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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.

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Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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Conclusion: The conclusion of the study should be highlighted.

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EDITORIAL

2021 Issue 6 at a Glance:

This issue of our journal features 6 original articles, 1 review, and 4 case reports on different topics, as well as a letter to the editor and its reply.

Saá et al. reported in their study titled "Association Between Skin Findings and Ocular Signs in Rosacea" that the prevalence of ocular involvement in rosacea patients was 74.5%, the most common findings were lid margin erythema and meibomian gland dysfunction, and patients with low visual acuity presented to dermatology clinics with papules, pustules, and rhinophyma. Interestingly, 2 of the 51 patients were diagnosed as having ocular cicatricial pemphigoid (see pages 338-343).

In their study titled "Effects of *Myrtus communis* L. Extract and Apocynin on Lens Oxidative Damage and Boron Levels in Rats with a High Fat-Diet", Kuru Yaşar et al. showed that a high-fat diet increased serum triglyceride and total cholesterol levels, body weight, and lens malondialdehyde level and decreased reduced glutathione and boron levels and superoxide dismutase and catalase activity in lens homogenates. However, they reported that treatment with *Myrtus communis* L. extract and apocynin increased levels of boron, reduced glutathione, and catalase activity in lens homogenates, and therefore suggested that they may reduce oxidative stress in the lens (see pages 344-350).

Ekici Tekin et al. reported in their study titled "Follow-up Findings of Non-infectious Pediatric Uveitis Patients" that of 46 uveitis patients under 16 years of age, 45.7% were found to have a rheumatologic disease (juvenile idiopathic arthritis in 23.9%) and 13% had moderate to severe vision loss. The authors reported that methotrexate was the most common treatment (87%) and adalimumab was added to treatment in resistant cases (73.9%) (see pages 351-357).

In their study evaluating the effect of visual quality of life on depression and anxiety levels in patients with Behçet uveitis, Eser Öztürk et al. assessed 105 patients using the Beck Depression Inventory, State-Trait Anxiety Inventory, and Visual Functioning Questionnaire (VFQ-25) and showed that of the 58 patients who completed the questionnaires completely, 31% had symptoms of depression, 58.6% had symptoms of anxiety, and visual quality of life was associated with the development of depression (see pages 358-364).

In a study by Garlı et al. titled "Evaluation of the Effect of Intravitreal Dexamethasone (Ozurdex®) Implant on Intraocular Pressure in Vitrectomized and Non-Vitrectomized Eyes with Macular Edema", non-vitrectomized eyes were found to have significant increases in mean IOP at 1-3 days, 1 month, 2 months, and 3 months after receiving the first dose compared to before the first dose, whereas in vitrectomized eyes a significant increase in mean IOP was only seen at 6 months after the first dose. Antiglaucomatous medication was initiated in 17.2% of the patients due to elevated IOP (see pages 365-372).

A survey by Önder Tokuç et al. on intravitreal injection techniques and treatment protocols among the members of the Turkish Ophthalmological Association revealed that 13% of physicians prescribed prophylactic antibiotics before injection, 63.8% used antibiotics drops immediately after injection, and 91.8% of the physicians prescribed topical antibiotics. In addition, most intravitreal injection procedures were performed in an operating room (65.3%) or clean room (33.6%) and most of the surgeons worked under sterile conditions (see pages 373-380).

In the review selected for this issue, titled "Evolving Techniques and Indications of Descemet Membrane Endothelial Keratoplasty", Evren Kemer et al. summarized new DMEK techniques, size and shape modifications, graft placement techniques, and tips for difficult cases such as eyes with prior glaucoma surgery or failed penetrating keratoplasty, in light of the recent literature (see pages 381-392).

In a case report by Berges Marti et al. titled "Palytoxin-Related Keratoconjunctivitis Assessed by High-Resolution Anterior Segment Optical Coherence Tomography", a 63-year-old man who rubbed his eyes after handling zoanthid corals without gloves was found to have bilateral ring-shaped corneal stroma infiltration, epithelial defect, and marginal stromal infiltration on slit-lamp examination and stromal hyperreflectivity and Descemet's folds on anterior segment optical coherence tomography (OCT). Treatment included topical dexamethasone, topical antibiotics, oral doxycycline, and umbilical cord serum eye drops (see pages 393-397).

Straatsma syndrome is the triad of myelinated retinal nerve fibers, myopia, and amblyopia, and can also be associated with strabismus, nystagmus, hypoplastic optic nerve, and iris heterochromia. In a case report titled "Straatsma Syndrome: Should Visual Prognostic Factors Be Taken into Account? A Case Report", Sevik et al. presented two patients with Straatsma syndrome who showed different responses to occlusion therapy and discussed their treatment responses according to the prognostic factors for post-occlusion visual acuity reported in the literature (see pages 398-402).

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EDITORIAL

In a case report by Kılıç Müftüoğlu et al. titled "Bilateral Sequential Paracentral Acute Middle Macuopathy", a 57-year-old man presenting with complaints of a black spot in his left eye and visual acuity of 20/200 was diagnosed as having paracentral acute middle maculopathy based on a hyperreflective band pattern at the level of the inner nuclear layer and inner plexiform layer in the left eye on SD-OCT. The patient developed paracentral acute middle maculopathy in the other eye 1 year later (see pages 403-406).

Persistent fetal vasculature syndrome is characterized by abnormal regression of the fetal hyaloid system and may occur in various forms. In a case report titled "Pseudo-hyaloidal Stalk in Anterior Persistent Fetal Vasculature: A Report of Two Cases", Özdemir Zeydanlı et al. discussed two atypical cases associated with posterior capsule defect and ectopic lens material located along Cloquet's canal, along with the possible underlying mechanisms (see pages 407-411).

We hope that the articles selected for this issue will be interesting and enjoyable reading.

Respectfully on behalf of the Editorial Board,

Banu Bozkurt, MD

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Original Article

Association Between Skin Findings and Ocular Signs in Rosacea

Francisco Lucero Saá, Federico Cremona, Pablo Chiaradia

Hospital de Clínicas José de San Martin, Universidad de Buenos Aires (UBA), Department of Ophthalmology, Buenos Aires, Arjantin

Abstract

Objectives: To report the most frequent signs in ocular rosacea and evaluate their association with skin findings.

Materials and Methods: Fifty-one patients diagnosed with rosacea by a trained dermatologist were evaluated by an ocular surface specialist. A complete ophthalmological examination was performed.

Results: In our study, the prevalence of ocular signs in patients with rosacea was 74.5%. The average age at presentation was 50 years and women were more affected than men. The most common findings were lid margin erythema, meibomian gland dysfunction, and blepharitis. Fifteen patients had decreased visual acuity due to complications related to rosacea such as leukoma and corneal neovascularization. Interestingly, patients that had the lowest visual acuity presented with dermatological signs of papules and pustules (p=0.001) and rhinophyma (p=0.023). Two patients who showed subepithelial fibrosis and fornix foreshortening were diagnosed as having ocular cicatricial pemphigoid (OCP) by immunohistopathological analysis of conjunctival specimens.

Conclusion: Ocular compromise is common in rosacea. Our study shows that there might be a relationship between the severity of ocular involvement and certain subtypes of cutaneous disease. Rosacea and OCP may coexist. In cases that present with conjunctival fibrotic changes, a diagnostic biopsy is mandatory.

Keywords: Rosacea, ocular rosacea, ocular cicatricial pemphigoid, ocular surface disease, dry eye disease

Introduction

Rosacea is a chronic inflammatory skin syndrome that most commonly affects middle-aged, fair-skinned adults. Clinical signs include central face involvement manifesting with erythema, telangiectasias, papules, pustules, and rhinophyma. However, rosacea can also present with ocular morbidity. Recent studies suggest that the worldwide prevalence of rosacea is 5.46% in the adult population.[1] The disease usually follows a pattern of repeated remissions and exacerbations. Although it was historically classified into four major subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) that could overlap and progress from one to another, the classification criteria was recently updated to include only two features that may be considered diagnostic: Persistent centrofacial erythema showing periodic intensification, and phymatous changes. Even though ocular involvement is not diagnostic of rosacea, it is considered a major phenotype and can also occur in the absence of dermatologic disease in 20% of cases.[2,3,4] Ocular signs include lid margin erythema and telangiectasias; anterior blepharitis and meibomian gland dysfunction (MGD); styes and chalazia; corneal erosion, vascularization, and thinning; scleritis and sclerokeratitis.[2,3,4,5] The treatment consists mainly of avoiding the external stimuli that exacerbate the disease and controlling the chronic inflammation. Although ocular involvement may initially respond to warm compresses, lid hygiene, and artificial tears, some patients may require the prescription of oral antibiotics such as tetracyclines;[6] immunomodulation

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with topical cyclosporine;[7] topical azithromycin;[8] or in-office procedures such as intense pulsed light therapy[9] and meibomian gland probing.[10] Surgical treatment may be necessary in some cases with severe corneal neovascularization, leukoma, progressive corneal thinning, and spontaneous perforation.[11]

The aim of this study was to report the prevalence, clinical signs, and therapeutic modalities for ocular rosacea in our country and attempt to identify which skin phenotypes are associated with more severe ocular disease. We also report two cases of the coexistence of rosacea and ocular cicatricial pemphigoid (OCP).

Materials and Methods

A descriptive, observational, retrospective, and cross-sectional study was performed. All voluntary adult patients of both sexes who were previously diagnosed with rosacea by a trained dermatologist in our institution and provided informed consent to participate were included consecutively. Patients with ocular or systemic pathology other than rosacea that was associated with diminished visual acuity or dry eye disease and/or had required any ocular surgical treatment were excluded. Contact lens wearers were also excluded from the study. All patients meeting the inclusion criteria were evaluated by a cornea and ocular surface specialist in the Ophthalmology Division of the Hospital de Clínicas "José de San Martín" in Buenos Aires between August 31, 2017 and May 31, 2018. The project was approved by the Ethics Committee of the Hospital de Clínicas of the University of Buenos Aires (date: 16.09.2015) and conducted in accordance with the guidelines of the Declaration of Helsinki (Fortaleza 2013).

The age and gender of every admitted patient were recorded. According to the most prevalent skin signs in each case, the patients were classified as having erythematotelangiectatic, papulopustular, or phymatous rosacea. A complete ophthalmological exam was performed, including best corrected visual acuity and slit-lamp biomicroscopy. A 1% sodium fluorescein solution was used to stain the tear film. First, tear film break-up time (TBUT) was measured. A TBUT longer than 10 seconds was considered normal, less than 10 seconds was noted as diminished TBUT. Each eye was measured three times and the results were averaged. Afterwards, fluorescein corneal staining was assessed with a standardized 4-point scale (0: none, 1: mild, 2: moderate, 3, severe). Meibomian gland function was evaluated in the upper and lower lid based on the expressibility of secretions upon digital compression of an area including five gland orifices. The results were classified on a 4-point scale according to the number of glands expressing meibum (0: all five glands, 1: three to four glands, 2: one to two glands, 3: zero glands).

A decrease in visual acuity due to corneal complications related to rosacea (corneal thinning, scarring, infiltrates, and neovascularization) was considered an indicator of more severe ocular involvement. Patients were divided into those with and without ocular rosacea. All patients who presented with palpebral erythema and telangiectasias were classified in the ocular rosacea group.

Statistical Analysis

The groups were compared using chi-square or Fisher's t-test for categorical variables and Student's t-test or Mann-Whitney U test for numerical variables. A p value <0.05 was used to evaluate statistical significance.

Results

A total of 102 eyes of 51 patients with a dermatological diagnosis of rosacea were analyzed. The more affected eye of each patient was selected for statistical analysis; in cases where the degree of involvement was the same, the right eye was selected. The study patients were predominantly female (84.2%) and the average age at presentation was 50 years (range: 18-84).

Ocular signs of rosacea were detected in 38 patients (74.5%). Slit-lamp biomicroscopy in these patients showed lid margin erythema and telangiectasia (100%), MGD (94.7%), anterior blepharitis (73.7%), chalazia (23.0%), corneal neovascularization (10.5%), peripheral corneal infiltrates (10.5%), keratitis (7.9%), corneal ulcer (7.9%), and scarring (7.9%) (Table 1). Fifteen patients had decreased visual acuity due to rosacea-related complications such as leukoma and corneal neovascularization; 3 of them (7.9%) required keratoplasty. Interestingly, among these patients, those who had the lowest visual acuity presented with dermatological signs of papules and pustules (p=0.023); and rhinophyma (p=0.017). Two patients who presented with subepithelial fibrosis and fornix foreshortening were diagnosed as having OCP by immunohistopathological analysis of conjunctival specimens.

The most commonly used treatments were artificial tears (65.8%), oral doxycycline (60.5%), corticosteroid-antibiotic ointment (57.9%), and lid hygiene (39.5%). However, 7.9% of patients with ocular rosacea required a corneal transplant due to decreased visual acuity related to corneal complications.

Case 1

An 18-year-old woman presented with skin rosacea showing papules and pustules (Figure 1). Ophthalmological examination revealed a visual acuity of counting fingers in both eyes due to bilateral corneal neovascularization and leukoma. Slit-lamp biomicroscopy also showed intense blepharitis and MGD. Treatment with oral doxycycline, topical ciprofloxacin/dexamethasone ointment, and artificial tears was initiated. One month later, systemic and local involvement was stabilized and keratoplasty was performed in both eyes. Systemic treatment with oral doxycycline and corticosteroids was maintained for 6 months. Eighteen months after keratoplasty, the right eye developed mild graft rejection that responded well to topical prednisolone.

Case 2

A 22-year-old woman presented with skin rosacea including papules, pustules, and rhinophyma (Figure 2A). Ophthalmological evaluation showed a best corrected visual

Table 1. Comparison between group 1 (with ocular rosacea) and group 2 (rosacea without ocular involvement)			
	Group 1 (n=38)	**Group 2 (n=13)**	**p**
Males, n (%)	6 (15.8)	1 (7.7)	0.662
Age (years), mean (range)	50 (18 -84)	41 (19-64)	0.086
Erythema and telangiectasia, n (%)	38 (100)	0 (0)	0
Meibomian gland dysfunction, n (%)	36 (94.7)	11 (84.6)	0.266
Blepharitis, n (%)	28 (73.7)	4 (30.8)	0.008
Chalazia, n (%)	9 (23.7)	6 (15.8)	0.414
Keratitis, n (%)	3 (7.9)	0 (0)	0.405
Peripheral corneal infiltrates, n (%)	4 (10.5)	0 (0)	0.295
Corneal ulcer, n (%)	3 (7.9)	0 (0)	0.405
Neovascularization, n (%)	4 (10.5)	0 (0)	0.295
Corneal scarring, n (%)	3 (7.9)	0 (0)	0.295

acuity of 20/40 in the right eye and 20/60 in the left eye. Slit-lamp biomicroscopy revealed intense MGD and blepharitis, corneal neovascularization, and scarring (Figure 2B, C). Initially, treatment with oral doxycycline, topic ciprofloxacin/dexamethasone ointment, and artificial tears was initiated. Due to a poor response to treatment, a short course of oral corticosteroids was needed to control the disease. The patient now presents periodic relapses that respond well to oral doxycycline 100 mg/day in 30-day courses.

Case 3

A 65-year-old man presented with intense skin rosacea including papules, pustules, and rhinophyma (Figure 3A). Ophthalmological examination revealed a best corrected visual acuity of counting fingers in both eyes. Slit-lamp biomicroscopy showed blepharitis, MGD, fornix foreshortening, conjunctival scarring, corneal neovascularization, and leukoma in both eyes. Conjunctival immunohistochemistry revealed OCP. Systemic immunosuppression with methotrexate was initiated. Rosacea was treated with oral doxycycline, topical antibiotic/dexamethasone ointment, cyclosporine 0.05%, and preservative-free artificial tears. Keratoplasty was performed in the left eye. No graft rejection was observed in the first 5 years of follow-up (Figure 3B).

Discussion

In this study we present a series of 51 patients with a clinical diagnosis of rosacea who were evaluated in the Ophthalmology Department of the Hospital de Clínicas "José de San Martín". Currently, there is no gold standard for the diagnosis of ocular rosacea and every patient with cutaneous rosacea may have some degree of ocular compromise.[12] Because erythema is considered a diagnostic sign of skin disease and it is usually accompanied by telangiectasias in the lid margin, all patients in our study with palpebral erythema and telangiectasias were classified in the ocular rosacea group. We found the prevalence of ocular signs to be 74.5%, similar to that reported in other studies.[4] The mean age at presentation for rosacea was 50 years, also similar to the literature,[11] and most patients were women. The most common ocular signs were erythema and telangiectasias of the lid margin, MGD, and anterior blepharitis. More serious manifestations of ocular involvement such as keratitis, corneal infiltrates, ulcers, leukomas, and corneal neovascularization occurred with low frequency. These results are consistent with the findings in other series.[4,5,11]

Severe dry eye can be caused by MGD. Meibomian gland loss in rosacea can be assessed objectively with meibography. Atrophy

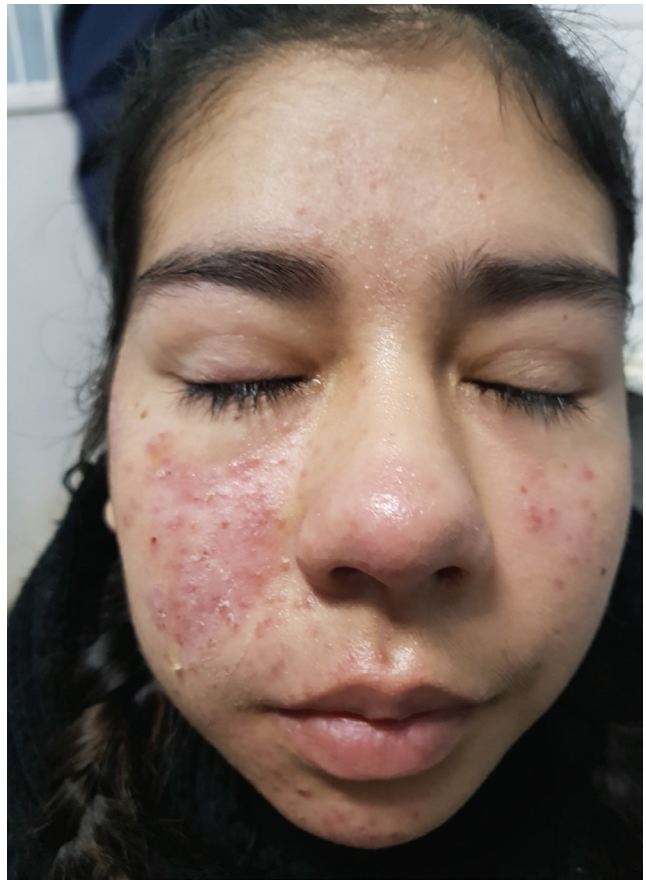

Figure 1. Woman with skin rosacea presenting with papules and pustules

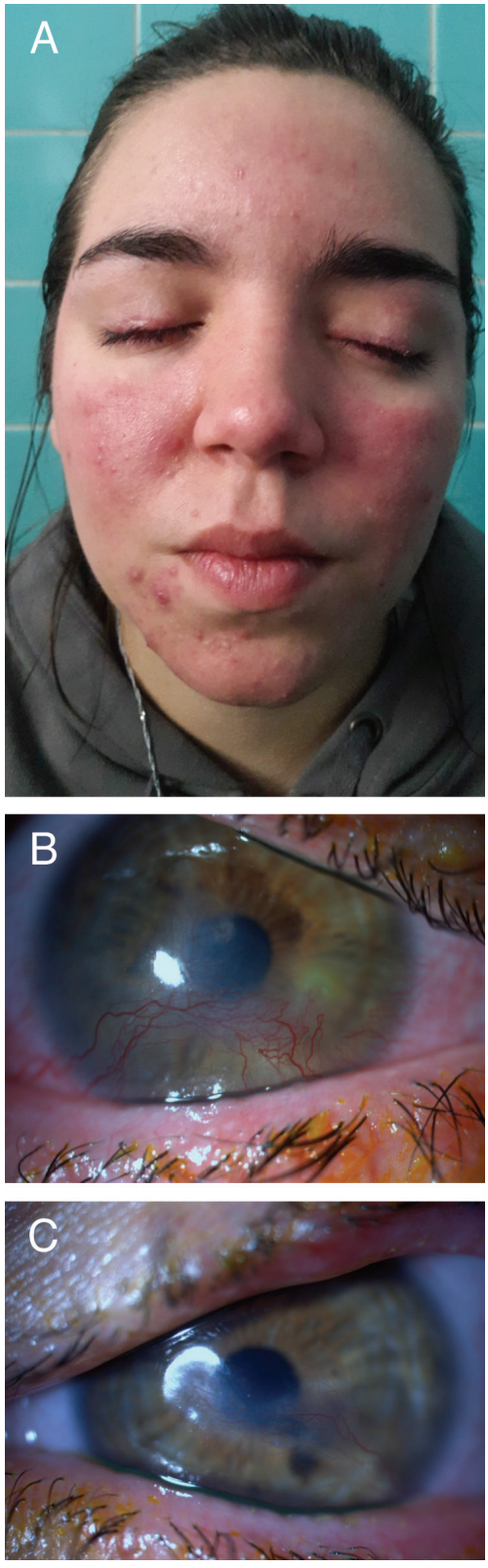

Figure 2. Woman with skin rosacea presenting with papules, pustules, and mild rhinophyma (A). Both the right eye (B) and left eye (C) showed intense blepharitis, meibomian gland dysfunction, corneal scarring, and neovascularization

has been correlated to impaired gland function, including diminished TBUT and an altered tear lipid layer pattern. Meibography using infrared light technology allows for the detection of gland dropout, shortening, dilation, and distortion, and is very important in the diagnosis and follow-up of patients with MGD.[13,14] Unfortunately, it was not possible in our center.

In cases of severe corneal compromise producing low visual acuity or spontaneous perforation, keratoplasty may be needed. Akpek et al.[11] published a series of 131 cases in which 6 patients underwent corneal transplantation (4.6%). In our study, 3 of 38 patients (7.9%) in the ocular rosacea group required keratoplasty. Interestingly, one of those patients also showed signs of cicatricial conjunctivitis and a conjunctival biopsy confirmed OCP. Such an association might have been partly responsible for the need for keratoplasty in that particular patient.

Ocular rosacea can be accompanied by signs of chronic cicatricial conjunctivitis and is a well-known cause of pseudopemphigoid. Several studies describe pseudopemphigoid

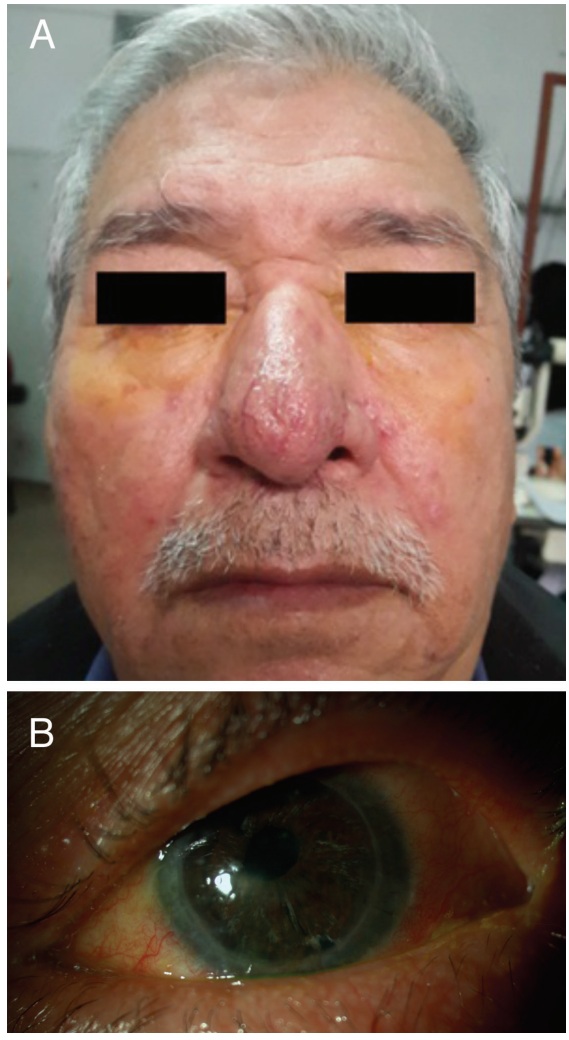

Figure 3. Man showing signs of severe skin rosacea with papules, pustules, and rhinophyma (A). Keratoplasty was performed in the left eye, which shows a paracentral leukoma (B)

associated with rosacea.[11,15,16] Furthermore, Thorne et al.[17] identified rosacea as responsible for 20% of cases, with immunohistopathological confirmation. We identified two cases of associated OCP in patients with ocular rosacea. This suggests that these two diseases can coexist. OCP is an autoimmune disease that involves a type 2 hypersensitivity reaction. Both environmental factors and genetic susceptibility might be involved in loss of tolerance to the components of the basement membrane zone.[18] As has been proposed for other diseases that may coexist with OCP, ocular surface injuries related to rosacea could expose basement membrane epitopes of damaged conjunctiva, which might act as neoantigens that precipitate the autoimmune response.[19] Although further research is needed, all patients who present with conjunctival fibrotic changes should be thoroughly analyzed to rule out OCP.

To date, a reliable correlation between the severity of skin findings and ocular involvement has not been established.[12] However, Keshtcar-Jafari et al.[20] reported an association between facial erythema and ocular involvement. Furthermore, Whitfeld et al.[21] suggested that there would be a correlation between the presence of *Staphylococcus epidermidis* and ocular compromise because the same pathogen was isolated on the lid margin and in the pustules of patients with papulopustular rosacea. We found a significant association between the severity of ocular findings, assessed as a diminished visual acuity due to rosacea corneal involvement, and the presence of rhinophyma, papules, and pustules. As it has been mentioned before, rosacea manifests with relapses and remissions. Special attention should be given to ocular involvement during exacerbations, as progression of skin disease could lead to more severe ocular damage. Early referral to the ophthalmologist in these cases might prevent visual loss.

As in other case series,[5,7] the most commonly used treatments included artificial tears (65.8%), oral doxycycline (60.5%), and antibiotic ointment combined with topical corticosteroids (57.9%).

Study Limitations

The main limitation of our study is the relatively small number of patients.

Conclusion

Ocular compromise in rosacea is common. Our study shows that there might be a relationship between the severity of ocular involvement and specific cutaneous signs. On the other hand, rosacea and ocular mucous membrane pemphigoid may coexist. In patients presenting with conjunctival fibrotic changes, we believe that a diagnostic biopsy is imperative.

Ethics

Ethics Committee Approval: The project was approved by the Ethics Committee of the Hospital de Clínicas of the University of Buenos Aires (date: 16.09.2015).

Informed Consent: It was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: F.L.S., F.C., P.C., Concept: F.L.S., F.C., P.C., Design: F.L.S., F.C., P.C., Data Collection or Processing: F.L.S., F.C., P.C., Analysis or Interpretation: F.L.S., F.C., P.C., Literature Search: F.L.S., F.C., P.C., Writing: F.L.S., F.C., P.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Effects of *Myrtus communis* L. Extract and Apocynin on Lens Oxidative Damage and Boron Levels in Rats with a High Fat-Diet

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Abstract

Objectives: Nutritional obesity causes oxidant damage in the body and cataract formation in the lenses by increasing the formation of free radicals. *Myrtus communis* leaf extracts (Myr) have antioxidant properties, and apocynin (Apo) is an effective NADPH-oxidase inhibitor. The data on tissue boron levels are quite lacking. The aim of this novel study was to investigate the effects of Myr and Apo treatment on boron levels and oxidative lens damage in rats fed a high-fat diet (HFD).

Materials and Methods: Wistar albino male rats were randomly divided into four groups: the control group, HFD group, HFD + Myr group, and HFD + Apo group. Body weight and blood lipids were determined before and after the experiment. After decapitating the rats, the lenses were removed and homogenized. Catalase (CAT) and superoxide dismutase (SOD) activities and boron, malondialdehyde (MDA), and reduced glutathione (GSH) levels in the lens homogenates were determined.

Results: The HFD increased serum triglyceride ($p<0.05$), total cholesterol level ($p<0.001$), body weight ($p<0.001$), and lens MDA levels ($p<0.01$) and decreased lens GSH ($p<0.05$) and boron level ($p<0.01$), SOD ($p<0.001$), and CAT activity ($p<0.001$). However, Myr and Apo treatment reduced the rats' body weight ($p<0.001$), serum triglyceride ($p<0.05$), and total cholesterol level ($p<0.001$) and increased lens boron ($p<0.01$; $p<0.001$), GSH levels ($p<0.05$; $p<0.01$), and CAT activity ($p<0.001$).

Conclusion: Both Myr and Apo may be able to reduce oxidative stress in the lenses of obese rats caused by HFD by increasing boron levels.

Keywords: Obesity, lens, boron, antioxidants, *Myrtus communis*, apocynin

Introduction

Obesity is described as excessive or abnormal fat accumulation and is known to cause diabetes, hypertension, dyslipidemia, sleep apnea, respiratory problems, osteoarthritis, cardiovascular disease, and cancer. One of the mechanisms related to obesity and its associated comorbidities is the formation of excess oxidants and reactive oxygen species (ROS).[1] Various studies have indicated that increased ROS formation in a high-fat diet (HFD) causes oxidant damage in the lens and cataract development.[2,3]

ROS are produced during normal cellular oxygen metabolism and are essential for numerous enzymatic reactions and biological functions. However, in some pathological conditions, they appear in excessive amounts and cause harmful effects at cellular level.[4] Peroxidation of polyunsaturated fatty acids in biomembranes often occurs through exposure to ROS. Malondialdehyde (MDA)

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is generated by the peroxidation of fatty acids containing three or more double bonds. MDA, which is one of the major end products of lipid peroxidation, is frequently used in evaluating oxidant damage.[5] Cells try to protect themselves from the harmful effects of ROS by developing various antioxidant systems. Endogenous antioxidants include catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH). Dietary antioxidants contribute significantly to the endogenous antioxidant system in relieving oxidative stress.[6]

Plant phytochemicals have been shown to exhibit preventive activity against oxidative stress in various animal models.[7,8] *Myrtus communis*, commonly known as myrtle, is among the edible foods and medicinal plants found in the Mediterranean and the Black Sea regions (including Turkey) and grows mainly in swamps and forests.[9] *M. communis* leaf extracts (Myr) have been reported to have anti-inflammatory, antibacterial, and antioxidant properties.[10,11] Nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase is a multi-enzyme complex that catalyzes the one-electron reduction of molecular oxygen to the superoxide anion. Therefore, this reaction is the major source of ROS.[12] Apocynin (Apo) which can be obtained from the root of the *Apocynum cannabinum* plant, is a potent NADPH oxidase inhibitor.[13]

The biological importance of boron is increasingly coming to light.[14,15] Although boron is not yet considered an essential element for humans, it is classified as a possible essential element.[16] The data on tissue boron levels, boron metabolism, and boron mechanism of action are quite lacking. There is no previous study in the literature that determines lens boron levels.

The aim of this study was to investigate the effects of Myr and Apo treatment on boron levels and oxidative lens damage in rats fed an HFD. To our knowledge, this study is the first to evaluate boron levels in the lens, and our results show that an HFD, Myr, and Apo can affect lens boron levels.

Materials and Methods

Animals and Conditions

The study was conducted in 2-month-old male Wistar albino rats (n=20) supplied by the Marmara University Application and Research Center for Experimental Animals. The rats were housed in an air-conditioned room with light-dark cycles of 12h:12h and constant relative humidity (65-70%) and temperature (22±2 ºC). Ethical approval was obtained from the Marmara University Animal Care and Use Committee (30.03.2019).

Plant samples and preparation of *Myrtus communis* extract

The plant samples used in this study were collected from the city of Manisa (Turgutlu region) in 2010. The samples were identified by a botanist in the Marmara University, Faculty of Pharmacy. Voucher specimens were deposited in the Herbarium of Marmara University, Faculty of Pharmacy (MARE no: 13006). *M. communis* leaves (100 g) were dried in the shade at room temperature. The dried pulverized leaves were extracted with 96% EtOH using a Soxhlet apparatus. They were then evaporated in a vacuum at 40 ºC until dry. This extract was stored in a dark container in the refrigerator (4 ºC) until use.

Study Groups

After a 7-day acclimation period, the rats were weighed and randomly divided into four groups as follows:

- Control group (n=5): Rats were fed a standard rat diet for 16 weeks.
- HFD group (n=5): Rats were fed an HFD including 45% fat for 16 weeks.
- HFD + *M. communis* L. group (n=5): Rats were fed an HFD for 16 weeks and received Myr (100 mg/kg) via orogastric gavage during the last 4 weeks.
- HFD + Apo group (n=5): Rats were fed an HFD for 16 weeks and received Apo (Merck, Darmstadt, Germany) (25 mg/kg, in 15% dimethyl sulfoxide) via intraperitoneal injection during the last 4 weeks.

Biochemical Analysis

At the end of 16 weeks, the rats were weighed again and decapitated. Blood samples were collected for measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels and the lenses were removed and homogenized in 0.9% of NaCl solution to prepare 5% lens homogenates. The lens homogenates were stored at -80 ºC until assaying. Boron, reduced GSH and MDA levels, SOD, and CAT activities in the lens homogenates were determined using the modified carminic acid[17], Beutler [18], Ledwozwy et al.[19], Mylorie et al.[20], and Aebi[21] methods, respectively.

Statistics Analysis

Statistical analysis was done using GraphPad Prism 5.0 (GraphPad Software, San Diego, USA). All data were expressed as mean ± standard error. Analysis of variance (ANOVA) was used for multiple comparisons followed by Tukey's post-hoc test. A p-value less than 0.05 was considered significant.

Results

This study used an HFD-induced obesity model. Weight values at the beginning and end of the experiment are shown in Figure 1. At the end of week 16, rats in the HFD group were significantly heavier than those in the control group ($p<0.001$), whereas treatment with Myr and Apo significantly reduced this increase in weight.

The total cholesterol, triglyceride, and HDL-cholesterol of rats at week 16 are shown in Figure 2. Rats in the HFD group had higher triglyceride ($p<0.05$) (Figure 2a) and total cholesterol levels ($p<0.001$) (Figure 2b) and lower HDL-cholesterol levels ($p<0.001$) (Figure 2c) than the control group. Rats that received Myr and Apo also had significantly lower total cholesterol and triglyceride levels and significantly higher HDL-cholesterol levels than those in the HFD group.

At the end of 16 weeks, lens MDA levels were significantly higher in the HFD group than in the control group ($p<0.01$) (Figure 3a). Lens MDA levels of Apo-treated rats were significantly lower than those of the control group ($p<0.05$)

and the HFD group (p<0.001). Moreover, the lens MDA levels of the Apo-treated group were significantly lower than those of the Myr-treated group (p<0.001). Lens GSH levels in the HFD group were significantly lower than those of the control group (p<0.05) (Figure 3b). Lens GSH levels were significantly higher in the Apo-treated (p<0.01) and Myr-treated (p<0.05) groups than in the HFD group. Lens CAT (Figure 3c) and SOD (Figure 3d) activities were significantly lower in the HFD group than in the control group (p<0.001). There was no significant difference in SOD activity between the Apo-treated and HFD groups. However, the Myr-treated group had higher SOD activity than the HFD group (p<0.05). Lens CAT activity in the Myr- and Apo-treated groups was significantly higher than in the control and HFD groups (p<0.001).

Lens boron levels in the HFD, Myr-treated, and Apo-treated groups were significantly lower than those of the control group (p<0.001). Moreover, lens boron levels in the Myr-treated (p<0.05) and Apo-treated (p<0.001) groups were higher than those of the HFD group (Figure 4).

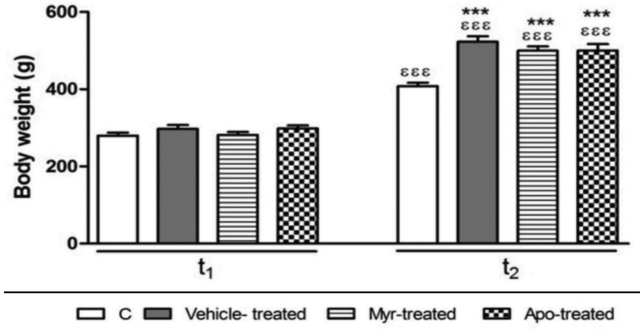

Figure 1. Body weight of the groups recorded at the beginning (t1) and end (t2) of the study
C: Control group, HFD: High-fat diet group, Myr-treated: HFD + *Myrtus communis* L. extract, Apo-treated: HFD + apocynin group. Values are given as mean ± standard error. ***: p<0.001: significantly different compared to t1, ***: p<0.001: significantly different compared to the control group.

Discussion

It is known that HFD is strongly associated with obesity. HFDs have been used for decades to induce dyslipidemia and obesity in rodents.[22] In the present study, body weight was significantly higher in HFD-fed rats (45% fat) compared to the control group (standard rat diet). However, this increase in body weight was less pronounced in the Myr- and Apo-treated groups. Similar to our study, it has been shown that Myr treatment (200 and 400 mg/kg) in rats[23] and Apo treatment (5 mM, dissolved in drinking water) in mice reduced weight gain in animals receiving an HFD.[24] It has been shown that polyphenols and flavonoids regulate the activity of PPAR-γ (peroxisome proliferator-activated receptor), the inhibition of angiogenesis in adipose tissue, and the SREBP (sterol regulatory-element binding proteins) pathway.[25,26] Myr is rich in polyphenols and flavonoids. Therefore, it is thought that it can reduce body weight. It has been suggested that Apo can achieve this by preventing insulin resistance.[27]

In recent years, the use of plant extracts and plant-derived compounds has been increasing in research studies for the prevention and treatment of many cardiovascular diseases.[28] Rosa et al.[29] reported that the semi-myrtucommulone and myrtucommulone-A compounds in Myr has antiatherogenic effects. Meng et al.[27] showed that Apo significantly improved dyslipidemia in mice with HFD-induced obesity. In the present study, the total cholesterol and triglycerides levels of rats fed an HFD were significantly higher than those of the control group, while their levels of HDL cholesterol were lower. However, triglyceride and total cholesterol levels were significantly lower in the Myr and Apo treatment groups than in the HFD group, while HDL cholesterol was higher.

Oxidative damage is an important factor that causes cataracts, which are responsible for almost half of all cases of human blindness worldwide. Generally, oxidation is considered to be a key feature of cataract formation.[30] HFD may contribute to cataract formation by increasing ROS in the lens.[2,3] A case-

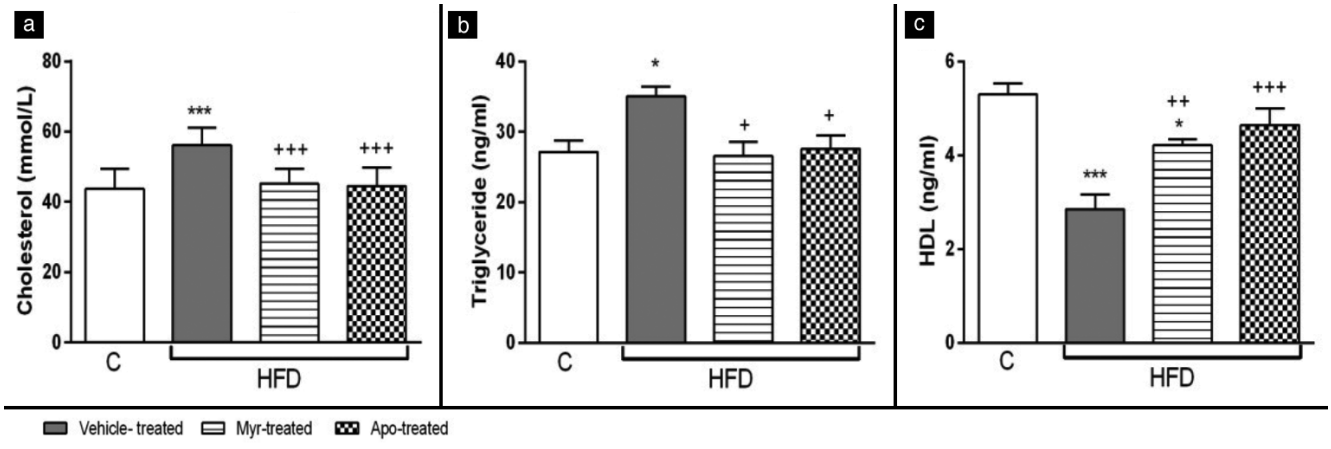

Figure 2. Total cholesterol (a), triglyceride (b), and HDL-cholesterol (c) levels
C: Control group, HFD: High-fat diet group, Myr-treated: HFD + *Myrtus communis* L. extract, Apo-treated: HFD + apocynin group. Values are given as mean ± standard error. *p<0.05, ***p<0.001: significantly different from the control group. +p<0.05, ++p<0.01, +++p<0.001: significantly different from the HFD group

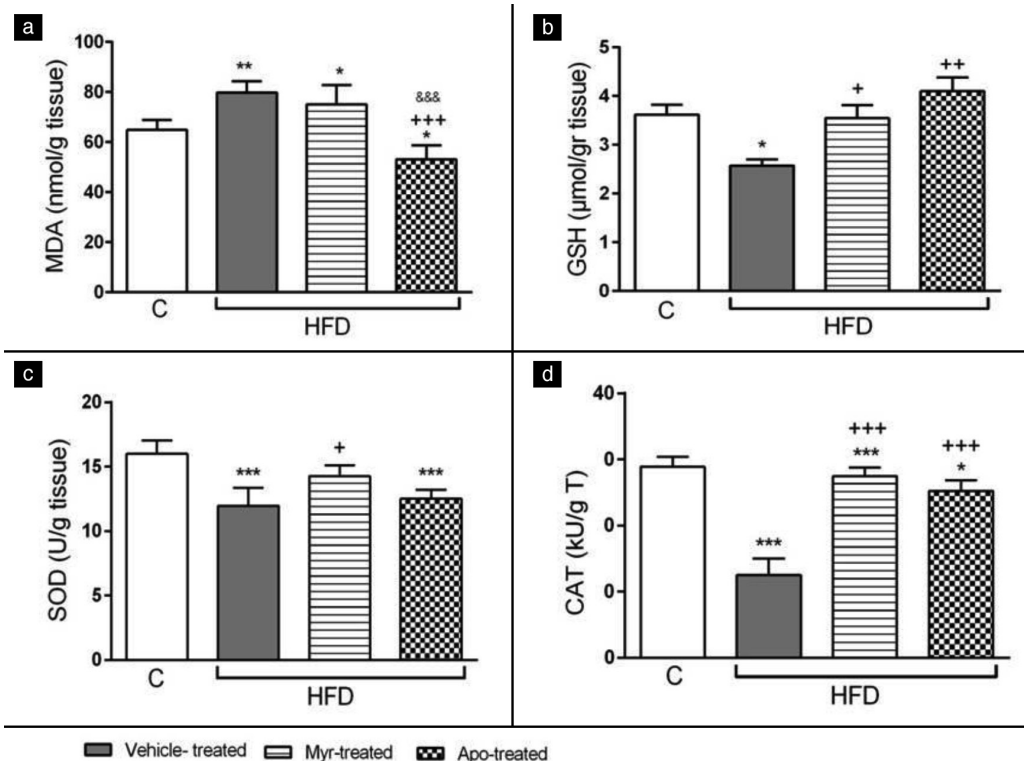

Figure 3. Lens malondialdehyde (MDA; a) and glutathione (GSH; b) levels and superoxide dismutase (SOD; c) and catalase (CAT; d) activities
C: Control group, HFD: High-fat diet group, Myr-treated: HFD + *Myrtus communis* L. extract, Apo-treated: HFD + apocynin group. Values are given as mean ± standard error. *p<0.05, **p<0.01, ***p<0.001: significantly different from the control group. +p<0.05, ++p<0.01, +++p<0.001: significantly different from the HFD group. &&&: p<0.001: significantly different from the HFD+Myr group

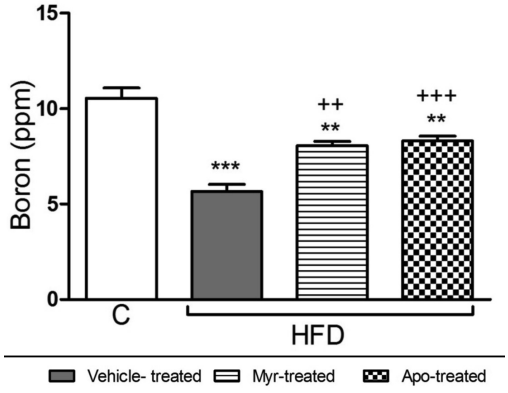

Figure 4. Lens boron levels
C: Control group, HFD: High-fat diet group, Myr-treated: HFD + *Myrtus communis* L. extract group, Apo-treated: HFD + Apocynin group. Values are given as mean ± standard error. **p<0.01, ***p<0.001: significantly different from the control group. ++p<0.01, +++p<0.001: significantly different from the HFD group

control study evaluating the relationship between diet and cataract risk showed that the risk of cataract increased with total dietary fat intake (p<0.001).[31]

Ocular tissues contain many antioxidants such as enzymes, proteins, ascorbic acid, glutathione, cysteine, and tyrosine to protect against excess ROS. The lens is a tissue that is particularly vulnerable to oxidative damage.[32] It is also known that in cataract patients, the level of hydrogen peroxide (H_2O_2) in the lens may triple compared to a healthy lens.[33] It has been shown that SOD protects the lens from oxidative damage from H_2O_2 in rats.[34] It is known that GSH in the lens contributes to the preservation of lens transparency.[35] GSH protects thiol groups in lens proteins against ROS. This is very important for the normal function of the lens epithelium Na/K-ATPase enzyme, which affects cell permeability.[35] It is known that NADPH oxidase is the main source of ROS and Apo is an effective NADPH oxidase inhibitor.[36] As the major end product of lipid peroxidation, MDA is considered a toxic compound in the eye due to its high cross-linking ability with the lipid membrane.[37] In the present study, tissue oxidative damage was monitored with lens MDA levels. In rats fed an HFD, lens MDA levels were significantly higher than those of the control group. This result shows that HFD increases oxidative damage. Moreover, lens MDA levels in the Apo treatment group were significantly lower than in the control and HFD groups. Furthermore, lens GSH and CAT activity in the Apo treatment group were significantly higher than in the HFD group. These results show that Apo can protect the lens from oxidative damage. In another study, treatment with 2.4 g/L Apo (in drinking water) for 5 weeks in mice fed an HFD reduced systemic and hepatic oxidative stress.[27] It was also reported that cataract progression was reduced in rabbits given 20 mg/kg/day Apo intraperitoneally.[38]

Various studies have shown that *M. communis* has antimicrobial, anti-inflammatory, and antioxidant effects.[39,40,41] In the literature, studies showing the effect of *M. communis* on lens antioxidant status are limited. In streptozotocin-induced diabetic rats, *M. communis* extract was shown to increase lens GSH ($p<0.05$) and MDA levels ($p<0.05$).[42] In the present study, lens MDA levels did not differ significantly between the HFD and Myr-treated groups. However, GSH levels, CAT and SOD activities were significantly higher in the Myr-treated group than in the HFD group.

Boron is present in human tissues and body fluids as a natural result of boron intake from food and drinking water.[14] Studies on the distribution of boron in tissues are limited in the literature.[15] Data on the mechanism of action of boron is insufficient. It is reported that boron may react with cis-hydroxyl group-containing biomolecules such as polysaccharides, adenosine-5-phosphate, pyridoxine, flavins (e.g., flavin adenine dinucleotide), dehydroascorbic acid, and pyridine (e.g., NAD+ or NADP).[14] Having low atomic weight and being able to make compounds with organic molecules are thought to be important for the biological function of boron. It is also thought that boron may be effective in hormone receptors and trans-membrane signals, cell membrane functions, and stability.[43]

Boron compounds ingested orally are rapidly converted to boric acid in the gastrointestinal tract and are nearly completely absorbed and distributed to the tissues through the blood.[14] Studies have shown that 84-85% of dietary boron is excreted in urine. Although it is known that the distribution of boron into tissues involves passive diffusion and/or sodium-dependent borate carrier-1 (NaBC1), it has not been fully elucidated yet.[44] Studies are needed to determine how boron is transported to the lens. In rats, the "no observed adverse effect level" (NOAEL) for developmental effects of boron is 9.6 mg boron/kg body weight/day. The oral lethal dose (LD50) for boron in rats is 400-700 mg/kg.[45,46] The available human exposure studies are very limited due to geographical conditions and dietary differences, and the toxic oral reference dose and recommended dietary allowance (RDA) of boron for humans have not been clearly established. However, it is known that it is not possible to exceed the safe intake level (20 mg/day) and toxic dose (500 mg/day) through dietary and water intake.[47]

There is no previous study in the literature that examines lens boron levels. Therefore, we could not compare these results. However, it has been shown that the boron level decreases in plasma, kidney, brain, and liver tissue of rats receiving malathion, which induces oxidative stress. Boron levels in these tissues were found to be considerably lower than our lens boron levels.[48] Similar to the above study, lens boron levels also decreased with an HFD in the present study. Various studies have shown that boron plays a role in energy and lipid metabolism. It increases thermogenesis by causing the expression of uncoupling proteins in adipose tissue[49] and inhibits transcription activity of SREBP.[50] In rats fed an HFD, it has been shown that increased boron intake reduces body weight by altering serum L-carnitine and insulin-like growth factor 1 levels.[51] In humans, it has been reported that high dietary boron intake increases serum and saliva boron levels and reduces body weight, serum low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, total cholesterol, and triglyceride levels.[44]

Study Limitations

A limitation of the present study was that we did not determine boron intake by food and water. Drinking water from the same source was given to all groups. Therefore, boron intake by water can be assumed to be similar for all groups. However, the boron intake of the HFD group may have been lower than that of the treated HFD groups. The reason for the increased boron levels may arise from both the antioxidant properties of Myr and Apo, as well as from boron intake with Myr. Increased boron levels may enhance the effects of Myr and Apo. The increase in lens boron level in HFD + Apo group rats suggests that boron may be important in preventing lens oxidative damage. Boron can be a mediator in the prevention of lens oxidative damage. Further studies evaluating the effects of boron supplements on HFDs and lens boron levels are needed.

Conclusion

Both Apo and Myr may be able to reduce oxidative stress in the lenses of HFD-induced obese rats by increasing boron levels. More detailed studies are needed to elucidate boron's distribution and mechanism of action in the lens and whether it has any effect on cataract formation. Boron levels may be a novel indicator of reduced oxidative stress.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Marmara University Animal Care and Use Committee (30.03.2019).

Informed Consent: Informed consent is not necessary because our study is an experimental study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ş., F.E., Concept: G.Ş., F.E., A.Y., Design: G.Ş., F.E., A.Y., Data Collection or Processing: A.Ş., G.Ş., F.E., A.Y., Analysis or Interpretation: R.K.Y., D.K., A.Ş., G.Ş., F.E., A.Y., Literature Search: R.K.Y., D.K., A.Y., Writing: R.K.Y., D.K., A.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Follow-up Findings of Non-infectious Pediatric Uveitis Patients

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Abstract

Objectives: In this study, we aimed to describe the demographic and clinical findings of children with uveitis at a tertiary pediatric rheumatology and ophthalmology center.

Materials and Methods: A retrospective cross-sectional study was conducted with 46 patients who were diagnosed with uveitis before the age of 16 years and were followed regularly for at least 6 months between January 2013 and June 2019. Demographic data, uveitis characteristics, underlying diseases, systemic treatment modalities, drug side effects, complications, and surgical intervention were evaluated.

Results: Eighty-three eyes of 46 patients were included in the study. The mean age at diagnosis of uveitis was 9.2±4.5 (1.6-15.6) years, and the mean uveitis follow-up period was 54±41 (6-191) months. Twenty-one patients (45.7%) had uveitis associated with rheumatologic diseases. Juvenile idiopathic arthritis was the most common disease (23.9%). Visual acuity was categorized as moderately impaired in 6 eyes (7.2%), severely impaired in 4 eyes (4.8%), and blindness in 1 eye (1.2%). Methotrexate (87%) was the most frequently used systemic immunosuppressive agent in treatment. Adalimumab (73.9%) was added to treatment in resistant cases. Thirty-five patients (76.1%) had complications in at least 1 eye secondary to uveitis or uveitis treatment. Posterior synechiae (11 eyes, 13.2%) was the most common complication during treatment.

Conclusion: In order to preserve visual acuity, pediatric uveitis should be recognized early and especially persistent/chronic cases should be started on effective systemic treatment immediately.

Keywords: Uveitis, immunosuppressive therapy, adalimumab, tocilizumab, complication

Introduction

Uveitis basically refers to an inflammatory condition of the highly vascularized and pigmented uveal layer of the eye, although the vitreous, retina, and retinal vascular structures can also be affected by the inflammatory process due to their close anatomical proximity. In a broad sense, the term uveitis suggests intraocular inflammation.

Pediatric uveitis, which accounts for approximately 10-15% of uveitis series, poses unique challenges in terms of diagnosis, follow-up, and treatment.[1,2,3] The insidious nature of uveitis in childhood and pediatric patients' inability to express their

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complaints adequately and cooperate with eye examination can delay the diagnosis. More importantly, pediatric uveitis tends to be more severe and become chronic. All of these factors increase the frequency of complications that can lead to vision loss.[3,4] Therefore, patients with refractory uveitis require pediatric rheumatology follow-up both to initiate systemic treatment and detect underlying rheumatologic disease.

In this study, we evaluated the demographic data, uveitis characteristics, underlying rheumatologic diseases, treatment modalities, complications during follow-up, and adverse drug effects in uveitis patients being followed in the ophthalmology and pediatric rheumatology departments.

Materials and Methods

After obtaining approval from the Pamukkale University Ethics Committee for this retrospective cross-sectional study, we reviewed the records of 57 uveitis patients who were diagnosed with non-infectious uveitis in the ophthalmology department and were referred to the pediatric rheumatology department for etiological studies and systemic therapy between January 2013 and June 2019. Inclusion criteria were being diagnosed with uveitis before the age of 16 years, being followed up for at least 6 months, attending follow-up visits regularly, and having no missing data. Forty-six patients who met these criteria were included in the study.

The patients' demographic data, uveitis characteristics, underlying diseases, systemic treatment modalities, adverse drug effects, uveitis complications, and surgical history were evaluated. Most recent best corrected visual acuities assessed by Snellen chart were noted. Intraocular pressure and anterior and posterior examination findings were recorded. Level of vision was classified according to World Health Organization criteria.[5] Best corrected visual acuity of 3/60 or worse in the better-seeing eye was considered blindness; between 3/60 and ≤6/60 was severe impairment, and between 6/60 and ≤6/18 was moderate impairment.[6]

Uveitis was categorized according to the criteria specified by the International Uveitis Working Group. Patients were grouped according to these criteria as anterior uveitis (primary site of inflammation is anterior chamber; presence of iritis, iridocyclitis, and anterior cyclitis), intermediate uveitis (primary site of inflammation is vitreous; presence of pars planitis, posterior cyclitis, hyalitis), posterior uveitis (primary site of inflammation is retina/choroid; presence of choroiditis, chorioretinitis, retinitis, neuroretinitis), and panuveitis (involvement of all regions).[7]

The patients' uveitis was classified according to anatomic location (anterior, intermediate, posterior, panuveitis), affected eye (right, left, bilateral), and etiology.

Follow-up frequencies are determined in our center as specified in the guidelines. The follow-up interval was 2-3 months for patients with stable uveitis, less than 3-4 weeks while tapering topical steroids, and less than 2 months while tapering systemic therapy.[8]

Controlled uveitis was defined as inactive uveitis or the presence of up to grade 1+ anterior chamber cells provided that there were no new complications secondary to inflammation. The presence of grade 1+ or more anterior chamber cells or the appearance of new signs/complications of inflammation was regarded as loss of control of uveitis.[7,8]

Juvenile idiopathic arthritis (JIA) was diagnosed based on the International League of Associations for Rheumatology diagnostic criteria; Behçet's disease was diagnosed according to the pediatric Behçet diagnostic criteria published in 2015; the diagnosis of tubulointerstitial nephritis and uveitis (TINU) was made by demonstrating renal pathology on biopsy; and the diagnosis of sarcoidosis was made clinically.[9,10]

Results

A total of 83 eyes of 46 patients were included in the study. The patients' demographic characteristics, unilateral/bilateral involvement rates, uveitis locations, and complication and surgical intervention rates are summarized in Table 1. The mean age at uveitis diagnosis was 9.2±4.5 years (median: 8.3, range: 1.6-15.6) and the mean duration of uveitis follow-up was 54±41 months (median: 49, range: 6-191).

Uveitis was associated with rheumatologic disease in 21 patients (45.7%) and was idiopathic in 25 patients (54.3%) (Table 2). JIA was the most common systemic disease (23.9%) and only caused anterior uveitis (11 patients). JIA was oligoarticular in 8 patients, polyarticular in 2 patients, and enthesitis-related in 1 patient. Uveitis was diagnosed after the diagnosis of JIA in 8 patients, simultaneously in 2 patients, and before the onset of joint findings in 1 patient.

Two patients had suspected sarcoidosis initially presenting as isolated uveitis with no systemic organ involvement and the other two patients had inherited sarcoidosis (Blau syndrome) and early-onset adult sarcoidosis. Of the 4 patients followed for Behçet uveitis, all had oral aphthae, 2 had genital aphthae, and 1 had skin and vascular involvement. Both patients with TINU developed anterior uveitis while being followed for creatinine elevation.

Best corrected visual acuity was 0.29±0.59 LogMAR (median: 0.1, range: 0-3) at the first visit and 0.15±0.30 LogMAR (median: 1, range: 0-1.3) at the last visit (p=0.04, Wilcoxon). Visual acuity was categorized as moderately impaired in 6 eyes (7.2%), severely impaired in 4 eyes (4.8%), and blindness in 1 eye (1.2%). The mean number of attacks was 3.6±2.3 (median: 3, range: 1-9).

Local uveitis treatment was effective in only 2 patients (4.3%) patients; the 44 patients (95.7%) whose disease could not be controlled with local treatment were given short-term systemic steroid at 1-2 mg/kg/day (maximum 60 mg/day), and 10 patients (21.7%) received a periocular steroid injection. Of 44 patients (95.7%) with complicated uveitis at diagnosis (n=7), systemic corticosteroid-resistant uveitis (n=27), or additional systemic disease (n=10), 40 patients (87%) were started on methotrexate 15 mg/m^2/week (subcutaneous, maximum 25 mg/

dose) and 4 (8.4%) were started on azathioprine 1-2 mg/kg/day (oral, maximum 150 mg/day). Twenty-five of the patients treated with methotrexate had anterior uveitis, 10 had intermediate uveitis, 2 had posterior uveitis, and 3 had panuveitis. Of the patients treated with azathioprine, 2 had anterior uveitis and 2 had panuveitis (Table 3). The mean duration of methotrexate use, the most preferred systemic immunosuppressive agent, was 42.40±41.68 months (median: 28.50, range: 3-190).

Uveitis could not be controlled in 34 patients (73.9%) under systemic immunosuppressive therapy. Most cases of uveitis that did not respond to immunosuppressive therapy were idiopathic and anterior uveitis (Table 4). An anti-TNF agent (adalimumab) was added to treatment for these patients (Table 3). Adalimumab was administered at 24 mg/m^2 every 2 weeks (subcutaneous, maximum 40 mg/dose) for a mean duration of 31.50±21.39 months (median: 27, range: 6-84). In 10 patients (21.7%) whose uveitis attacks continued while receiving adalimumab, the treatment frequency was increased and injections of the same dose were given weekly. In 6 patients, attacks were controlled after a mean of 11.67±5.28 months (median: 12, range: 6-20), after which treatment was continued at the normal injection interval (every 2 weeks). One patient with refractory macular edema despite a year of adalimumab therapy was started on an interleukin-6 antagonist (tocilizumab) at 8 mg/kg/2 weeks (intravenous infusion, maximum 400 mg/dose) as an alternative treatment.

Table 1. The patients' demographic and clinical characteristics

Sex	Female	20 (43.5%)
	Male	26 (56.5%)
Ocular involvement	Unilateral	9 (19.6%)
	Bilateral	37 (80.4%)
Uveitis location	Anterior	27 (58.7%)
	Intermediate	12 (26.1%)
	Posterior	2 (4.3%)
	Panuveitis	5 (10.9%)
Complication	Yes	35 (76.1%)
	No	11 (23.9%)
Surgical intervention	Yes	13 (28.3%)
	No	33 (71.7%)

Five patients with controlled uveitis are being followed without medication. Medication-free follow-up was possible after local treatment and short-term systemic steroid therapy in 2 patients, after 12 months of methotrexate therapy in 2 patients, and after 108 months of methotrexate and 54 months of adalimumab therapy in 1 patient. The other patients with controlled uveitis were followed up with treatment as follows: As 2 patients using adalimumab and methotrexate had no attacks for 24 months of adalimumab therapy, adalimumab was discontinued and methotrexate therapy was continued. The frequency of adalimumab was increased to 3 weeks in both patients. During the treatment discontinuation phase, first adalimumab and then methotrexate were discontinued. In the first stage, treatment intervals were extended and then the doses were reduced. All uveitis patients who reached the treatment discontinuation stage were in the idiopathic uveitis category.

Extraocular complications that occurred during systemic treatment included intolerance (methotrexate, n=6, 13%) and liver toxicity (azathioprine, n=1, 2.2%). Three patients using biological agents were treated with isoniazid for 9 months due to positive screening test (without any signs of disease).

Complications secondary to uveitis or uveitis treatment were detected in at least one eye of a total of 35 patients (76.1%), including at the time of diagnosis in 7 patients. These complications were glaucoma, cataract, posterior synechiae, band keratopathy, macular edema, and retinal detachment (Figure 1). The most common complication that developed during treatment was posterior synechia (n=11). As a result of complications, 2 patients (4.3%) underwent cataract surgery, 3 patients (6.5%) underwent glaucoma surgery, and 2 patients (4.3%) underwent both cataract and glaucoma surgery.

Discussion

In this study we examined our experience with non-infectious pediatric uveitis. Almost half (45.7%) of our uveitis patients had an underlying rheumatologic disease, and nearly all of them required the addition of systemic steroids and immunosuppressants. Moderate vision loss was present in 7.2%, severe vision loss in 4.8%, and blindness in 1.2% of the patients in our study.

Table 2. Distribution of uveitis location and complications according to underlying disease

		Diagnosis					Total
		Idiopathic	**JIA**	**Sarcoidosis**	**TINU**	**BD**	
Uveitis location	Anterior	11 (23.9%)	11 (23.9%)	3 (6.5%)	2 (4.3%)	0	27 (58.7%)
	Intermediate	11 (23.9%)	0	0	0	1 (2.2%)	12 (26.1%)
	Posterior	1 (2.2%)	0	0	0	1 (2.2%)	2 (4.3%)
	Panuveitis	2 (4.3%)	0	1 (2.2%)	0	2 (4.3%)	5 (10.9%)
Complication	Yes	21 (45.6%)	7 (15.2%)	3 (6.5%)	1 (2.2%)	3 (6.5%)	35 (76.1%)
	No	4 (8.7%)	4 (8.7%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	11 (23.9%)
Total		25 (54.3%)	11 (23.9%)	4 (8.7%)	2 (4.3%)	4 (8.7%)	46 (100%)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, BD: Behçet's disease

Pediatric uveitis is reported at a frequency of 10-15% in case series and is often idiopathic, bilateral, and manifests as anterior uveitis.[1,2,3] In our patient group, 80.4% of cases were bilateral, 54.3% were idiopathic, and 58.7% of patients had anterior uveitis.

Although uveitis is reported slightly more frequently in females than males, the female to male ratio among our patients was 1:1.3 (20 girls, 26 boys).[4,11,12] Similarly, a recent publication from Turkey reported this ratio to be 1:1.1 in non-infectious pediatric uveitis.[13]

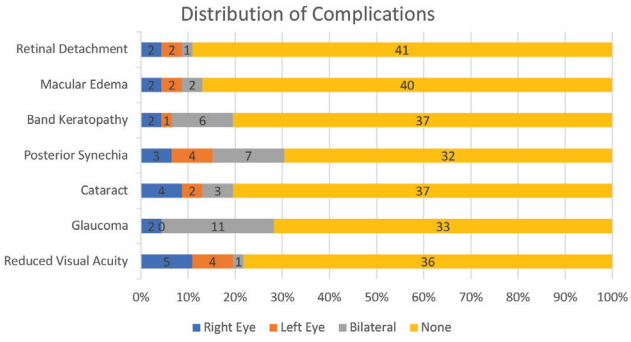

Figure 1. Complication rates

In a review of pediatric uveitis, Tugal-Tutkun[3] stated that uveitis series from North America and Europe showed rates of 35-50% for anterior uveitis, 10-20% for intermediate uveitis, 15-25% for posterior uveitis, and 10-20% for panuveitis. The prevalence of anterior uveitis has been reported to be 46-62% in recent publications.[4,11,12] In our series, the rate of anterior uveitis was 58.7%, close to the upper limit of the range specified in current reports. Anterior uveitis was idiopathic in 23.9% of cases and associated with the underlying pathologies of JIA in 23.9%, sarcoidosis in 6.5%, and TINU in 4.3% of patients. In another recent publication from our country, the two most common etiologies of pediatric uveitis were idiopathic in 47.8% and JIA in 36.9% of patients.[14] A retrospective study in Finland reported an anterior uveitis rate of 93%, which was attributed to JIA in 61% of patients.[15] Our cases of intermediate uveitis (26.1%) were predominantly pars planitis (23.9%). Intermediate uveitis was reported to be the most frequent form (34.2%) in another study from Turkey but was not detected in any patients in a Japanese study, while non-infectious intermediate uveitis was observed at rates of 25.6% and 19.9% in studies conducted in Brazil and the USA, respectively.[4,11,12,13] Posterior uveitis (4.3%) and panuveitis (10.9%) were less common in our study.

Anterior uveitis was present in 100% of patients with JIA and TINU and 75% of patients with sarcoidosis, whereas

Table 3. Distribution of immunosuppressive therapies by indication

Immunosuppressive therapy	Primary systemic disease	Uveitis				Total
		Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	
Methotrexate	10	17	7	2	4	40
Azathioprine	0	3	1	0	0	4
Adalimumab	1	20	6	2	5	34
Infliximab	0	1	0	0	0	1
Tocilizumab	0	0	0	1	0	1

Table 4. Distribution of uveitis refractory to immunosuppressive therapy according to underlying disease and uveitis location

		Treatment non-response	Treatment response	Total
Underlying disease	Idiopathic	18 (39.1%)	7 (15.2%)	25 (54.3%)
	JIA	10 (21.7%)	1 (2.2%)	11(23.9%)
	Sarcoidosis	4 (8.7%)	0	4 (8.7%)
	TINU	0	2 (4.3%)	2 (4.3%)
	BD	2 (4.3%)	2 (4.3%)	4 (8.7%)
	Total	34 (73.9%)	12 (26.1%)	46 (100%)
Uveitis location	Anterior	21 (45.7%)	6 (13%)	27 (58.7%)
	Intermediate	8 (17.4%)	4 (8.7%)	12 (26.1%)
	Posterior	2 (4.3%)	0	2 (4.3%)
	Pan	3 (6.5%)	2 (4.3%)	5 (10.9%)
	Total	34 (73.9%)	12 (26.1%)	46 (100%)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, BD: Behçet's disease

isolated anterior uveitis was not seen in any Behçet's patients. Involvement rates in Behçet's disease were 25% intermediate, 25% posterior, and 50% panuveitis.

In this series, which had a final visual acuity of 0.15±0.30 LogMAR, the prevalence of legal blindness (3/60 or worse) was determined to be 1.21%. In pediatric uveitis studies conducted in Turkey, Yüce et al.[16] reported a visual acuity of 20/200 or worse in 4 eyes and 20/40 or worse in 18 of 64 eyes with pediatric uveitis, and Yalçındağ et al.[13] reported a visual acuity of 20/200 or worse in 8 eyes and between 20/200 and 20/40 in 16 eyes. Recent studies have indicated that the rate of legal blindness among uveitis patients has decreased from 19-69.6% to 7.7-9.7%.[4,12,17,18,19] In a French pediatric uveitis series, there were no legally blind patients but 9 (6%) had monocular blindness.[20] This improvement is believed to be related to the increasing use of biological agents in the treatment of uveitis over the last decade.

Complications are common in pediatric uveitis due to its tendency for chronification and recurrence. The frequency of one or more complications in recent pediatric uveitis series is reported as approximately 70%.[4,12] Complications occur secondary to treatment in addition to the primary disease. In recent series, the most common complications were cataract (44-52%), followed by secondary glaucoma (23-33%), band keratopathy (13-37%), and posterior synechia (19-54%).[4,12] Gautam Seth et al.[21] reported complication rates of 24% for cataract, 18.29% for band keratopathy, and 6.29% for glaucoma in their series. In our study, 76.1% of our patients developed at least one complication, with synechia (30.4%) and glaucoma (28.3%) being the most common. Seven patients (19%) whose cataract and glaucoma could not be controlled with medical therapies were treated surgically. Two patients underwent cataract surgery, 3 underwent glaucoma surgery, and 2 patients underwent combined cataract and glaucoma surgery. Yalçındağ et al.[13] reported a complication rate of 26.1% and surgical treatment rate of 2.8% in their series, while Ferrara et al.[12] reported that the surgical treatment rate was 8-46% in the literature and 38% in their series. In a recent study from Turkey, 34% of patients had complications, the most common of which was posterior synechia (18.6%), and 8 eyes (5.1%) underwent surgical treatment due to complications.[14]

In treatment management, the presence of complications and systemic disease accelerates the transition from local treatment to systemic treatment. The general tendency in systemic treatment is to use systemic steroids as first-line therapy. Depending on the threat to vision and the underlying systemic disease, the first treatment may be an anti-TNF agent. However, in cases of nonresponse, steroid dependence, or the need for long-term treatment for systemic disease, a second immunosuppressive therapy should be added to enable discontinuation of the steroid within a reasonable time due to its adverse effects.[3,22] Methotrexate is usually the first choice of immunosuppressive, as it is both safe and effective in patients with pediatric uveitis.[22,23] In our study, 44 patients (95.7%) who did not respond to local treatments were given short-term systemic steroid therapy. Forty patients (87%) needed additional methotrexate and 4 patients (8.7%) patients needed azathioprine. However, treatment was discontinued in 6 patients (13%) who could not tolerate methotrexate and 1 patient (2.2%) receiving azathioprine due to liver toxicity. Treatment was continued with a biologic agent. In contrast, uveitis could only be controlled with methotrexate in 7 patients (15.2%) and with azathioprine in 1 patient (2.2%).

Adalimumab was initiated in 34 patients (73.9%) whose uveitis did not respond to immunosuppressive therapy. Of these, 1 patient who required emergency surgery was given infliximab followed by adalimumab. Three JIA patients using etanercept due to severe joint involvement were switched to adalimumab when they developed uveitis. Biologic agents are revolutionary in the treatment of refractory ocular inflammation that cannot be controlled with disease-modifying agents. Infliximab and adalimumab are highly effective in the treatment of refractory pediatric uveitis.[24] Although adalimumab therapy has the advantage of being safer and easier use in pediatric patients, infliximab provides satisfactory results in cases where a rapid effect is desired and emergency surgery is required.[25] In our series, the adalimumab treatment interval was reduced from 2 weeks to 1 week in 10 patients (21.7%) whose attacks were not adequately controlled despite all of these treatments. Although there are very few examples in the literature of weekly adalimumab therapy in refractory uveitis, our patients benefited from this approach.[26,27] In 6 patients whose uveitis could be controlled, the treatment frequency was returned to normal and treatment was discontinued in 1 patient during follow-up. The response time to weekly adalimumab was quite heterogeneous, with a mean of 11.67±5.28 months (range: 6-20). While 3 patients continued weekly treatment, 1 patient was switched to tocilizumab because of persistent macular edema despite weekly treatment. This patient's symptoms were controlled and macular edema regressed after 4 months of tocilizumab therapy. Favorable outcomes in adult uveitis have suggested that tocilizumab may also be used in refractory pediatric cases. In addition, the use of abatacept, rituximab, and tocilizumab for anti-TNF-refractory uveitis is included in the 2018 uveitis treatment recommendations of the SHARE group.[28] Pediatric patients with underlying rheumatologic disease or who are nonresponsive to local therapies and need systemic immunosuppressants should be followed up in collaboration with a rheumatologist.

Caution in terms of infection is recommended when administering biologic agents that have been recently introduced and have even more limited pediatric use. Screening for diseases such as tuberculosis, hepatitis B, and hepatitis C is necessary before initiating anti-TNF therapy.[29] Annual follow-up for hepatitis B and tuberculosis is recommended. TNF inhibitors increase the risk of tuberculosis infection and reactivation.[30] During our follow-up, 3 patients with large indurations on purified protein derivative test were given prophylaxis to prevent reactivation. In addition to these, no latent or opportunistic infections were encountered.

Study Limitations

A limitation of our study is that it was designed as a retrospective, single-center study. In addition, our uveitis series did not include any patients who responded rapidly to local therapies and thus did not require systemic treatment. Especially in young children, it may not be possible to perform examinations used to detect subclinical posterior segment findings due to the lack of cooperation, which may cause misclassification in terms of anatomic location.

Conclusion

As pediatric uveitis can cause vision loss if not treated appropriately, early recognition, initiation of effective systemic treatment in refractory and chronic cases, and close follow-up for complications are essential. In cases where uveitis cannot be controlled even with standard immunosuppressive therapy and biologic agents, increasing the dosing frequency of anti-TNF may have therapeutic benefit. For patients with systemic diseases that can lead to the development of uveitis, pediatric rheumatologists should inform the families about uveitis and its symptoms and refer them to regular eye examinations for uveitis screening.

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Ethics

Ethics Committee Approval: Pamukkale University Non-Invasive Clinical Research Ethics Committee approval number: 60116787-020/75663.

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Authorship Contributions

Surgical and Medical Practices: Z.E.T., G.O.Y., S.A., E.N.Ç., S.Y., Concept: Z.E.T., E.N.Ç., S.Y., Design: Z.E.T., E.N.Ç., S.Y., Data Collection or Processing: Z.E.T., G.O.Y., S.A., Analysis or Interpretation: Z.E.T., E.N.Ç, S.Y., Literature Search: Z.E.T., Writing: Z.E.T.

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Original Article

The Effect of Vision-Related Quality of Life on Depression and Anxiety in Patients with Behçet Uveitis

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Abstract

Objectives: To evaluate the effect of vision-related quality of life on depression and anxiety in patients with Behçet uveitis.
Materials and Methods: The Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI) I-II, and the Visual Functioning Questionnaire (VFQ)-25 were used to evaluate 105 patients being followed for Behçet uveitis. Sociodemographic data and VFQ-25 scores were compared between the groups with and without depression and anxiety. Regression analysis was performed to determine the relationship between the variables.
Results: Forty-eight (82.8%) men and 10 (17.2%) women who completed the questionnaires were included in the study. The mean age of the patients was 37.76±11.14 (18-65) years and the mean duration of uveitis was 8.57±7.43 (1-27) years. The mean VFQ-25 composite, BDI, STAI-I, and STAI-II scores were 74.90±18.50 (18.79-97.04), 10.76±8.90 (0-43), 42.52±6.23 (25-55), and 46.53±6.80 (27-58), respectively. Of 58 patients, 31% had depressive symptoms and 58.6% had anxiety symptoms. VFQ-25 composite score was lower in the depressive group than in the group with no depression (p=0.030), while there was no significant difference in this score between the groups with and without anxiety. Regression analysis revealed a negative relationship between total VFQ-25 composite score and depression.
Conclusion: In our study, high rates of depression and anxiety were detected in patients with Behçet uveitis. Patient-reported visual functioning was associated with depression. In patients with Behçet uveitis, it is important to evaluate vision-related quality of life as well as visual acuity.
Keywords: Behçet uveitis, depression, anxiety disorder, vision-related quality of life

Introduction

Behçet's disease is a chronic inflammatory disease that can involve the mucocutaneous, ocular, vascular, pulmonary, gastrointestinal, genitourinary, and central nervous systems and is characterized by recurrent episodes and spontaneous remission. More than two-thirds of patients have sight-threatening ocular involvement, which usually presents with attacks of bilateral panuveitis and retinal vasculitis.[1,2,3]

Ocular inflammatory diseases are known to affect both physical and mental health.[4,5] In addition to the chronic and sight-threatening course of the disease, systemic therapies[6] and inflammatory cytokines that cross the blood-brain barrier have also been reported to lead to behavioral changes.[7]

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Behçet's disease can lead to a significant deterioration in quality of life and even mental problems such as depression and anxiety disorder due to its recurrent course and threat to vision, the need for treatment with immunosuppressive and biological agents, and other systemic symptoms.[8,9]

The aim of this study was to screen patients being followed for Behçet uveitis in our center for depression and anxiety and to evaluate the effect of age, education level, uveitis duration, visual acuity, and vision-related quality of life on depression and anxiety levels.

Materials and Methods

Between October 2016 and October 2017, 105 patients with Behçet uveitis who were followed in the Ophthalmology Uvea-Behçet outpatient clinic of Ondokuz Mayıs University and had clinically inactive disease or were in remission were given the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI-I and -II), and the Visual Functioning Questionnaire (VFQ-25). The patients' sociodemographic characteristics were evaluated with a semi-structured sociodemographic form. The patients were asked to complete the questionnaires at the clinic or to fill them out at home and bring them to their next visit. Uveitis duration and localization, systemic treatment received, and best corrected visual acuity in the better-seeing eye and fellow eye were obtained from the patients' records. In patients with bilateral involvement and a difference in visual acuity of at least one Snellen line between the eyes, the eye with better visual acuity was included in the better-seeing eye group and the fellow eye was included in the worse-seeing eye group. If both eyes had equal visual acuity, data from a single eye was evaluated in the better-seeing eye group. In patients with unilateral involvement, the affected eye was included in the worse-seeing eye group. Clinical inactivity was defined as the presence of up to grade 0.5+ cells in the anterior chamber and vitreous, the absence of vitreous haze, and the absence of posterior segment inflammation findings such as retinitis, retinal vasculitis, and papillitis. Remission was defined as disease inactivity lasting more than three months despite discontinuation of treatment.[10]

The study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University and conducted in accordance with the Declaration of Helsinki.

Assessment Tools

Visual Functioning Questionnaire (VFQ-25)

The VFQ-25 is a 25-question self-report instrument used to assess vision-related quality of life. Patients grade the severity of their visual symptoms or the difficulty of various activities. The items aim to measure the effects of visual impairment in the domains of general health, general vision, ocular pain, distance activities, near activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, color vision, and peripheral vision. A score for each subscale is calculated by averaging the scores for the relevant items. The VFQ-25 total score is calculated as the sum of the vision-related scores (excluding the general health subscale) and ranges from 0 to 100. Higher scores are associated with better quality of life.[11] Toprak et al.[12] translated the VFQ-25 into Turkish and conducted the validity study of the Turkish version.

Beck Depression Inventory (BDI)

The BDI is a 21-item self-report scale used to assess symptoms of depression. Each item has four response options scored between 0 and 3. Total scores of 0-13 are interpreted as no depression, 14-19 as mild depression, 20-28 as moderate depression, and 29-63 as severe depression.[13] Using a cut-off value of 13, the BDI was reported to have a sensitivity of 90% and a specificity of 99% in depression screening.[14] A validity-reliability study was conducted among university students in our country.[15]

State-Trait Anxiety Inventory (STAI-I and -II)

The STAI-I and STAI-II are self-report scales, each comprising 20 items containing positively or negatively worded statements that are scored between 1 and 4. The total score varies between 20 and 80, with higher scores reflecting higher anxiety. Studies indicate that a score of 40 or above indicates a clinical level of anxiety.[16] Oner[17] translated the STAI into Turkish and performed the validity-reliability study.

Statistical Analysis

The data were analyzed using SPSS version 21.0 (IBM Corp, Armonk, NY) software. For quantitative variables, mean, standard deviation, minimum, and maximum values were presented. Mann-Whitney U test was used for intergroup comparisons. Regression analyses were done to determine relationships between variables.

Results

Five of the 105 patients surveyed did not return the questionnaires. Thirty-two patients who did not complete the questionnaires fully and 10 patients still receiving interferon therapy were excluded from the study. Therefore, the data of 58 patients consisting of 48 men (82.8%) and 10 women

(17.2%) with a mean age of 34.76±11.14 (18-65) years were included in the statistical analysis.

The mean duration of uveitis was 8.57±7.43 (1-27) years. Fifty-three (91.4%) of the patients had posterior segment involvement. Highest level of education completed was elementary school for 16 patients (27.6%), middle school for 9 patients (15.5%), high school for 22 patients (37.9%), and university for 11 patients (19%). Seven patients were not receiving any systemic treatment, 30 patients were being treated with conventional agents, and 21 patients were being treated with anti-TNF-α agents. Three patients were currently using antidepressants, while 14 patients had a history of antidepressant drug use. Ten of the patients reported receiving emotional support from their spouse, three patients received emotional support from friends, and three patients said they had seen a psychiatrist, while 42 patients stated that they did not receive any emotional support.

The mean visual acuity was 0.86±0.22 (0.2-1.0) Snellen in the better-seeing eye and 0.40±0.31 (0.0-0.9) Snellen in the worse-seeing eye. The patients' mean BDI, STAI-I, and STAI-II scores were 10.76±8.90 (0-43), 42.52±6.23 (25-55) and 46.53±6.80 (27-58), respectively. Mean VFQ-25 scores were 74.90±18.50 (18.79-97.04) for total score, 40.08±19.27 (0-100) for general health, 66.55±12.64 (40-80) for general vision, 67.67±21.72 (25-75) for ocular pain, 77.87±21.72 (25-100) for distance activities, 74.07±22.33 (16.66-100) for near activities, 86.85±21.26 (25-100) for vision-specific social functioning, 62.09±28.69 (12.50-100) for vision-specific mental health, 64.87±28.62 (12.50-100) for vision-specific role difficulties, 77.15±28.85 (8.33-100) for vision-specific dependency, 85.64±13.60 (50-100) for driving, 90.94±17.95 (25-100) for color vision, and 78.44±23.62 (0-100) for peripheral vision.

The patients were grouped according to their BDI scores. Eighteen patients (31.0%) whose BDI score was above 13 were included in the depression group and 40 patients (68.9%) whose BDI score was 13 or lower were included in the no depression group. When evaluated according to BDI score, depressive symptoms were mild in 10 patients (17.2%), moderate in 5 patients (8.6%), and severe in 3 patients (5.2%). There was no significant difference between patients with and without depression in terms of age, sex, education, uveitis duration, or visual acuity. There was also no significant difference between the two groups in terms of anxiety scores measured by STAI-I

Table 1. Comparison of sociodemographic characteristics, visual acuities, and VFQ-25, STAI-I, and STAI-II scores between patients with and without depressive symptoms

		Depression +	Depression -	p
Age (years)		37.00±9.80 (21-53)	38.10±11.80 (18-65)	0.980
Gender (M/F)		16/2	32/8	0.650
Education level (primary/secondary or university)		8/10	17/23	1.000
Uveitis duration (years)		7.72±7.11 (2-27)	8.95±7.63 (1-27)	0.649
Visual acuity (better-seeing eye)		0.84±0.26 (0.2-1.0)	0.87±0.20 (0.2-1.0)	0.917
Visual acuity (worse-seeing eye)		0.41±0.31 (0.0-0.8)	0.40±0.31 (0.0-0.9)	0.872
VFQ-25	Total	66.35±21.61 (18.79-91.93)	78.74±15.75 (42.19-97.04)	**0.030**
	General health	31.94±14.36 (0-50)	43.75±20.21 (25-100)	**0.028**
	General vision	62.22±13.53 (40-80)	68.50±11.89 (40-80)	0.093
	Ocular pain	54.86±20.17 (25-100)	73.44±20.05 (37.5-100)	**0.003**
	Distance activities	70.83±26.85 (25-100)	81.04±18.49 (33.33-100)	0.210
	Near activities	64.58±23.41 (16.66-100)	78.35±20.73 (33.33-100)	**0.031**
	Social functioning	77.08±28.52 (25.00-100)	91.25±15.56 (37.50-100)	0.052
	Mental health	52.08±27.54 (12.50-93.75)	66.60±28.38 (18.75-100)	0.061
	Role difficulties	50.00±30.92 (12.50-100)	71.56±25.16 (25.00-100)	**0.013**
	Dependency	71.29±30.14 (16.66-100)	79.79±28.24 (8.33-100)	0.227
	Driving (n=28)	84.93±13.13 (50-100)	87.50±15.34 (58.33-100)	0.460
	Color vision	86.11±23.04 (25-100)	93.12±14.96 (50-100)	0.238
	Peripheral vision	66.67±29.70 (0-100)	83.75±18.39 (50-100)	**0.030**
STAI-I		42.33±5.53 (34-55)	42.60±6.57 (25-54)	0.649
STAI-II		48.94±6.16 (39-58)	45.45±6.88 (27-58)	0.094

VFQ-25: Visual Functioning Questionnaire-25, STAI: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory

and II. The depression group had significantly lower VFQ-25 total score and general health, ocular pain, vision-specific role difficulties, and peripheral vision subscale scores (Table 1).

Thirty-four patients (58.6%) scored above the recommended cut-off for the STAI-I (≥40) and 46 patients (79.3%) scored above the recommended cut-off for the STAI-II (≥40). We evaluated whether patients whose anxiety scores were above and below the cut-off differed in terms of VFQ-25 subscale scores. When grouped according to the STAI-I, the only significant differences were in the general health (p=0.047) and dependency (p=0.040) domains; when grouped according to the STAI-II, there was no significant difference in any VFQ-25 score.

VFQ-25 total score and general health, general vision, distance activities, near activities, color vision, and peripheral vision subscale scores were lower in patients over 30 years of age (p=0.027, p=0.021, p=0.003, p=0.008, p=0.001, p=0.036, and p=0.007, respectively). VFQ-25 total score and scores for distance vision, vision-specific social functioning, and vision-specific mental health were significantly lower in patients with lower education (p=0.047, p=0.018, p=0.027, p=0.045, respectively). Patients with visual acuity of 0.5 or worse in the better-seeing eye had longer uveitis duration (mean 17.00±7.91 years for ≤0.5 and mean 7.22±6.47 years for >0.5) and significantly lower VFQ-25 total score and distance activities, near activities, social functioning, mental health, dependency, driving, and color vision subscale scores (p=0.003, p=0.019, p=0.020, p=0.042, p=0.005, p=0.023, p=0.031, p=0.008, and p=0.033, respectively). There was no difference in depression and anxiety scores in any group. Patients with posterior segment involvement had significantly lower VFQ-25 total score and distance activities score (p=0.050 and p=0.009, respectively). Depression scores were higher in patients with posterior segment involvement, while anxiety scores did not differ significantly (Table 2).

The linear regression analysis performed to determine the relationship between VFQ-25 total score and depression score revealed a significant negative correlation. There was a 1.5-point decrease in BDI score for each 10-point increase in VFQ-25 total score (odds ratio: -0.15, 95% confidence interval: -0.26 to -0.04, p=0.009). Logistic regression analysis was performed to evaluate predictors of depression. We observed an association between VFQ-25 total score and depression. There was no statistically significant relationship between

Table 2. Comparison of VFQ-25, BDI, STAI-I, and STAI-II scores in terms of age, education level, uveitis duration, uveitis location, and visual acuity

	Total VFQ-25 score	BDI score	STAI-I score	STAI-II score
Age (years)				
<30 (n=18)	83.66±12.34 (52.25-96.48)	8.89±11.509 (0-43)	42.56±6.94 (25-52)	45.06±7.30 (27-55)
>30 (n=40)	70.96±19.56 (18.79-97.04)	11.60±7.46 (0-32)	42.50±5.98 (26-55)	47.20±6.56 (35-58)
P value	**0.010**	0.465	0.814	0.367
Education level				
Primary education (n=25)	69.33±18.67 (18.79 -97.04)	11.20±7.31 (0-32)	43.20±6.04 (35-55)	47.76±6.72 (35-58)
Secondary education or university (n=33)	79.36±18.16 (32.25-96.48)	10.42±10.03 (0-43)	42.00±6.42 (25-52)	45.61±6.83 (27-58)
P value	**0.047**	0.357	0.747	0.225
Uveitis duration				
<10 years (n=37)	76.35±18.39 (18.79-96.48)	11.27±9.69 (0-43)	42.27±6.87 (25-55)	47.14±7.03 (27-58)
>10 years (n=21)	72.35±18.87 (32.25-97.04)	9.86±7.43 (0-32)	42.95±5.03 (34-50)	45-48±6.41 (35-58)
P value	**0.344**	0.733	0.752	0.364
Uveitis location				
Anterior uveitis (n=5)	89.64±4.51 (83.86-96.12)	4.20±3.50 (0-8)	41.20±4.66 (37-48)	49.20±5.40 (43-559
Posterior or panuveitis (n=53)	73.51±18.73 (18.79-97.04)	11.38±9.20 (0-43)	42.64±6.38 (25-55)	46.28±6.91 (27-58)
P value	**0.050**	**0.047**	0.517	0.343
Visual acuity in the better-seeing eye				
>0.5 (n=50)	81.37±15.52 (34.00-97.04)	10.48±8.68 (0-43)	42.54±6.42 (25-55)	47.04±6.85 (27-58)
<0.5 (n=8)	65.73±18.79 (18.79-94.00)	12.50±10.66 (0-32)	42.38±5.26 (36-50)	43.38±5.99 (35-52)
P value	**0.001**	0.603	0.868	0.136

VFQ-25: Visual Functioning Questionnaire-25, STAI: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory

Table 3. Logistic regression analysis of predictors of depression in patients with Behçet uveitis

	OR	95% CI	p
Age	-0.018	0.90-1.06	0.650
Uveitis duration	-0.018	0.87-1.10	0.754
Education level	-0.385	0.17-2.71	0.585
VFQ-25 total score	-0.042	0.92-0.99	**0.027**
STAI-I score	0.005	0.89-1.12	0.940
STAI-II score	0.088	0.98-1.21	0.092

OR: Odds ratio, CI: Confidence interval, VFQ-25: Visual Functioning Questionnaire-25, STAI: State-Trait Anxiety Inventory

depression and patient age, uveitis duration, education level, anxiety scores, or visual acuity in the better-seeing eye (Table 3).

Discussion

In this study, we screened patients with Behçet uveitis for depression and anxiety disorder and examined the effects of vision-related quality of life on depression and anxiety scores.

In depression screening performed with the BDI, we determined that 18 (31%) of the patients scored above the cut-off score of 13 points. This rate has varied between 8.1% and 54% in survey studies of patients with uveitis.[18,19,20,21,22] This wide range may be related to cultural differences, as well as the differences in disease activity, assessment tools used, and cut-off points specified in the studies. Maca et al.[19] found that BDI scores were above the normal limit in 31.6% of the patients in their study of HLA-B27+ patients. They also reported that patients assessed during an acute attack had higher scores. In a study comparing patients experiencing acute anterior uveitis attacks with healthy controls, BDI score was above the cut-off value in 54% of the patients and 9% of control subjects. Pain caused by the attack and the decrease in visual acuity were shown to be the main reasons for this increase in depressive state.[18] Their assessment of patients during an acute attack as well as using a cut-off point of 10 may explain the high depression rate in their study. In a study conducted in Thailand, which had the lowest reported rate of depression (8.1%), the authors attributed the low rate to cultural differences and their use of a different assessment tool.[22] The presence of chronic disease, bilateral involvement, oral corticosteroid use, and treatment with multiple immunomodulatory drugs have been shown to affect the rate of depression.[21] Onal et al.[20] from Turkey reported a depression rate of 37.3% in patients with active uveitis. Tanriverdi et al.[23] conducted a depression screening in Behçet's patients with ocular involvement and determined that patients with uveitis had a higher mean BDI score than the control group.

Studies also indicate that vision-related quality of life is impaired in patients with uveitis.[5,24] Schiffman et al.[5] reported that patients with uveitis had lower VFQ-25 total scores than all test groups (patients with age-related macular degeneration, diabetic retinopathy, glaucoma, cataract, and cytomegalovirus infection) except patients with low vision. In multivariate regression analyses, they reported that poor visual acuity, bilateral involvement, and more intense immunosuppressive therapy were associated with lower visual functioning scores.[5] In a study by Onal et al.[24] conducted in patients with Behçet uveitis, VFQ-25 domain scores differed significantly according to age, education level, uveitis activity, uveitis severity, and visual acuity. In our study, we found that older age, low education level, posterior segment involvement, and low visual acuity were associated with lower VFQ-25 total score.

In this study aiming to elucidate the effect of vision-related quality of life on the psychological state of patients with Behçet uveitis, we observed that VFQ-25 total score and general health, ocular pain, near activities, role difficulties, and peripheral vision subscale scores were significantly lower in the depression group. Similarly, previous studies have demonstrated significantly lower scores in all VFQ-25 domains except for driving and color vision scores in patients with depression.[20,21] Onal et al.[20] reported a relationship between depression and visual acuity in the better-seeing eye and attributed this to the fact that vision in the better-seeing eye was an indicator of visual potential. However, in our study, there was no difference in visual acuity between the depression and no depression groups. Qian et al.[21] showed that decreased visual acuity was associated with an increase in BDI scores in bivariate analyses. However, they reported that this effect disappeared in regression analyses and that VFQ-25 total score was a better indicator of depression. In other studies in the literature, VFQ-25 scores were found to be associated with depression, whereas visual acuity was not as strongly related.[25,26] This is because Snellen visual acuity does not fully reflect vision, but represents only one parameter of visual function. The fact that only patients with active disease were included in the study by Onal et al.[20] may explain the significant results in their analyses.

According to the logistic regression analysis in our study, only VFQ-25 total score was a significant predictor of depression. Qian et al.[21] identified VFQ-25 total score, inadequate emotional support, change in immunomodulatory therapy, and oral corticosteroid use as predictors of depression in their study. In our study, we observed no significant

difference between patients with and without depression in terms of emotional support. In addition, because our study did not include patients with active disease and none of our patients were using steroids at doses higher than the maintenance dose, we did not evaluate the steroid effect.

Consistent with other studies, we detected no statistically significant relationship between sociodemographic characteristics and depression in our study.[20,21,22]

We determined that 34 patients (58.6%) had state anxiety scores above the cut-off according to the STAI-I and 46 patients (79.3%) had trait anxiety scores above the cut-off according to the STAI-II. Onal et al.[20] found that approximately 50% of patients had high state anxiety scores. Tanriverdi et al.[23] reported that Behçet's patients with ocular involvement had higher depression scores as well as higher anxiety scores than healthy individuals.

We observed that patients evaluated as having anxiety disorder according to their state anxiety scores had statistically significantly lower scores only in the general health and dependency subscales. Onal et al.[20] reported that VFQ-25 total score and nearly all subscale scores were lower in the anxiety disorder group compared to the group without anxiety disorder. Considering that disease activity may cause an increase in state anxiety and further impairment of vision-related quality of life, the inclusion of patients with active uveitis in their study may have led to a significant difference in more subscale scores.

Study Limitations

The main limitation of our study is the small patient sample. Furthermore, the patients were only evaluated using questionnaire screening, with no psychiatric evaluation for depression and anxiety disorder. In addition, as only patients in remission or with inactive disease were included in our study, the effect of disease activity on their scores was not evaluated.

Conclusion

This study emphasizes the need to evaluate subjective loss of function associated with vision loss in patients with Behçet's uveitis in addition to performing visual acuity tests. Our findings suggest that patient-reported vision-related quality of life is an important predictor of depression and is more valuable than Snellen visual acuity. Using the same instruments to assess patients with non-Behçet uveitis involving the posterior segment and comparing with the data of patients with Behçet uveitis will aid in determining the relationship between our results and Behçet's disease. Ophthalmologists should be aware that visual functioning is associated with depressive symptoms and anxiety levels in patients with Behçet uveitis and should refer these patients for appropriate psychosocial support to increase their quality of life.

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Ethics

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Authorship Contributions

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Original Article

Evaluation of the Effect of Intravitreal Dexamethasone (Ozurdex®) Implant on Intraocular Pressure in Vitrectomized and Non-Vitrectomized Eyes with Macular Edema

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Abstract

Objectives: This study aimed to retrospectively evaluate the intraocular pressure (IOP) change in vitrectomized and non-vitrectomized patients receiving 0.7 mg intravitreal dexamethasone implant to treat macular edema due to different indications.

Materials and Methods: The patients' diagnoses, IOP values before receiving the intravitreal dexamethasone implant and in follow-up examinations at 1-3 days, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months after implantation, pachymetry values, medications used, and history of vitrectomy surgery were recorded.

Results: A total of 134 eyes of 112 patients between 46 and 85 years of age who received intravitreal dexamethasone implants were evaluated. Seventeen eyes (12.7%) were vitrectomized and 117 (87.3%) were not vitrectomized. In non-vitrectomized eyes, the mean IOP was 14.01±2.36 mmHg before and 14.8±2.96 at 1-3 days, 16.71±3.97 at 1 month, 17.88±5.27 at 2 months, 15.54±3.35 at 3 months, 15.1±3.24 at 6 months, and 14.61±3.71 mmHg at 12 months after receiving the first dose. In this group, the increases in mean IOP at 1-3 days, 1 month, 2 months, and 3 months were significant compared to the mean IOP before the first dose ($p<0.05$). In vitrectomized eyes, only the increase in mean IOP at 6 months was significant compared to the mean IOP before the first dose ($p<0.05$). Twenty-three of the 134 eyes (17.2%) were prescribed 1-3 medications due to IOP elevation (one drug for 73.9%, two drugs for 17.4%, and three drugs for 8.7% of these eyes).

Conclusion: The IOP increase that occurs as a side effect of intravitreal dexamethasone administration is generally mild and temporary in both vitrectomized and non-vitrectomized eyes, regardless of indication. There was no cumulative effect in patients who received two or three doses.

Keywords: Intravitreal, dexamethasone, glaucoma, macular edema

Introduction

Corticosteroids are used topically, periocularly, or intravitreally in the treatment of many inflammatory and autoimmune ocular diseases. One of the complications of intravitreal steroid administration is elevated intraocular pressure (IOP). Ocular hypertension has been defined as an IOP ≥25 mmHg or ≥10 mmHg above baseline.[1] Ocular hypertension can be a direct result of increased intraocular volume or may occur due to the adverse effect of steroids on aqueous drainage weeks or months after administration.[2] Risk factors include glaucoma, young age, development of ocular hypertension after a previous injection, uveitis, and high-dose steroid use. Detecting secondary ocular hypertension is essential because most cases are asymptomatic and it can lead to permanent vision loss if left untreated.

The dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) is injected into the vitreous cavity with a 22-gauge needle, contains 0.7 mg dexamethasone, and releases corticosteroid for

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an average of 6 months.[3] In animal studies it was observed that the intravitreal dexamethasone (IVD) concentration peaked after 2 months and decreased rapidly between 2 and 3 months. After 6 months, the intravitreal concentration reaches an undetectable level.[4]

In this study, we evaluated the IOP changes in vitrectomized and non-vitrectomized eyes treated with 0.7 mg IVD implant due to macular edema for different indications.

Materials and Methods

Ethical approval for the study was obtained from the ethics committee of the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital. In this retrospective, single-center clinical study, we evaluated patients between 20 and 85 years of age who were followed up in the retina unit of our hospital's ophthalmology clinic and underwent IVD implantation in one or both eyes due to macular edema of varying etiology between April 2016 and January 2018. Each intravitreal implant was administered under topical anesthesia using a 22-gauge injector. Exclusion criteria were as follows: presence of known glaucoma (primary open-angle glaucoma, uveitic glaucoma, neovascular glaucoma, angle closure glaucoma); receiving any intravitreal injection within 3 months before receiving the first IVD implant; an IOP higher than 21 mmHg before implantation; use of systemic or topical corticosteroids; receiving subTenon or subconjunctival steroid; presence of uncontrolled diabetes mellitus with >10% HbA1c; presence of iris neovascularization or intravitreal hemorrhage; having undergone laser therapy, additional ocular surgery, or trauma during follow-up; history of ocular cytomegalovirus or herpes infection; and presence of infectious uveitis or retinitis. Each patient's diagnosis, age, IOP values before IVD implantation, and IOP and pachymetry values measured with a tonometer/pachymeter (Canon TX-20P, Canon Medical Systems, Japan) between 8:30 and 11:00 AM at 1-3 days, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months after implantation were recorded. In addition, history of pars plana vitrectomy and indication (e.g., diabetic retinopathy, retinal detachment, macular hole, intravitreal hemorrhage), need for IOP-lowering medication after IVD implantation, and the number of medications initiated were noted. The patients included in the study were divided into two main groups, vitrectomized and non-vitrectomized. Non-vitrectomized patients were divided into subgroups according to etiology: diabetic macular edema (DME), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), non-infectious uveitis, and macular edema associated with retinitis pigmentosa (RP). All vitrectomized patients had completed panretinal photocoagulation treatment for proliferative diabetic retinopathy (DRP) and did not receive silicone oil or gas.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA) software package. The Shapiro-Wilk test was used to test whether the study data were normally distributed. In addition to descriptive statistical methods (mean, standard deviation, frequency), Mann-Whitney U test was used to compare quantitative data between two groups for parameters that did not show normal distribution. Within-group comparisons were performed with paired samples t-test for normally distributed parameters and Wilcoxon signed rank test for non-normally distributed parameters. Pearson correlation analysis was used to examine relationships between normally distributed parameters. Statistical significance was accepted at $p<0.05$.

Results

A total of 134 eyes of 112 patients between the ages of 46 and 85 years who underwent IVD implantation in the retina unit of our clinic between April 2016 and January 2018 were included in the study. Of these, 17 eyes (12.7%) were vitrectomized and 117 (87.3%) were non-vitrectomized. In the non-vitrectomized eyes, IVD implantation was performed for the diagnosis of DME (n=65), BRVO (n= 32), CRVO (n= 10), non-infectious uveitis (n= 8), and RP (n=2). Because the IVD implant provides corticosteroid release for an average of 6 months, the second or third IVD implants were administered 5-6 months after the last dose if the macular edema persisted. Panretinal photocoagulation for a diagnosis of PDR was completed in all vitrectomized eyes. IVD was performed in 16 of these eyes due to DME and in 1 eye due to macular edema associated with BRVO. The distribution of diagnoses is shown in Table 1.

In non-vitrectomized eyes after the first IVD dose (n=117), IOP was 25 mmHg in 1 eye with DME at 1-3 days and in 1 eye with DME at 1 month. At 2 months after the first dose, IOP was in the 30-40 mmHg range in 1 eye with DME, 30 mmHg in 1 eye with BRVO, in the 25-30 mmHg range in 2 eyes with BRVO and DME, and 25 mmHg in a total of 5 eyes with DME (n=2), BRVO (n=2), and uveitis (n=1). One eye with DME had an IOP of 25 mmHg at 3 months, and 1 eye with DME had an IOP of 40 mmHg at 9 months. After the second dose (n=30), IOP was 30 mmHg in 1 eye with DME at 1-3 days, 30-40 mmHg in 2 eyes with DME and 25-30 mmHg in 1 eye with CRVO at 2 months, and 25 mmHg in 1 eye with BRVO at 3 months.

Among the vitrectomized eyes, none had IOP values of 25 mmHg or higher after the first dose of IVD (n=17), whereas IOP was 25 mmHg in 1 eye with DME at 1 month and 25-30 mmHg in 1 eye with DME at 2 months after the second dose of IVD (n=5). IOP higher than 25 mmHg was not observed after the third dose of IVD in any non-vitrectomized (n=10) or vitrectomized (n=1) eyes. The numbers of eyes with IOP values of 25 mmHg and higher according to group are shown in Table 2.

A total of 23 (17.2%) of the 134 eyes (21/117 non-vitrectomized, 2/17 vitrectomized) required IOP-lowering medication. Of these, 1 medication was initiated in 73.9%, 2 medications in 17.4%, and 3 medications in 8.7% of the eyes. IOP elevation that required surgical intervention was not observed in any of the eyes.

In non-vitrectomized eyes, the mean IOP was 14.01±2.36 mmHg before the first dose and 14.8±2.96 at 1-3 days, 16.71±3.97 at 1 month, 17.88±5.27 at 2 months, 15.54±3.35 at 3 months, 15.1±3.24 at 6 months, and 14.61±3.71 mmHg at 12 months after the first dose (Table 3). In non-vitrectomized eyes, the increases in mean IOP at 1-3 days, 1 month, 2 months, and 3 months were statistically significant compared to the mean IOP before the first IVD implant ($p<0.05$). Mean IOP at 6 months, 9 months, and 12 months did not differ significantly from mean IOP before the first dose ($p>0.05$). In non-vitrectomized eyes, there was no statistically significant change in mean IOP at 1-3 days, 1 month, 3 months, or 6 months after the second dose ($p>0.05$) but mean IOP at 2 months was significantly increased compared to before the second dose ($p<0.05$) (Table 4). In non-vitrectomized eyes, the increase in mean IOP from before to 1-3 days after the second dose was significantly greater than the increase in mean IOP at the same period after the first dose ($p<0.05$). However, the change in mean IOP at 1, 3, and 6 months compared to before implantation did not differ significantly between the first and second doses ($p>0.05$). Non-vitrectomized eyes showed no significant change in mean IOP at 1-3 days or 1, 2, 3, 6, and 9 months after the third dose ($p>0.05$).

Because the eyes were not homogeneously distributed in the vitrectomized and non-vitrectomized patient groups, as expected in real life conditions, and because the etiopathology and course of macular edema can vary, we also analyzed the eyes in our study in subgroups according to their diagnosis. In non-vitrectomized eyes treated with IVD due to DME (n=65), the mean IOP was 13.98±2.45 mmHg before the first dose and 15.00±3.12 at 1-3 days, 17.42±4.07 at 1 month, 18.08±5.41 at 2 months, 15.76±3.10 at 3 months, 15.14±3.41 at 6 months, 16.05±6.51 at 9 months, and 13.86±4.09 mmHg at 12 months. The increase in IOP was statistically significant at 1-3 days, 1 month, 2 months, and 3 months compared to the mean IOP before the first dose ($p<0.05$). Among these eyes that received a second IVD implant (n=13), the change in mean IOP was not significant at 1-3 days (16.31±4.70 mmHg), 1 month (15.80±3.90 mmHg), 2 months (29.00±9.64 mmHg), 3 months (19.63±2.72 mmHg), or 6 months (15.14±2.80 mmHg) compared to the mean IOP before the second dose (16.46±2.79 mmHg) ($p>0.05$). Of these eyes that received a third IVD implant (n=4), there was also no significant change in mean IOP at day 1-3 (14.50±1.73 mmHg), 1 month (16.67±3.22mmHg), or 3 months (13.00±1.41 mmHg) compared to the mean IOP before the third dose (15.75±2.63 mmHg) ($p>0.05$).

Table 1. Distribution of the diagnoses of patients who underwent intravitreal dexamethasone implantation

	Non-vitrectomized		Vitrectomized	
Diagnosis	**n**	**%**	**n**	**%**
DME	65	55.6	16	94.1
BRVO	32	27.4	1	5.9
CRVO	10	8.5	0	0
UVEITIS	8	6.8	0	0
RP	2	1.7	0	0
Total	117	100	17	100

DME: Diabetic macular edema, BRVO: Branch retinal vein obstruction, CRVO: Central retinal vein occlusion, RP: Retinitis pigmentosa

In the non-vitrectomized eyes treated with the IVD implant due to BRVO-related macular edema (n=32), the mean IOP was 14.22±2.17 mmHg before the first dose and 15.09±2.35 at 1-3 days, 15.83±3.99 at 1 month, 18.18±5.96 at 2 months, 14.79±2.96 at 3 months, 14.83±2.82 at 6 months, 14.71±3.90 at 9 months, and 14.75±2.75 mmHg at 12 months. Only the increase in IOP at 2 months was statistically significant compared to the mean IOP before the first dose ($p<0.05$). Among these eyes that received a second IVD implant (n=11), the changes in mean IOP at 1-3 days (14.55±2.66 mmHg), 1 month (18.29±3.15 mmHg), 2 months (19.67±5.86 mmHg), 3 months (19.40±3.58 mmHg), and 6 months (19.33±2.08 mmHg) were not statistically significant compared to the mean IOP before the second dose (14.91±2.39 mmHg) ($p>0.05$). In the non-vitrectomized eyes that received an IVD implant due to CRVO (n=10), the mean IOP was 14.10±2.60 mmHg before the first dose and 14.30±3.34 at 1-3 days, 16.00±4.03 at 1 month, 15.50±1.29 at 2 months, 16.89±4.78 at 3 months, and 19.00±2.83 mmHg at 12 months. There was no significant change in mean IOP at 1-3 days, 1 month, 2 months, 3 months, and 12 months compared to before the first dose or at 1-3 days, 1 month, 3 months, and 6 months compared to before the second dose ($p>0.05$).

In the non-vitrectomized eyes that received an IVD implant due to uveitis-related macular edema (n=8), the mean IOP was 13.25±2.55 mmHg before the first dose and 12.63±3.20 at 1-3 days, 14.75±2.50 at 1 month, 18.50±5.07 at 2 months, 13.33±3.79 at 3 months, and 15.00±2.00 mmHg at 12 months. The changes in mean IOP at 1-3 days, 1 month, 2 months, 3 months, and 12 months were not statistically significant compared to the mean IOP before the first dose ($p>0.05$). In the 2 non-vitrectomized eyes treated with IVD implant due to RP-related macular edema, the changes in mean IOP at 1-3 days (15.00±1.41 mmHg) and 1 month (16.00±0.00 mmHg) were not statistically significant compared to the mean IOP before the first dose (14.00 ±1.41 mmHg) ($p>0.05$). When compared according to diagnosis, no statistically significant difference was observed in terms of IOP changes at 1-3 days, 1 month, 2 months, 3 months, or 6 months compared to pre-implant IOP values with the first or second doses of IVD in non-vitrectomized eyes ($p>0.05$) (Table 5).

In the vitrectomized eyes treated with IVD due to DME (n=16), the mean IOP was 14.63±3.01 mmHg before the first dose and 13.56±2.83 at 1-3 days, 14.27±2.90 at 1 month, 15.71±3.50 at 2 months, 15.80±4.52 at 3 months, 18.29±3.20 at 6 months, 15.67±4.51 at 9 months, and 15.00±1.41 mmHg at 12 months. The changes in mean IOP at 1-3 days and at 1, 2, 3, 6, 9, and 12 months were not significant ($p>0.05$). Among these eyes that received a

second IVD implant (n=5), the changes in mean IOP at 1-3 days (17.20±3.35 mmHg), 1 month (19.00±4.97 mmHg), 2 months (20.00±6.00 mmHg), 3 months (20.67±2.3 mmHg), and 6 months (17.00±1.41 mmHg) were not statistically significant compared to the mean IOP before the second dose (15.60±4.34 mmHg) (p>0.05). Only one vitrectomized eye underwent IVD implantation for a diagnosis of BRVO. This eye received a single dose and showed no significant change in IOP at 1, 3, or 6 months (p>0.05).

Discussion

Corticosteroid-induced ocular hypertension is a complication seen in patients with a previous diagnosis of glaucoma or a family history of glaucoma. Elevated IOP values during corticosteroid therapy usually return to normal when treatment is interrupted. However, glaucomatous optic neuropathy may develop if the diagnosis is missed. Therefore, it is essential to closely monitor patients receiving corticosteroid therapy, especially children and patients with a family history of ocular hypertension or glaucoma. Studies have shown that IOP increases 1-2 months after intravitreal 4 mg triamcinolone injection and that this increase continues for approximately 3 months in non-vitrectomized eyes.[5,6] In a retrospective study evaluating 68 IVD implants in 38 eyes, 7 cases with IOP values above 21 mmHg were reported.[7] In the GENEVA study, IOP of 25 mmHg or higher was detected in 16% of patients treated with IVD, with the maximum increase on day 60 and return to pre-implantation levels on day 180.[8] These transient IOP increases did not require treatment or were controlled with short-term topical antiglaucomatous drops. Only 5 patients needed surgical intervention or laser trabeculoplasty. In another retrospective study evaluating 92 eyes, 50% of cases showed transient IOP elevation that did not require treatment, whereas 46.7% required glaucoma treatment and only 1 patient required glaucoma surgery.[9]

Chin et al.[10] reported in their study that IOP elevation was an important side effect of IVD implantation that was generally mild/moderate and transient. In a 3-year randomized controlled study examining patients who underwent 0.7 mg IVD implantation with DME as the indication, 144 (41.5%) of a total of 347 patients needed to start antiglaucomatous drops, 4 (1.2%) were treated with laser or surgical procedures, and only 1 case (0.3%) required incisional glaucoma surgery.[11] In our study, IOP elevation was controlled with topical antiglaucomatous drops in 23 (17.2%) of 134 eyes. None of these patients required glaucoma surgery. After the first dose of IVD, IOP peak values were observed at 2 months in the non-vitrectomized group and at 6 months in the vitrectomized group, while IOP values normalized in both groups after 6 months. After the second IVD dose, peak IOP was observed at 2 months in the non-vitrectomized group and at 3 months in the vitrectomized group, with IOP values again normalizing after 6 months in both groups. The findings in the non-vitrectomized group are consistent with the pharmacokinetics demonstrated in animal studies.[4] IOP elevation was also shown to peak at 2 months after IVD implantation in the GENEVA study[8] and in studies by Mazzarella et al.[9] and Meyer and Schönfeld.[12] In another retrospective study evaluating 59 eyes of 52 patients treated with IVD, it was reported that IOP elevation showed no cumulative effect in patients who received more than one implant.[10] In a 2015 study evaluating 15 eyes of 12 patients, there were 3 cases of IOP elevation controlled with topical treatment after the first, second, and third IVD doses.[13] In our study, there was no significant difference in IOP changes at 1, 3, and 6 months between the patients who received a single dose and those who

Table 2. Numbers of eyes in the vitrectomized and non-vitrectomized groups with IOP values of 25 mmHg or higher after receiving the first and second doses. In the non-vitrectomized group, IOP values of 25 mmHg or higher were recorded after the first dose in 13 eyes (8 with DME, 4 with BRVO, and 1 with uveitis) and after the second dose in 5 eyes (3 with DME, 1 with CRVO, and 1 with BRVO); in the vitrectomized group, IOP values of 25 mmHg or higher were recorded after the second dose in 2 eyes with DME

Non-vitrectomized (n=117)						**Vitrectomized (n=17)**	
IOP (mmHg)	**25**	**25-30**	**30**	**30-40**	**40**	**25**	**25-30**
First dose							
1-3 days	**1**	0	0	0	0	0	0
1 month	**1**	0	0	0	0	0	0
2 months	**5**	**2**	**1**	**1**	0	0	0
3 months	**1**	0	0	0	0	0	0
9 months	0	0	0	0	1	0	0
Second dose							
1-3 days	0	0	**1**	0	0	0	0
1 month	0	0	0	0	0	**1**	0
2 months	0	**1**	0	2	0	0	**1**
3 months	**1**	0	0	0	0	0	0

IOP: Intraocular pressure, DME: Diabetic macular edema, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion

received two doses. Eyes in our study that received multiple IVD implants showed a transient, mild to moderate increase in IOP with no statistically significant cumulative effect after the second and third doses. When compared by clinical diagnosis, there was no statistically significant difference in mean IOP values.

Pars plana vitrectomy (PPV) can be beneficial in the treatment of various conditions, such as diabetic retinopathy, retinal detachment, macular hole, epiretinal membrane, and intravitreal hemorrhage. IVD implantation is often necessary after PPV surgery. Viscosity decreases in vitrectomized eyes. It has been shown that intravitreal drugs such as anti-VEGF, triamcinolone, and amphotericin B are cleared from the vitreous faster in vitrectomized eyes.[15,16,17] A study conducted in monkey eyes demonstrated that the half-life of bevacizumab was reduced by 60% in vitrectomized eyes compared to non-vitrectomized eyes.[18] Niwa et al.[19] also showed that both intravitreal ranibizumab and aflibercept had shorter half-lives in vitrectomized eyes. These results suggest that the efficacy of intravitreal drug therapy may vary in non-vitrectomized and vitrectomized eyes. However, in a study conducted with rabbit eyes that received 0.7 mg IVD, a similar pharmacokinetic profile was observed in vitrectomized and non-vitrectomized eyes.[20]

The Ozurdex CHAMPLAIN study group published the results of a study evaluating the safety and efficacy of IVD for 26 weeks in 55 vitrectomized eyes of patients with DME in 2011. According to their report, 16% of the cases had elevated IOP. The proportion of patients with IOP values of 25 mmHg or higher was 9% at week 8 and decreased to 0% at week 26. In the same study, only 1 vitrectomized patient had IOP higher than 35 mmHg at week 8, while 17% of the cases required antiglaucomatous medication.[21] In their study evaluating the outcomes of IVD implant therapy in patients with DME, Çevik et al.[14] reported elevated IOP (25-30 mmHg) requiring medical treatment in 1 of 9 vitrectomized eyes and 2 of 31 non-vitrectomized eyes. In another study evaluating the results of IVD implantation in patients with DME, IOP values between

Table 3. IOP values (mmHg) after the first dose of intravitreal dexamethasone in non-vitrectomized and vitrectomized eyes

Surgery	IOP	n	Mean ± SD	Median	p
Non-vitrectomized	Preop	117	14.01±2.36	14	0.012*
	1-3 days	117	14.8±2.96	14	
	Preop	87	14.15±2.39	14	0.000*
	1 month	87	16.71±3.97	16	
	Preop	51	14.31±2.15	14	0.000*
	2 months	51	17.88±5.27	17	
	Preop	72	14.21±2.63	14	0.008*
	3 months	72	15.54±3.35	15	
	Preop	49	14.24±2.56	14	0.111
	6 months	49	15.1±3.24	15	
	Preop	30	14.33±2.43	14	0.973
	9 months	30	14.6±6.8	14	
	Preop	23	14.13±2.4	14	0.626
	12 months	23	14.61±3.71	14	
Vitrectomized	Preop	17	14.35±3.12	14	0.089
	1-3 days	17	13.41±2.81	14	
	Preop	12	13.75±3.11	14	0.680
	1 month	12	14±2.92	14	
	Preop	7	14.71±3.4	14	0.340
	2 months	7	15.71±3.5	16	
	Preop	11	14.36±3.75	14	0.441
	3 months	11	15.82±4.29	16	
	Preop	8	15.13±3.98	14	0.040*
	6 months	8	17.75±3.33	18	
	Preop	3	17±4.36	14	0.785
	9 months	3	15.67±4.51	16	
	Preop	2	18±5.66	14	0.655
	12 months	2	15±1.41	15	

Wilcoxon signed rank test, *p<0.05, IOP: Intraocular pressure, Preop: Before implantation, SD: Standard deviation

Table 4. IOP values (mmHg) after the second dose of intravitreal dexamethasone in vitrectomized and non-vitrectomized eyes

Surgery	IOP	n	Mean ± SD	Median	p
Non-vitrectomized	Preop	30	15.8±2.58	15	0.108
	1-3 days	30	14.8±3.84	14	
	Preop	16	15.81±1.91	15	0.378
	1 month	16	16.63±3.65	16.5	
	Preop	7	16.43±3.55	15	0.028*
	2 months	7	24.86±8.13	24	
	Preop	18	16.61±2.57	15	0.116
	3 months	18	18.39±3.74	17	
	Preop	12	16.08±2.91	15	0.664
	6 months	12	16.67±3.42	16	
Vitrectomized	Preop	5	15.6±4.34	14	0.593
	1-3 days	5	17.2±3.35	18	
	Preop	4	12.75±1.5	14	0.144
	1 month	4	19±4.97	19	
	Preop	3	15.33±5.77	15	0.109
	2 months	3	20±6	20	
	Preop	3	15.33±5.77	15	0.180
	3 months	3	20.67±2.31	22	
	Preop	2	17±7.07	17	1.000
	6 months	2	17±1.41	17	

Wilcoxon signed rank test, *p<0.05, IOP: Intraocular pressure, Preop: Before implantation, SD: Standard deviation

Table 5. Evaluation of changes in intraocular pressure measured before and after the first and second doses of intravitreal dexamethasone in non-vitrectomized eyes according to diagnosis

	CRVO	DME	UVEITIS	BRVO	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
First dose					
Preop - 1-3 days	0.2±2.97	1.02±3.24	-0.63±3.25	0.88±2.78	0.786
Preop - 1 month	2.13±4.79	3.30±4.33	-0.25±2.06	1.65±4.53	0.350
Preop - 2 months	0.00±2.71	3.88±5.57	4.25±2.22	3.88±6.01	0.564
Preop - 3 months	2.78±5.33	1.51±3.49	-1.00±1.00	0.68±3.45	0.452
Preop - 6 months	-	0.77±4.56	-	0.75±2.56	0.737
Second dose					
Preop - 1-3 days	-3.6±3.65	-0.15±3.34	-	-0.36±2.62	0.149
Preop - 1 month	-1.33±6.11	-0.40±2.70	-	2.86±3.93	0.311
Preop - 2 months	-	11.67±8.62	-	5.00±5.29	0.449
Preop - 3 months	-0.50±7.00	2.50±3.30	-	3.20±4.55	0.497
Preop - 6 months	1.05±9.19	-0.86±1.86	-	3.33±0.58	0.127

Kruskal-Wallis Test; CRVO: Central retinal vein occlusion, DME: Diabetic macular edema, BRVO: Retinal vein branch obstruction, IOP: Intraocular Pressure, Preop: Before implantation, SD: Standard deviation

21 and 35 mmHg were measured in both vitrectomized and non-vitrectomized eyes 1 to 3 months after administration and were controlled with topical treatment alone.[22] Özdemir et al.[23] also showed in their study that vitrectomized eyes receiving IVD for a diagnosis of DME had significant IOP elevation at 1, 3, and 6 months after implantation. In a retrospective study of 59 vitrectomized and 127 non-vitrectomized eyes, the frequency of IOP higher than 25 mmHg or at least 10 mmHg over baseline was 21.3% in non-vitrectomized eyes and 29.3% in non-vitrectomized eyes, IOP-lowering medication was required in 26.0% of non-vitrectomized eyes and 28.8% of vitrectomized eyes, and there was no significant difference between vitrectomized and non-vitrectomized eyes in terms of the incidence of ocular hypertension in patients with DME.[24] In the present study including 117 non-vitrectomized eyes, IOP after the first IVD dose was measured as 25 mmHg in 1 eye with DME at 1-3 days; 25 mmHg in 1 eye with DME at 1 month; 30-40 mmHg in 1 eye with DME, 30 mmHg in 1 eye with BRVO, 25-30 mmHg in 2 eyes with BRVO and DME, and 25 mmHg in a total of 5 eyes with DME (n=2), BRVO (n=2), and uveitis (n=1) at 2 months; 25 mmHg in 1 eye with DME at 3 months; and 40 mmHg in 1 eye with DME at 9 months. In the 30 non-vitrectomized eyes that received a second IVD dose, IOP was measured as 30 mmHg in 1 eye with DME at 1-3 days; 30-40 mmHg in 2 eyes with DME and 25-30 mmHg in 1 eye with CRVO at 2 months; and 25 mmHg in 1 eye with BRVO at 3 months. Among the 17 vitrectomized eyes in our study, we detected no significant IOP elevation after the first dose of IVD, while of the 5 vitrectomized eyes that received a second IVD dose, IOP was measured as 25 mmHg in 1 eye with DME at 1 month and 25-30 mmHg in 1 eye with DME at 2 months. We determined that the changes in IOP at 1-3 days, 1 month, 2 months, and 3 months after the first IVD dose were significant in non-vitrectomized eyes that underwent IVD implantation due to DME. In addition, we observed significant IOP elevation at 2 months in non-vitrectomized eyes that underwent IVD implantation due to BRVO-related macular edema. In the non-vitrectomized group, IOP measurements were found to be significantly higher at 1-3 days, 1 month, 2 months, and 3 months after IVD implantation, while there was no significant difference in vitrectomized eyes at these time points, which is inconsistent with the postoperative IOP elevation seen as a complication of vitrectomy surgery. We believe these results may be due to the fact that all of our vitrectomized patients had completed panretinal photocoagulation treatment for proliferative DRP and were not given silicone oil or gas, and had no intraoperative complications. This result may also be related to the more rapid vitreous clearance of IVD due to decreased viscosity in vitrectomized eyes, as demonstrated with other intravitreally administered drugs such as anti-VEGF, triamcinolone, and amphotericin B.[15,16,17]

In a study evaluating IVD implantation in vitrectomized patients with uveitis-related macular edema, the frequency of IOP elevation was 47.1%. IOP was measured as 22-30 mmHg and 30-40 mmHg in 7 eyes (41.1%) and 1 eye (5.9%), respectively, and returned to normal with medical treatment 8 weeks after implantation, with only 1 case required filtering surgery.[25] In addition, in a study examining 42 eyes undergoing IVD implantation for the indication of macular edema associated with non-infectious uveitis, IOP elevation over 21 mmHg was reported in 8 (36.4%) of 22 non-vitrectomized eyes and 12 (60%) of 20 non-vitrectomized eyes.[26] In the 8 non-vitrectomized eyes in our study that were treated with IVD for macular edema associated with non-infectious uveitis, IOP was measured as 25

mmHg in 1 eye at 2 months after the first dose and was below 25 mmHg in the other eyes. We detected no significant change in IOP levels at 1-3 days, 1 month, 2 months, 3 months, and 12 months after implantation.

Dexamethasone, fluocinolone acetonide, and triamcinolone were shown to activate different gene expression patterns in the human trabecular network.[27] The pharmacological activity of dexamethasone differs from that of triamcinolone. Dexamethasone is less lipophilic than triamcinolone and does not accumulate in the trabecular network to the same degree, and thus has a less pronounced IOP-elevating effect compared to triamcinolone.[28,29] When compared with the literature data, our findings support that IVD implants may be safer than intravitreal fluocinolone administration in terms of IOP elevation that may require glaucoma surgery.[30,31,32]

Conclusion

In this study we evaluated IOP changes in patients who underwent IVD implantation for the treatment of macular edema for various indications by grouping the eyes as those with and without a history of vitrectomy and also dividing them into subgroups according to their diagnosis. We observed that both vitrectomized and non-vitrectomized eyes that received the IVD implant generally had mild and transient IOP elevation that was independent of the indication for implantation and showed no cumulative effect in eyes that received second and third doses. This study has some limitations because it was conducted retrospectively and in a single center. The long-term prognosis of eyes with elevated IOP is unknown. These cases should be closely followed due to the risk of glaucoma in the future. A strength of our study is that we compared a large group of patients who received IVD implants for various indications by classifying them as vitrectomized and non-vitrectomized and dividing them into subgroups according to diagnosis. Studies with larger patient groups and more comprehensive follow-up may yield more definite results. Prospective clinical studies are needed to evaluate the safety of IVD implantation.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the ethics committee of the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., S.A.K., Concept: S.A.K., B.A., M.G., Design: B.A., M.G., S.A.K., Data Collection or Processing: M.G., A.Ç., Analysis or Interpretation: S.A.K., B.A., M.G., Literature Search: M.G., A.Ç., Writing: M.G., S.A.K.

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Original Article

Survey of Intravitreal Injection Techniques and Treatment Protocols Among Members of the Turkish Ophthalmological Association

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Abstract

Objectives: To describe the intravitreal injection (IVI) techniques, practices, and treatment protocols of ophthalmologists in Turkey from May 20, 2020 to June 4, 2020.

Materials and Methods: All members of the Turkish Ophthalmological Association were contacted by e-mail to complete an anonymous, 47-question internet-based survey.

Results: Thirteen percent of the participants prescribed prophylactic antibiotics pre-injection, 63.8% (406/636) used antibiotic drops immediately after injection, and 91.8% prescribed topical antibiotics. The majority of IVI procedures were performed in an operating room (65.3%) or clean room (33.6%). Most surgeons used sterile gloves, masks, sterile drape, sterile fenestrated cover, and sterile eyelid speculum. Multispecialists (M) preferred to wear sterile gloves more than retina specialists (RS) (99.0% vs. 95.3%; p=0.004). Also, M prescribed antibiotics more than RS (93.7% vs. 88.8%; p=0.029). RS dilated the pupil more frequently than M (48.3% vs. 39.0%) (p=0.020). RS were more familiar to use different quadrants (right p=0.012; left p=0.001). Most surgeons (82.8%) did not perform injections in both eyes on the same day.

Conclusion: Ophthalmologists in Turkey employ a wide range of techniques in care before, during, and after IVI. In addition, IVI techniques and treatment protocols differed between RS and M. Further research is needed to elucidate best practice patterns.

Keywords: Intravitreal injections, survey, retina specialists, anti-VEGF

Introduction

Intravitreal injections (IVI) are widely used by ophthalmologists for the treatment of various retinal diseases. The IVI technique was first described in 1911 and has been used to administer anti-vascular endothelial growth factors, corticosteroids, and other drugs for many years.[1,2] There are several published guidelines describing the indications and procedures of IVI.[3,4,5] However, there is no consensus among clinicians on the intravitreal injection technique or pre-injection and post-injection care.

The aim of this study was to determine the personal preferences of ophthalmologists in Turkey regarding IVI procedures.

Materials and Methods

All members of the Turkish Ophthalmological Association were contacted via e-mail in May 2020 to complete a 47-question internet-based survey. Three reminder e-mails were sent to the participants who had not completed the survey. SurveyMonkey (www.surveymonkey.com; SurveyMonkey, San

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Mateo, CA) was used for the data collection. The final results were collected on June 4, 2020. Thirty-five questions related to injection and follow-up procedures were evaluated. In the first 3 questions, participants were asked about demographic data (institution, society membership). The fourth question asked if the participant had experience with IVI. Participants who did not have any experience with IVI were directed to the end of the questionnaire. Reimbursement regulations in Turkey indicate 3 consecutive monthly injections of bevacizumab for the treatment of diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion. Therefore, there was no question about the timing of IVI in the survey. Protocol differences regarding the injection techniques were also evaluated. Participants were divided into the retina specialist-only group (RS) and multispecialty group (M) and protocol differences were compared between groups.

Statistical Analysis

All P values were derived from chi-square tests using SPSS software version 20 (IBM Corp, Armonk, NY). The research protocol was initially submitted to the Institutional Ethics Committee and Review Board of the University of Kocaeli (registration number: KAEK 2020/219).

Results

A total of 892 ophthalmologists answered the questionnaire. Of these, 232 participants reported having no experience related to IVI. The other 660 participants who were actively performing IVI were included in our analysis of practice patterns.

Demographic Data

The participants' institutions are presented in Table 1. RS accounted for 30.6% (273/891) of all participants. The responses of RS and M are evaluated in Table 2. Of all respondents, 4.4% (39/882) were members of the Turkish Ophthalmological Association Medical Retina Society, 2.4% (21/882) were members of the Turkish Ophthalmological Association Vitreoretinal Surgery Society, and 4.4% (39/882) were members of both the Medical Retina and Vitreoretinal Surgery societies. The remaining 88.8% (783/882) of the participants were not members of any society.

Pre-injection Practices

Only 13.0% (84/646) of the participants prescribed prophylactic antibiotics before IVI. There was no statistically significant difference in prophylactic antibiotic use between RS and M (10.9% vs. 14.2%, respectively, p=0.216). In terms of setting, 65.3% (422/646) of the participants performed IVI in an operating room (OR), 33.6% (217/646) in a clean room (CR), and 1.1% (7/646) in an office or other setting. There was no significant difference between RS (OR: 61.5%, CR: 36.6%, office-others: 1.9%) and M (OR: 68.0%, CR: 31.5%, office/other: 0.5%) (p=0.083). Nearly all participants (97.8%; 633/647) administered topical anesthetics, 2 participants (0.3%) preferred peribulbar anesthesia, whereas 12 participants (1.9%) did not perform anesthesia before IVI. There was no difference in topical anesthesia use between RS and M (96.9% vs. 98.5%, respectively, p=0.448).

Most surgeons draped before IVI, with 56.7% (367/647) saying they used a sterile drape and 34.9% (226/647) using a fenestrated towel. The rest of the surgeons did not use any covering. There was no significant difference in draping practices between RS (sterile drape: 55.3%; fenestrated towel: 34.2%; no covering: 10.5%) and M (sterile drape: 57.5%; fenestrated towel: 35.6%; no covering: 7.0%) (p=0.281).

Ninety-six percent (624/650) of the participants used a sterile eyelid speculum during the procedure. There was no difference in eyelid speculum use between RS and M (96.1% vs. 95.9%, respectively, p=0.886).

Povidone iodine (PI) antisepsis on the conjunctiva was used by almost all surgeons (98.9%, 643/650). However, different concentrations of PI were preferred by the participants (1% PI with frequent repetition: 11.4%; 5% PI: 71.9%; 10% PI: 15.7%). There was no difference in the PI concentrations used by RS (1% PI: 9.3%; 5% PI: 74.0%; 10% PI: 15.9%, no PI: 0.8%) and M (1% PI: 12.8%; 5% PI: 70.3%; 10% PI: 15.6%; no PI: 1.3%) (p=0.515). There was also variation in the contact time of PI on the conjunctiva (30 s: 25.9%, 60 s: 28.0%, 90 s: 14.6%, 180 s: 31.5%) but there was no difference in PI contact time between RS (30 s: 24.2%, 60 s: 27.7%, 90 s: 15.6%, 180 s: 32.4%) and M (30 s: 27.2%, 60 s: 28.2%, 90 s: 14.0%, 180 s: 30.6%) (p=0.804).

Nearly all participants (97.5%, 630/646) wore sterile gloves during IVI. The use of sterile gloves was higher in M (99.0%) than RS (95.3%) (p=0.004). Similarly, nearly all participants wore masks (98.3%). Eighty-one percent (523/646) of the participants said they cover their noses with the mask and all stated the importance of covering the nose. In addition, 72.4% (467/645) of the participants wore special surgical clothes. There was no difference between RS and M in terms of mask use (96.9% vs. 99.2%, respectively) (p=0.087) or the use of special surgical clothes (68.5% vs. 75.1%, respectively) (p=0.065).

Most surgeons (82.8%, 535/646) did not perform injections in both eyes on the same day. RS preferred same-day bilateral injection more frequently than M (21.8% vs. 14.2%, p=0.013). Most of the surgeons who performed bilateral same-day injections used a sequential procedure (79.6%, 86/108). There was no significant difference in sequential procedure use between RS and M (85.5% vs. 73.6%) (p=0.126).

Table 1. Institutions of the participants (n=890)

	n	%
School of medicine	239	26.9
Private practice	219	24.6
Training and research hospital	194	21.8
Public hospital	147	16.5
City hospital	48	5.4
Foundation university	46	5.2
Clinic	42	4.7

Pupil dilation before IVI was practiced by 42.7% of participants overall (276/646) and was significantly more common among RS than M (48.3% vs. 39.0%) (p=0.020).

Injection Practices

The most common quadrant for right eye injection was the superotemporal quadrant (78.5%, 499/636) followed by the inferotemporal (18.2%, 116/636), superonasal (2.2%, 14/636), and inferonasal (1.1%, 7/636) quadrants. Quadrant preferences were similar for the left eye. M preferred mostly the superotemporal quadrant (right: 82.5%, left: 74.1%), followed by the inferotemporal quadrant (right: 15.2%, left: 14.7%), superonasal quadrant (right: 1.8%, left: 9.7%), and inferonasal (right: 0.5%, left: 1.6%) quadrant. RS preferred mostly the superotemporal quadrant (right: 72.2%, left: 59.1%), followed by the inferotemporal quadrant (right: 23.0%, left: 21.4%), superonasal quadrant (right: 2.8%, left: 9.7%), and inferonasal quadrant (right: 2.0%, left: 0.5%). There was a significant difference in quadrant preference between RS and M (right: p=0.012, left: p=0.001)

When performing injections, 70.9% (449/633) of the participants said they hold the needle perpendicular to the globe. The tendency to use this needle position was higher in M than RS (74.0% vs. 66.4%, respectively, p=0.039).

Post-injection Practices

Most participants (93.1%, 591/632) did not use indirect ophthalmoscopy to evaluate retinal and optic nerve perfusion after injection. There was no significant difference in the use of indirect ophthalmoscopy between RS and M (5.6% vs. 7.9%, respectively, p=0.091).

Evaluation for central retinal artery occlusion (CRAO) after injection was performed using hand motion and finger counting by 42.5% (270/636) of participants and with light perception assessment by 17.1% (109/636) of participants. Another 2.2% (14/636) of participants used indirect ophthalmoscopy and 6.1% (39/636) of participants evaluated the retina 30 minutes after injection with a biomicroscope. The other 32.1% (204/636) of the participants did not check for CRAO. RS evaluated CRAO after injection more than M (76.6% vs. 62.0%, p=0.001)

Table 2. Comparison of intravitreal injection practice patterns between retina specialists (RS) and multispecialists (M)

	RS		M (n=		
	n	%	n	%	p value
Antibiotics before injection	28/257	10.9	55/387	14.2	0.216
Uses an operating room	158/257	61.5	263/387	68.0	0.091
Wears mask	249/257	96.9	313/387	99.2	0.087
Wears sterile gloves	245/257	95.3	383/387	99.0	**0.004**
Wears special surgical clothes	176/257	68.5	290/386	75.1	0.065
Uses sterile drape and fenestrated towel	230/257	89.4	361/388	93.0	0.111
Uses sterile eyelid speculum	248/258	96.1	374/390	95.9	0.886
Dilates pupil	124/257	48.3	151/387	39.0	**0.020**
Uses topical anesthetic drops before injection	249/257	96.9	382/388	98.5	0.448
Uses 5% povidone iodine before injection	191/258	74.0	274/390	70.3	0.296
Performs same-day bilateral injection	56/257	21.8	55/387	14.2	**0.013**
Uses superotemporal quadrant-right	182/252	72.2	315/382	82.5	**0.002**
Uses superotemporal quadrant-left	149/252	59.1	283/382	74.1	**0.000**
Holds the needle perpendicular to the globe	166/250	66.4	282/381	74.0	**0.039**
Uses indirect ophthalmoscopy	14/251	5.6	30/382	7.9	0.091
Checks for central retinal artery occlusion	193/252	76.6	237/382	62.0	**0.001**
Covers the eye until discharge	170/252	67.5	216/382	56.5	**0.006**
Uses antibiotic drops immediately after injection	153/252	60.7	251/382	65.7	0.201
Prescribes antibiotics for home use	223/251	88.8	358/382	93.7	**0.029**
Prescribes antibiotics for 1 week	95/223	42.6	196/355	55.2	**0.003**
Examines patients on postoperative day 1	102/251	40.6	198/380	52.1	**0.006**
Performs same-day injections	107/230	46.5	131/339	38.6	0.062

Statistically significant results shown in bold

A majority of the participants (63.8%, 406/636) administered antibiotic drops immediately after injection, 24.7% (157/636) used povidone iodine drops, and 0.2% (1/636) used topical anesthetic drops. 11.3% (72/636) of surgeon did not use drops after injection. There was no significant difference in use of drops after injections between RS (antibiotic drops: 60.7%, povidone iodine drops: 28.2%, no drops: 10.7%, topical anesthetic drops: all of but one) and M (antibiotic drops: 65.7%, povidone iodine drops: 22.5%, no drops: 11.8%, topical anesthetic drops: 0.0%) (p=0.208).

Nearly all participants (92.9%) covered the eye with a sponge, with 60.9% (287/636) reporting that they covered the eye until discharge and 32.1% (204/636) applying the sponge for 24 hours. More RS than M covered the eye until discharge (67.5% vs. 56.5%, respectively, p=0.006), whereas more M than RS preferred to cover the eye for 24 hours (56.5% vs. 36.1%, respectively, p=0.006)

Most of the participants (85.8%, 545/635) prescribed fluoroquinolone group antibiotics, 6.0% (38/635) prescribed aminoglycoside group antibiotics, and 8.2% (52/635) did not perform any antibiotherapy. M prescribed antibiotherapy more than RS (93.7% vs. 88.8%, respectively, p=0.029). Almost half of the participants prescribed antibiotics for 1 week and rest prescribed for 24 or 72 hours. M prescribed antibiotics for 1 week more than RS (55.2% vs. 42.6% respectively, p=0.003).

After the IVI procedure, 47.6% (301/633) of the participants examined the patients on postoperative day 1, 7.3% (46/633) on postoperative day 3, and 13.6% (86/633) both on postoperative day 1 and at postoperative 1 week. Approximately one-third of the surgeons (200/633) called the patients at postoperative 1 month and 81.1% (146/180) instructed patients to visit the clinic in case of any complaints. M examined patients on postoperative day 1 more than RS (52.1% vs. 40.6%, respectively, p=0.006), while RS examined patients at postoperative 1 month more than M. (38.7% vs. 26.8%, respectively, p=0.002). There was no significant difference between RS and M in terms of informing patients they should visit the clinic in case of any complaints (RS: 79.6%, M: 82.4%, p=0.176).

Injection Protocol

While 42.3% of participants reported performing IVI immediately after deciding to treat with IVI, the other participants scheduled an extra appointment for IVI. MS tended to perform IVI in another appointment more than RS, but the difference did not reach statistical significance (46.5% vs. 38.6%, p=0.062).

Almost half of all ophthalmologists examined patients monthly during the loading phase (first 3 injections), 24.7% (141/570) examined the patients on injection day, and 22.1% (126/570) examined patients only at 1 month after the loading phase. There was no significant difference in examination practices between RS (monthly: 53.3%, injection day: 24.9%, after loading phase: 21.8%) and MS (monthly: 52.8%, injection day: 24.8%, after loading phase: 22.4%) (p=0.986).

For patients with AMD, the most frequent treatment approach was 3 initial monthly injections, followed by pro re nata (PRN) treatment (64.5%). There was no significant difference in preference of AMD treatment protocol between R (PRN: 62.8%, treat and extend [TREX]: 35.5%, other: 1.7%) and M (PRN: 66.1%, TREX: 31.9%, other: 2.1%) (p=0.651).

Approximately half of the surgeons assumed that patients with AMD receive 6-7 injections per year, while this number was assumed to be 1-3, 4-5, and 8 or more by 6.2%, 33.9%, and 11.3% of participants, respectively. More RS than M assumed 6-7 injections yearly for AMD (60.2% vs. 40.5%, p=0.000).

For patients with DME, 42%, 38%, 11%, and 9% of participants assumed 6-7, 1-3, 4-5, and 8 or more injections per year, respectively. More RS than M assumed 6-7 injections for DME (49.4% vs. 36.5%, p=0.002).

Discussion

Several guidelines for intravitreal drug injections have been published in recent years.[6,7] However, pre-injection preparation, injection technique, and post-injection care preferences vary in daily practice. In this study, we report the preferred IVI techniques of surgeons in Turkey.

Topical Antibiotics

Most participants did not use prophylactic antibiotics before IVI. Similarly, 76.8% of members of the American Society of Retina Specialists (ASRS) did not prescribe pre-injection antibiotics in a 2018 survey.[8] A report of the American Academy of Ophthalmology in 2014 stated that there is insufficient evidence supporting the use of prophylactic antibiotics to reduce the risk of endophthalmitis.[9] According to a EURETINA expert consensus report in 2018, perioperative antibiotic use was also not considered standard care.[6] Furthermore, recent studies suggest that antibiotic prophylaxis may lead to antibiotic resistance.[10,11]

Almost two-thirds (63.8%) of our respondents used topical antibiotic drops immediately after injection. In contrast, the rate of antibiotic use always or frequently immediately after injection was limited to 16.6% in the recent ASRS survey.[8] In our survey, the rate of prescribing antibiotics for home use was very high at 91.8%. In the ASRS survey, this rate was 33%. Antibiotics were prescribed for home use more frequently and for longer duration by the multispecialty group than the retina specialist group. This may be related to retina specialists' ability to manage complications that may occur after IVI.

Guidelines do not recommend perioperative antibiotics.[3,6] However, in the real world, 33% of ASRS members prescribed antibiotics after injections. This may be due to a lack of trust in guideline recommendations. Usage rates among Turkish surgeons were also higher than elsewhere in the world. This is associated with surgeons' reluctance to take risks and to avoid malpractice allegations.

Use of Masks, Gloves, and Drapes

Nearly all (91.65%) of the surgeons used a sterile drape. This rate is much higher than ASRS 2018 data (10.9%). Studies

suggest that sterile covers isolate the mouth and nose of patients and may reduce patient-induced transmission.[12,13] However, the EURETINA 2018 consensus report noted that there is not enough evidence to reduce the risk of postoperative infection using sterile drapes, and they can be used according to surgeon preference.[14]

Most of the participants wore masks (98.30%) and sterile gloves (97.52%) before the procedure. In the ASRS survey 2018 data, only 32.9% of the participants wore masks and 54.8% wore gloves (50.4% sterile gloves). Forty-one percent of salivary isolates constitute *Streptococcus* species[15] and post-IVI endophthalmitis are mostly caused by streptococci.[16,17] Production of oropharyngeal droplets is thought to cause contamination of the sterile infection site.[15] Studies show that wearing a mask during injection and adopting a "no talking" policy significantly reduces the formation of bacterial colonies on culture plates.[18] The EURETINA 2018 consensus report recommended wearing a mask.[6] Most of the participants in our study (81.0%) also preferred to cover the nose while wearing a mask. It was especially emphasized that the use of effective masks or respirators (covering both the mouth and nose) during the COVID-19 pandemic is effective in preventing aerosol formation and transmission.[19]

Interestingly, the rate of wearing sterile gloves was lower in the retina specialist group. This may also be related to retina specialists' higher level of confidence regarding the management of complications such as endophthalmitis. The World Health Organization's hand hygiene guideline recommends hand hygiene and wearing gloves before surgical interventions.[20] However, no study has directly evaluated the effect of sterile or non-sterile gloves and surgical hand washing before IVI in reducing the risk of endophthalmitis.

The vitreous is a rich medium for low-virulence bacteria and has immune privilege. Therefore, we believe that IVI should be considered an aseptic procedure.

Anesthesia

In the presented survey, the most commonly used anesthesia was topical drops (97.8%). Consistent with our results, Canadian retina specialists and ASRS members also preferred topical drops before injection.[8,21] Although there is a lack of evidence regarding the anesthesia technique before IVI, topical anesthesia is recommended because it is the least invasive anesthesia method.

Eyelid Speculum

Nearly all of our participants (96%) used a sterile eyelid speculum. This was similar to the preferences of Canadian surgeons (91%).[21] During IVI it is necessary to prevent involuntary closure of the lids and needle contamination by the eyelashes. An increase in the rate of endophthalmitis was reported when adequate lid retraction was not achieved.[22] In the 2018 ASRS survey, 73% of all members used an eyelid speculum, which showed a decline from 92% in 2011. This was associated with the more frequent use of bimanual retraction technique.[23]

Antisepsis

Nearly all (98.9%) surgeons used PI antisepsis in the conjunctiva. This rate was similar to those reported in Canada, ASRS members (92.2%), and the United Kingdom.[8,21,24] Most of the surgeons (71.9%) preferred to use a 5% PI solution. PI has broad-spectrum microbicidal activity and is important for antisepsis. It reduces the pathogen load on the ocular surface prior to the surgical procedure and its use on the conjunctiva and periocular skin before IVI is strongly recommended.[20,25] In order to achieve a bactericidal effect at PI concentrations in this range, it is necessary to wait 30-120 seconds after a single application, and a single application is sufficient.[25] The 2018 EURETINA consensus report suggested using 5% PI for 30 seconds before IVI.[6]

Injection Setting

The preferred setting for IVI was an operating room for 65.3% of the surgeons and a clean room for 33.6% of the surgeons. In contrast, IVIs are performed mainly as an office procedure in the United States and Canada, with a low incidence of post-injection endophthalmitis. A previous study indicated no significant difference between the office and operating room in terms of the incidence of endophthalmitis in IVIs.[26] In the 2018 EURETINA report, IVIs were reported to have similar risk in terms of infection frequency.[6]

Injection Practices

Most surgeons preferred the superotemporal quadrant (78.5% in the right eye, 68.2% in the right eye), followed by the inferotemporal quadrant (18.2% right, 17.3% left). In contrast, the inferotemporal quadrant was preferred by a majority of Canadian retina specialists (63%) and ASRS members (61.8% right, 61.0% left). Recent guidelines leave the choice of injection quadrant to the surgeon's preference.[14] An advantage of performing IVI in the inferotemporal quadrant may be that it prevents the drug from interfering with the patient's vision. Conversely, if retinal detachment occurs after injection, the superotemporal quadrant may be more advantageous for pneumatic retinopexy. The retina specialists in our study are more familiar with using different quadrants because of their vitreoretinal surgery experience, and therefore may choose each quadrant separately.

Approximately 70% of the participants held the needle perpendicular to the globe. This method has been preferred by most surgeons for many years. However, recent studies indicate that the tunnel technique is superior in the prevention of vitreous reflux.[27] The tunnel technique involves inserting the needle at a 30 degree angle to the globe, then raising it perpendicular to the center. This approach may prevent trapping of the vitreous in the sclera, which is called vitreous wick syndrome, and/or bacterial entry into the vitreous.

Injection Protocol

More than half (58.0%) of the participants stated that they were not able to administer the injection on the same day they decided on the treatment. The rate of same day injection was

higher in the retina specialist group. This may be explained by the fact that retina specialists have more experience with IVI.

In our study, 64.5% of the participants stated that they examined the patients monthly and followed up with a PRN regimen after the first 3 injections for AMD. Another 33.6% of the participants said they followed a TREX regimen, treating monthly until patients' eye were dry and then extending the treatment interval at subsequent visits. Recent studies have confirmed that the TREX regimen maintains or improves visual acuity in patients with AMD.[28,29] The number of examinations each year is lower in the TREX protocol than in the PRN protocol.[28] Studies indicate that the longer treatment intervals in the TREX protocol reduce patient anxiety.[28] Unlike American surgeons, our survey results demonstrate low usage of the TREX protocol for AMD in Turkey

Many surgeons in our study estimated that patients with AMD and DME require 6-7 injections per year. However, different results were obtained in real-life case studies in Turkey for AMD. The Bosphorus Retina Study Group stated in a real-life study conducted between 2013 and 2014 that the average annual number of injections was 4.1 for AMD.[30,31] This suggests that the annual number of injections estimated by surgeons is not consistent with real-life practice.

Other Practices

Most of the participants preferred not to inject both eyes in the same appointment (82.8%). However, this rate differed in North America, as 71.5% of ASRS members and 57% of Canadian retina specialists were reported to prefer bilateral injection on the same day.[8,21] Recent studies suggest that bilateral IVI does not increase the rate of adverse events compared to unilateral injections.[32,33] The latest EURETINA guideline recommends same-day bilateral injection using separate equipment for each eye (sequential injections).[6] The lower preference for same-day bilateral injections among ophthalmologists in Turkey may be related to the obligatory application of an initial 3 consecutive monthly injections of bevacizumab due to reimbursement regulations. In addition, dispensing multiple syringes from a single bevacizumab bottle may increase the risk of endophthalmitis.

Only 57.3% of the participants dilated the pupil before injection. This rate was much lower than Canadian retinal specialists (83%).[21] There is currently no consensus to widen pupil before IVI. The 2018 EURETINA guideline states that the decision for pupil dilation before IVI depends on the practitioner. This guideline recommends pupil dilation for physicians who are newly performing IVI to enable immediate examination of retinal and optic nerve perfusion. In contrast, retina specialists preferred to dilate the pupil more frequently than multispecialists in our survey.

Over two-thirds (67.2%) of the surgeons evaluated retinal and optic nerve perfusion immediately after the injection. This rate was higher than in the ASRS survey (56.0%). It is known that a short-term increase in intraocular pressure occurs after IVI.[34] Visual acuity test (finger counting or hand movement test), intraocular pressure measurement, or direct visualization of the optic nerve can be performed to assess ischemic optic nerve damage and check for perfusion. Although light perception indicates the presence of central retinal artery perfusion, the most reliable method of ensuring arterial perfusion is direct imaging.[34,35]

Almost half of the surgeons (47.6%) reported performing clinical examination on postoperative day 1, whereas 31.6% did not perform an examination. Most surgeons (81.1%) who did not prefer clinical examination verbally informed the patients about potential complications, and a smaller group (11.7%) said they used an information form. In recent years, telephone contact has been more commonly used for the follow-up and reporting of complications after IVI.[35] According to a United States expert panel from 2014, patients should be informed before discharge about the symptoms of possible post-injection complications such as endophthalmitis, retinal detachment, and intraocular hemorrhage, and 24-hour contact information should be provided to the patient.[14]

Conclusion

In this study, the response rate was 90% and our results showed that ophthalmologists in Turkey have varying preferences regarding IVI techniques. Furthermore, their practices differ in some ways from those of Canadian surgeons and ASRS members. In many countries, IVI is considered a surgical procedure and is performed in an operating room. In the United States, IVI is performed as an office-based procedure to reduce costs and accommodate the large number of patients. Office-based procedures are generally performed in the examination room without using a sterile drape, sterile gloves, sterile surgical clothes, or mask. The results of our survey are more similar to European surgeon practices.[36]

The results of this study are generally compatible with IVI guidelines, except for the high rate of postoperative antibiotic prescription and performing bilateral intravitreal injections on the same day.

IVI are generally administered only by retina specialists around the world, which differs from the practice of surgeons in Turkey. Current healthcare practices allow IVI to be performed not only by retina specialists, but also by other ophthalmologists. This may lead to differences in IVI practices of our country. These discrepancies should be considered when performing retrospective studies to examine the efficacy and safety of IVI. More evidence-based medicine is required to identify IVI techniques that combine safety and efficacy.

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Ethics

Ethics Committee Approval: The research protocol was initially submitted to the Institutional Ethics Committee and Review Board of the University of Kocaeli (registration number: KAEK 2020/219).

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Authorship Contributions

Surgical and Medical Practices: V.L.K., E.Ö.T., Concept: V.L.K., E.Ö.T., Design: V.L.K., E.Ö.T., Data Collection or Processing: V.L.K., E.Ö.T., Analysis or Interpretation: V.L.K., E.Ö.T., F.Ş., Literature Search: V.L.K., E.Ö.T., F.Ş., Writing: V.L.K., E.Ö.T., E.B.

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Review

Evolving Techniques and Indications of Descemet Membrane Endothelial Keratoplasty

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Abstract

Endothelial keratoplasty has replaced traditional penetrating keratoplasty for the treatment of corneal endothelial dysfunction. It offers faster, more predictable, stable visual recovery and low rejection rates while the surgery itself is less invasive. Descemet membrane endothelial keratoplasty (DMEK) is currently the gold standard for the treatment of Fuchs endothelial dystrophy, bullous keratopathy, and corneal edema after cataract surgery. Its favorable long-term outcomes are increasingly reported by large study groups. This review summarizes the current literature on new DMEK techniques, including size and shape modifications, new graft delivery techniques, and surgical pearls for challenging cases like eyes with glaucoma, glaucoma tubes, and failed penetrating keratoplasties.
Keywords: Corneal transplantation, DMEK, hemi-DMEK, quarter-DMEK, DMEK in complicated cases

Introduction

Endothelial keratoplasty (EK) offers great advantages for the treatment of patients with endothelial dysfunction. It can be performed for Fuchs endothelial dystrophy, pseudophakic or aphakic bullous keratopathy, posterior polymorphous dystrophy, iridocorneal endothelial syndrome, or failed penetrating keratoplasty (PK). It provides more rapid visual recovery, lower rejection rates, better refractive outcomes, and greater structural integrity than traditional PK.[1,2,3,4] Moreover, it provides a closed system that prevents PK's most dreadful complication: intraoperative suprachoroidal hemorrhage.[5,6]

Modern EK techniques include mainly Descemet stripping automated EK (DSAEK), Descemet membrane EK (DMEK), and pre-Descemet EK (PDEK).[7] In 2006, Melles[1] first introduced DMEK that selectively replaces the Descemet membrane (DM) and endothelium, resulting in an anatomically accurate procedure. DMEK poses some technical challenges, such as the need for careful graft preparation and meticulous graft orientation techniques, which result in a steep learning curve.[8] Despite this, DMEK has gained popularity in the last decade, and various modifications have been introduced that are gradually improving the surgical technique or donor preparation in challenging situations.[9]

As DMEK surgery became more popular, more information on its mid- and long-term results also became available. Recently, Birbal et al.[10] reported outcomes for a cohort of 500 DMEK eyes with a 5-year graft survival probability of 0.90 and 82% of eyes achieving a best-corrected visual acuity (BCVA) of 20/25. The endothelial loss was 37% in the first 6 months, 40% at 1 year, and 55% at 5 years. Allograft rejection rates were as low as 1.7-2.8% compared to 5% in DSAEK and 14% in PK.[10] Woo et al.[5] compared DMEK survival at 5 years (97.4%) with DSAEK (76.4%) and PK (54.6%). Even after 10 years, pioneering DMEK surgery cases maintained excellent visual acuities with low rejection rates, further supporting DMEK as the gold standard treatment for corneal endothelial diseases.[11]

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In this review, we will discuss new perspectives, various indications of DMEK, and elucidate the surgical steps of DMEK in challenging cases in light of recent scientific publications.

New Techniques of Graft Preparation and Insertion

Hemi-DMEK

DMEK provides fast visual recovery in the treatment of endothelial dysfunction. However, a donor corneal tissue with good endothelial cell density is required for the procedure.[12,13] Due to the worldwide shortage of suitable donor tissue for EK procedures, the idea of splitting the donor tissue into two or more grafts while keeping similar surgical success evolved (Table 1).[14] Lam et al.[15] were the first to describe a half-moon (semicircular) hemi-DMEK technique. In regular DMEK surgery, an 8.0 mm graft is sufficient to achieve corneal clarity. A hemi-DMEK graft utilizes a larger diameter graft, like 11-12 mm, and divides it into two. This way, the surface area of a hemi-DMEK graft and the number of transplanted corneal endothelial cells are comparable to regular DMEK. Although it is advantageous in terms of tissue efficiency, it presents some challenges in preparation and intraocular graft positioning. In this technique, after mounting the corneoscleral buttons endothelial side up, uveal remnants are removed and the DM is loosened with a knife in the central direction. Then the buttons are separated into two halves and the DM is removed from the posterior stroma as two half-moon shaped grafts without any trephination.[16] Except for the diameter of the graft, a routine DMEK surgery is performed. While orienting the graft, the widest diameter is aligned to the longest horizontal meridian so that the largest part of the graft covered the pupillary area (Figure 1a).

The healing period also has unique properties. Some denuded corneal stroma is left after surgery because of the mismatch between the descemetorhexis area and the graft. Clinically, the postoperative corneal edema resolves in 12 months and the denuded area is covered with endothelial cells. It is still not clear whether the posterior denuded stroma is covered via the migration of donor or recipient endothelial cells.[17] Müller et al.[18] showed that endothelial cell density was decreased by 59% in the first year and stayed stable for 3 years. Visual acuity was improved, and no complications were seen intraoperatively or postoperatively. The corneas were clear and presented with stable pachymetry in 1- and 3-year clinical follow-ups.[18,19] Hemi-DMEK led to similar outcomes to conventional DMEK; therefore, it may be a promising technique due to its potential to double the number of endothelial transplants from the same donor cornea.

Quarter-DMEK

The idea of stromal repopulation by host endothelial cells after a complete Descemet graft detachment or "descemetorhexis only" (descemetorhexis without EK) surgery helped to design a technique called "quarter-DMEK."[20,21] Since host cellular migration is slow in patients with descemetorhexis only, quarter-DMEK could be described as a hybrid technique that combines the advantage of DMEK (achieving rapid corneal clearance) with DM endothelial transfer (DMET) (stimulates peripheral host endothelium). One donor cornea can yield four endothelial grafts by this procedure. Zygoura et al.[20] evaluated the outcome of quarter-DMEK applied in 12 patients with central Fuchs endothelial dystrophy. As in hemi-DMEK, the corneoscleral buttons were mounted endothelial side up, uveal remnants were removed, and the DM was loosened with a knife in a central direction. However, the buttons were then separated into four equal parts and the DM was removed from the posterior stroma as four equal grafts. All DM grafts were rolled with the endothelium on the outside and kept in an organ culture medium until transplantation. After a 7-8 mm descemetorhexis under air, routine DMEK surgery was performed with the graft oriented centrally (Figure 1b). They followed the patients for 6 months and reported that all of the eyes reached a BCVA of ≥20/40 (≥0.5) and 11 of 12 eyes (92%) achieved a BCVA of ≥20/25 (≥0.8). The rebubbling rate was 33% within the first 2 months. However, they showed a quick drop in endothelial cell density in the first month. Extensive endothelial cell migration and error of measurement at the graft edges could be the reason for this drop. The authors also described a higher tendency for corneal clearance along the cut edges of the grafts compared to the "limbal" rounded edge, which may reflect different cell migration patterns in different graft areas. It was hypothesized

Table 1. Modifications of standard Descemet membrane endothelial keratoplasty (DMEK) surgery

Type of DMEK	Difference from standard DMEK	Advantage	Disadvantage	Defined by
Hemi-DMEK	Uses half of a larger sized graft	2 grafts from one donor	Challenges with graft preparation and positioning	Melles et al.[1]
Quarter-DMEK	Uses a quarter of a larger sized graft	4 grafts from one donor	Challenges with graft preparation and positioning	Melles et al.[1]
¾-DMEK	Uses three quarters of a larger sized graft	Can be used in the presence of tubes in the anterior chamber	Challenges with graft preparation and positioning	Melles et al.[1]
E-DMEK (EndoGlide)	The graft is prepared the same way but folded "endothelium-in"	Easier unfolding, especially in challenging cases	Requires special cartridge for delivery	Mehta et al.
H-DMEK (Hybrid)	Similar to E-DMEK, the graft is prepared with a thin stroma that acts like a carrier	Easier unfolding, especially in challenging cases	Requires 4.5 mm corneal incision, challenging graft preparation	Woo et al.[5]

DMEK: Descemet membrane endothelial keratoplasty

that the repopulating cells at the rounded graft edges were probably host endothelial cells.

Birbal et al.[22] reported the clinical outcomes of 19 patients with central Fuchs endothelial dystrophy. These patients showed good visual outcomes, and the visual acuities were stable for 2 years postoperatively. Eight of 19 eyes (42%) required rebubbling due to significant graft detachment. Good outcomes of quarter-DMEK were also reported by Oganesyan et al.[23] Quarter-DMEK may be comparable to conventional DMEK in terms of visual acuity outcomes and increase the availability of endothelial grafts.[22]

E-DMEK

Despite the many advantages of DMEK, technical difficulties in graft insertion and unfolding led to a new surgical technique called EndoGlide-DMEK (E-DMEK).[24,25] This technique features several differences in graft preparation and insertion. In this technique, the graft is prepared in a standard manner,

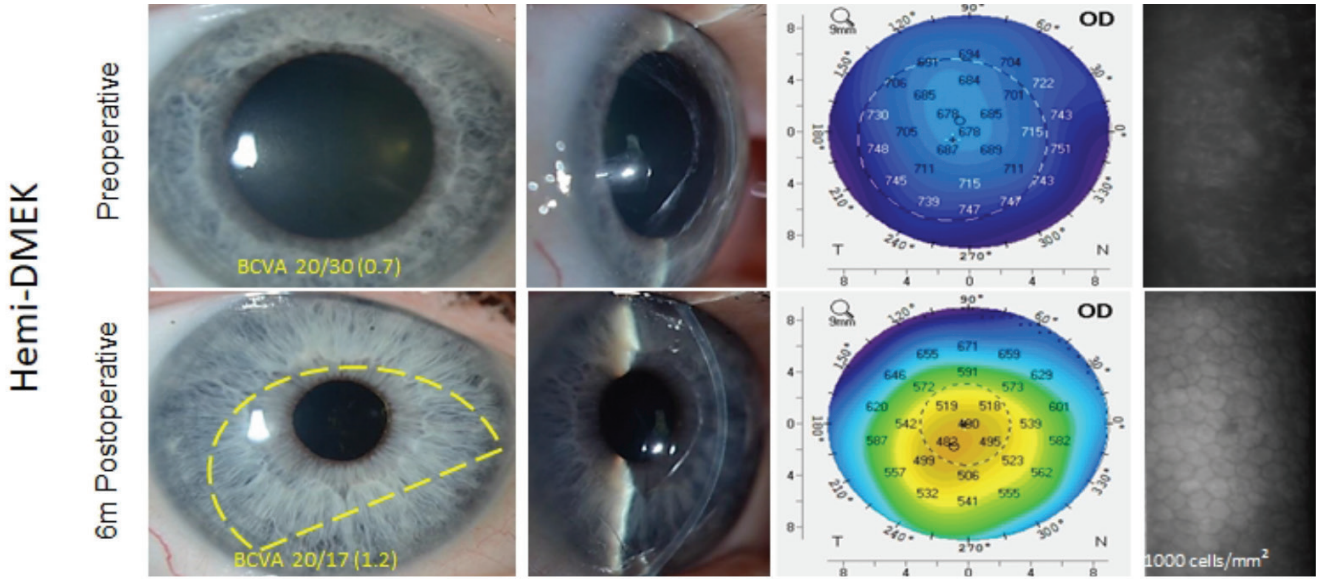

Figure 1a. Slit-lamp images, pachymetry maps, and specular microscopy images before and after hemi-DMEK (Descemet membrane endothelial keratoplasty). Images obtained preoperatively and at 6 months postoperatively are shown. The dashed yellow lines show the position of the hemi-DMEK grafts

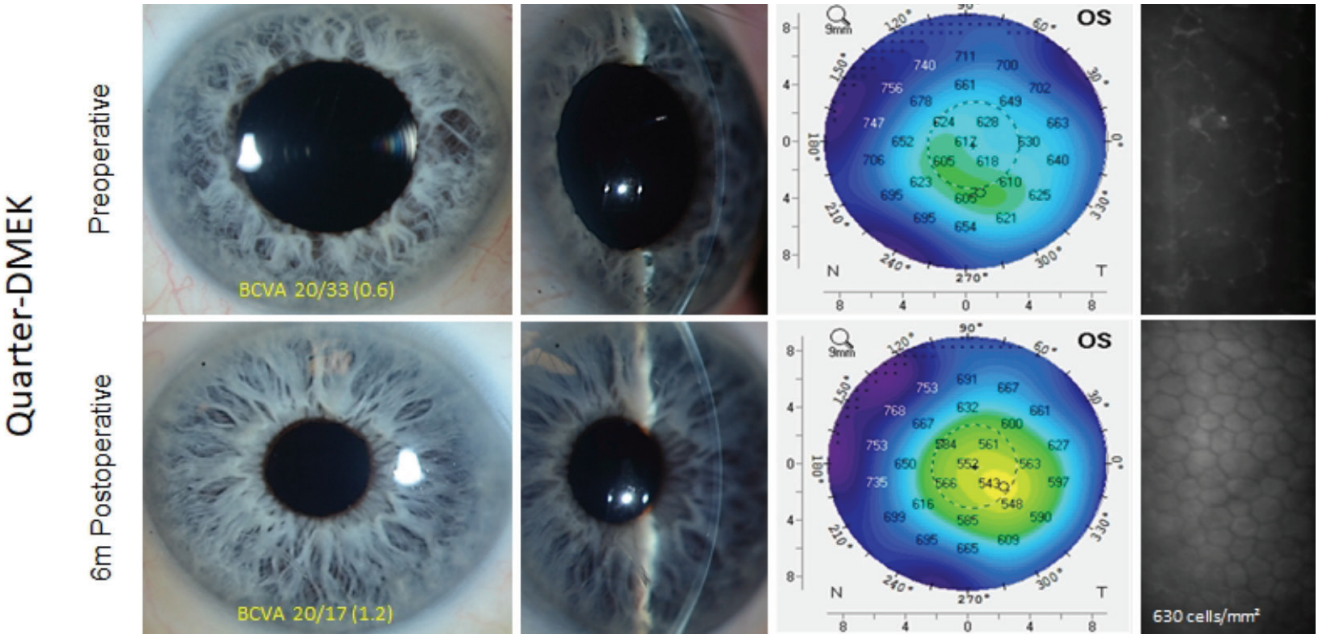

Figure 1b. Slit-lamp images, pachymetry maps, and specular microscopy images before and after quarter-DMEK (Descemet membrane endothelial keratoplasty). Images obtained preoperatively and at 6 months postoperatively are shown

but it is tri-folded in an endothelium-in fashion using a forceps rather than the natural endothelium-out orientation. It is then loaded in a cartridge and inserted through a corneal incision (Figure 2a-f). Rather than being injected, it is pulled into the anterior chamber (AC) by grasping with a forceps from the opposing corneal incision. Once an endothelium-in graft enters the AC, it unfolds easily with fewer maneuvers. Keeping the AC shallow is critical for this technique as the graft would scroll back to the endothelium-out orientation in a deep AC. E-DMEK is especially designed for challenging cases like those with abnormal anterior segment anatomy, gross peripheral anterior synechia, drainage devices, and filtering blebs. It is similar to DSAEK graft insertion, so it may be technically easier for surgeons who are accustomed to DSAEK surgery during the transition to DMEK surgery.

Tan et al.[24] showed both *ex vivo* and clinical results of E-DMEK. In an *ex vivo* study, DMEK grafts were stained with calcein acetoxymethyl, tri-folded in the endothelium-in fashion, and placed into the EndoGlide. Then they were pulled through and unfolded in imaging dishes simulating a real surgery. Mean endothelial cell loss was 15.2%±5.4% in 9 human corneas. In a clinical series, endothelial cell loss was 33.6% (range 7.5%-80.4%) among 69 eyes with at least 6 months follow-up. Rebubbling and primary graft failure rates were 11.6% and 1.5%, respectively. In conclusion, they suggested E-DMEK was a safe and promising alternative to standard DMEK due to its good clinical outcomes.

H-DMEK

Woo et al.[26] developed a new technique called hybrid DMEK (H-DMEK). They used the DSAEK pull-through donor inserter and donor stroma as a carrier while performing DMEK. In this technique, pre-cut DSAEK donor tissue from the eye bank that was approximately 150 µm in thickness was utilized. During graft preparation, a Tan DMEK stripper was used for lamellar dissection of the DM from the underlying stroma, but the DM was not completely removed from the stroma. The DMEK graft and stromal carrier were loaded into the EndoGlide inserter device in a double-coil endothelium-in configuration. The glide was inverted so that the graft would be placed in an endothelium-down fashion. It was inserted through a scleral tunnel into the AC. The DMEK graft edge was pulled with forceps from the nasal paracentesis incision into the AC, completely detaching from the donor stroma and leaving the stroma behind.

H-DMEK is similar to E-DMEK as the graft is placed in an endothelium-in fashion. The difference is the presence of a thin stromal component during graft preparation. The thin stroma acts like a carrier of the DMEK graft. This difference makes it easier to handle and fold the graft while placing it in the basin. The need for a 4.5 mm incision to deliver the graft into the AC and more complicated steps in graft preparation are potential disadvantages.

Eighty-five eyes of 79 patients with Fuchs endothelial dystrophy or bullous keratopathy were involved in the clinical study. Of the eyes without pre-existing ocular pathology, 44.7% and 57.1% showed a BCVA of 20/25 or better at 6 and 12 months postoperatively, respectively. Endothelial cell loss was 32.2% at 6 months. The authors suggested that this technique might be useful in complicated cases.[26]

DMEK in Vitrectomized Eyes

Although DMEK surgery is gaining popularity for endothelial dysfunction, vitrectomized eyes undergoing DMEK still pose a challenge. Due to the lack of posterior support of the vitreous, the AC is mostly deep, and graft unfolding can be difficult. Excessive manipulation of the donor tissue while

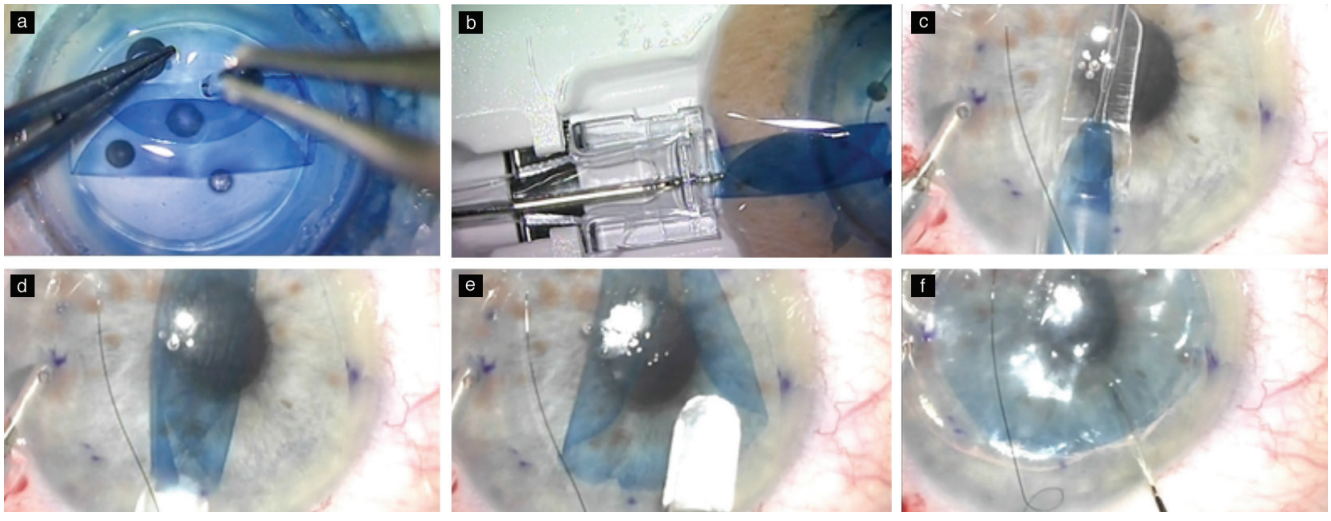

Figure 2. Steps of the Endoglide Descemet membrane endothelial keratoplasty (E-DMEK) procedure. a) Formation of tri-fold using the no endothelium touch technique. b) Loading the DMEK graft into the DMEK Endoglide using 23G straight forceps. c) Inserting the DMEK Endoglide into the anterior chamber (AC) through a 2.6 mm clear corneal incision. Pre-placed tissue will be used. The double-port 23G AC maintainer (ASICO) ensures the AC can be deepened as needed; d) As the graft is pulled in, it will spontaneously unfold endothelium side down in a deep AC because it naturally wants to scroll endothelium-out. e) As the graft opens, the cornea can be gently tapped to enhance the opening of the posterior leaves of the graft if needed. f) Once the graft has opened, the bubble is enlarged with more gas

unfolding may lead to graft failure.[27] Additionally, the injected air bubble used to tamponade the graft toward the stroma may be less effective due to a fluctuating iris-lens diaphragm.[28] As injected air tends to move posteriorly, recurrent globe collapse is a significant problem. Furthermore, the DMEK graft may dislocate into the vitreous cavity.[29,30] However, the challenges should not discourage surgeons from proceeding with DMEK, as some surgical modifications have been described for these eyes to improve the outcome. The main philosophy for DMEK graft unfolding relies on a shallow and stable AC. Moreover, donor age is important in these eyes. Age-dependent decrease in elastin levels, change in collagen composition, and increase in nonenzymatic glycosylation cause an increase in DM rigidity.[31] Therefore, older donor grafts unfold more easily and are more appropriate for these eyes.

Yoeruek et al.[32] tried a new maneuver for unfolding the graft in high myopic vitrectomized eyes. After inserting the DMEK graft, they performed equatorial digital indentation and corneal tapping for unfolding. During this maneuver, they avoided using air injection above or below the graft.[32] After centration and unfolding, air was injected below the graft for apposition against the posterior stroma. The AC was filled totally with air. They first published their results in a case series with 6 Fuchs endothelial dystrophy and 4 bullous keratopathy eyes.[32] Three of 10 eyes had graft detachment and required rebubbling, but they showed no graft failure during the follow-up period. Although this technique worked quite well for Fuchs endothelial dystrophy and bullous keratopathy eyes, they had difficulties in vitrectomized eyes. Their retrospective clinical study of 20 vitrectomized eyes that underwent DMEK surgery showed that 13 of them had significant intraoperative complications.[29] Intraoperative corrective measures were quite difficult in a few cases, and iatrogenic intraocular damage was encountered in some of them. Unfolding the graft was quite difficult. Eleven eyes had graft dislocation and two had iatrogenic primary graft failure.

Sorkin et al.[27] performed DMEK in vitrectomized eyes using posterior pars plana infusion. In this technique, after DMEK grafts were prepared with an "F" marking,[33] a 23-gauge trocar was inserted at the inferotemporal quadrant, 3.0 mm from the limbus. Infusion pressure was set between 5-26 mmHg depending on the stability of the AC. After descemetorhexis, a glass pipette or intraocular lens (IOL) injector was used to deliver the graft. The pars plana infusion was turned on and off to maintain optimal eye pressure and a shallow AC. This facilitated graft unfolding and positioning. Yoeruek's tapping technique (corneal tapping with external digital pressure application) was used during the unfolding.[32] After the graft was unrolled and positioned, the posterior infusion was turned off and the AC was filled with air. The trocar was extracted from the eye, and corneal incisions and any leaky sclerotomy sites were sutured. The authors performed this technique on 12 vitrectomized eyes and had one graft detachment, which required rebubbling.[27] No graft failure was experienced during the follow-up period. Another study by the same group evaluated the long-term outcomes up to 2 years.[28] They reported 5 of 15 eyes had retinal complications, including retinal detachment, retinoschisis, and cystoid macular edema. Although using posterior pars plana infusion could potentially reduce intraoperative and postoperative complications in vitrectomized eyes, the authors also cautioned that using an infusion could increase retinal complication risks.

Some of the vitrectomized eyes may also have sutured IOLs. In these patients, several maneuvers may be required to unfold the DMEK graft.[32,34] These eyes are monocameral, and this situation may lead the graft to migrate to the posterior cavity. Additionally, the globe is prone to collapse, which makes graft unfolding quite difficult.[27,29,35] Hayashi et al.[36] described a modified technique called the "double-bubble technique in DMEK for vitrectomized eyes." It was the modification of a small air bubble-assisted unrolling maneuver (Dapena maneuver).[37] In this technique, after inserting the DMEK graft, one small air bubble was placed over the graft for unfolding, and the other large bubble was injected beneath the graft for fixation. If peripheral edges were not attached, they applied bubble-bumping maneuvers to unfold the edges. Despite the unfolding time being relatively long, all of the surgeries were successful. In the follow-up period, one eye required rebubbling.

Although using 23-gauge infusion helps to stabilize the globe, unfolding the donor graft is still a problem due to its strong recurling tendency. The equatorial digital indentation and corneal tapping techniques are helpful mainly in partially vitrectomized eyes. Eyes with completely removed vitreous still pose several challenges. In the normal eye, the vitreous applies a counter-pressure and limits the motion of the iris-lens diaphragm. As iris-lens diaphragm stability is necessary for DMEK surgery, Yoeruek et al.[38] described a new technique using a temporary diaphragm for easier graft unfolding. Following descemetorhexis, a hydrophilic methacrylate sheet measuring 12.8 mm with holes in the periphery was implanted into the AC to create a double AC. A DMEK graft was injected into the AC over the hydrophilic methacrylate sheet and unfolded. Under continuous air injection through a 30-gauge cannula, the hydrophilic methacrylate sheet was removed. Sulfur hexafluoride gas at a concentration of 20% was preferred for longer tamponade. Seven eyes of 7 patients who underwent DMEK by this method showed no complications intraoperatively or postoperatively. Karadağ et al.[39] tried using the posterior corneal stroma instead of a hydrophilic methacrylate sheet for the same purpose.

Saad et al.[40] described the C-press technique in 11 eyes of 11 patients who underwent DMEK. They reported that their experience with pars plana infusion and double-bubble technique in vitrectomized eyes were not reproducible in all cases; therefore, another new approach was required. Following descemetorhexis and DMEK graft insertion into the AC, correct graft orientation was ascertained by intraoperative optic coherence tomography. A cannula was then inserted inside the graft (Descemet side) and moved right and left to open it by irrigating with balanced salt solution. At the same time, a second cannula held in the other hand pressed externally on the central cornea. Shallowing the

AC with this pressure helped the graft to remain open. Then the first cannula was removed and 20% SF6 gas was injected. No intraoperative complications were experienced; however, 2 cases needed rebubbling for partial graft detachment. Lower unfolding time and complication rates were advantages of this technique.

These evolving techniques show that we do not have a standard, straightforward approach suitable for all vitrectomized eyes. It is advisable to get familiar with different methods so they can be readily applied when needed.

DMEK After Failed PK

After PK, secondary graft failure and late endothelial decompensation are likely to increase with the aging graft. In the past, the only options were repeating PK and implanting keratoprosthesis for managing failed PK.[41,42] Recently, EK has allowed restoration of endothelial function in failed PK grafts and decreased the need for a full-thickness graft. This reduces the risk of rejection and refractive changes and avoids the complications associated with "open-sky" surgery.[43,44,45,46] DMEK has acceptable outcomes in patients with failed PK. However, recent literature shows that it is associated with a high postoperative graft detachment rate, ranging between 26-100%.[45,46,47,48] Nevertheless, since the DMEK graft is thin and flexible, a better apposition could be achieved with DMEK-grafts compared to the "stiffer" DSAEK graft. Also, DMEK grafts should better fit the irregular posterior surface and PK wound and could cover more surface area.[49] Lavy et al.[46] evaluated the clinical outcomes of 11 DMEK surgeries for secondary PK failure. They described some surgical modifications and specific manipulations while performing DMEK in these patients. A corneal incision 3.0 mm wide was made in the host peripheral corneal rim without penetrating PK graft to avoid potential host-graft wound dehiscence. Descemetorhexis was started in the central area of the PK graft and was enlarged in a curvilinear pattern, like capsulorhexis, under air using a reverse Sinskey hook. The remaining part of the surgery was routine DMEK surgery (Figure 3a). The authors mentioned that circular scarring at the PK graft-host junction sometimes blurred the edges of the DMEK graft, and visualization was not always possible. Four of 11 eyes required rebubbling, and 7 of 11 eyes were clear at their last visit. Additionally, they showed that graft attachment could be achieved in eyes with failed PK grafts through interface scarring that was detected in histopathological specimens after the patient's death. The specimens with areas of detachment clinically showed a layer of newly formed fibrotic tissue extending from the PK wound area to the central and peripheral graft areas. Although the scar tissue formation may be a normal wound-healing process, the fibrotic response was more aggressive than in primary DMEK eyes, resulting in diffuse interface haze. Overall, three important points were emphasized: there may be delayed DMEK graft detachment, which may need rebubbling. Second, oversized DMEK grafts were more prone to detach. Third, pressurizing the eye adequately at the end of the surgery is critical. Otherwise, hypotony could lead to detachment of the graft.

Pasari et al.[42] reviewed 93 DMEK procedures performed in 84 eyes of 77 patients with failed PK. Stripping was done within the edge of the PK wound and avoiding the graft-host junction. Failed PK graft diameter, recipient horizontal corneal white-to-white diameter, and AC depth were evaluated intraoperatively to select the donor graft diameter. The graft was oversized, same-sized, or undersized. The 4-year graft survival rate of these patients was found to be 76%. They also showed that previous glaucoma surgery was the only risk factor for graft failure. Additionally, rebubbling rates changed depending on graft size. The rates were 53% when the DMEK graft diameter was oversized, 27% when same-sized, and 33% when undersized.

DMEK surgery under a failed PK may be challenging due to DM tags or stromal fibers caused by traumatic DM stripping. The maneuvers may affect DM graft adhesion and increase graft detachment risk. Some authors claimed DMEK could be done without removing the DM of the failed graft.[50] Alio Del Barrio et al.[51] performed non-Descemet stripping DMEK (NS-DMEK) and recommended either matched or undersized 0.25-0.50 mm grafts to avoid the PK donor-host junction. They also used SF6 tamponade to decrease the risk of graft detachment. All eight patients in the study achieved full PK transparency within two weeks. One patient required rebubbling, and one required PK re-suturing due to host-donor junction dehiscence. With this technique, DMEK surgery in failed PK patients was simplified and intraoperative complications were avoided.

Recently, femtosecond laser-assisted descemetorhexis has been recommended in patients with failed PK who do not have stromal scarring and have normal AC anatomy.[27,52,53] Sorkin et al.[54] performed femtosecond laser-assisted DMEK for failed PK in 8 patients. In this technique, descemetorhexis was planned 0.25 mm smaller than the PK graft to prevent graft dehiscence and incomplete incision.[55] The Intralase iFS femtosecond laser platform enabled a precisely located deep vertical ring cut.[53] Then, the DM was removed from the stroma using a reverse Sinskey hook. Deep dissection into the stroma was avoided. The remainder of the surgery was similar to standard DMEK. In this study, no cases required re-bubbling, and only one eye (12.5%) had a small graft detachment, which did not affect corneal clarity and vision. The same group compared manual (M) and femtosecond laser-assisted (F) DMEK for failed PK.[56] They showed that F-DMEK was effective and safe in failed PK patients, and rebubbling rates were lower than for M-DMEK. Primary failure was lower in F-DMEK; however, there was no significant difference compared to M-DMEK. Visual outcomes and postoperative cell densities were similar between the groups. Although the precise reason for the reduced detachment rate is unclear, they suggested that F-DMEK could lead to complete removal of the host's DM with less remnant Descemet tags and islands. In addition, the host DM peripheral to the descemetorhexis remains undamaged. While

F-DMEK looks promising, the data is currently limited to 10 patients.

DMEK in Eyes with Prior Glaucoma Surgery

Glaucoma predisposes a high risk for graft failure in either PK, DSAEK, or DMEK due to both surgical and immunological challenges. Technically it is more challenging to position a DMEK graft in the setting of previous glaucoma surgery because these eyes usually have comorbidities like synechia, aphakia, tubes, or pupillary abnormalities that need several surgeries.[57] It is harder to keep the air in the AC. These technical difficulties also result in prolonged surgical time and extra maneuvers, resulting in increased endothelial loss which leads to secondary graft failure. Lysis of anterior synechia and trimming the tube are some of the additional techniques used in these complex eyes. Immunologically, eyes also lose their immune privilege after glaucoma surgery because it alters the aqueous composition.[58]

Arevena et al.[57] reported early outcomes of DMEK in eyes with previous trabeculectomy or a drainage device. Surprisingly, they did not encounter secondary failures in the first postoperative year. After Birbal et al.[59] described the decrease of graft survival from 89% at 1 year to 67% at 2 years, similar studies on this subject emerged. Pasari et al.[42] showed graft survival probability gradually decreased from 78% at 1 year to 39% at 3 years. Sorkin et al.[60] investigated graft survival at 4 years based on previous studies showing a possible downward trend of graft survival over time. They found a survival drop over the third and fourth postoperative years, with cumulative 2-, 3-, and 4-year DMEK survival probability rates of 60%, 43%, and 27%, respectively.[28,57,61] Although eyes without glaucoma drainage devices (GDD) have better graft survival than eyes with GDD, they are more prone to graft failure than the control group, suggesting that glaucoma itself affects the long-term survival of DMEK grafts. Beyond graft failure, they found a significantly high rejection rate compared to the control group (19.6% vs. 2.3%, p=0.01).[60] The baseline high inflammatory status of eyes with previous glaucoma surgery due to disruption of the blood-aqueous barrier may be one of the reasons leading to this difference.

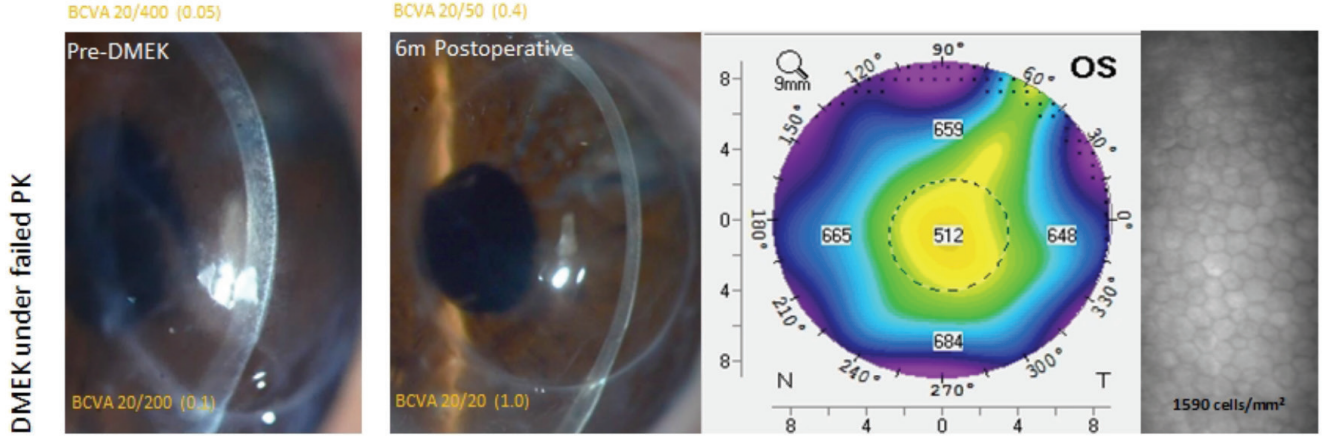

Figure 3a. Slit-lamp images before and after Descemet membrane endothelial keratoplasty, postoperative pachymetry map and specular microscopy image of an eye with a failed penetrating keratoplasty graft

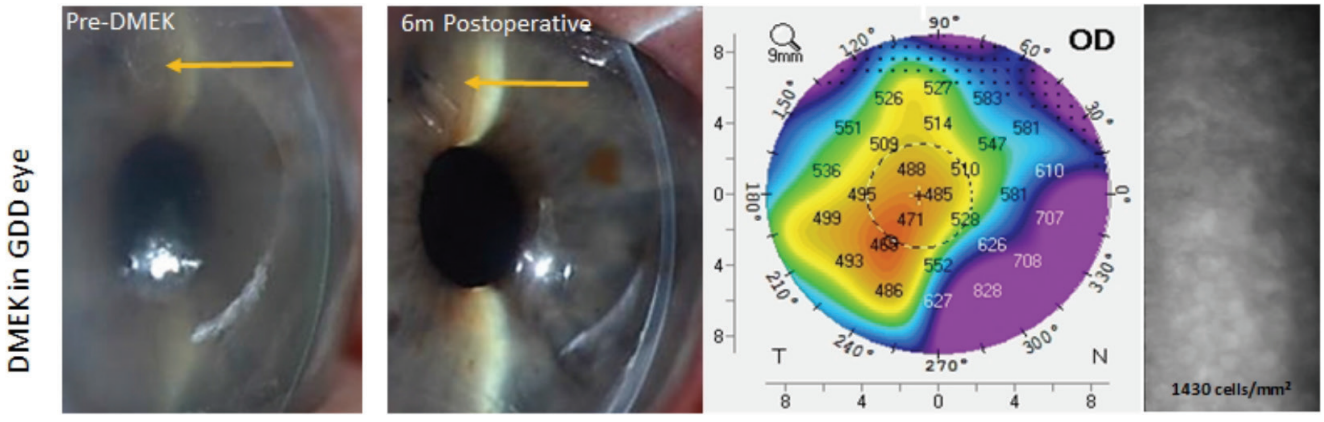

Figure 3b. Slit-lamp images before and after Descemet membrane endothelial keratoplasty, postoperative pachymetry map and specular microscopy image of an eye with a glaucoma drainage device superotemporally (orange arrows)

Endothelial cell loss is another important consideration in patients with prior glaucoma surgery. In addition to rejection-related cell loss, alterations of the aqueous environment may also contribute to ongoing cell loss in these eyes.[58] Aravena et al.[57] showed that endothelial cell loss was higher in the surgery group (44.6%±17.8%) than in the medically treated group (29.9%±12.0%) and the control group (32.7%±11.3%, p=0.001). Some potential factors such as inflammation, oxidative stress, and increased plasma proteins are included in endothelial apoptosis after glaucoma surgery.[62,63] Sorkin et al.[60] touched on another point about the trend of endothelial cell loss. Endothelial cell loss was highest in the first 6 postoperative months (about 44%), which was not different from other DMEK cases. After that, endothelial cell loss was higher in patients with glaucoma, about 12%-22%. The significant difference in endothelial cell loss continued throughout follow-up.

Apart from glaucoma surgery itself, the tube's position is quite important for graft survival and endothelial cell loss. Intermittent tube-uveal contact may result in corneal endothelial damage. Therefore, some technical modifications are recommended for GDD patients. The area of the GDD should be avoided while creating a 3.0 mm clear corneal incision at 12 o'clock position, and the superior conjunctiva was avoided for future glaucoma surgery. During graft insertion, contact between graft and tube should be prevented. The tube could be trimmed for better graft positioning. Additionally, Descemet graft unfolding should be performed over the tube, not over the iris (Figure 3b). This could be difficult in some cases; therefore, a modified "three-quarter DMEK technique" (3/4-DMEK) was designed and evaluated in three patients by Oganesyan et al.[64] All of the patients had previous Ahmed valve implantation and were pseudophakic. During graft preparation, the DM was stripped from the posterior stroma and put over a soft contact lens. Two perpendicular cuts with a keratome (MANI Inc, Tokyo, Japan) helped separate a quarter of the graft and create a 3/4-DMEK graft. In the host cornea, an 11-12 mm diameter descemetorhexis was performed, sparing the area under the GDD. While unfolding the graft, the missing 1/4-graft area was adjusted to the region of the tube, and the 3/4-DMEK graft was positioned centrally. The AC was filled 100% with air. All of the DMEK surgeries were uneventful, and grafts were stable up to postoperative 24 months. Endothelial cell loss was similar to previous studies (range 49%-64%) within the first year, as with conventional DMEK.[59,60,65] The absence of the graft under the tube prevented direct tube contact with the graft and may be beneficial for the graft's postoperative survival. Possible cell migration from the graft to the recipient stroma was minimized by leaving the host DM intact under the tube. Despite the promising results of this technique, they suggested the need for long-term follow-ups and larger case series.

The mechanical effect of the GDD, active filtration of air through filtering ostium or tube, and posterior escape of air through a large iridectomy are some of the factors blamed for high graft detachment and rebubbling rates (22.0%-23.5%).[57,59] Contrary to this popular belief, Sorkin et al.[60] did not find increased detachment and rebubble rates in these patients. They also stated that preoperative visual potential estimation of glaucomatous eyes was a challenge due to unknown adequate IOP control and prolonged standing corneal edema. Despite this challenge, 85% of patients had improved visual acuity, and none had a primary failure.

Although DMEK in patients with previous glaucoma surgery seems to have challenges, it should be performed by considering some critical steps and modifications. Graft survival is reduced not only in DMEK but in all other keratoplasty techniques. Therefore, these patients should be given the opportunity to undergo DMEK despite the risk of future re-grafting.

DMEK and Cataract Surgery

Although triple DMEK (simultaneous DMEK, cataract surgery, and IOL implantation) is often preferred in phakic patients, this procedure may lead to a refractive shift that is difficult to predict. Some recent studies have shown that a small hyperopic shift could be observed after DMEK.[66,67,68,69] Hence during IOL selection, these studies suggested a -0.50 to -1.0 D refractive target to provide emmetropia or slight myopia after DMEK. However, some individual cases showed large hyperopic and myopic shifts, particularly in advanced Fuchs endothelial dystrophy cases due to anterior curvature changes.[66] Apart from accurate IOL selection, endothelial cell density loss and DMEK graft detachment rate are other areas of concern in these cases.[70,71,72,73]

In recent studies, several approaches have been performed during triple DMEK. Laaser et al.[71] targeted -0.75 D refractive power for IOL selection. They did not find any adverse effect on endothelial cell function or graft adhesion due to the triple procedure. Schoenberg et al.[73] targeted a -0.50 D shift from IOL calculation due to +0.50 D hyperopic shift expectation after DMEK. The spherical equivalent median value was 0.0 D (range -0.25 to 0.25) postoperatively, and no astigmatic change was seen.

The average endothelial cell loss after 6 months was 26% to 40% in recent studies.[70,71,72] The difference was not significant between pseudophakic and triple DMEK eyes.[70,74] Better visual outcomes were seen in triple DMEK eyes. Although visual outcomes are promising, overhydration of the cornea and viscoelastic use during cataract surgery may interfere with graft attachment in triple DMEK.[70] Eliminating the use of viscoelastic during graft insertion is quite important. Another critical point is that the second eye's refractive shift may follow that of the first eye. Therefore, the first eye could be a reference point for the second eye's future surgery.[75]

The need for toric IOLs to neutralize corneal astigmatism could be a major concern in a triple procedure. Yokogawa et al.[76] evaluated 15 eyes of 10 patients with cataract extraction, toric IOL placement, and DMEK surgery for Fuchs corneal dystrophy. Keratoscopy measurements were obtained from Scheimpflug corneal imaging, and an online toric calculator was used to determine the cylinder power of the toric IOLs. The spherical

target varied between -0.50 and -1.00 D due to the mild mean hyperopic shift seen with DMEK surgery. Postoperatively, 61.5% of eyes gained uncorrected distance visual acuity better than 20/40 and mean best spectacle-corrected distance visual acuity (logMAR) increased from 0.21±0.15 to 0.08±0.12 ($p<0.01$). The refractive astigmatism was also significantly decreased from 2.23±1.10 D (range 0.75-4.25 D) to 0.87±0.75 D (range 0.00-3.00 D) postoperatively ($p<0.01$). In one eye, no improvement was observed due to rotational misalignment by 43 degrees. The prediction error of astigmatism at the corneal plane was 0.77±0.54 D (range 0.10-1.77 D). Four eyes with preoperative with-the-rule corneal astigmatism had postoperative against-the-rule refractive astigmatism. The authors emphasized the importance of rechecking the IOL alignment after DMEK graft placement to avoid clockwise rotation of the IOL.

In the absence of cataract, phacoemulsification may be delayed as a future option after DMEK.[77] However, if phacoemulsification after DMEK is required, its potential impact on graft function should be taken into account. Since DMEK grafts tend to adhere stronger to the recipient posterior stroma than "virgin" DM, manipulations during cataract surgery may not create a potential risk for DMEK graft dislocation.[78] Musa et al.[79] reviewed phacoemulsification outcomes after DMEK and did not show any graft dislocation or detachment in those eyes. The refractive outcome was mostly within ±0.50 D.[72,79,80] However, donor endothelial cell density decreased significantly in eyes with previous DMEK.[79] This study included high-risk eyes (e.g., multiple intraocular surgeries, advanced glaucoma). It was mentioned that DMEK graft endothelium resistance to trauma may not be as good as "virgin" endothelium.

A hyperopic shift due to DMEK is an expected result. Some specific adjustments may be required in the triple procedure. However, cataract surgery after DMEK is more predictable. Therefore, no particular nomograms are obligatory in this situation.

DMEK in Complex Anterior Segment Changes

Other than the standard indication of Fuchs endothelial dystrophy, DMEK can serve as a routine procedure in endothelial decompensation even in complex preoperative situations such as the presence of anterior synechia of the iris, large iris defects, iridocorneal-endothelial (ICE) syndrome, aphakia, subluxated posterior chamber IOL, AC IOL, phakic IOL, and acute corneal hydrops. The main objective in these situations is to reconstruct the iris and iris-lens diaphragm intraoperatively or preoperatively while treating the patients with DMEK. The graft size should be selected according to available space, e.g., eyes with anterior synechia may require a smaller graft diameter.[81]

Weller et al.[82] presented 24 complex eyes with endothelial decompensation. They performed DMEK in eyes with ICE syndrome, aphakia, subluxated posterior chamber (PC) IOL, and AC IOL. The eyes with ICE syndrome (3 eyes) had anterior synechia that interfered with the opening of the chamber angle, corectopia, and a shallow AC. Synechiolysis was required in two eyes with DMEK, and rebubbling was performed in two eyes. However, no graft failure developed in follow-up visits. In eyes with aphakia, stabilizing the iris-lens diaphragm by implanting a scleral sutured PC IOL was performed as the initial step. In eyes with IOL subluxation or AC IOLs, IOL explantation and implantation of a scleral sutured PC IOL or scleral suture-fixation of the existing IOL were applied. Further surgical procedures such as pupilloplasty or anterior vitrectomy were performed if necessary. DMEK was performed after a mean of 5±4 months. Four eyes required rebubbling but no graft failure was observed during postoperative examinations. The authors emphasized the importance of graft diameter in ICE syndrome depending on the extent of the synechia. Free retrocorneal surface is significant in the determination of graft diameter. Additionally, the authors suggested a two-step procedure for eyes with IOL problems to prevent graft dislocation in a destabilized AC.

In another study, eight eyes with either ICE (4 eyes) or posterior polymorphous corneal dystrophy (4 eyes) underwent DMEK.[83] Three of the eyes had goniosynechiolysis and one eye had iridoplasty with DMEK. BCVA increased in all of the eyes. No graft failure or graft rejection was observed during follow-up visits. DMEK only replaces the diseased central endothelium; however, it does not heal ICE syndrome or posterior polymorphous dystrophy. The pathological endothelial cells persist at the peripheral cornea after surgery. These cells may induce corneal decompensation in the future, although the graft border could be a mechanical barrier delaying migration from the periphery to the central cornea. Treatment of glaucoma in ICE syndrome may be challenging. Hohberger et al.[84] presented a case with micro bypass Xen Gel stent after DMEK. They concluded that microinvasive surgery after DMEK has less adverse effects and provides good IOP regulation.

Conclusion

Data from the Eye Bank Association of America shows that between 2004 and 2014, the rate of PK decreased to half (from 95% to 42%) and was replaced by lamellar keratoplasty techniques (5% to 55%).[85] The volume of EK procedures has been doubling every year since 2011.[85]

Fuchs endothelial dystrophy (47.7%) is the most common cause of endothelial failure, followed by corneal edema after cataract surgery (17.8%) that needs EK. DMEK offers significantly better graft survival of 98.7% in these eyes than DSAEK (78.4%) and PK (73.5%) in Fuchs endothelial dystrophy. PK results in eight-fold higher rejection rates compared to DMEK.[5]

For challenging cases like eyes with glaucoma, failed grafts, and vitrectomized eyes, DMEK still offers quick visual recovery, better graft survival, and lower rejection rates compared to traditional PK.

Although it has a learning curve, the literature on new techniques of DMEK is expanding tremendously, making it possible to perform DMEK in a variety of challenging situations.

This review summarized different approaches such as using different graft sizes (hemi-DMEK, quarter-DMEK), different graft folding techniques (endothelium-in delivery methods), new unfolding techniques (using a diaphragm in vitrectomized eyes), new positioning techniques (3/4-DMEK in eyes with glaucoma shunts), and double layers of DM in cases of failed PK. Hopefully, more standardized innovative modifications will enable cornea surgeons to treat endothelial dysfunction in almost any situation with confidence and great success.

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Case Report

Palytoxin-Related Keratoconjunctivitis Assessed by High-Resolution Anterior Segment Optical Coherence Tomography

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Abstract

Palytoxin (PTX) is produced by corals such as zoanthid corals. Here we present a case of bilateral PTX-induced keratoconjunctivitis. A 63-year-old man presented to the emergency department with symptoms of red eye, purulent discharge, and foreign body sensation in both eyes. On slit lamp examination, epithelial defects in both eyes with a ring-shaped corneal stromal infiltrate in the right eye and a marginal stromal infiltrate in the left eye were noted. High-resolution anterior segment optical coherence tomography (HR-AS-OCT) showed stromal hyperreflectivity and Descemet folds. Bacterial, fungal, and amoebic cultures were taken. Empirical treatment with topical dexamethasone as well as antibiotics and systemic doxycycline was started. The next day the patient stated that he had been handling zoanthid coral without gloves and had rubbed his eyes afterward. Bilateral PTX-induced keratoconjunctivitis was diagnosed. His eyes were irrigated abundantly with saline solution, and umbilical cord serum eye drops were added to the treatment. Treatment was tapered according to improvement of the corneal infiltrates and epithelial defects. After four months, the stromal infiltrates were resolved but corneal scars persisted in both eyes. HR-AS-OCT showed anterior stromal hyperreflectivity corresponding to corneal leucomas. PTX can cause ocular adverse effects such as keratolysis and corneal inflammation, and in some cases can lead to corneal perforation. It can also produce systemic adverse effects, hence the importance of the preventive measures when handling corals that can produce this toxin.
Keywords: Palytoxin, zoanthid, toxic keratoconjunctivitis, umbilical cord serum eye drops, high-resolution anterior segment optical coherence tomography

Introduction

Palytoxin (PTX) is a deadly marine toxin produced by many species of *Palythoa* coral. This coral, in the order Zoantharia, is commonly found in domestic aquariums due to its fast growth and low maintenance requirements.[1]

Ocular exposure to PTX can lead to surface toxicity. A wide variety of presentations have been reported in literature, from superficial punctate epitheliopathy to corneal perforation as a result of corneal melt. This exposure can be from direct contact with the coral, contact with contaminated water, or by rubbing the eyes with a toxin-contaminated hand after handling zoanthid coral. Management is based on recommendations according to the severity of the case; a surgical intervention such as a corneal transplant may be necessary in cases of ulceration that result in corneal perforation.[2,3,4,5,6,7]

We report a case of bilateral PTX-induced chemical keratoconjunctivitis, assessed by high-resolution anterior

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segment ocular coherence tomography in which umbilical cord blood serum (UCBS) eye drops were added as a complementary treatment.

Case Report

A 63-year-old man with no ophthalmologic history presented with a 3-day history of bilateral foreign body sensation, red eye, and purulent discharge. On examination, the visual acuity (VA) was 20/200 in the right eye (OD) and 20/100 in the left eye (OS). Slit-lamp examination showed intense conjunctival hyperemia and follicular tarsal reaction in both eyes (OU). A 7x5-mm central corneal epithelial defect associated with a ring-shaped corneal stromal infiltrate was noted in the OD (Figure 1A, B). There was a grade 2+ anterior chamber reaction. The OS presented a 2x4-mm corneal epithelial defect and an inferior marginal infiltrate (Figure 1C). A grade 1+ anterior chamber inflammation was observed. Corneal edema and Descemet's membrane folds were present in OU. There was no limbal ischemia and no foreign bodies were noted in either eye. Intraocular pressure and fundus examination were unremarkable in OU. High-resolution anterior segment optical coherence tomography (HR-AS-OCT) was performed in OU. Hyperreflectivity in the corneal stroma and Descemet's membrane folds were observed with no thinning of the corneal stroma (Figure 1D, E).

Cultures for bacteria, fungi, and *Acanthamoeba* were performed and empirical therapy was initiated with fortified topical antibiotics (vancomycin 50 mg/mL and ceftazidime 50 mg/mL) every hour, combined dexamethasone and chloramphenicol 0.5/10 mg/mL ointment once a day, as well as oral doxycycline 100 mg twice a day.

The next day, the patient's VA was unchanged. On examination, the conjunctival hyperemia persisted, while the corneal epithelial defect size and the circumferential infiltrate (OD) and marginal infiltrate (OS) were stable.

The patient reported that 6 days before presentation, he had removed a zoanthid coral from a rock in a domestic aquarium without wearing gloves and rubbed his eyes afterwards. He did not present systemic symptoms. The patient was diagnosed with PTX-induced keratoconjunctivitis based on clinical history. The toxin was not isolated. The patient's eyes were irrigated with saline solution in order to remove any remaining toxin from the ocular surface. Topical treatment with dexamethasone drops every 3 hours was started, fortified antibiotic drops were reduced to 4 times a day, and UCBS eye drops every 2 hours were added, and ascorbic acid 100 mg daily was added to his doxycycline systemic treatment.

Over the following days, slit-lamp examination revealed improvement of the corneal epithelial defects, especially in his OS, and the infiltrate density decreased (Figure 2A-D). HR-AS-OCT showed persistent hyperreflectivity in the corneal stroma and Descemet's membrane folds (Figure 2E, F).

Fortified antibiotics were replaced with moxifloxacin 5 mg/mL 3 times a day and a therapeutic contact lens was applied in the OD. Culture results were negative.

One week later, his VA was 20/200 in the OD and 20/40 in the OS. The epithelial defect in the OD was smaller and the infiltrate density had decreased. The epithelial defect

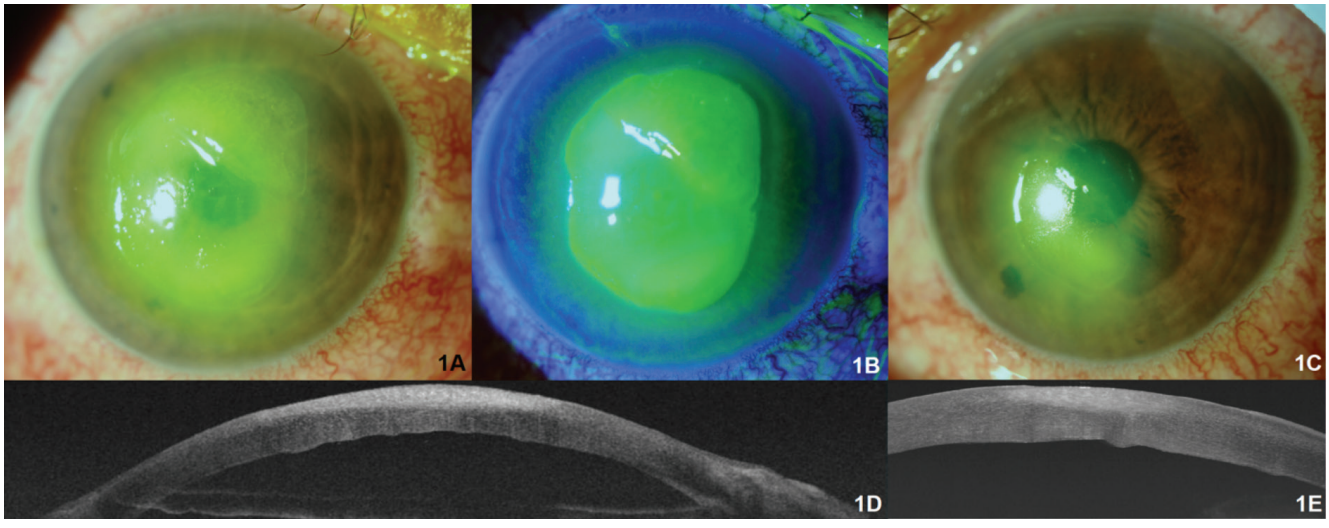

Figure 1. Slit-lamp photography and high-resolution anterior segment optical coherence tomography (HR-AS-OCT) before starting treatment. Slit-lamp photography of the right eye (OD) showed a ring-shaped stromal corneal infiltrate (A) and a 7x5-mm central corneal epithelial defect (stained with topical fluorescein, B). Slit-lamp photography of the left eye (OS) showed inferior marginal corneal infiltrate (C). HR-AS-OCT revealed Descemet's membrane folds and areas of strong hyperreflectivity with irregular and poorly defined borders corresponding to the corneal infiltrate in the anterior half of the corneal stroma in the OD (D) and the superficial third of the corneal stroma in the OS (E)

was healed in the OS, although corneal haze remained in the area where the infiltrate had been. Topical dexamethasone was tapered over 4 months; moxifloxacin was discontinued in OU and the UCBS eye drops were stopped when the epithelial defects were resolved.

At examination 4 months later, best-corrected visual acuity was 20/40 in the OD and 20/32 in the OS. Slit-lamp examination showed persistent corneal scarring in OU; we noted a ring-shaped anterior stromal scar in the OD and faint nasal anterior stromal leucoma in the OS (Figure 3A, B). Corneal topography demonstrated a non-uniform corneal steepening corresponding to irregular astigmatism in OU (Figure 3C, D). On HR-AS-OCT, a subepithelial area of increased reflectivity was observed in OU where the corneal scar was located (Figure 3E, F).

Discussion

Some corals, such as *Palythoa* in the order Zontharia, can release a toxin called PTX. It is a lethal toxin whose toxicity is mainly due to its profound vasoconstrictive effect and the release of norepinephrine by sympathetic nerve terminals. The toxin is also known to act on the sodium-potassium ATPase pump, converting it into a non-specific ion channel and causing intracellular calcium accumulation and cellular death. Moreover, it has been suggested that the signaling pathway triggered by PTX leads to actin filament system distortion.[1]

Exposure to PTX can be dermal (by direct contact with a coral or by contacting contaminated aquarium water), inhalational (usually while cleaning or eradicating the coral from home aquariums), or oral. This can lead to a systemic intoxication, manifesting with systemic symptoms such as dyspnea, rhabdomyolysis, and renal failure.[4,8,9]

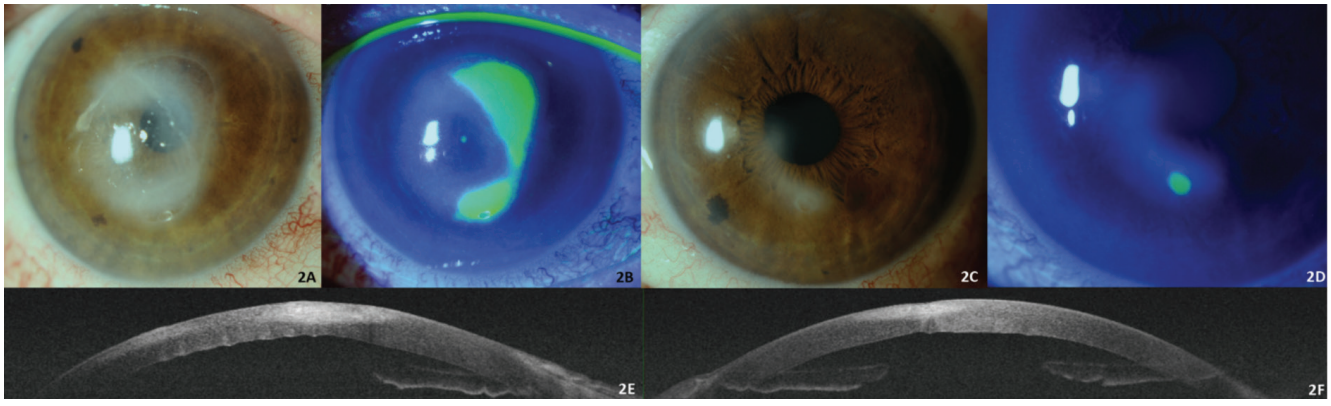

Figure 2. Slit-lamp photography and high-resolution anterior segment optical coherence tomography (HR-AS-OCT) on day 5 of treatment. Slit-lamp photography in the right eye (OD) showed the ring-shaped stromal corneal infiltrate (A) and the corneal epithelial defect with topical fluorescein staining (B). Slit-lamp photography in the left eye (OS) showed inferior marginal corneal infiltrate (C) and corneal epithelial defect with topical fluorescein staining (D). HR-AS-OCT revealed areas of hyperreflectivity in the anterior corneal stroma with more defined borders and Descemet's membrane folds in the OD (E) and OS (F)

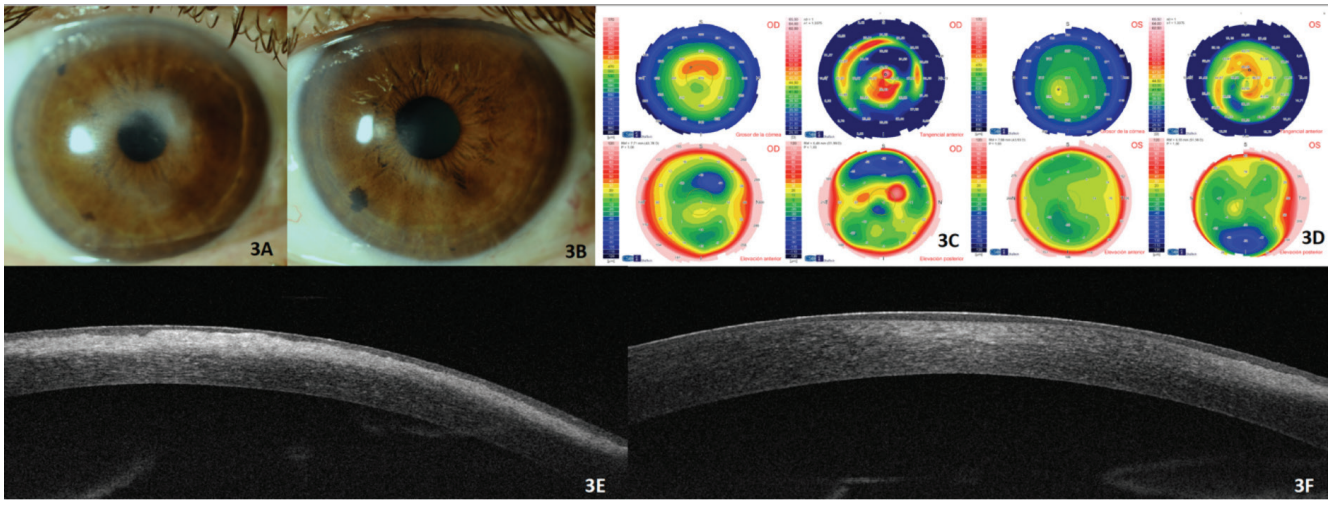

Figure 3. Slit-lamp photography, high-resolution anterior segment optical coherence tomography (HR-AS-OCT), and corneal topography at 4 months. Slit-lamp photography showed a ring-shaped stromal corneal leucoma in the right eye (OD, A) and nasal corneal scarring in the left eye (OS, B). Corneal topography in the OD and OS revealed irregular astigmatism (C, D) and HR-AS-OCT demonstrated thinner subepithelial hyperreflectivity with defined borders corresponding to the corneal scar (E, F)

Some cases of PTX ocular toxicity have been reported in the literature. The symptoms described are non-specific and include foreign body sensation, red eye, ocular pain, and decreased visual acuity. The most common ocular signs described are conjunctival hyperemia, circumferential corneal inflammatory infiltrate, and Descemet's membrane folds. Other ocular manifestations observed are conjunctival and limbal ischemia, punctate bulbar and tarsal conjunctival hemorrhages, superficial corneal punctate epitheliopathy, corneal erosions, corneal infiltrates, corneal melting and perforation, and anterior chamber reaction.[2,3,4,5,6]

Ocular exposure to PTX can occur by direct contact with the coral, contact with contaminated water, or rubbing the eyes after handing coral without gloves. In the presented case, the patient rubbed his eyes after manipulating zoanthids without using gloves.

Direct cellular toxicity of PTX and concomitant cytokine and protease activity causes keratocyte death and the degradation of collagen and proteoglycans. The subsequent inflammatory response can lead to epithelial defects, corneal melting, nerve damage, and corneal infiltrates. Disruption of the actin pathway slows the natural therapeutic process, interrupting the cell phenotype change from keratinocyte to myofibroblast.[2,5,6]

There are a limited number of case reports in the literature, so there is no defined treatment protocol. It has been reported that initial therapy should include eliminating the toxin by rinsing the eyes, with each eye irrigated individually. Treatment with topical corticosteroids is highly recommended in the early stages, together with prophylactic antibiotic therapy. Furthermore, it is also important to perform bacterial, fungal, and amoebic cultures. Artificial tears and autologous serum or UCBS eye drops should be added to the treatment. In our case, we did not use autologous serum because it takes 2 weeks to prepare in our center, but instead opted for UCBS eye drops, which can be obtained immediately as the patient needed. The use of oral corticosteroids, oral doxycycline, or ascorbic acid can be useful in cases with significant inflammation to reduce keratolysis and complications. In cases of persistent epithelial defects, the use of a therapeutic contact lens, amniotic membrane transplant, or tarsorrhaphy can be considered. Corneal transplant may be performed in cases of corneal perforation.[2,3,4,5]

PTX keratoconjunctivitis is a clinical diagnosis, based on a clinical examination, negative cultures for an infectious cause, and a temporal relation to toxin exposure.[2] Even so, the differential diagnosis from bacterial keratitis is very important. The differential diagnosis must also include other entities such topical nonsteroidal anti-inflammatory drugs (NSAID) toxic keratolysis, ophthalmia nodosa from mechanical irritants, and keratoconjunctivitis due to other toxic exposures, for example plant debris such as *Epipremnum aureum*.[2,7,10]

An early diagnosis is crucial to determine appropriate treatment and help avoid complications that involve permanent visual defects such as eye perforation, limbal stem cell failure, or extensive corneal scars.

In the presented case, we observed severe involvement in the OD and moderate involvement in the OS that had relatively good outcomes without the need for surgical intervention. Assessment with HR-AS-OCT allowed us to monitor corneal thickness to detect corneal thinning that would lead to a risk of corneal perforation and therefore more aggressive therapeutic management. It also let us analyze the depth of the corneal infiltrate and the leukoma. Unlike other reported cases, UCBS eye drops were added to the topical treatment and were found to facilitate healing of the corneal epithelial defects and reduce symptoms. Moreover, this case, as well as other cases reported in literature, shows the importance of taking a detailed clinical history and careful clinical assessment to diagnose this entity given the potential ocular and systemic complications related to PTX. In addition, it is important to know the effect of the toxin and how to prevent exposure by using protective equipment (goggles, gloves, face shield, air mask with activated charcoal filters) when handling zoanthids.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.M., S.M-N., J.O., D.A-R, F.T-V., Concept: M.B.M., S.M-N., Design: M.B.M., S.M-N., Data Collection or Processing: M.B.M., M.G-M., Analysis or Interpretation: M.B.M., S.M-N., J.O., Literature Search: M.B.M., D.A-R., F.T-V., Writing: M.B.M., D.A-R., M.G-M.

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Case Report

Straatsma Syndrome: Should Visual Prognostic Factors Be Taken into Account? A Case Report

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Abstract

Straatsma syndrome is the triad of myelinated retinal nerve fibers, myopia, and amblyopia and may be associated with strabismus, nystagmus, hypoplastic optic nerve, and heterochromia iridum. The degree of anisometropia, presence of strabismus, extent of myelination, and macular involvement have been reported to be associated with poor visual acuity after occlusion therapy for amblyopia in this syndrome. Here we present two cases of Straatsma syndrome with different responses to occlusion therapy and discuss their treatment responses according to prognostic factors for post-occlusion visual acuity.

Keywords: Amblyopia, myelinated retinal nerve fibers, straatsma syndrome, prognostic factors

Introduction

Straatsma syndrome was originally described by Straatsma et al.[1] in 1979 in a case series of 4 patients with unilateral myopia, amblyopia, and strabismus associated with myelinated retinal nerve fibers (MRNF). With the growing literature, the triad of MRNF, myopia, and amblyopia is now accepted as Straatsma syndrome.[2] However, additional findings such as strabismus, nystagmus, hypoplastic optic nerve, and heterochromia iridum have also been reported and do not preclude the diagnosis of this syndrome.[2,3,4] There is even a reported variation of the triad with hyperopia instead of myopia, called "reverse Straatsma syndrome."[5] Although it is generally unilateral, bilateral cases of traditional and reverse Straatsma syndrome have also been reported.[2,6]

The challenging part of the syndrome is treating amblyopia. Several factors are reported to be associated with poor visual outcomes after occlusion therapy, including a high degree of anisometropia, strabismus, extensive myelination, and macular involvement.[3,7,8,9]

This report presents two cases of traditional Straatsma syndrome and discusses the patients' responses to occlusion therapy according to the literature knowledge.

Case Reports

Case 1

An 8-year-old girl was referred to our clinic with a 1-year history of blurred vision in the right eye (RE). Her family history was unremarkable. On examination, the patient's best-corrected visual acuity (BCVA) was 6/120 in the RE and 6/6 in the left eye (LE). Cycloplegic refraction was -3.00 diopters (D) in the RE and -0.25 D in the LE. Pupillary reflexes were equal and symmetric with no relative afferent pupillary defect. Cover-uncover and alternate cover tests were normal for both distance and near fixation. Bilateral slit-lamp examination and Goldmann applanation tonometry were unremarkable. Dilated fundus examination of the RE revealed 5 clock hours of MRNF along the superior arcade and 4 clock hours of MRNF along the inferior arcades with the macula spared, normal foveal reflex, and normal optic disc

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(Figure 1a). Dilated fundus examination of the LE was normal (Figure 1b). Spectral-domain optical coherence tomography (SD-OCT; Heidelberg Spectralis, Heidelberg Engineering GmbH, Germany) showed hyperreflective MRNF that cast a shadow obscuring the outer retinal details in the affected areas (Figure 1c) and normal fovea in the RE (Figure 1d). Fundus autofluorescence (FAF) imaging (Heidelberg Spectralis, Heidelberg Engineering GmbH, Germany) in the RE revealed hypoautofluorescence in the corresponding areas of MRNF (Figure 1e). SD-OCT and FAF were unremarkable in the LE. Axial lengths evaluated with optical biometer (Lenstar, Haag-Streit, Koeniz, Switzerland) were 25.02 mm in the RE and 22.96 mm in the LE.

Four hours per day LE occlusion therapy with best spectacle correction was initiated for anisometropic amblyopia associated with Straatsma syndrome. However, despite patient compliance and the parents' active engagement with the occlusion regimen, 1 year following initial presentation, the patient's BCVA remained 6/120 in the RE.

Case 2

A 6-year-old boy presented to our clinic for routine examination. Patient history revealed that spectacle correction and occlusion therapy were recommended by another clinic 1 year ago, but the patient did not tolerate the therapy. Family history was unremarkable. On examination, his BCVA was 6/6 in the RE and 6/30 in the LE. Cycloplegic refraction was -1.00 D and -3.25 D in the RE and LE, respectively. Pupillary reflexes were equal and symmetric with no relative afferent pupillary defect. Bilateral slit-lamp examination and Goldmann applanation tonometry were unremarkable. Cover-uncover and alternate cover tests were normal for both distance and near fixation. Dilated fundus examination of the RE was normal (Figure 2a). Dilated fundus examination of the LE revealed 6 clock hours of MRNF along the superior arcade with minimal obliteration of the optic disc superiorly, spared macula, and normal foveal reflex (Figure 2b). SD-OCT showed hyperreflective MRNF that cast a shadow obscuring the outer retinal details at the affected sites (Figure 2c) and normal fovea in the LE (Figure 2d). FAF imaging revealed hypoautofluorescence in the corresponding areas of MRNF in the LE (Figure 2e). SD-OCT and FAF were unremarkable in the RE. Axial lengths evaluated with optical biometer were 24.40 mm in the RE and 25.51 mm in the LE.

Three hours per day RE occlusion therapy with best spectacle correction was initiated for anisometropic amblyopia associated with Straatsma syndrome. With patient compliance and parents' active engagement with the occlusion regimen, the patient's BCVA improved 2 lines to 6/15 in the LE at 1 year after initial presentation.

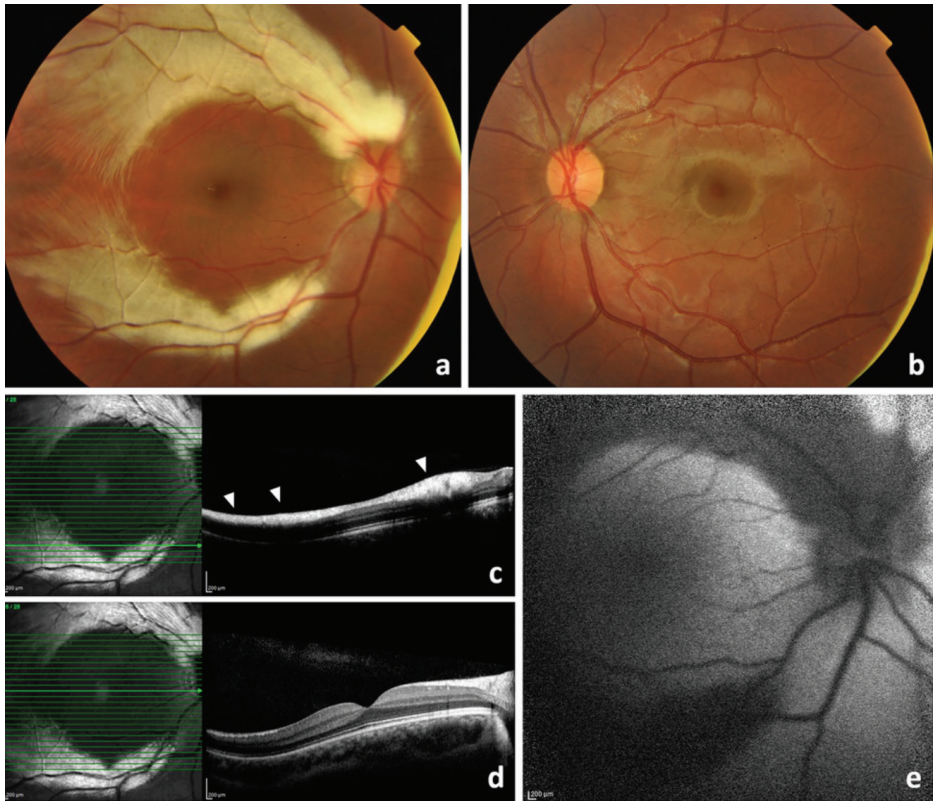

Figure 1. Color fundus photographs, spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) images of patient 1. a) Right fundus image showing myelinated retinal nerve fibers (MRNF). b) Left fundus image appears normal. c) SD-OCT scan passing through a retinal section containing hyperreflective MRNF (arrowheads) along the inferior temporal vascular arcade. d) SD-OCT scan passing through the normal fovea. e) FAF showing hypoautofluorescence in the areas corresponding to the MRNF

Discussion

MRNF are rare lesions that were observed in only 0.98% of individuals and 0.54% of eyes in the large study of 3968 consecutive autopsies conducted by Straatsma et al.[10] They are mostly seen as white to gray-white striated patches with feathery borders following the distribution of the retinal nerve fibers. They are generally isolated findings, but can also be associated with various ocular and systemic abnormalities.[3] MRNF are commonly asymptomatic, and their effect on visual function is highly variable depending on the lesion's location and extent.[3]

Patients with MRNF often demonstrate axial myopia rather than refractive myopia.[1] In the literature, there is no consensus about whether the blurred image created by myelination initiates the vicious cycle of axial myopia and amblyopia or whether the axial elongation of the globe causes late closure of the lamina cribrosa, leading to myelination and amblyopia.[3,11,12,13] According to animal studies and observational clinical studies, the growth of the eye is influenced by the quality of the retinal image not just at the fovea but across a wide area of the retina.[14] On the other hand, the theory that elongation of the globe is caused by poor retinal image quality conflicts with cases of reverse Straatsma syndrome (hyperopia with amblyopia, MRNF, and strabismus) and suggests that the etiological relationship between myelination and myopia may not be a strong association.[5,6]

The most critical and challenging part of Straatsma syndrome is the associated amblyopia and its treatment. There are several factors related to poor visual outcomes after occlusion therapy for amblyopia in Straatsma syndrome. An important prognostic

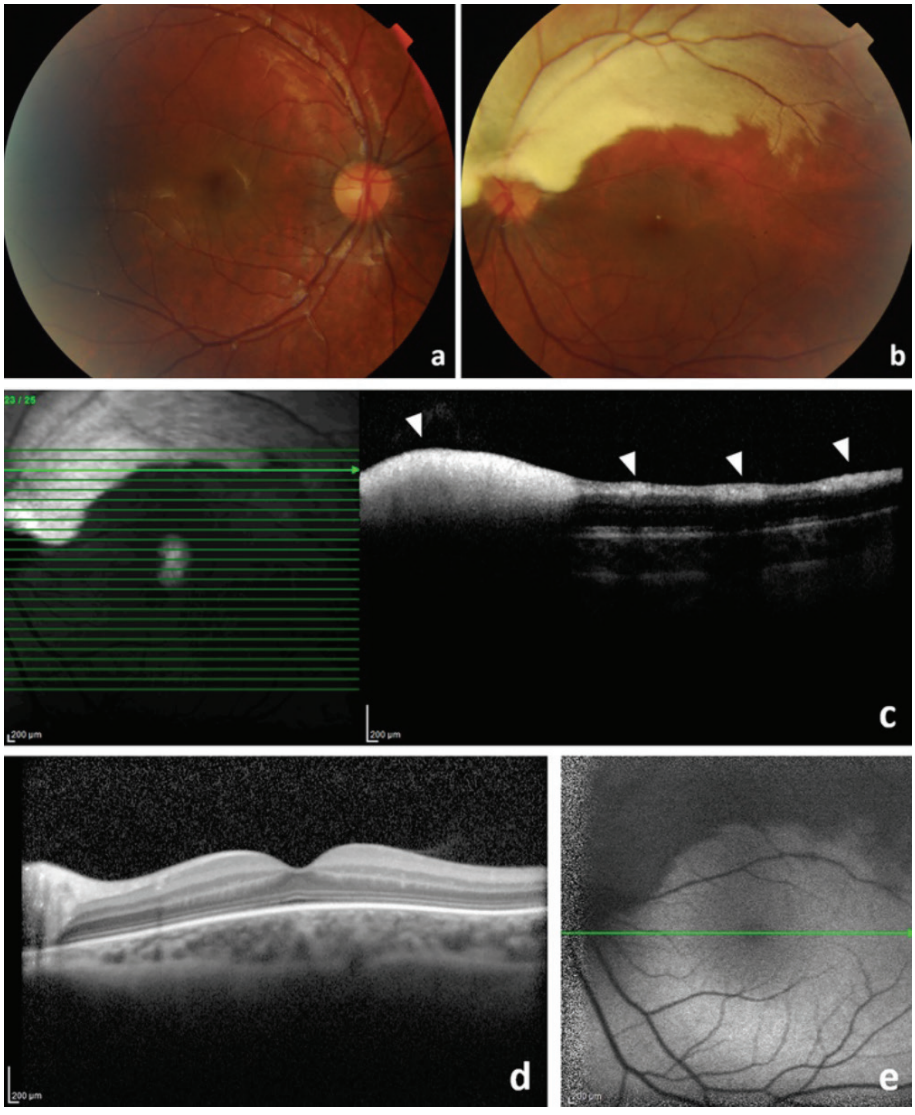

Figure 2. Color fundus photographs, spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) images of patient 2.
a) Right fundus image showing normal appearance. b) Left fundus image showing myelinated retinal nerve fibers (MRNF). c) SD-OCT scan passing through a retinal section containing hyperreflective MRNF (arrowheads) along the superior temporal vascular arcade. d) SD-OCT scan passing through the retinal section indicated by the green line in panel corresponding to the normal fovea. e) FAF showing hypoautofluorescence in the areas corresponding to the MRNF

factor according to the major series in the literature seems to be the degree of anisometropia. In a case series by Hittner and Antoszky[7], patients with higher degrees of anisometropia (an average of -13.00 D) tended to have lower post-treatment visual acuity than patients with lower degrees of anisometropia (an average of -3.75 D). Other studies also reported similar trends.[3,8,9] In our cases, although anisometropia was relatively low in both patients (-2.75 D in patient 1 and -2.25 D in patient 2), the higher anisometropia in patient 1 was also associated with a worse post-treatment visual outcome. However, it should be noted that the lower initial visual acuity in patient 1 may have affected this outcome.

In patients with isolated anisometropic amblyopia, occlusion therapy often produces variable results. Because of poor visual acuity outcomes despite aggressive therapy in MRNF patients, Ellis et al.[11] postulated that an organic etiology might also be present in these patients in addition to functional amblyopia. Abnormal macular appearance on fundus examination was also reported in several papers before the era of OCT, suggesting an organic etiology underlying poor post-treatment visual acuity.[3,7,11] In a recent case series of 3 patients with Straatsma syndrome, poor visual acuity was associated with loss or disturbance of the ellipsoid zone (EZ), and it was postulated that organic pathology in patients with poor prognosis might be related to that.[15] However, in both of our cases, the EZ was intact (Figure 1d and 2d). Therefore, we believe that while the expectation of inadequate treatment response in a patient with impaired EZ is rational, an intact EZ should not be assumed to be associated with good treatment response.

Accompanying strabismus has also been associated with poor visual outcome and a higher degree of myopia in Straatsma syndrome patients.[3,9] There was no strabismus in our presented cases, but as can be appreciated, a high degree of anisometropia and amblyopia can lead to strabismus in cases such as our patient 1, and strabismus alone should not be regarded as an independent factor for treatment response.[9]

According to their location, three types of MRNF have been described: type 1 (the most common), along the superior temporal arcade; type 2 (the least common), along both temporal arcades; and type 3, with no continuity with the optic disc.[11] Among them, type 2 MRNF was usually associated with a worse prognosis.[10,11] Although not included in this classification, rare cases of macular involvement with extensive MRNF have also been reported and associated with severe photophobia and vision loss.[16] According to this classification, patient 1 in our report corresponded to type 2 MRNF and, consistent with the literature, had poor visual prognosis after occlusion therapy. However, in a recent case report of a patient with BCVA of 20/400 and 30 prism diopter (PD) esotropia with type 2 MRNF in fundus examination, extensive occlusion therapy and contact lens correction was reported to be effective in improving BCVA to 20/30 and esotropia to 12 PD.[4]

Studies have shown that more extensive areas of MRNF may be associated with higher myopia and poor visual acuity.[8,13] In a study of 12 patients with MRNF, poor post-treatment visual acuity was associated with the extent of myelination around the fovea on a clock hour scale. According to the study, patients with 5 clock hours or less of retinal involvement showed the best improvement, and patients with 9 clock hours or more of retinal involvement showed the worst results.[8] Similarly, in our cases, the patient with 9 clock hours involvement (patient 1) had the worst outcome. However, this classification should be approached with caution because it does not show all retinal involvement on an area basis.

In conclusion, Straatsma syndrome seems to be generally associated with poor visual outcomes, especially in patients with poor post-treatment visual acuity predictors such as deep anisometropia, strabismus, type 2 myelination, extensive myelination, and macular involvement. However, there are several reports of unexpectedly good responses in the literature, even in patients with these predictive factors.[4,17] Therefore, we believe that all patients with Straatsma syndrome should be approached optimistically and provided aggressive amblyopia treatment with appropriate refractive correction.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.O.S., A.A., Ö.Ş., Design: M.O.S., A.A., Ö.Ş., Data Collection or Processing: M.O.S., N.F.K., Analysis or Interpretation: M.O.S., A.A., Ö.Ş., Literature Search: M.O.S., N.F.K., Writing: M.O.S., N.F.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Bilateral Sequential Paracentral Acute Middle Maculopathy

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Abstract

We aim to present a case with bilateral sequential paracentral acute middle maculopathy (PAMM). A 57-year-old man presented with paracentral scotoma in the left eye. The patient's multimodal imaging findings were consistent with PAMM in the left eye. Extensive systemic work-up revealed hypertension and a history of cerebrovascular event. One year after initial presentation, the patient had a subsequent decrease in visual acuity in the right eye and developed optical coherence tomography findings consistent with PAMM, whereas the left eye showed resolved PAMM findings. Although rare, PAMM can occur bilaterally. Clinicians should monitor unilateral PAMM patients with systemic vasculopathy for involvement in the fellow eye.

Keywords: PAMM, paracentral acute middle maculopathy, hypertension, cerebrovascular event

Introduction

Paracentral acute middle maculopathy (PAMM) is a recently defined retinal entity characterized by a hyperreflective parafoveal band at the level of the inner nuclear layer (INL) on spectral-domain optical coherence tomography (SD-OCT) corresponding to ischemia in the deep retinal capillary plexus.[1]

PAMM can be isolated or associated with several retinovascular and systemic diseases such as retinal artery or vein occlusion (RVO), diabetic retinopathy, Purtscher retinopathy, and sickle-cell retinopathy.[2,3,4] Despite the substantial number of unilateral PAMM cases in the literature, there is little information on the bilateral involvement of PAMM. Herein, we aim to report a patient who presented with acute PAMM in one eye and subsequently developed PAMM in the fellow eye during follow-up.

Case Report

A 57-year-old man presented complaining of a black spot in his left eye for 2 months. At presentation, his best corrected visual acuity (BCVA) was 20/200 in the left eye and 20/20 in the right eye. Biomicroscopic slit-lamp and dilated fundus examinations were within normal limits except for the presence of grade 2 nuclear sclerosis in both eyes. Fundus fluorescein angiography (FA) showed normal perfusion of the retinal vessels with no abnormal fluorescence or leakage in both eyes (Figure 1A, B). SD-OCT showed a hyperreflective band pattern at the level of the INL and inner plexiform layer (IPL) in the left eye and apparently normal retinal structures in the right eye (Figure 1C, D). His medical history included hypertension for the last 5 years and a previous cerebrovascular event. He was taking 160 mg valsartan, 12.5 mg hydrochlorothiazide, and

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100 mg acetylsalicylic acid. At presentation, his blood pressure was 140/90 mmHg. The patient's SD-OCT findings were consistent with PAMM in the left eye. Accordingly, the patient underwent an extensive systemic work-up including carotid artery Doppler and orbital color Doppler imaging, metabolic panel, blood count, and cardiology and hematology consultations for underlying disease. The systemic work-up was unremarkable.

The patient missed several follow-up visits, then returned 1 year after his initial presentation with complaints of a black spot in the fellow eye for 1 month. Visual acuity was 20/25 in the left eye and 20/60 in the right eye. No retinal lesion was seen in dilated fundus examination. FA was within normal limits in both eyes (Figure 2A, B). On SD-OCT, a hyperreflective lesion was noted at the INL and IPL level in the right eye with signs of chronic PAMM in the left eye (Figure 2C, D). OCT angiography showed decreased perfusion of the deep capillary plexus with normal perfusion of the superficial capillary plexus in the right eye (Figure 2E-H). Microperimetry showed paracentral scotomas corresponding to the retinal lesions seen on SD-OCT in both eyes (Figure 3). In light of his previous retinal findings in the left eye, patient was diagnosed as bilateral PAMM. His BCVA was 20/25 in both eyes at final visit.

Discussion

Herein, we document a patient with a history of hypertension and cerebrovascular event who presented with PAMM in one eye and later developed PAMM in the fellow eye. Initially, the first eye showed characteristic acute PAMM findings, then had signs of chronic (resolved) PAMM in the form of INL thinning associated with outer plexiform layer disruption/elevation. The subsequent development of INL thinning corresponding to the original PAMM lesion suggests that ischemia of the intermediate and deep capillary plexuses may be the primary etiology.

Though PAMM has been associated with various ocular and systemic conditions, a recent study reported that the condition may occur even in asymptomatic patients with unknown systemic disease.[5] In a recent study, chronic PAMM lesions were detected in 89.9% of hypertensive patients and 16.7% of healthy individuals.[5] Moreover, the likelihood of developing chronic PAMM lesions was significantly higher in patients with mild hypertension, which may suggest that these lesions are the earliest changes in retinal microcirculation before changes in OCTA parameters become apparent. In another study, the prevalence of resolved PAMM lesions in the fellow eyes of

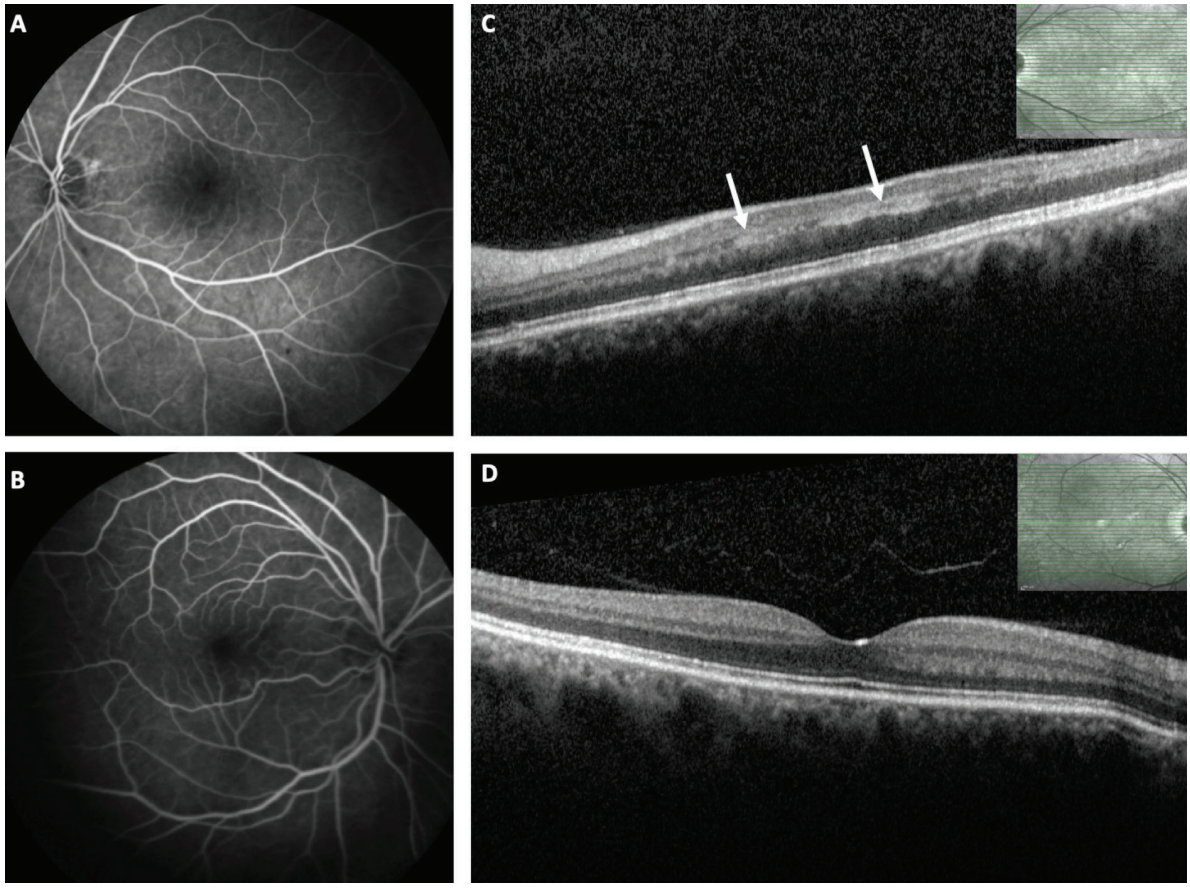

Figure 1. Fundus fluorescein angiography shows complete perfusion of the retinal vessels without abnormal leakage in both eyes at initial visit (A, B). Spectral domain optical coherence tomography (SD-OCT) scans of the left eye demonstrate a hyperreflective parafoveal band at the level of the inner nuclear and inner plexiform layers (C). The right eye of the patient shows no abnormality on SD-OCT (D)

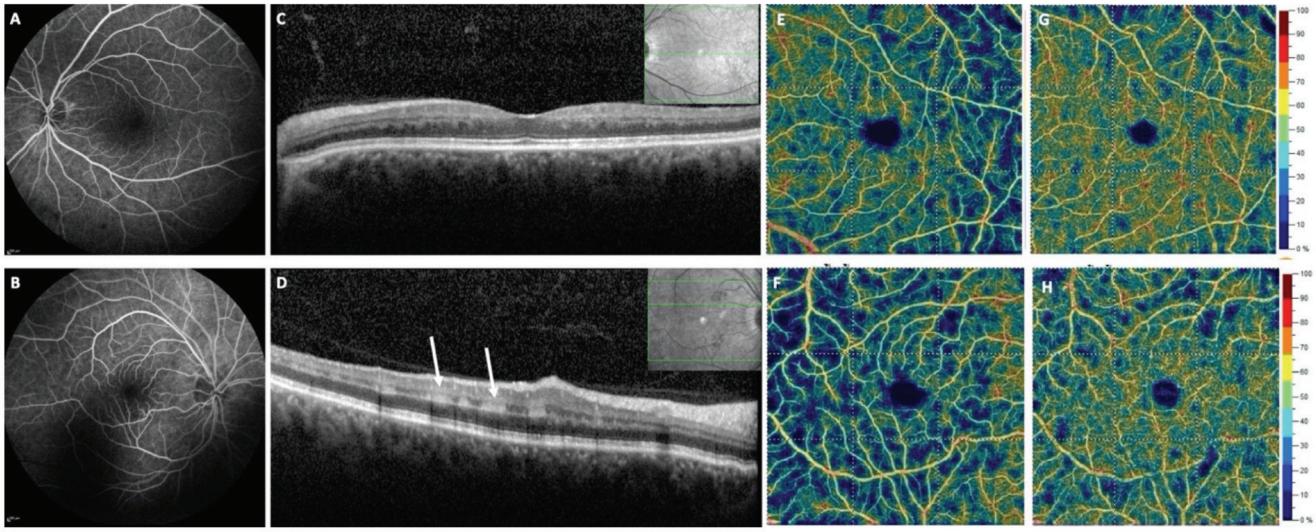

Figure 2. Fundus fluorescein angiography shows complete perfusion of the retinal vessels in both eyes (A, B). Spectral domain optical coherence tomography (SD-OCT) scan of the left eye shows inner nuclear layer thinning associated with outer plexiform layer elevation consistent with resolved paracentral acute middle maculopathy (PAMM) (C). SD-OCT scan of the right eye reveals a hyperreflective parafoveal band at the level of the inner nuclear and inner plexiform layers corresponding to acute PAMM (D). OCT angiography shows normal perfusion of the deep and superficial capillary plexuses in the left eye (E, G) and decreased perfusion of the deep capillary plexus but normal perfusion of the superficial capillary plexus in the right eye (F, H)

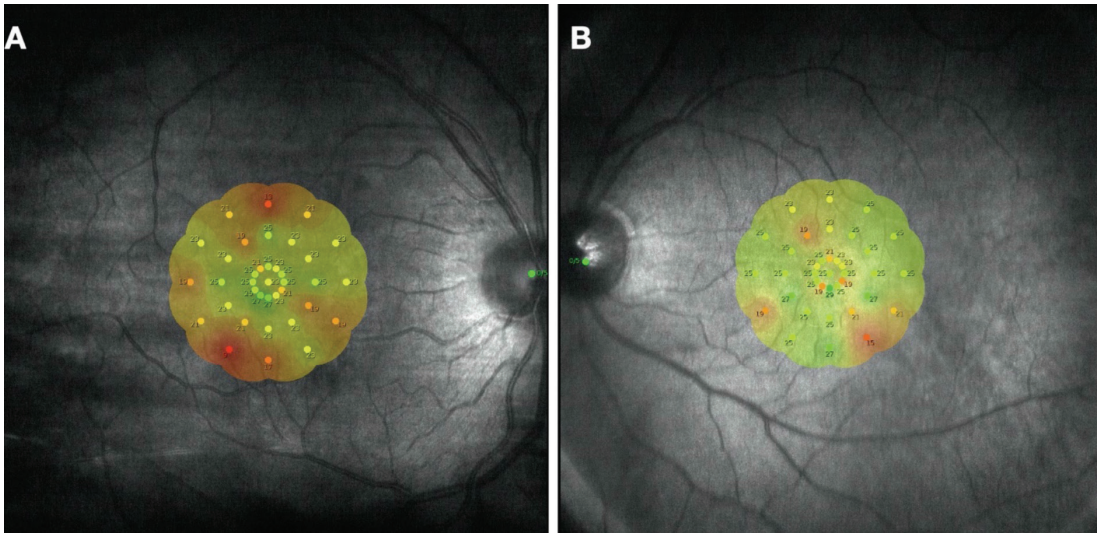

Figure 3. Retinal sensitivity maps containing interpolated retinal sensitivity measures. Microperimetry images show decreased retinal sensitivity in red (A, B)

patients with unilateral RVO was found to be as high as 71.2%, whereas 19.3% of age-matched healthy individuals displayed similar findings.[6]

In conclusion, patients with systemic vascular pathologies are at risk for developing bilateral PAMM, which may occur sequentially. These patients should be monitored closely for involvement of the fellow eye.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.K.M., E.Ö.T., V.L.K., Concept: İ.K.M., E.Ö.T., V.L.K., Design: İ.K.M., E.Ö.T., V.L.K., Data Collection or Processing: İ.K.M., E.Ö.T., V.L.K., Analysis or Interpretation: İ.K.M., E.Ö.T., V.L.K., Literature Search: İ.K.M., E.Ö.T., V.L.K., Writing: İ.K.M., E.Ö.T., V.L.K.,

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Case Report

Pseudo-hyaloidal Stalk in Anterior Persistent Fetal Vasculature: A Report of Two Cases

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Abstract

Persistent fetal vasculature (PFV) syndrome is characterized by abnormal regression of the fetal hyaloid system and may occur in various forms. In this report, two atypical cases associated with posterior capsular defect and ectopic lens material located along Cloquet's canal are discussed. Ultrasonography of these patients presenting with bilateral total cataracts revealed a hyaloidal stalk extending from the optic nerve head to the retrolental area. During lensectomy, it was observed that lens particles were moving anteriorly from the central mid-vitreous to the aspiration port and that the posterior capsule was developmentally defective. There was no pathological vascular remnant, rather the lens material partially filled Cloquet's canal through the opening in the posterior capsule and created a pseudo-stalk appearance on the preoperative ultrasonography. We aim to discuss possible mechanisms underlying these cases, which may help to improve our understanding of the PFV spectrum.

Keywords: Congenital cataract, Cloquet's canal, persistent fetal vasculature, persistent hyperplastic primary vitreous, anatomical variation

Introduction

Persistent fetal vasculature (PFV), previously known as persistent hyperplastic primary vitreous, is a congenital developmental abnormality caused by failed regression of the primary vitreous and hyaloid vasculature.[1] Although typically characterized by the presence of a vascularized retrolental plaque or a hyaloidal stalk extending from the optic disc to the posterior lens capsule, PFV refers to a much broader spectrum of ocular abnormalities with varied clinical presentations and numerous anatomical variations.[1,2,3] This variation in the spectrum may even include regression of the hyaloid vasculature after causing various pathologies in the eye, as shown in the literature.[4]

Here, we report two cases with bilateral congenital cataracts associated with developmental posterior capsule defects and ectopic lens material located in Cloquet's canal, which we interpret as a possible expression of an abnormal fetal hyaloid system in the gestational period. We aimed to discuss the possible underlying mechanisms, which may help to improve our understanding of the PFV spectrum.

Case Report

Patient 1 was a 2-month-old boy who was referred to our clinic due to bilateral congenital cataract. He was born full term via normal spontaneous delivery. There were no fetomaternal complications in the pre- or perinatal period nor was he confined to the hospital. Family history was remarkable for an older sibling with bilateral congenital cataracts, the clinical and surgical details of which were not known. Laboratory work-up for

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TORCH (*Toxoplasma*, other agents, rubella, cytomegalovirus, and herpes simplex virus) titers, serum glucose, phosphate, calcium, and urine studies were negative and pediatric evaluation yielded no associated systemic anomalies. Ocular examination revealed near-total white cataract with only a thin peripheral rim of clarity in both eyes (Figure 1a). There was no fibrovascular structure visible within or behind the lens. The corneas were of equal and normal size, and no associated microphthalmia was present. B-scan ultrasonography showed a hyperechoic band extending from the optic nerve head to the posterior lens surface, representing a persistent hyaloidal stalk and leading to the diagnosis of anterior PFV (Figure 1b).

Patient 2 was a 3-month-old boy who was similarly referred due to bilateral congenital cataract. The patient was born full term via cesarean section. The parents were consanguineous and the mother had an infection of unknown cause during pregnancy. The family history was otherwise insignificant. Blood and urine work-up were unremarkable and no systemic abnormalities were identified. Ocular examination showed near-total cataract with a thin peripheral clear zone in both eyes and there was no visible fibrovascular structure within or behind the lens, microcornea, or microphthalmia, similar to patient 1 (Figure 2a, b). B-scan ultrasonography revealed a small stalk emerging from the optic nerve head towards the anterior vitreous in both eyes. Based on these findings, the diagnosis of anterior PFV was made (Figure 2c, d).

Surgical Procedure and Anatomical Findings

The patients underwent combined lensectomy-vitrectomy in both eyes. A limbal approach was utilized in the first patient, and pars plana entries were used in the second patient. Procedural steps and surgical findings were similar in all four eyes, as follows: Following entries, the anterior lens capsule was opened centrally and the lens material was aspirated using a vitrector (Figure 1c). During lensectomy, we noticed lens particles were moving anteriorly from the central mid-vitreous towards the aspiration port, and the central part of posterior capsule was observed to be developmentally defective, with margins demarcated and slightly fibrosed, and have coalescent white opacities (Figure 1d, 2e, f). Additionally, the distance between the anterior and posterior capsule was reduced. The posterior capsule defect (PCD) was gently trimmed with the vitrector to clear the visual axis, and epithelial debris on the capsular leaflets was cleared. In patient 1, it was impossible to clear all of the dot-like opacities that were firmly adhered to the capsules and some of them had to be left in place. Complete aspiration of the lens material revealed that there was no fetal vascular hyaloidal structure extending from the disc, but instead lens material had partially filled Cloquet's canal through the opening in the posterior capsule and created a pseudo-stalk appearance on the preoperative ultrasonography (Figure 1e). The retina was normally attached; hence only core vitrectomy was performed (Figure 1f, 2g, h). The peripheral retina, pars plana, and plicata were normal, free of any pathology in both patients. The eyes were left aphakic and fitted with bilateral contact lenses in the postoperative period and followed up for 16 months (Patient 1) and 8 months (Patient 2). Patient 1 had a secondary proliferation of the capsular epithelium blocking the pupillary axis in the right eye within 4 months and had a second operation to clear the opacities, which resulted in a clear axis for a 12-month follow-up period. There was no problem or complication noted in either eye of patient 2 during follow-up. Visual acuity was noted as central, steady, and maintained bilaterally in both patients, and nystagmus was observed in patient 2. Both patients had esotropia in the right eye, and 2 hours/day occlusion therapy to the left eye was initiated but discontinued after observing the development of alternating deviation.

Discussion

Developmental defects of the posterior capsule are rare and have been reported in association with congenital cataracts in a few studies.[5,6,7] Vajpayee and Sandramouli[5] were the first in the literature to report a pre-existing PCD in a patient with congenital cataract. More recently, Vasavada et al.[6] reported on 400 eyes that had congenital cataract surgery, 6.75% of which had a preexisting PCD. The authors demonstrated several features commonly found in these eyes to ease the identification of a preexisting PCD, such as well-demarcated, thick defect margins and white dots on the capsule and anterior vitreous. However, all these reports described the location of the lens in its natural position, anterior to the posterior capsule. In contrast, we observed a significant amount of lens material displaced posterior to the PCD and along Cloquet's canal, mimicking the presence of a hyaloid stalk. These findings were similar to those observed by Tandon et al.[7] in a recent case report. The authors presented an 8-week-old patient with bilateral congenital cataracts that were displaced into the anterior/middle vitreous in association with a pre-existing PCD. Similarly, they reported a small posterior stalk in one eye. However, unlike our observations, it was poorly defined and did not extend to the anteriorly located lenticular opacity. The cataract type was less dense as well, mainly in the form of subcapsular opacities. The presence of a denser, more diffuse cataract and a more prominent stalk on ultrasound may suggest an earlier onset in our patients.

The exact underlying mechanism of developmental PCDs is unknown. Several studies pointed out that PCDs may initially begin as posterior lenticonus.[4,6,7] Therefore, proposed mechanisms to explain the development of posterior lenticonus (i.e., embryologic hyaloid artery traction on the posterior capsule, inherent weakness of the capsular wall) are likely to be triggering factors in the formation of PCD as well.[4,6,8] However, unlike the classical posterior lenticonus formation, PCD appears to occur at an accelerated pace and results in a full-thickness defect.

We believe that in the presented cases, an abnormal hyaloid artery and tunica vasculosa lentis system exerted some traction on the posterior capsule, causing the capsule

to stretch outwards and weaken, and as the axial length of the globe increases, proportionally increased traction on the capsule finally led to the development of a PCD. The possible migration of the lens material through the PCD into Cloquet's canal in the presented cases suggests a somewhat different course from the previously reported cases of PCD where the lens material is in its natural position or slightly displaced in the retrolental space or anterior vitreous. The underlying mechanism might be PCD formation much earlier in the gestational period, before lenticular development is complete, either due to inherent weakness of the posterior capsule or stronger traction or both. Indeed, the dense total cataract with slightly fibrosed edges of the PCD in the presented cases may reflect a more chronic time course. Although the lack of a persistent hyaloid artery remnant in our patients appears to contradict the mechanism proposed here, the literature suggests that as the eye continues to grow, the hyaloid vasculature may resorb even after causing lenticular and capsular changes, leaving no evidence of its involvement in the pathology.[4] Additionally, our cases did not have microphthalmos or microcornea. As the normal growth of the eye depends on expansion of the secondary vitreous along with involution of the hyaloid vasculature, we can speculate that the hyaloid system formed a PCD early in development, then regressed without interrupting the growth process of the eye, and as the hyaloid vasculature regressed, lens material filled Cloquet's canal through the PCD.

In conclusion, persistent fetal vasculature may present with minimal or even no visible fetal vascular remnants.[4,9] We

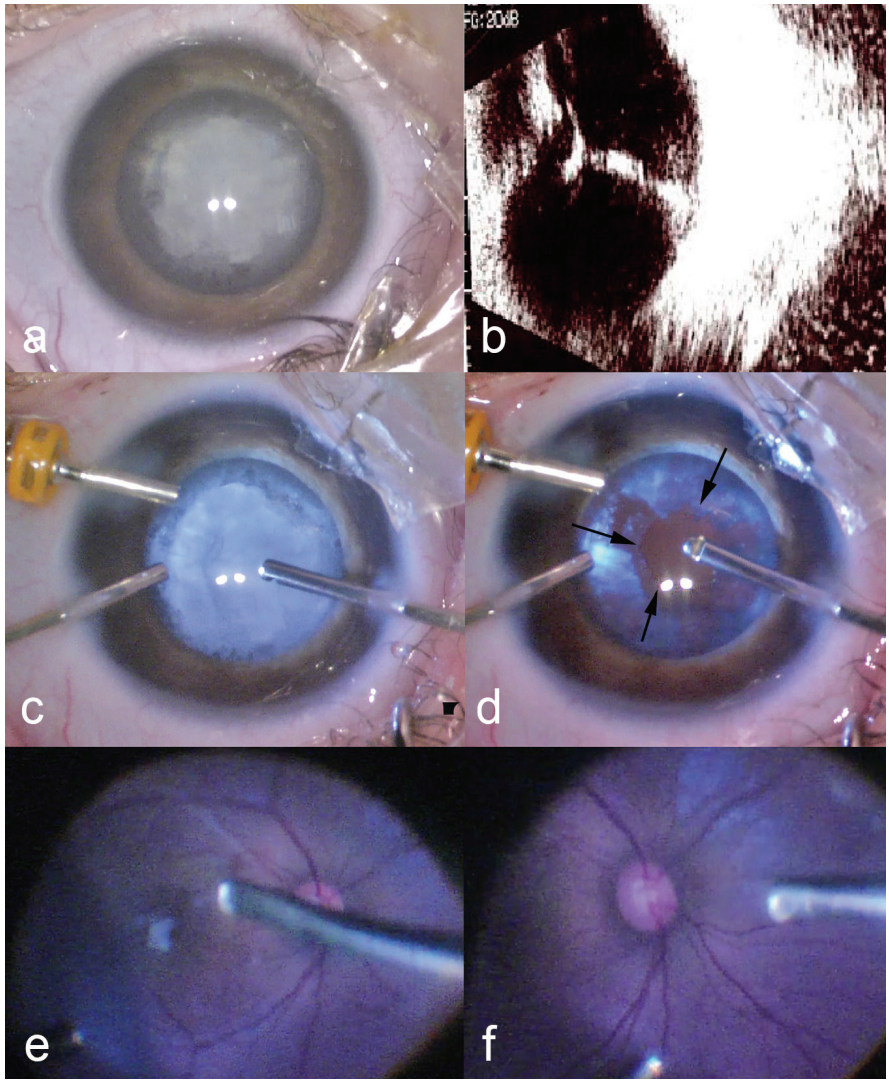

Figure 1. (a) Images of the right eye of patient 1 under the operating microscope showing white cataract in the center surrounded by a relatively clear zone in the periphery. (b) B-scan ultrasonography indicates a highly prominent hyperechoic stalk extending from the optic disc to the posteriorly bulging posterior lens surface. (c) The cataractous lens is located relatively posteriorly in the anterior vitreous. (d) A well- demarcated posterior capsular defect (arrows) and accompanying white dots are seen. (e) Lens particles along Cloquet's canal are removed during central core vitrectomy. (f) The retina is attached and the optic disc is normal without any stalk

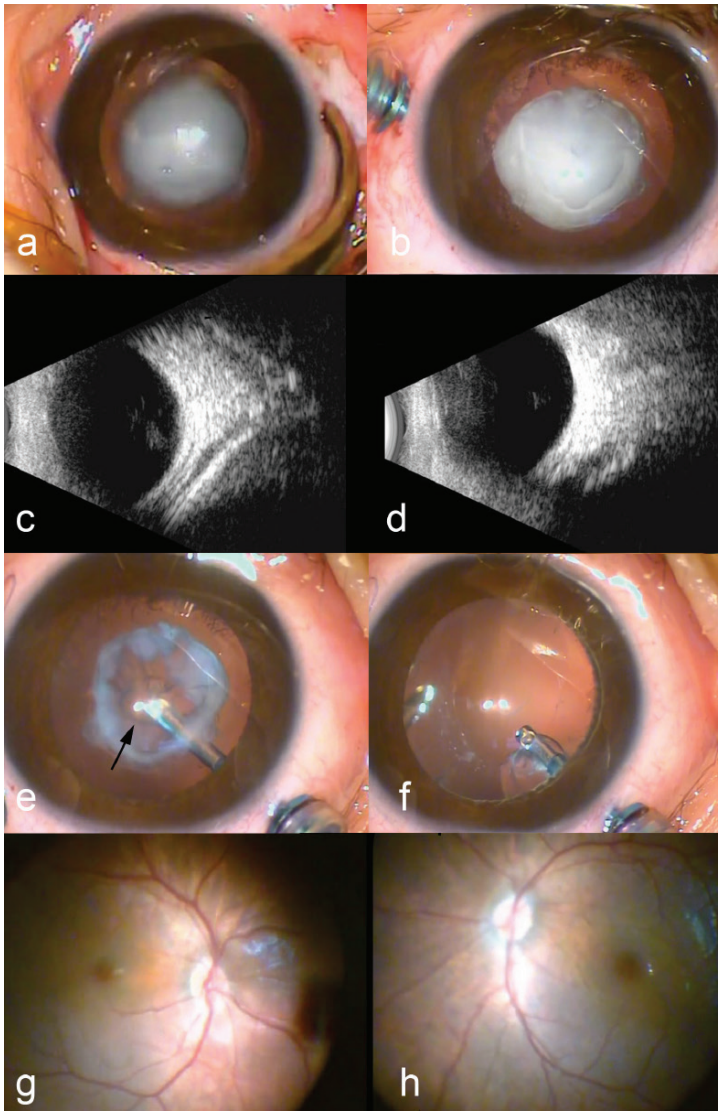

Figure 2. Images of the right (a, c, e, g) and left eye (b, d, f, h) of patient 2. (a, b) A white near-total cataract is seen in the center of the lens in both eyes with a thin clear zone at the periphery. A small hyperechoic stalk could be identified extending from the optic disc and the back of the lens (c, d). A posterior capsular defect (arrows) is evident in the right (e) and left eye (f). Following cataract removal, the retina is observed to be attached and optic discs are normal in both eyes (g, h)

hypothesize that ectopic congenital cataracts with PCD are on the milder end of the PFV spectrum, caused by abnormal regression of the fetal hyaloid system. More evidence is necessary to confirm this pathogenesis. As congenital cataracts may present with complex morphological variations, a meticulous assessment should be made preoperatively, and surgeons should be prepared for a possible vitreoretinal surgery.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.Ö.Z., A.B.T., H.T.A., Ş.Ö., Design: E.Ö.Z., A.B.T., H.T.A., Ş.Ö., Data Collection or Processing: E.Ö.Z., A.B.T., H.T.A., Ş.Ö., Analysis or Interpretation: E.Ö.Z., A.B.T., H.T.A., Ş.Ö., Literature Search: E.Ö.Z., A.B.T., H.T.A., Ş.Ö., Writing: E.Ö.Z., A.B.T., H.T.A., Ş.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor re: "Lipemia Retinalis Diagnosed Incidentally After Laser Photocoagulation Treatment for Retinopathy of Prematurity"

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Keywords: Lipemia retinalis, premature infant, HIV

Dear Editor,

In the October 2021 issue of the Turkish Journal of Ophthalmology, Öztürk et al.[1] presented an interesting case of lipemia retinalis (LR) in a Turkish preterm infant diagnosed incidentally after laser photocoagulation therapy for retinopathy of prematurity. We believe that Öztürk et al.[1] should consider prenatally acquired human immunodeficiency virus (HIV) infection in the case in question, based on the following point. Globally, HIV infection is still a major health threat. Though HIV/AIDS cases in Turkey were recorded at a level of zero in 2020 according to World Bank data, which is compiled from officially recognized sources,[2] it was previously reported that the epidemiologic profile of HIV-infected individuals is changing in Turkey.[3] Most neonatal HIV infections are the result of vertical transmission.[4] The neonatal population has weaker immunity compared to adults; therefore, if they contract HIV infection, they are at greater risk of rapid disease progression, with significant morbidity and mortality rates.[4] Among emerging HIV-associated complications, hyperlipidemia is increasingly recognized. A substantial number of HIV-infected children were found to have persistent elevation of serum lipid levels, potentially putting them at risk for life-threatening events.[5] Among these events, cases of LR have been reported only among HIV-positive adults.[6] Accordingly, we believe that an underlying HIV infection should be seriously considered in the case in question, and arranging for CD4 count and viral load estimations and fourth-generation antigen/antibody immunoassays in the mother and her studied preterm infant would be warranted. If these tests were to disclose HIV positivity, the presented case could be considered a novel case report of HIV-associated neonatal LR.

Peer-review: Externally peer reviewed.

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Reply to Letter to the Editor re: "Lipemia Retinalis Diagnosed Incidentally After Laser Photocoagulation Treatment for Retinopathy of Prematurity"

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Keywords: Lipemia retinalis, premature infant, HIV

Dear Editor,

We are thankful for the opportunity to respond to the issue raised in the letter to the editor that was recently directed to us. We would also like to thank the authors of the letter for their interest in our case report presenting a preterm infant with lipemia retinalis (LR) diagnosed incidentally after laser photocoagulation treatment for retinopathy of prematurity, and for taking their valuable time to express their concerns.[1]

In their letter, the authors rightly recommended a detailed study for prenatally acquired human immunodeficiency virus (HIV) infection for the presented case, as there may be a strong relationship between HIV infection and dyslipidemia. This association has been described previously in the scientific literature.[2,3,4,5,6] Such publications have especially emphasized the potential association between lipid metabolism disorders and antiretroviral therapy with protease inhibitors or nucleoside reverse transcriptase inhibitors used in the medical treatment of patients with HIV infection. However, markedly elevated levels of total cholesterol, low-density lipoprotein, and triglyceride may be found in HIV patients related to the virus itself.[5,6] In the presented case, we tested for blood-borne diseases including hepatitis B and C, as well as HIV just before laser photocoagulation therapy in the routine work-up done before interventions performed in the operating room, and the blood test for HIV infection resulted negative. However, the authors' valuable insight should be heeded, and all infants diagnosed with LR should undergo testing for prenatally acquired HIV infection.

Peer-review: Externally peer reviewed.

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We wish you every success in your academic career.

Respectfully yours

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