conjunctivitis in children with PIMS, episcleritis and isolated cases of retinal vasculitis and retrobulbar optic neuritis. COVID-19 PCR was negative in all of them, while SARS-CoV-2 IgG antibodies were positive. Therefore, ophthalmic complications seem to occur in a convalescent and non-infectious phase of the disease. Wider studies are needed to confirm this hypothesis, but meanwhile ophthalmologists must keep in mind these potential clinical presentations of COVID-19 infection. To date, the pathogenic origin of these lesions remains unknown. SARS-CoV-2 enters the cells via the angiotensin-converting enzyme II (ACE-2) which is only present in the retina and aqueous humour (Lock et al. 2019). This warned us about the possibility of anterior uveitis or posterior pole involvement. So far, no other cases have been reported. Other hypothesis, mentions an autoimmune mechanism as a type I interferons response to coronavirus or the increased levels of serum interleukin 6. More exhaustive studies should now be designed to our better understanding of the disease. Attention should be devoted to children, mainly in the convalescence phase of the infection. SARS-CoV-2 tests should be included in the differential diagnosis of ocular pathology in children who present episcleritis or retinal vasculitis, as well as neuro-ophthalmological manifestations such as optic neuritis or cranial nerve paresis, which may be triggered by viral infections. Further studies are needed to delve into the current state of knowledge.

Declarations

Funding

Not applicable.

Conflict of interest

Not applicable.

Availability of data and material

All data and material concerning the patients included in this case series are accessible if required under the data protection statements.

Code availability

Numerical coding.

Funding

Not applicable.

Ethics approval

The presented study has been approved by the Ethics Committee of Hospital Universitario La Paz.

Consent to participate

All patients that were included gave their consent to participate in the present study.

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Table 1

	Gender	Age	COVID-19 contact	Systemic findings	Ocular symptoms	VA RE	VA LE	Ocular surface	Fundus exam	PCR	IgM	IgG
1	M	11	No	Chilblains	No	1	1		Retinitis			Positive
2	M	17	No	Cutaneous purpura	No	1	1			Positive		
3	M	13	Yes	Kawasaki like S.	No							Positive
4	M	6	Yes	Kawasaki like S.	No	1	1	Conjunctivitis				Positive
5	M	13	No	Kawasaki like S.	No	1	1	Conjunctivitis			Positive	Positive
6	M	4	Yes	Kawasaki like S.	No							Positive
7	F	6	No	Kawasaki like S.	No	1	1	Conjunctivitis				Positive
8	F	14	Yes	Pneumonia	No	1	1			Positive		
9	M	9	No	Kawasaki like S.	No	1	1					Positive
10	M	11	No	Pneumonia	No	1	1					Positive
11	M	6	Yes	Pneumonia	No	1	1			Positive		Positive
12	M	10	No	Pneumonia	No	1	1			Positive	Positive	
13	M	13	No		Quadrantanops	1	1	Episcleritis				Positive
14	M	0	Yes	Pneumonia	No	1	1			Positive		Positive
15	F	17	Yes	Pneumonia	No	1	1				Positive	Positive
16	M	0	Yes	Pneumonia	No	1	1				Positive	Positive
17	M	7	No		No	1	1	Conjunctivitis Episcleritis		Positive		

Figures

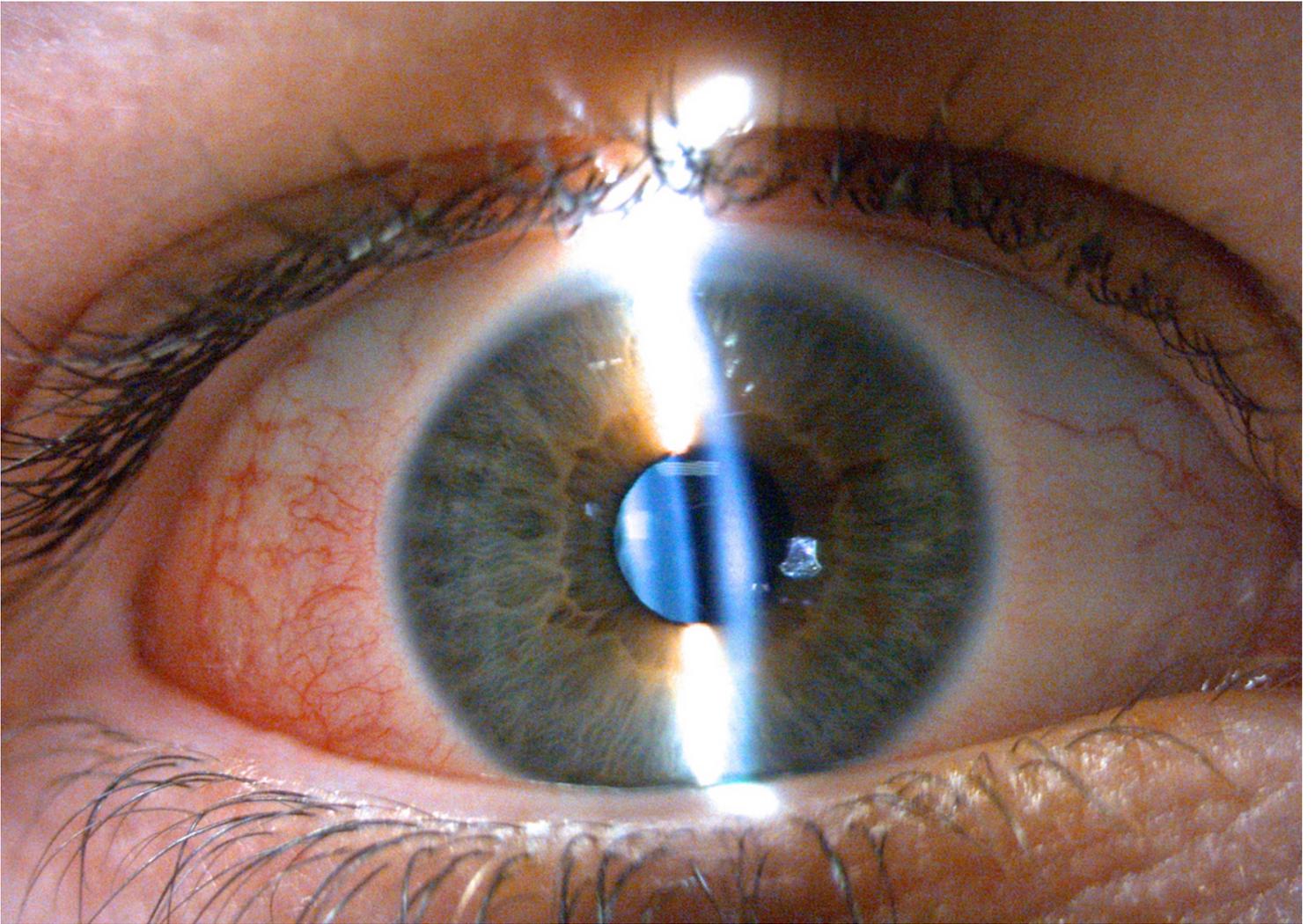


Figure 1

A caption was not provided with this version

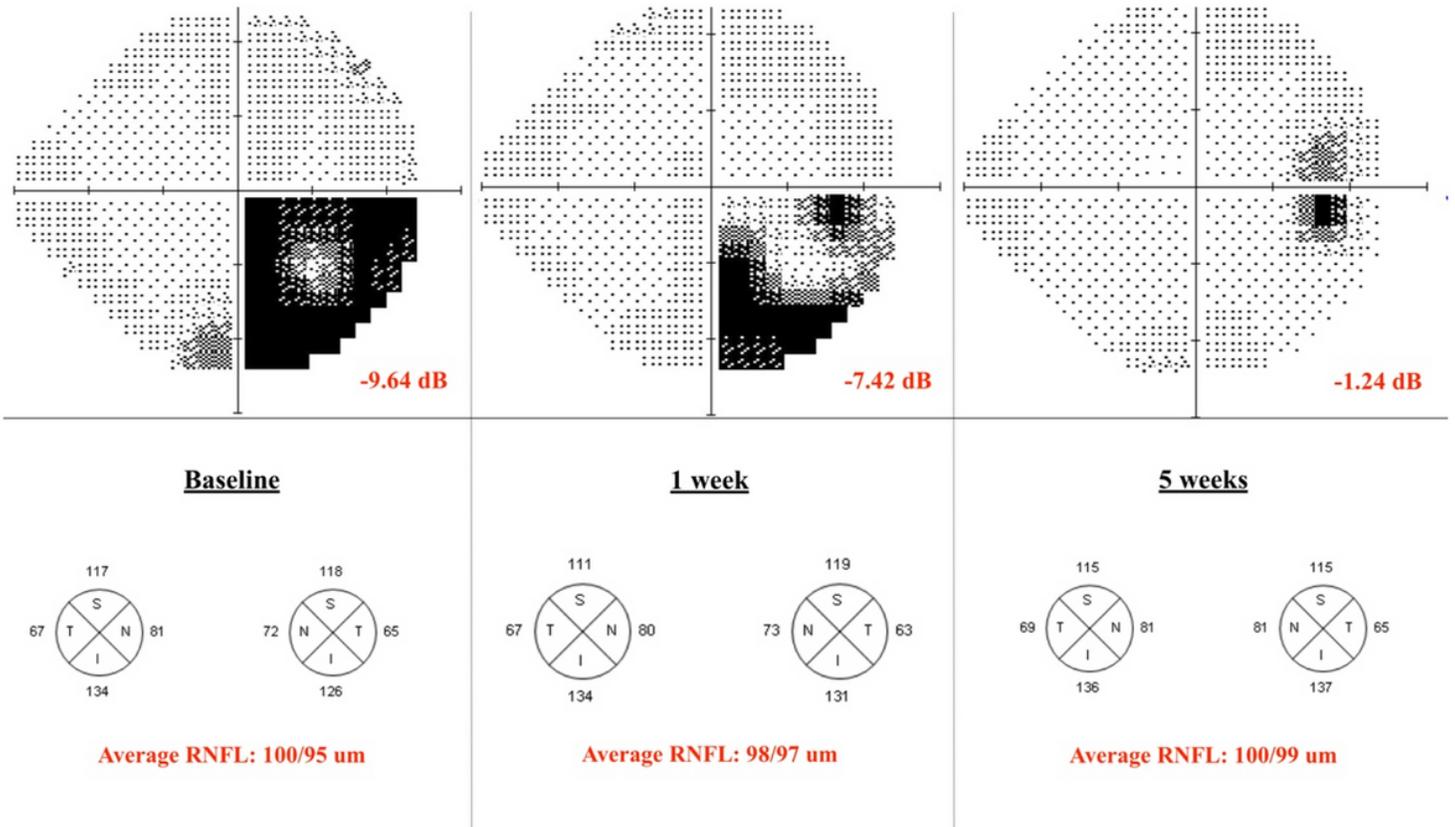


Figure 2

A caption was not provided with this version