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Ziya KAPRAN
Private Practice, İstanbul, Turkey

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CONTENTS

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EDITORIAL

2022 Issue 6 at a Glance:

Esteemed colleagues,

In its sixth issue of 2022, the Turkish Journal of Ophthalmology features eight original studies, a review, and three case reports.

A clinical study by Altan-Yaycıoğlu et al. reports the ocular complications of allogeneic hematopoietic stem cell transplantation (allo-HSCT) procedures. Early diagnosis and treatment are essential for graft-versus-host disease after allo-HSCT, which is an increasingly frequent procedure with expanding indications as well as improved success, and ophthalmologists will be an indispensable stakeholder in this process.

A study by Doğan et al. entitled "The Effect of Prolactinoma on Tear Film Functions" provides a look at benign pituitary tumors, especially prolactinomas, which cause a typical visual field loss in the form of bitemporal hemianopsia, from the point of view of another undesired outcome: dry eye.

A study by Akça Bayar et al. examining the effects of intracameral drugs and dyes on corneal endothelial apoptosis by *in vivo* and *in vitro* analyses in experimental animals is an important reference. The study showed that intracameral adrenaline, trypan blue, and lidocaine injections caused histopathological toxicity in the corneal endothelium. Therefore, caution seems warranted in the use of the intracameral drug administration route, which has been recommended as an alternative to the application of drugs to the ocular surface and has become popular in "dropless cataract surgery."

Prolonged contact lens use is a well-known risk factor for dry eye. However, Şimşek et al. observed a significant increase in ocular surface disease index and dendritic cell density using silicone-hydrogel contact lenses for period as short as 1 month. Fortunately, these latest-generation contact lenses did not cause significant changes in corneal sensitivity, tear secretion, meniscus volume, or subbasal corneal nerve density, reflectivity, and tortuosity in the short term.

In their study of 120 diabetic patients without retinopathy or reduced visual acuity, Shah et al. showed that contrast sensitivity decreased with longer duration of diabetes and increased glycosylated hemoglobin level. The study demonstrated that contrast sensitivity testing is a much better indicator of metabolic control than retinal imaging or visual acuity testing and suggests that contrast sensitivity testing should also be added to the follow-up criteria for type 2 diabetes patients with disease duration longer than 5 years and HbA1c levels above 8%.

Ataş et al. investigated bacillary layer detachment (BLD), a common tomographic finding, in 58 eyes of 29 patients diagnosed with acute Vogt-Koyanagi-Harada disease. They reported that BLD was more common in severely affected eyes but because it resolved rapidly with treatment, its presence did not affect long-term visual function.

Acute retinal necrosis is an ophthalmological emergency that requires immediate treatment after diagnosis. Delayed diagnosis and especially the administration of corticosteroids before starting antiviral therapy allow retinal necrosis to spread. In their large series of 48 patients, Aksu-Ceylan et al. found that early diagnosis and early initiation of antiviral therapy were critical in terms of final vision.

The comprehensive vision screening with axial length, spherical equivalent, and corneal curvature parameters conducted in 1382 school children by Gopalakrishnan et al. is a strong study because normative data for Indian children in this age group have not been previously determined. The general distribution of ocular biometry parameters in children in India will be an important reference for studies on myopia and associated risk factors.

The review article for this issue, written by Mirzayev and Gündüz, comprehensively addresses the heading of "Hamartomas of the Retina and Optic Disc" with rich visual support including the modalities of ultrasound, fundus autofluorescence, optical coherence tomography, optical coherence tomography angiography, and fluorescein angiography. Although some do not require treatment, if complications such as vitreous hemorrhage, macular exudation, retinal detachment, macular hole, epiretinal membrane, and choroidal neovascularization occur, it seems prudent to follow-up the retinal and optic disc hamartomas that require treatment in light of this review.

Menteş and Değirmenci used multimodal imaging in their case report of a pediatric patient with pigmented paravenous retinochoroidal atrophy (PPRCA) and cystoid macular edema (CME). They reported that the occurrence of CME without ocular inflammation was an unusual finding for PPRCA and that chronic or latent inflammation may be involved in the etiology of PPRCA.

Dermatofibrosarcoma protuberance is a locally aggressive and infiltrative malignant tumor that occurs most commonly on the trunk and least commonly in the head and neck region and has a relatively

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EDITORIAL

high recurrence rate. Aslan Kaya et al. present the case of a 44-year-old woman with tearing of the right eye and swelling in the medial canthus for 15 years, and their comprehensive approach to diagnosis and treatment compensates for the lack of a review on this subject.

The scleral fixation sutures of posterior chamber intraocular lenses can create pseudoblebs with Seidel-positive cystic filtration. In their case report, Hoang and Clement describe filtering pseudoblebs secondary to persistent posterior chamber intraocular lens in a patient with Marfan syndrome and discuss the relationship between pseudoblebs and previous ocular surgeries. The filtration was stopped by patching with scleral grafts, constituting a successful treatment example.

As we say farewell to 2022 with articles featuring examples of comprehensive diagnosis and successful treatment, even in rare and challenging diseases, I wish for the new year to bring more health and peace.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

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Original Article

Age-Related Differences in the Clinical Patterns of Ocular Graft-Versus-Host Disease

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Abstract

Objectives: To evaluate age-related differences in clinical patterns of ocular graft-versus-host disease (GVHD).
Materials and Methods: In this cross-sectional study, patients diagnosed with ocular GVHD were evaluated in two groups: Group I included those aged 18 years or younger and Group II included those over 18 years of age. Demographic and clinical information were recorded and compared between the groups.
Results: Forty eyes of 20 patients were included (11 patients were in Group I and 9 patients were in Group II). Follow-up was at least 6 months. All patients had burning, dryness, and foreign body sensation. Conjunctival hyperemia, cicatricial conjunctivitis, and limbal stem cell disease (LSCD) was observed more frequently in Group II. In addition to non-preserved artificial tears, cyclosporine A 0.05% (65%) and autologous/allogeneic serum eye drops (80%) were given and silicone plugs were inserted (28%). In Group I, an improvement in GVHD scoring and best corrected visual acuity was observed after 6 months of treatment ($p<0.0005$).
Conclusion: In ocular GVHD, conjunctival cicatrization and limbal stem cell deficiency might be observed more often in adults. Topical cyclosporine, autologous/allogenic serum drops, and punctal plugs are helpful in moderate or more severe cases. With early diagnosis and treatment, an improvement in clinical signs and visual acuity might be observed, particularly in younger patients.
Keywords: Conjunctiva, cornea, dry eye, graft-versus-host disease, meibomian gland dysfunction

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is used for many hematologic malignancies and non-malignant disorders. The expansion of indications as well as the success of the procedure has resulted in a rise in the number of procedures performed. Allo-HSCT is thought to work by inducing an immune response to malignant cells.[1] Graft-versus-host disease (GVHD), which can be acute or chronic, is the leading cause of morbidity and mortality following allo-HSCT. Approximately 30-70% of HLA-matched patients develop chronic GVHD.[2] Chronic GVHD is a pleiotropic multi-organ inflammatory syndrome that has the potential to affect all mucosal surfaces, including the ocular, oral, vaginal, and gastrointestinal mucosa.[3]

Ocular involvement is observed in 60-90% of patients with chronic GVHD.[4] The prevalence of ocular GVHD is increasing with improved survival rates after allo-HSCT. Ocular GVHD primarily affects the ocular surface, cornea, conjunctiva, eyelid, and lacrimal gland. According to the diagnostic criteria, the new onset of dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy are distinctive manifestations of ocular GVHD.[3] Ocular dry eye disease (DED) in ocular GVHD usually develops within 6 to 9 months after allogeneic GVHD.[5] Symptoms include irritation, burning, pain, redness, photophobia, blurred or decreased vision, excessive tearing, and the sensation of having sand or grit in the eyes.

In our clinical practice, we observed some differences in the clinical features of ocular GVHD in children and adults. A previous study on the oral complications of chronic GVHD reported that adult patients develop more extensive symptoms compared to children.[6] Thus, in the present study, we aimed to evaluate the clinical patterns of patients diagnosed with ocular GVHD and investigate differences in the frequency of these patterns by age.

Materials and Methods

In this cross-sectional observational study, patients with a history of allo-HSCT who were referred to the ophthalmology clinic due to eye-related complaints and received a diagnosis of ocular GVHD were evaluated. The study was conducted according to the criteria of the Declaration of Helsinki. Institutional review board approval was obtained (#BTEDK-12/20). Patients were examined between April 2017 and December 2019 by two doctors (R.A.Y. and Y.A.A.) who agreed on the classification criteria of the diagnostic protocols (Table 1).[3] Follow-up of at least 6 months was mandatory for inclusion in the study.

Patients were divided into two groups: children (Group I) and adults (Group II). In our country, patients under the age of 18 years are considered children according to Ministry of Health regulations. Thus, patients who were 18 years or younger were included in Group I, and patients over the age of 18 years were included in Group II. All patients were evaluated for history, subjective complaints, clinical findings, and treatment modalities. Their age, sex, indication for HSCT, relevant medical and ocular history, use of systemic medications, and previous topical ocular treatments were noted. Best-corrected visual acuity (BCVA), slit-lamp and fundus examination findings, and intraocular pressure were recorded. Data were recorded at baseline (day 0) and 6 months (day 180).

According to our observation, ocular GVHD does not necessarily affect both eyes. In a study on ophthalmic studies, it was stated that if inter-eye correlation is low, data obtained from both eyes should be analyzed.[7] Therefore, we decided to include both eyes of the patients for evaluation.

BCVA was measured using Snellen visual acuity charts in decimal values and converted to LogMAR units for statistical comparison.

Subjective symptoms were assessed by asking specific questions about tearing, dry/gritty feeling, burning, irritation, foreign body sensation, redness, subjective pain, photophobia, and blurred vision. The Ocular Surface Disease Index questionnaire could not be used with children and thus was not included in the evaluation. Instead, we asked the patients to grade their symptoms from 0 to 4 (0, no complaints; 1, mild complaints not affecting daily activities; 2, moderate complaints slightly affecting daily activities; 3, severe complaints affecting daily activities; and 4, unable to open eyes due to photophobia and pain).

The ocular surface was evaluated with slit-lamp before and following unpreserved fluorescein application. A yellow barrier filter and cobalt blue illumination was used to evaluate punctate staining of the cornea and conjunctiva. Corneal staining was scored from 0 to 3 as none, mild, moderate, or diffuse. Tear film break-up time (TBUT) was measured, and a value less than 5 seconds was considered abnormal. Aqueous tear production was assessed by Schirmer test without anesthesia.

The prevalence and severity of clinical symptoms and signs were evaluated. The severity of dry eye was evaluated with corneal fluorescein staining, Schirmer test, TBUT, and subjective symptoms, and scoring was performed according to the proposed grading system.[8]

Table 1. Ocular graft-versus-host disease scoring according to the National Institutes of Health consensus development project[3]

Score	Symptoms
Score 0	No symptoms
Score 1	Mild dry eye symptoms not affecting activities of daily living (requiring eye drops OR asymptomatic signs of keratoconjunctivitis sicca)
Score 2	Moderate dry eye symptoms partially affecting activities of daily living (requiring drops >3 times per day OR punctal plugs), without vision impairment
Score 3	Severe dry eye symptoms significantly affecting activities of daily living or unable to work (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca

Additionally, topical medications used were noted from the patients' records. Some patients received topical autologous/allogenic serum. For preparation, the blood was obtained either from the patient or a relative and was screened using standard tests to check for blood-borne diseases. Under sterile conditions, 20 mL of whole blood was collected by venipuncture of an antecubital vein. The blood was immediately centrifuged at 1500 rpm for 10 minutes to obtain serum. The serum was then diluted with balanced salt solution for a final concentration of 30% and divided into five vials. Patients were instructed to keep four vials in a deep freezer, and the fifth in a freezer at 4 °C. Each vial was used for one week after thawing.

Statistical Analysis

Prevalence rates of clinical signs and symptoms and treatment modalities were given. The study parameters were also compared between the two groups. Comparison was performed with chi-square test or paired Student's t-test, as applicable. A probability value (p) of 0.05 was accepted as clinically significant.

Results

Forty eyes of 20 patients were included. Eleven patients (4 female, 7 male) with a median age of 12 years (mean 11.45±5.07 years, range 3-17) were included in Group I. Nine patients (4 female, 5 male) with a median age of 45 years (mean 44.44±1.64 years, range 25-61) were included in Group II. The mean follow-up time at the ophthalmology clinic was longer in Group I (mean 15.67±18.88 months) compared to Group II (8.82±5.78 months); however, the difference was statistically insignificant (p=0.13, Student's t-test).

In Group I, the indication for HSCT was thalassemia major in 4 patients, acute lymphoblastic leukemia in 3, acute myeloblastic leukemia in 2, and aplastic anemia in 2 patients. In Group II, the indication for HSCT was acute myeloblastic leukemia in 6 patients, acute lymphoblastic leukemia in 1, and aplastic anemia in 1, and myelofibrosis in 1 patient. Stem cells were obtained from related donors for 14 patients (7 patients in Group I and 7 patients in Group II) and matched unrelated donors for 6 patients (4 patients in Group I and 2 patients in Group II). The interval between HSCT and ophthalmic examination was 15.05±12.79 months (range 4-48) in Group I and 23.89±22.48 months (range 8-84) in Group II. Although the interval was longer in Group II, the difference was statistically insignificant (p=0.06, Student's t-test).

The patients' subjective complaints are listed in Table 2. All patients had burning, dryness, and foreign body sensation, and most had photophobia (95%), redness (95%), blurred vision (85%), and tearing (80%). When we investigated the difference in complaints, tearing was significantly more frequent in Group I compared to Group II (p=0.000). Although statistically insignificant, itching was more prevalent in Group II (p=0.067).

The GVHD scoring distribution according to the National Institutes of Health classification (Table 1) is shown in Figure 1.[3] As all patients presented with ocular symptoms, none of the patients was Score 0. Following 6 months of treatment (day 180), the scores were statistically better in Group I (p<0.0005), as 10 patients moved from score 3 to score 2. In Group II, one patient with Score 3 improved to Score 2, and the difference was insignificant (p=0.331).

The BCVA in Group I was 0.49±0.39 at presentation (day 0), which increased significantly to 0.33±0.29 at 6-month (day 180) follow-up (p=0.004). In Group II, although an improvement was observed from 0.23±0.37 at day 0 to 0.16±0.26 at day 180, the difference was not significant (p=0.087).

The clinical findings at presentation are shown in Table 3. Meibomian gland dysfunction (MGD) was present in all except

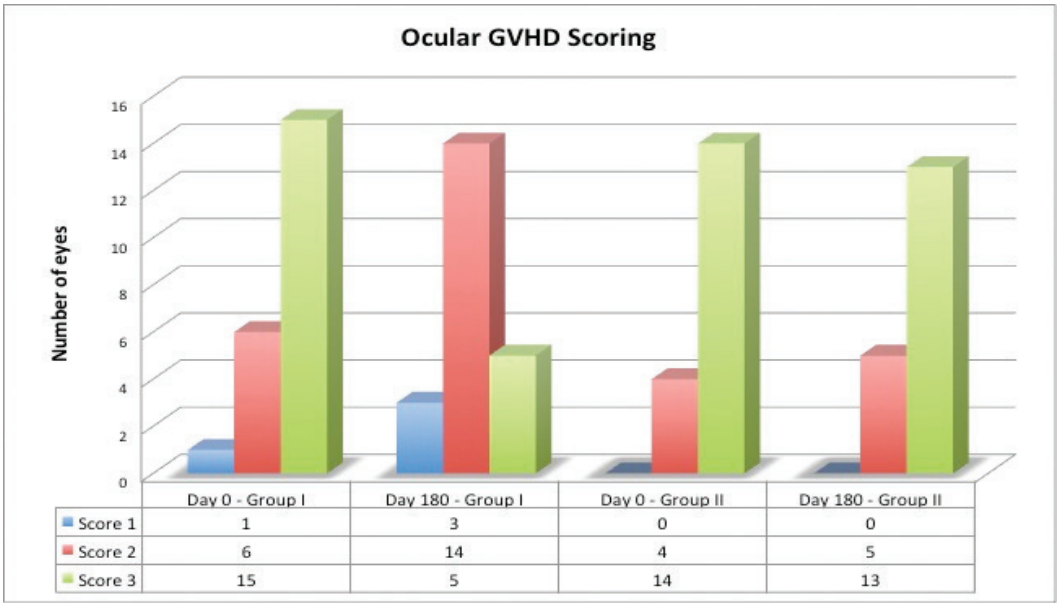

Figure 1. The distribution of cases according to ocular graft-versus-host disease clinical score (number of eyes with each score shown below the graph)

1 patient (95%). Conjunctival hyperemia was observed less often in Group I compared to Group II (p=0.004). Six eyes (15%) had pseudomembrane. Cicatricial conjunctivitis was significantly more frequent in Group II (67% vs. 32%, p=0.028). Limbal stem cell disease was observed only in patients in Group II (44%, p=0.000). Corneal epithelial staining was detected in 36 eyes (90%). The degree of staining was mild in 5 eyes, moderate in 11 eyes, and diffuse in 20 eyes. Five eyes of 5 patients had persistent corneal epithelial defects; 3 of them used bandage contacts for 1 month and the other 2 healed in 2 weeks' time. Five eyes (12.5%) had keratitis. Of these, the etiologic pathogen was bacteria in 3 eyes, herpes virus in 1 eye, and *Candida* in 1 eye.

Table 2. The subjective complains of patients aged 18 years and younger (Group I) and those over 18 years of age (Group II)

	Total (n=40)		Group 1 (n=22)		Group 2 (n=18)		p
	n	%	n	%	n	%	
Photophobia	38	95	22	100	16	89	0.109
Tearing	32	80	22	100	10	56	0.000*
Burning	40	100	22	100	18	100	1.000
Dryness	40	100	22	100	18	100	1.000
Itching	30	75	14	64	16	89	0.067
Foreign body sensation	40	100	22	100	18	100	1.000
Redness	38	95	22	100	16	89	0.109
Pain	10	25	4	18	6	33	0.271
Blurred vision	34	85	20	91	14	78	0.247

n: Number of eyes, *Statistically significant

Table 3. The clinical findings of patients aged 18 years and younger (Group I) and those over 18 years of age (Group II)

	Total (n=40)		Group 1 (n=22)		Group 2 (n=18)		p
	n	%	n	%	n	%	
Periorbital pigmentation	30	75	14	64	16	89	0.067
Trichiasis	1	2.5	1	4,5	0	0	0.360
Ptosis	1	2.5	1	4,5	0	0	0.360
Lagophthalmos	4	10	2	9	2	11	0.832
Conjunctival hyperemia	34	85	14	64	18	100	0.004*
Pseudomembrane	6	15	4	18	2	11	0.533
Cicatricial conjunctivitis	19	48	7	32	12	67	0.028*
Meibomian gland dysfunction	38	95	22	100	16	89	0.109
Filamentary keratitis	16	40	8	36	8	44	0.604
Corneal epithelial staining	36	90	18	82	18	100	0.057
Keratitis	5	12.5	2	9	3	17	0.471
Limbal stem cell disease	8	20	0	0	8	44	0.000

n: Number of eyes, *Statistically significant

During follow-up, cataract developed in 4 eyes of 2 patients in Group II (53 and 61 years of age). In addition, intraocular pressure was elevated in 2 eyes in Group II, one with herpetic and the other with fungal keratitis.

The management strategies are shown in Table 4. All eyes were prescribed frequent non-preserved artificial tears, 18 eyes (45%) received lubricant gels, and 10 (25%) were given eye drops containing coenzyme Q10 (Visudrop®, Visufarma). Short-term loteprednol was used at the start of cyclosporine A therapy to relieve complaints of burning and hyperemia. A total of 26 eyes (65%) received cyclosporine 0.05% (Restasis®, Allergan or Depores®, Deva), 26 eyes (65%) used a dexpanthenol-containing gel (Recugel®, Bausch&Lomb), and 6 eyes (15%) received topical matrix regenerating agent (Cacicol®, Laboratories Thea). Oral doxycycline was given only to Group II in 44% of patients.

Overall, 32 eyes (80%) were given autologous/allogeneic serum eye drops, which resulted in improvement in corneal epithelial problems. In Group II, autologous serum was used in 16 eyes (89%). In Group I, allogeneic serum was preferred because some children were afraid of venipuncture and some were underweight. Therefore, allogeneic serum was used in 16 (73%) of the eyes in Group I.

In Group II, temporary or silicone punctal plugs were inserted in 11 patients, amniotic membrane transplantation was performed in 1 eye with fungal keratitis, and cataract surgery was performed in 4 eyes of 2 patients.

Table 4. The recommended treatment for patients in our study group

	Total (n=40)		Group I (age ≤18) (n=22)		Group II (age >18) (n=18)		p
	n	%	n	%	n	%	
Artificial tears (polyvinyl + povidone, or sodium hyaluronate, or trehalose)	40	100	22	100	18	100	1
Sodium hyaluronate + lipid components	8	20	6	27	2	17	0.203
Carbomer gel	24	45	18	82	6	33	0.002*
Coenzyme Q10	10	25	8	36	2	17	0.067
Dexpanthenol	26	65	12	55	14	78	0.125
Cyclosporine A 0.05%	26	65	10	45	16	89	0.180
Cacicol®	6	15	0	0	6	33	0.003*
Moxifloxacin	22	55	10	45	12	67	0.180
Loteprednol	28	70	10	45	18	100	0.0002*
Tetracycline	8	20	0	0	8	44	0.0005*
Autologous/allogenic serum	32	80	16	73	16	89	0.204
Punctual plugs	11	28	0	0	11	61	0.00002*

n: Number of eyes, *Statistically significant

Discussion

Ocular GVHD can affect the whole lacrimal functional unit, leading to lacrimal gland dysfunction, MGD, and ultimately dry eye syndrome as a result of reduced tear production, excessive tear evaporation, and associated corneal and conjunctival inflammation.[9] In the present study of patients with ocular GVHD, MGD and DED were observed in patients approximately 19 months after allo-HSCT. Although the clinical features were similar at all ages, conjunctival hyperemia, cicatrization, and limbal stem cell disease were more frequent in Group II, which consisted of patients older than 18 years of age. Topical treatment was started immediately with non-preserved artificial tears, and cyclosporine A 0.05% and autologous/allogeneic serum were given when necessary. This treatment approach assisted in the improvement of symptoms, clinical findings, and BCVA, with statistically significant improvements seen in Group I.

The lacrimal gland is one of the organs most susceptible to damage caused by chronic GVHD. In the initial phase, T-cells and other inflammatory cells preferentially target the medium-sized ducts in the lacrimal gland. Immune-mediated fibrosis frequently obstructs the ducts of lacrimal and meibomian glands, as well as the nasolacrimal duct.[9] An increase in stromal fibroblasts, fibrosis of the glandular interstitium, T-cell infiltration of the periductal area, and activation of fibroblasts have been observed.[10] Extensive destruction of the lacrimal gland, including ductal fibrosis, ductular stenosis, and reduced secretory capacity, leads to tissue atrophy.[11] The disease process involving destruction and fibrosis of the conjunctival and lacrimal glands contributes to decreased production of aqueous and mucinous tears, resulting in keratoconjunctivitis sicca.[12]

The most reported symptom of ocular GVHD is dry eye, which typically develops 6 to 9 months after allogeneic HSCT.[5] The interval between HSCT and ophthalmic examination ranged between 4 and 84 months in our study group (mean 19.03±18.12 months). The timing of the development of chronic GVHD was proposed to correspond to the tapering or discontinuation of immunosuppressive treatment.[13] Signs and symptoms include fluctuating vision, burning, foreign body sensation, pain, red irritated eyes, photophobia, and excessive tearing.[11] Similarly, all patients in our study had burning, dryness, and foreign body sensation, and most had photophobia, redness, blurred vision, and tearing. Interestingly, tearing was significantly more prevalent in younger patients, which is probably related to their reserve tear capacity.

Dry eye in ocular GVHD commonly presents with blepharitis and MGD.[14] The prevalence of meibomian gland involvement, with inflammatory cell infiltration, fibrotic changes, and ductal obstruction, was reported as 47.8%.[9] In the present study, MGD was observed in 95% of our patients. Our numbers are probably higher because we included only patients who were already diagnosed with ocular GVHD. Chronic ocular GVHD is an immunological process that may affect the meibomian gland structure more severely than other types of dry eye.[15] Ductal epithelial destruction due to lymphocyte aggregation, epithelial cell sloughing with lymphocyte infiltration, or pseudomembrane formation, and eventual extensive fibrosis around the meibomian gland orifices, ductules, ducts, and acini are observed.[16] On meibography, Hwang et al.[17] showed that aggressive destruction of the meibomian glands leads to meibomian gland loss in more than 80% of eyes.

Conjunctival involvement occurs in 9-41% of cases and is considered a sign of severe systemic impairment of chronic GVHD.[18] Conjunctival hyperemia, chemosis, and pseudomembrane formation are frequent in ocular GVHD.[19] Pseudomembranous conjunctivitis (grade 3) has been reported in 12-17% of patients. We encountered conjunctival hyperemia in 85% and pseudomembrane formation in 15% of our patients with ocular GVHD. Hyperemia was observed in all patients in Group II (>18 years of age) and was significantly more frequent than in the younger patients (Group I). Decreased goblet cell density, increased squamous metaplasia, severe goblet cell loss, and inflammatory cells were observed in the conjunctival biopsy of these patients.[20] We also observed cicatricial conjunctivitis in 48% of all eyes and more frequently in Group II (67%). Cicatrization of the conjunctiva may be palpebral, tarsal, or forniceal, leading to obliteration of the fornices, symblepharon formation, lid scarring, and extensive altered lid anatomy, including trichiasis, entropion, or ectropion development, lagophthalmos, eyelash loss, and lacrimal punctal stenosis.[21]

MGD aggravates ocular surface dryness by increasing tear film evaporation.[22] Therefore, DED with MGD leads to secondary conjunctival subepithelial changes, corneal epithelial changes as punctate keratopathy, filamentary keratitis, painful erosions, and secondary corneal infections. Less frequently, sterile corneal stromal necrosis and perforations have been reported.[2] Corneal fluorescein staining is recommended to diagnose and grade ocular GVHD.[8] Superficial punctate keratopathy is the most common corneal manifestation, as observed in 90% of our patients. Corneal neovascularization, persistent epithelial defects, corneal ulceration, and even perforation are reported.[19] *In vivo* confocal microscopy studies of ocular GVHD demonstrated higher density of dendritic cells and globular immune cells, a hyperreflective activated keratocyte network, and a lower density and higher tortuosity of sub-basal corneal nerves.[23] We observed keratitis in 12.5% of our patients, which was related to secondary infection and epithelial sloughing. Interestingly, limbal stem cell disease was observed only in Group II, accounting for 44% of the patients.

Treatment of ocular GVHD aims to reduce symptom severity, sustain disease activity control, and prevent tissue damage and disability.[24] Stepwise treatment is recommended, beginning with the simplest treatment and transitioning to increasingly aggressive interventions as needed. This approach can be listed as lubrication, tear preservation, prevention of tear evaporation, inflammation reduction, epithelial support, supportive care, and surgical intervention.[11]

Intense lubrication with non-preserved artificial tears and viscous ointment at bedtime is important to preserve the integrity of the ocular surface and dilute the inflammatory

mediators in the tear film.[11] Accordingly, every patient in our study was prescribed frequent artificial tear application.

Tear film evaporation can be reduced by improving meibomian gland expressibility with eyelid hygiene, warm compresses, moderate to firm massage, and lid margin cleansing. Topical antibiotic ointments and systemic tetracycline derivatives may provide additional benefits.[25] We used oral doxycycline in 8 eyes. Also, lipid-containing artificial tears could be added to the treatment, as in some of our patients.

Therapeutic options for ocular GVHD include anti-inflammatory agents such as topical corticosteroids and cyclosporine A, autologous/allogeneic serum eye drops, tacrolimus, tranilast, therapeutic contact lenses, and punctal occlusion.[14,26]

Reversible or permanent punctal occlusion may be provided for patients with severe dry eyes. Despite concerns that increased retention time of tears containing inflammatory cytokines may aggravate ocular surface inflammation, it has been shown to be a safe and effective treatment in ocular GVHD patients.[27] Because they are hard to insert and monitor, we did not prefer the use of punctual plugs in younger patients (Group I). However, 61% of adult patients (Group II) did receive punctal plugs.

Topical steroids promote lymphocyte apoptosis and suppress cell-mediated inflammation. They have been shown to be effective in reducing conjunctival inflammation with cicatricial changes in ocular GVHD.[20] However, considering the possible side effects of corticosteroids, they should only be used short term and with low frequency. We only used short-term loteprednol, usually in the commencement period of cyclosporine A.

Cyclosporine A acts via inhibition of T-cell activation and downregulation of inflammatory cytokines in the conjunctiva and lacrimal gland.[28] The reduction of anterior segment inflammation is thought to allow enhanced tear production. Cyclosporine also increases goblet cell density and decreases epithelial cell apoptosis. It was reported to bring about improvement in Schirmer scores, TBUT, and subjective complaints.[29] In a study of 16 patients (32 eyes) with GVHD, dry eye symptoms improved in 62.5% of patients, and corneal fluorescein staining improved in all eyes after 90 days.[30] Malta et al.[31] recommended initiating cyclosporine A prior to allogeneic stem cell transplantation to decrease lacrimal gland inflammation and thereby reduce post-transplant dry eye. Although a logical approach, we believe that further research is needed before integrating preoperative cyclosporine use into the routine treatment regimen. We started topical cyclosporine in mild to moderate cases (65%) and believe that some of the improvement in clinical signs and symptoms was related to its use.

Recently, topical tacrolimus has been shown to reduce local inflammation.[32] Unfortunately, tacrolimus and tranilast are not available for ophthalmic use in our country, so we were unable to use and observe their effects.

Blood-derived eye drops including autologous or allogeneic serum eye drops contain various factors such as epidermal growth factor, vitamin A, transforming growth factor-beta, and fibronectin.[33] Autologous serum eye drops showed marked suppression of apoptosis in the conjunctival and corneal epithelium. Albumin, the major protein in serum, improved ocular surface damage *in vivo,* and prevented apoptosis after serum deprivation in vitro.[34] Successful outcomes of autologous serum eye drops in patients with severe dry eye related to ocular GVHD have been reported. Rocha et al.[35] observed a beneficial effect of autologous serum eye drops in 2 cases with ocular GVHD. In a study of 14 patients with ocular GVHD and severe dry eye, significant improvement in symptom score, corneal staining score, and tear dynamics was observed following treatment with autologous serum eye drops.[36] In our study, 32 eyes (80%) were given autologous/allogeneic serum eye drops. Autologous serum was used in 89% of the eyes in Group II. In cases where autologous serum is not an option because the patient is young, is afraid of venipuncture, or has active systemic inflammation, allogeneic serum eye drops from healthy members are recommended.[37] We also used allogeneic serum in 73% of the eyes of pediatric patients (aged <18 years) in our study (Group I). We observed significant improvement in subjective complaints as well as clinical signs in both groups. A prospective study of allogeneic serum application for 4 weeks demonstrated marked improvement in symptoms and signs of patients with dry eyes related to ocular GVHD.[38] The authors argued that the amount of aqueous tears was not improved because of fibrosis in the lacrimal gland. However, even in moderate to severe cases, increased numbers of goblet cells probably result in improvement of ocular surface condition and dry eye symptoms. We believe that autologous/allogeneic serum could also be used in mild to moderate cases before the disease progresses.

Contact lens use is an option for ocular surface protection. Soft silicone hydrogels have high oxygen permeability, are suitable for extended wear, and can be used as bandage contact lenses. Besides providing symptomatic relief, they also help protect the cornea from frictional forces of the eyelids, the external environment, and tear film evaporation.[2] We used bandage silicone contact lenses in 2 patients for 2 weeks and for a 1-month period for the treatment of corneal epithelial defect. Although we do not have experience with scleral lenses such as the PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) and other commercially available designs, they have been shown to relieve the symptoms of ocular GVHD. These large-diameter rigid gas-permeable lenses cover most of the exposed surface, and the post-lens fluid reservoir provides continuous hydration of the ocular surface.[39]

Surgical interventions such as epithelial debridement, lateral tarsorrhaphy, amniotic membrane transplantation, forniceal reconstruction, limbal stem cell transplantation, and tectonic keratoplasty have been reported in some cases.[11,19] We needed to perform amniotic membrane transplantation in 1 eye and cataract surgery in 4 eyes in Group II.

After 6 months of treatment, clinical scoring and BCVA improved significantly in Group I. While Group II values were also better following treatment, the comparisons did not reach statistical significance. We believe these different results were related to the nature of histopathologic differences between

children and adults. In adults, the disease has a more severe course leading to cicatricial changes of the lacrimal glands, meibomian glands, and goblet cells. In children, these cells likely still have the potential to partially recover if treatment starts early. However, studies on histopathologic evaluation according to age are necessary to support this hypothesis.

The main limitation of our study is the small sample size, as ocular GVHD is a rare and overlooked condition. Further studies with larger sample sizes may help shed more light on the age-related clinical characteristics of this disease.

Conclusion

In conclusion, ocular GVHD is a disabling condition affecting both children and adult patients. It has a wide clinical spectrum from DED to sight-threatening surface inflammation. Patients' responses to topical treatment options are also variable. Non-preserved artificial tears are satisfactory only in mild cases. Topical cyclosporine is helpful in mild to moderate cases. Autologous/allogeneic serum drops should be the treatment of choice in mild to moderate cases. Allogeneic serum drops are also a good alternative in cases where autologous serum is not available. In adults, cicatricial changes such as conjunctival cicatrization and limbal stem cell disease were more common. After 6 months of treatment, pediatric patients showed significant improvement in clinical scoring as well as BCVA. Early diagnosis and intervention are imperative for optimal outcomes.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained (#BTEDK-12/20).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A.Y., Y.A.A., O.D., Concept: R.A.Y., Y.A.A., O.D., Design: R.A.Y., Y.A.A., O.D., Data Collection or Processing: R.A.Y., Y.A.A., O.D., Analysis or Interpretation: R.A.Y., Y.A.A., O.D., Literature Search: R.A.Y., Y.A.A., O.D., Writing: R.A.Y., Y.A.A., O.D.

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Original Article

The Effect of Prolactinoma on Tear Film Function

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Abstract

Objectives: To compare dry eye parameters in prolactinoma patients and healthy controls and evaluate their correlation with prolactin (PRL) levels and the duration of hyperprolactinemia.

Materials and Methods: Consecutive patients with prolactinoma and healthy controls were included in the study. Schirmer, tear break-up time (TBUT), tear osmolarity values, and ocular surface disease index (OSDI) scores were evaluated for each patient. Follow-up time and total duration of hyperprolactinemia were recorded for prolactinoma patients.

Results: The study included 39 eyes of 39 patients with prolactinoma and 39 eyes of 39 age- and gender-matched healthy controls. Prolactinoma patients showed lower Schirmer (14.1±8.4 vs. 24.8±8.9 mm; p<0.001) and TBUT values (7.0±3.2 vs. 11.6±2.6 s; p<0.001) and higher OSDI scores (20.6±16.6 vs. 5.8±2.4; p<0.001) compared to the healthy controls. While the mean osmolarity of the prolactinoma patients was 301.6±8.3 mOsm/L, it was 297.7±12.5 mOsm/L for the healthy controls (p=0.07). The duration of hyperprolactinemia in prolactinoma patients showed a negative correlation with Schirmer (r=-0.395; p=0.013) and TBUT values (r=-0.377; p=0.018) and a positive correlation with OSDI scores (r=0.337; p=0.036).

Conclusion: Prolactinoma patients had significantly lower Schirmer and TBUT levels and higher OSDI scores compared to the healthy controls, but no significant difference in tear osmolarity. The effect of high PRL levels on tear film function was duration-dependent.

Keywords: Prolactinoma, dry eye, Schirmer, tear osmolarity, tear break-up time

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Introduction

Prolactinoma is a pituitary adenoma which originates from prolactin (PRL)-producing cells of the pituitary gland. It occurs more frequently in middle-aged women, especially between the second and fifth decades. The female-to-male ratio of the disease was reported to be 10:1, and its prevalence is 100 per million cases.[1,2] With its benign nature, adenoma does not spread to local tissues or distant organs. Prolactinoma shows its effects in the body via hormonal differences or local pressure on the adjacent structures. Hyperprolactinemia disrupts reproductive hormone production and causes different signs and symptoms in both male and female patients. Amenorrhea, oligomenorrhea, galactorrhea, and hirsutism are among the most commonly observed symptoms in female patients. Erectile dysfunction, loss of libido, and gynecomastia are commonly observed in male patients. If prolactinoma remains undiagnosed, it can cause pressure signs such as headache, diplopia, and visual field loss.[1,2,3]

Dry eye disease (DED) is one of the most common causes of ocular irritation in adults.[4] Rheumatologic pathologies such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome may accompany DED or it may present as a primary ocular problem without any accompanying disease. The most frequent symptoms are common ocular irritation symptoms like burning, stinging, lacrimation, and red eyes. Schirmer's test, tear break-up time (TBUT), tear osmolarity, slit-lamp examination, and ocular surface disease index (OSDI) scores can be utilized in the diagnosis and grading of DED.[4,5]

DED is observed more frequently with older age, possibly due to a decrease in gonadal hormone levels during menopause.[6] Hyperprolactinemia inhibits gonadotropin-releasing hormone (GnRH) and follicle stimulating hormone (FSH), which in turn may cause a decrease in gonadal hormone levels. Androgen hormones are strong stimulating factors for meibomian gland function and important in the regulation of ocular surface inflammation.[7] Recent studies have suggested that androgen deficiency is a potential contributor to dry eye.[7,8] Previous in vivo studies showed the presence of prolactin-like molecules and PRL receptors in acinar cells and some interstitial cells of the lacrimal gland.[9] In one study, drug-induced hyperprolactinemia was related to a change in the collagenous structures of the lacrimal gland in rats.[10] Additionally, serum PRL levels have been shown to have strong negative correlations with tear film function in women undergoing hormone replacement therapy.[11] This growing body of evidence may indicate a possible role of hyperprolactinemia in tear film functions.

Our study aimed to compare dry eye parameters (Schirmer's test, TBUT, tear osmolarity, and OSDI scores) in prolactinoma patients to those of healthy controls and evaluate their correlation with PRL levels and duration of hyperprolactinemia.

Materials and Methods

The study included consecutive patients diagnosed with prolactinoma and healthy controls. All patients underwent a complete ophthalmological examination to exclude any coexisting ocular pathology other than DED that might affect the results of the tests. Only the right eyes of the patients were included in the study. Age, gender, and the follow-up duration since the diagnosis of prolactinoma were recorded. Patients who had any systemic diseases other than prolactinoma or were using any systemic or topical medication that might affect tear functions were excluded. Smokers and individuals with prolonged screen exposure (more than one hour per day) were excluded from the study. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from the patients before the examination.

Prolactinoma patients were included in the study regardless of their serum PRL levels on their screening day for the study. Therefore, both controlled and uncontrolled prolactinoma patients were included. Patients who had normal serum PRL levels during follow-up were considered controlled prolactinoma patients, whereas patients who had hyperprolactinemia on the day of screening and for at least 6 months in total during follow-up despite oral cabergoline therapy were regarded as uncontrolled prolactinoma patients. Hyperprolactinemia was defined as a PRL level >25 ng/mL in female patients and >20 ng/mL in male patients. The total duration of previous hyperprolactinemia (in months) was calculated from the patients' medical records.

Schirmer's test, TBUT values, and OSDI scores were recorded for each patient. Schirmer's test was performed without topical anesthesia at the same hour of the day for all patients. TBUT was performed after staining with a fluorescein strip at least 30 minutes after Schirmer's test. OSDI scores were calculated according to the patients' responses to the questionnaire. Tear osmolarity was measured with the TearLab Osmolarity System (TearLab, San Diego, CA, USA). The mean value of two measurements obtained at the same time was accepted as the tear osmolarity value. Tears were collected from the inferior lateral meniscus without any contact with the conjunctiva.

Statistical Analysis

Data distributions were evaluated for normality using the Shapiro-Wilk test. Student's t-test was used to compare the means of the groups with normally distributed data and the Mann-Whitney U test was used to compare those without normal distribution. For the correlation analysis, Spearman's correlation test was used. P values below 0.05 were accepted as statistically significant. SPSS version 21.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses.

Results

Thirty-nine eyes of 39 patients with prolactinoma and 39 eyes of 39 healthy controls were included in the study. The mean age was 39.6±13.5 years for the prolactinoma patients and 35.2±6.5 years for the control group (p=0.08). The female-to-male ratios of the groups were 24:15 and 23:16, respectively (p=0.817). Twelve patients (31%) had controlled and 27 patients (69%) had uncontrolled PRL levels. Twenty-six patients received oral cabergoline throughout follow-up.

The mean Schirmer value was 14.1±8.4 mm in the prolactinoma group and 24.8±8.9 mm in the control group (p<0.001). The prolactinoma and control groups' mean TBUT values were 7.0±3.2 s and 11.6±2.6 s (p<0.001) and their mean OSDI scores were 20.6±16.6 and 5.8±2.4, respectively (p<0.001). The results are shown in Table 1.

The patients' mean duration of hyperprolactinemia was 24.6±27.5 months (range: 3-117) and the mean serum PRL level was 28±32.4 ng/mL (range: 0.86-150) at the time of examination.

The correlation analysis results of the prolactinoma patients are shown in Table 2. The duration of hyperprolactinemia in prolactinoma patients showed a negative correlation with Schirmer (r=-0.395; p=0.013) and TBUT values (r=-0.377; p=0.018) and a positive correlation with OSDI scores (r=0.337; p=0.036).

Discussion

Prolactinoma is a pituitary adenoma that causes high serum PRL levels. Although the effect of androgen hormones on the lacrimal gland and tear function has been investigated extensively, the effect of elevated serum PRL on tear function in humans has not been evaluated yet. In this study, we showed that prolactinoma patients had significantly lower Schirmer and TBUT values and higher OSDI scores in comparison to the healthy controls. While the duration of hyperprolactinemia in these patients showed a negative correlation with Schirmer and TBUT values, it was positively correlated with OSDI scores.

High PRL levels cause a decrease in the levels of GnRH and FSH, which in turn might cause a decrease in the estrogen and androgen levels. Although androgens have been shown to increase the synthesis and secretion of lipids from the meibomian glands, estrogens have been shown to decrease lipid production.[12] The effect of sex steroids seems more complex. Azcarate et al.[7] showed that patients with decreased androgen levels after the development of andropause had high dry eye syndrome scores and lower TBUT values. Antiandrogen therapy was also linked to meibomian gland dysfunction and lipid tear deficiency.[8] Additionally, topical androgen therapies were also suggested for dry eye patients to provide symptomatic relief.[13] In addition to androgens, estrogens have been suggested to play an important role in the regulation of tear film function because of evidence that the frequency of dry eye syndrome increases dramatically in the postmenopausal period and estrogen replacement therapy improves tear film function.[14,15,16,17] Despite the conflicting results regarding the effect of estrogen replacement therapy on tear film function, a recent meta-analysis of 7 different studies showed that estrogen replacement therapy significantly improved Schirmer test results without any significant effect on TBUT.[14] However, the studies included in the meta-analysis had small sample sizes and even the treatment approach was

Table 1. Comparison of dry eye parameters in prolactinoma patients and healthy controls

	Prolactinoma (n=39)	Control (n=39)	p value
Schirmer (mm)	14.1±8.4	24.8±8.9	<0.001
TBUT (s)	7.0±3.2	11.6±2.6	<0.001
OSDI	20.6±16.6	5.8±2.4	<0.001
Osmolarity (mOsm/L)	301.6±8.3	297.7±12.5	0.07

TBUT: Tear break-up time, OSDI: Ocular surface disease index

Table 2. Correlation of PRL levels and duration of hyperprolactinemia duration with dry eye parameters

		Age	Schirmer	TBUT	Osm	OSDI	PRL	HPL Duration
Age		1.000						
	p	.						
Schirmer	r	-0.127	1.000					
	p	0.440	.					
TBUT	r	0.137	0.473**	1.000				
	p	0.405	0.002	.				
Osm	r	0.129	-0.145	-0.076	1.000			
	p	0.447	0.392	0.655	.			
OSDI	r	-0.090	-0.076	-0.574**	0.125	1.000		
	p	0.584	0.646	0.000	0.462	.		
PRL	r	0.096	0.301	-0.016	-0.078	0.230	1.000	
	p	0.561	0.063	0.925	0.648	0.160	.	
HPL duration	r	-0.058	-0.395*	-0.377*	0.097	0.337*	-0.121	1.000
	p	0.728	0.013	0.018	0.567	0.036	0.464	.

r: Correlation coefficient TBUT: Tear break-up time, Osm: Osmolarity, OSDI: Ocular surface disease index, PRL: Prolactin, HPL: Hyperprolactinemia
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

heterogeneous. Thus, further randomized controlled clinical trials are needed to clarify the effect of hormone replacement therapy on tear film function. All of these supporting findings may explain why prolactinoma caused dry eye syndrome.

Numerous studies showed the presence of PRL receptors on the acinar cells of the lacrimal gland and one study also showed the presence of PRL in the tear film.[9,18] A study on a PRL receptor knockout model showed that hyperprolactinemia caused a hyperfemale morphology, suggesting a role of PRL in dry eye syndromes.[19] Hyperprolactinemia in a mouse model was also shown to cause alterations in acinar cells (cellular disorganization, changes in their volume, and altered spacing between the acini) and the amount of collagen in the lacrimal gland in female mice.[10] Mathers et al.[11] showed that serum PRL levels had strong negative correlations with tear film functions in women under hormone replacement therapy. All of these findings support that PRL might have a direct regulatory negative effect on tear film function in the pathogenesis of dry eye syndrome in the prolactinoma patients in our study. Increased levels of serum PRL might have a negative effect on the production of the aqueous part of the tear film, while decreased sex steroids might have a negative effect on meibomian gland function, leading to a decrease in the Schirmer and TBUT values. However, the presence of PRL receptors in the human lacrimal gland and the presence of PRL in the human tear film should be studied extensively to support this hypothesis.

Although we showed decreased TBUT and Schirmer values and increased OSDI scores in prolactinoma patients, we observed no change in tear osmolarity levels in prolactinoma patients. This interesting finding might be explained as the effect of PRL not being related to the inflammatory status of the tear film. Instead, PRL might adversely impact only the production of the aqueous and lipid layers of the tear film, thereby affecting Schirmer and TBUT values without any effect on tear osmolarity, because tear osmolarity is related mostly to the release of the inflammatory cytokines, especially in patients with Sjögren's syndrome.[20]

After observing lower Schirmer and TBUT values and higher OSDI scores in prolactinoma patients, we further analyzed the duration of high serum PRL levels to evaluate its correlation with dry eye status. Our findings showed that the duration of hyperprolactinemia correlated negatively with Schirmer and TBUT values and positively with OSDI scores. Therefore, we concluded that the effect of high PRL levels was duration-dependent. Thus, patients with prolactinoma should be monitored for dry eye-related symptoms.

Study Limitations

Limitations of our study include the absence of serum estrogen and androgen levels of the patients, because the complex effect of prolactinoma on tear film function can be better analyzed with the consideration of sex steroid levels. Another limitation of the study is the exclusion of the patients' fellow eyes. We included only one eye to avoid the double organ bias. However, examination of both eyes for tear osmolarity difference between two eyes might have given important data related to the dry eye status of the patients. Future studies may also examine the tear osmolarity difference in prolactinoma patients.

Conclusion

In conclusion, here we showed that prolactinoma patients had lower Schirmer and TBUT levels and higher OSDI scores compared to the healthy controls, with no significant difference in tear osmolarity. The duration of high serum PRL levels showed a negative correlation with Schirmer and TBUT values and a positive correlation with OSDI scores. Thus, our study suggests that high serum PRL levels might disturb tear film functions in a duration-dependent manner and that patients with prolactinoma should also be questioned about dry eye-related symptoms. However, these findings should be improved with further studies on the effect of PRL on the lacrimal gland and tear film function.

Ethics

Ethics Committee Approval: İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee.

Informed Consent: Obtianed.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: O.K., Concept: C.D., Ü.Y.G., Design: C.D., Ü.Y.G., Data Collection or Processing: O.K., B.M., Analysis or Interpretation: B.M., Literature Search: O.K., B.M., Ü.Y.G., Writing: C.D., Ü.Y.G., O.K., B.M., Ö.A., G.İ.

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Original Article

Effects of Intracameral Drugs and Dyes on Corneal Endothelial Cell Apoptosis in a Rat Model: An *In Vivo* and *In Vitro* Analysis

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Abstract

Objectives: To evaluate the effects of intracameral drugs and dyes on rat corneal endothelial apoptosis and cell morphology.
Materials and Methods: The right eyes of 72 rats were injected intracamerally with 1% lidocaine, 0.01% adrenaline, triamcinolone acetonide (TA) 4 mg/mL, 1% trypan blue (TB), 0.5% indocyanine green (ICG), and fortified balanced salt solution as control. Corneal samples were taken 1 day and 1 week post-injection. Corneal endothelial apoptosis was assessed by the TUNEL technique, and the ratio of apoptotic cells in each group was compared with the control. Corneal endothelial cell morphology was evaluated in each specimen by transmission electron microscopy.
Results: The mean apoptotic endothelial cell ratio was significantly higher at 1 day and 1 week after intracameral adrenaline injection when compared to controls (p=0.03 and 0.021, respectively). TB caused a significantly higher apoptotic cell ratio when compared to controls at 1 week after injection (p=0.043). Lidocaine caused a higher apoptotic cell ratio compared to TA and ICG at 1 week, although not statistically significant (p=0.058, 0.09, 0.69, respectively). In all experimental specimens, transmission electron microscopy showed morphological changes associated with apoptosis.
Conclusion: This study showed that intracameral adrenaline, TB, and lidocaine injections may have toxic effects on corneal tissue, as indicated by ultrastructural and histopathological alterations. Therefore, these agents should be used with caution in intraocular surgery.
Keywords: Intracameral injection, corneal endothelium, apoptosis, TUNEL assay, morphology

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Introduction

Intracameral drugs frequently used in ophthalmic practice are useful tools for ocular anesthesia, pupil dilation, safe capsulorhexis, and control of intraocular inflammation. However, the effects and toxicity of these agents on the corneal endothelium are still under investigation.

Apoptosis is a form of cell death that occurs without damaging anatomical structures or disrupting physiological functions.[1,2] It is thought to play a key role in the modulation of corneal tissue through the induction of endothelial and epithelial cells.[3,4] One feature of apoptosis is the fragmentation of DNA, which can be detected in dying cells by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL). Previous studies have addressed various techniques to detect endothelial cell apoptosis induced by intracameral agents. However, the TUNEL technique has been studied in few reports.[5,6,7] It was shown that the TUNEL assay performed on the corneal endothelium allows better identification and quantification of apoptotic cells than other techniques.[8,9]

Previous data on intracameral agents are mostly from isolated reports of *in vivo* and *in vitro* studies. In this study, intracameral agents frequently used in intraocular surgeries were evaluated and compared in a single study using ultrastructural analysis. We aimed to demonstrate the effects of these drugs and dyes on corneal endothelial cell integrity using the TUNEL technique and transmission electron microscopy (TEM) in a rat model.

Materials and Methods

This animal study was performed in accordance with the Statement for the Use of Animals in Ophthalmic and Vision Research from the Association for Research in Vision and Ophthalmology, and the protocol was approved by the Institutional Animal Care and Use Committee of Başkent University Hospital in Ankara, Turkey (project no: DA 04/02).

The study was conducted with a total of 72 male Wistar albino rats aged 6 to 9 months and weighing between 301 and 457 g (mean: 357±23.6 g). Intracameral agents used were 0.05 mL of 1% preservative-free lidocaine, 0.01% adrenaline with preservative, triamcinolone acetonide (TA) 4 mg/mL, 1% trypan blue (TB), 0.5% indocyanine green (ICG) (25 mg ICG/0.5 mL aqueous solvent in 4.5 mL balanced salt solution [BSS]), and BSS alone. The rats were randomized and assigned to group 1 (adrenaline), group 2 (lidocaine), group 3 (TA), group 4 (ICG), group 5 (TB), and the control group (BSS). The rats were anesthetized with intramuscular injections of ketamine hydrochloride (Alfamine, Ege-Vet, Turkey) 60 mg/kg and xylazine hydrochloride (Rompun®, Bayer, Germany) 10 mg/kg before the procedure. In the right eye of each rat, the anterior chamber was entered through a long corneal tunnel in the superotemporal quadrant using an MVR knife, and 0.05 mL of aqueous humour was removed using a 30-gauge canula (Figure 1A,B). The same volume of an agent was injected intracamerally with a separate cannula, and the anterior chamber was not irrigated with BSS (Figure 2A-D). One agent was injected in each procedure. Topical ofloxacin 3 mg/mL was administered 3 times a day for 5 days after the injection.

For the euthanasia of the experimental rats, a high dose of intramuscular anesthetics or an intracardiac injection of potassium chloride was administered 1 day or 1 week after intracameral injection. In each group, 6 rats were sacrificed on day 1 and 6 rats at 1 week before their corneal samples were taken. Corneal transparency was clinically evaluated using a spotlight just before euthanasia. Immediately following death, the corneas were prepared for TUNEL staining and TEM analysis. The corneas were removed with a knife and scissors, leaving a 1 mm scleral rim, and the iris diaphragm was stripped from the corneal endothelium.

Preparation of the Corneal Samples

The corneas were divided into two parts, and one part was fixed in a glutaraldehyde fixative and the other part in a 4% formaldehyde solution for electron microscopic analysis. Formalin-fixed and paraffin-embedded 5 µm thick tissue sections were stained using the hematoxylin-eosin technique. DNA fragmentation was detected in situ by 3' end labelling using the ApopTag® Plus Peroxidase *In Situ* Apoptosis Kit (Oncor, Gaithersburg, MD, USA). TUNEL-stained apoptotic cells in the corneal samples were counted by the same person (B.B.) under a microscope using the 40x objective lens. Labelled cells were proportioned to the total number of cells and this was expressed as the rate of apoptosis. The percentage of apoptotic cells were scored as follows; grade 0: 0%, grade 1: 1-5%, grade 2: 5-25%, grade 3: 25-50%, and grade 4: ≥50%.

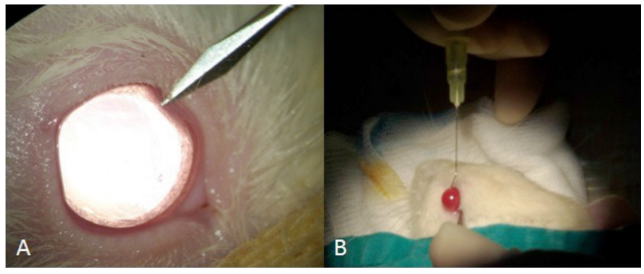

Figure 1. The anterior chamber was entered via the superotemporal corneal quadrant with an MVR knife (A) and 0.05 mL of aqueous humour was drained with a 30-gauge cannula (B) before injection of an intracameral agent

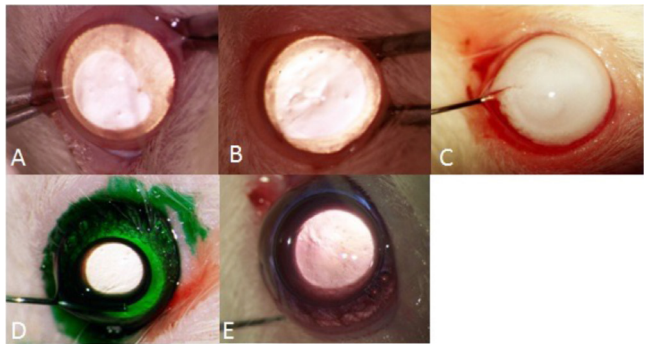

Figure 2. Intracameral injection of 1% preservative-free lidocaine (A), 0.01% adrenaline (B), triamcinolone acetonide 4 mg/mL (C), 0.5% indocyanine green (25 mg/0.5 mL aqueous solvent in 4.5 mL BSS) (D), and 1% trypan blue (E) into the rat anterior chamber

TEM Analysis

For the evaluation of corneal samples under TEM, the corneas were fixed for 24 hours in 2.5% glutaraldehyde solution in a phosphate buffer, post-fixed in 1% osmium tetroxide and 0.5% uranyl acetate, dehydrated through a graded sequence of acetone soaks, embedded in resin, sectioned and contrasted in 1% borax solution with 1% methylene blue and 1% azure II. After the ultrathin sections were cut, the material was counterstained with uranyl acetate and lead citrate. The specimens were initially embedded in dodecenyl succinic anhydride, Araldite CY212 (1:1, vol/vol), and benzyldimethylamine. The blocks were sectioned at 1 µm (thick section) and 0.05 µm (thin section) with an ultramicrotome. The thin sections were stained with uranyl acetate and lead citrate for examination with Carl Zeiss 906E (Oberkochen, Germany) TEM.

Statistical Analysis

The mean percentage of endothelial apoptotic cells in each group 1 day and 1 week after intracameral injection was compared with the control group. Data were analyzed using SPSS 11.0 for windows (SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was used to evaluate the differences between all groups, and differences between two groups were evaluated with the Mann-Whitney U test. P values less than 0.05 were considered statistically significant.

Table 1. The mean TUNEL-positive endothelial cell (apoptotic cell) ratio in each group at 1 day and 1 week after intracameral injections

	Post-injection day 1		Post-injection week 1	
Agent	**Mean ± SD**	**P value**	**Mean ± SD**	**P value**
Adrenaline	0.403±0.036	0.03	0.626±0.081	0.021
Lidocaine	0.188±0.015	0.42	0.361±0.026	0.058
TA	0.248±0.021	0.24	0.295±0.024	0.09
TB	0.233±0.03	0.18	0.428±0.032	0.043
ICG	0.210±0.04	0.76	0.318±0.027	0.69
BSS (control)	0.220±0.034	Ref.	0.316±0.03	Ref.

TA: Triamcinolone acetonide, TB: Trypan blue, ICG: Indocyanine green, BSS: Balanced salt solution, SD: Standard deviation

Results

The study examined 72 rats, and each group comprised 12 eyes. The mean ratio of TUNEL-positive apoptotic cells for each group 1 day and 1 week after intracameral injection is shown in Table 1. On postoperative day 1, the adrenaline group had a statistically significantly higher mean apoptotic cell ratio than the control group (p=0.03). The mean apoptotic cell ratios in the lidocaine, TA, TB, and ICG groups were not significantly different from the control group (p>0.05). At postoperative 1 week, the adrenaline and TB groups had statistically significantly higher mean apoptotic cell ratios than the control group and other agent groups (p=0.021 and 0.043, respectively). When apoptotic cell ratios were scored, apoptosis varying between grade 1 and grade 4 was detected in all agent groups at 1 day and 1 week after injection (Figure 3A-D). Grade 4 endothelial apoptosis was observed at 1 day and 1 week after injection only in the group given adrenaline (Table 2).

During the injection, minimal iris prolapse occurred in two rats. However, the iris was repositioned with proper

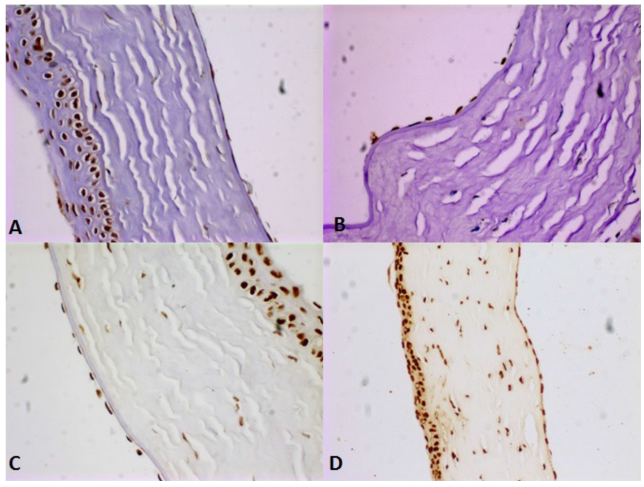

Figure 3. The effect of intracameral agents on endothelial cell apoptosis along the corneal folds was demonstrated by TUNEL technique. Cells with chromatin condensation were labelled and proportioned to the total number of cells. The rate of apoptosis was scored as Grade 0 (0%), Grade 1 (1-5%) (A), Grade 2 (5-25%) (B), Grade 3 (25-50%) (C), and Grade 4 (<50%) (D)

Table 2. The apoptotic scores in each rat corneal endothelium at 1 day and 1 week after the injection of intracameral agents

Agents	**Grade at 1 day post-injection (n=6)**						**Grade at 1 week post-injection (n=6)**					
Adrenaline	1	1	2	2	2	4	2	3	2	2	4	1
Lidocaine	1	1	2	1	1	1	3	3	2	1	2	1
TA	0	1	0	1	1	1	0	1	1	1	2	0
TB	0	2	1	0	1	1	1	3	2	2	3	1
ICG	2	1	1	1	2	0	3	1	2	0	2	1
BSS (control)	0	1	1	0	2	0	0	1	2	1	1	0

TA: Triamcinolone acetonide, TB: Trypan blue, ICG: Indocyanine green, BSS: Balanced salt solution

manipulation. Corneal edema was observed at 1 week in two rats with grade 4 apoptosis in the adrenaline group and one rat in the TB group. Minimal hemorrhage was observed in the anterior chamber in three rats on day 1. There was no sign of infection or endophthalmitis.

In TEM analysis, the control group displayed normal endothelium with intact cell junctions and organelles at 1 day and 1 week after BSS injection (Figure 4A). In the mid phase of apoptosis, the corneas showed chromatin clusters and mitochondrial swelling with vacuolization (Figure 4B). In the late apoptotic phase, chromatin condensation with mitochondrial swelling and shrinkage of the nucleus was observed (Figure 4C).

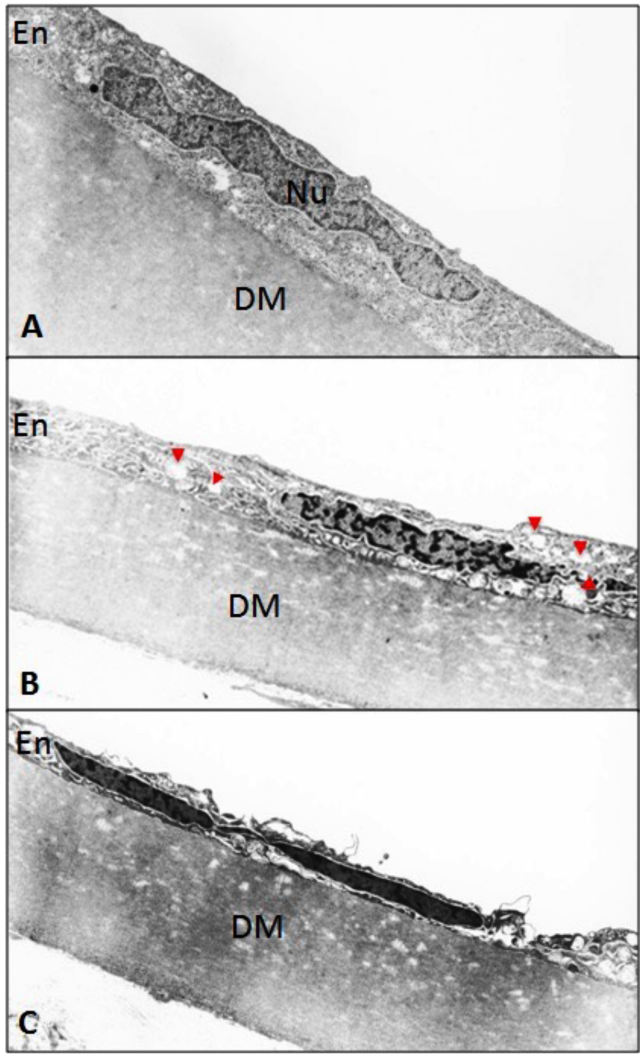

Figure 4. High-magnification transmission electron micrograph of rat corneal endothelium. The normal endothelium (En) is adherent to Descemet's membrane and the nucleus (Nu) appears long and undulated within the cell (A). The cells in the mid-phase of apoptosis show mitochondrial swelling, cytoplasmic vacuolization (arrows), and chromatin clustering (B). In the late apoptotic phase, the surface cell membrane is disrupted and chromatin condensation, mitochondrial swelling, and nucleus shrinkage are observed

Discussion

Our results showed that intracameral administration of adrenaline and TB induced significantly a higher rate of apoptotic response in the corneal endothelium. Lidocaine also caused more pronounced apoptotic changes in the first week, but there was no significant difference compared to the control group. Comparing day 1 and week 1 analyses, the proportion of apoptotic cells was higher after a week than after a day, suggesting that longer exposure may increase the apoptotic effect over time.

In the present study, TEM demonstrated the characteristic morphological features considered the hallmarks of apoptosis. These features include chromatin condensation, nuclear fragmentation, cytoplasmic vacuolization, and mitochondrial swelling, which were observed in the corneal endothelium 1 day and 1 week after drug administration.

Adrenaline is an agent used to provide rapid pupil dilation during intraocular surgery and minimize iris damage in patients with floppy iris syndrome.[10,11] Intracameral adrenaline use has been shown in numerous studies to be safe and effective.[12,13,14,15] However, there is still controversy regarding the possible endothelial toxicity. Liou et al.[16] observed that there were no significant changes in cell density or corneal thickness between rabbits that received intracameral injections of adrenaline and saline and that electron microscopic analysis showed healthy endothelial cells in all groups. Hong et al.[17] also showed that intracameral injection of adrenaline (up to 1%) did not affect the viability or morphology of endothelial cells in the rabbit cornea. In contrary, Hull et al.[18] reported that the endothelial damage caused by adrenaline was caused by the 0.1% bisulfite it contains, which is used to enhance the stability of the drug. Some studies also indicated that adrenaline has a high concentration of free radicals, which may contribute to endothelial toxicity.[19,20]

In our study, we observed corneal edema with grade 4 apoptosis in the adrenaline group at 1 week. Recently, toxic anterior segment syndrome was identified after an intracameral injection of 2.5% adrenaline and longer exposure was thought to be the cause.[21]

Lidocaine is an effective local anesthetic agent that acts on all nerve fibers in the anterior chamber. While some studies have indicated that low lidocaine concentrations do not affect corneal endothelial cells,[22,23] other studies have discussed the possibility of adverse effects to intraocular tissues at higher concentrations.[24,25,26,27] Cytotoxic effects have been demonstrated in relation to the concentration or duration of application of intracameral anesthetic agents.[22,23,25,26] It has been reported that 2% lidocaine with or without preservative induces a significant amount of apoptosis in rabbit corneal endothelium.[6,28] In terms of duration, Chang et al.[26] reported that a 1-minute exposure to 1% or 2% lidocaine appears to be safe for rabbit endothelial cells, but longer exposure may cause cytotoxicity. Atilla et al.[27] found that even a short exposure to intracameral lidocaine may result in histologic changes and functional defects in ocular tissues. Kim et al.[25] did not observe apoptosis in the rabbit endothelial cells 1 day after the administration of 1% lidocaine. However,

another study demonstrated apoptotic endothelial cell loss and morphologic changes which were temporary and resolved by 1 week.[6] According to our study, the risk of corneal endothelial cell apoptosis was increased by lidocaine relative to the risk presented by BSS exposure at 1-week analysis. This can be attributed to the longer time the agent remains in the anterior chamber.

TA is used to visualize and manage vitreous loss in the anterior chamber during complicated cataract surgery.[29,30,31] Furthermore, it has been shown to decrease postoperative inflammation and cystoid macular edema.[30] In a study by Oh et al.,[32] TA was administered into the anterior chamber of rabbit eyes, and their analysis showed no significant change in endothelial cell count after 2 hours. However, they observed a decreased amount of microvilli when TA was administered without resuspension. Another study showed cytotoxic effects on cultured rabbit endothelium, which was attributed to the preservative in the vehicle.[33] Histopathological studies conducted on retinal pigment epithelium cells also support the idea that the toxic effects of TA may be caused by 0.025% benzyl alcohol used as preservative.[34,35] In our study, no cytotoxic effect was observed due to TA at 1 day or 1 week after injection.

TB is used for capsulorhexis during cataract surgery. It is also used in staining and stripping the endothelium from the donor lenticule in deep anterior lamellar keratoplasty. Several clinical studies have tested TB toxicity on different structures of the anterior segment, and all have shown good biocompatibility with 0.1% TB.[36,37,38] Chung et al.[39] also evaluated the safety of 1% TB to improve visualization of the anterior capsule of a mature white cataract and found it to be safe. Although TB was shown to be feasible, there have been reports of toxicity related to dose and duration. *In vivo* and *in vitro* studies have demonstrated TB toxicity for corneal endothelium and corneal fibroblasts at higher concentrations and longer exposure periods.[37,40,41,42] Increasing the clinically used concentration resulted in a 38% to 55% decrease in the viability of endothelial cells. One study showed that intracameral TB injection may damage corneal tissue, as shown by oxidative stress parameters and histopathological assessment.[43] Teratogenic and carcinogenic potency has also been shown in animal studies.[44,45] Given these results, there is uncertainty as to whether TB is safe for corneal tissue. Briefly, TB is harmless to corneal cells at widely used concentrations, both in cataract surgery and in corneal tissue banks. However, extreme caution is advised at higher concentrations or longer exposures.

ICG is used as an intraocular stain in cataract and vitreoretinal surgery to improve the visualization of tissues. Intracameral administration is used for anterior capsular staining for safe capsulorhexis. Previous posterior segment studies have revealed that ICG may be toxic to the retina.[46,47] Clinical data showed that retinal glial cells, the nerve fiber layer, retinal ganglion cells, and the optic nerve can be damaged as a result of unknown mechanisms. The use of intracameral ICG tends to be well tolerated by the corneal endothelium during ophthalmic surgery. McEnerney and Peyman[48] demonstrated that ICG selectively stains dead corneal endothelial cells, and does not seem to be harmful to living cells. Holley et al.[49] indicated that the human corneal ultrastructure showed no harmful effects after ICG exposure in their TEM study. Our results based on an animal model also suggest that no toxic effects can be attributed to the dye. However, further research in the clinical setting is needed to document the effects of this stain.

The rats have a flat anterior chamber and thin iris stroma, which may lead to iris prolapse during injection. Among our subjects, only two rats had iris prolapse, and repositioning did not result in any endothelial contact or lens damage that could induce apoptosis. Events that cause inflammation in the anterior chamber may induce apoptosis. However, as all injections were performed by the same person using the same technique, we believe that all rats were subject to the same conditions.

Study Limitations

The present study has several limitations. Our objective was to investigate whether the doses of intracameral agents that are frequently used in clinical practice and determined to be safe in previous studies had an effect on apoptosis. Thus, we did not assess long-term effects or the effects of different doses of intracameral agents on endothelial cell function. Our study's primary objective was to explore the effects of anesthetic, mydriatic, and capsule staining agents in ocular surgery. Cefuroxime, on the other hand, has also been found to trigger apoptosis when administered intracamerally at the end of surgery.[50,51] This subject, however, was beyond the scope of our study.

Although rats are a common experimental model for studying the human cornea, human corneas may have different structural components and levels of endothelial stress than rat corneal endothelium. The rat cornea is thicker in the center and thinner in the periphery when compared to the human cornea.[52] Vasoactive intestinal peptide-positive parasympathetic nerve fibers identified in rat corneas but not in human corneas were reported to minimize corneal endothelium loss and improve corneal allograft survival following transplantation.[53] Human corneas, on the other hand, are protected from toxic injury by proteins and ion concentration in the aqueous humour, as well as a thicker endothelium mucin layer.[54,55] Furthermore, the use of viscoelastic and continuous irrigation during phacoemulsification can minimize these toxic effects. Additionally, the stromal component accounts for 90% of the human cornea, whereas it accounts for 70% in rats.[52] Thus, the disparity between the human eye and rat model could present difficulties in translating the findings. Future clinical trials are needed to support these results in humans. Also, it is known that DNA damage is not a unique feature of apoptosis and can also occur in necrosis. Therefore, using another independent method in conjunction with the TUNEL test may be essential to confirm and characterize apoptosis.

Conclusion

Intracameral injections of 1% lidocaine, 4 mg/mL TA, and 0.5% ICG did not cause damage to rat corneal endothelial cells. However, intracameral injection of 0.01% adrenaline or 1% TB

can induce microstructural changes in the corneal tissue. This should be considered when planning cataract or other ocular surgeries.

Ethics

Ethics Committee Approval: This animal study was performed in accordance with the Statement for the Use of Animals in Ophthalmic and Vision Research from the Association for Research in Vision and Ophthalmology, and the protocol was approved by the Institutional Animal Care and Use Committee of Başkent University Hospital in Ankara, Turkey (project no: DA 04/02).

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

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

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

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Original Article

Evaluation of Corneal Alterations After Short-Term Silicone Hydrogel Contact Lens Use by Confocal Microscopy

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Abstract

Objectives: To evaluate the corneal subbasal nerve morphology, corneal sensitivity, and anterior segment alterations in short-term silicone hydrogel contact lens (SiHCL) users by confocal microscopy.

Materials and Methods: The study included 25 right eyes of 25 male volunteers aged 25-30 years who had never used SiHCLs before. ocular surface disease index (OSDI), tear break-up time, Schirmer test, tear meniscus area, strip meniscometry tube, corneal sensitivity, and corneal subbasal nerve morphology were evaluated before and after 1 month of CL use.

Results: OSDI was 10.6±1.1 before CL use and 17.2±1.2 after 1 month of CL use ($p<0.01$). Schirmer test distance was 16.3±2.3 mm before and 14.3±1.9 mm after 1 month of CL use ($p>0.05$). Tear film break-up time was 7.1±0.4 s before and 6.2±0.3 s after CL use ($p>0.05$). The tear meniscus area was 0.026±0.002 mm^2 before and 0.024±0.001 mm^2 after 1 month of CL use ($p>0.05$). Strip meniscometry tube results were 5.4±0.9 mm before and 4.9±0.8 mm after 1 month of CL use ($p>0.05$). Corneal sensitivity values were 3.2±0.4 mm before and 2.95±0.3 mm after 1 month of CL use ($p>0.05$). Dendritic cell density evaluated by confocal microscopy was 14.84±3.1 cells/mm^2 before and 32.57±4.2 cells/mm^2 after 1 month of CL use ($p<0.01$). Subbasal nerve tortuosity was 0.92±0.2 before and 1.03±0.2 after 1 month of CL use ($p>0.05$). Subbasal nerve density was measured as 4726±310 pixels/frame before and 4570±272 pixels/frame after 1 month of CL use ($p>0.05$).

Conclusion: After a month of SiHCL use, no significant changes were observed in tear secretion, corneal sensitivity, tear meniscus volume, subbasal corneal nerve density, reflectivity, or tortuosity, while a significant increase was found in OSDI and dendritic cell density.

Keywords: Confocal microscope, contact lens, corneal sensitivity, subbasal cell density, ocular surface disease index

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Introduction

With the rising myopia rates and improved comfort resulting from advances in contact lens (CL) technology, silicone hydrogel contact lenses (SiHCLs) are now widely used to eliminate refractive errors.[1] Although the use of CLs is advantageous for users in social terms, it is known to be associated with various complications, including ocular infections such as keratitis, which can cause permanent visual impairment.[2] Their frequent use in routine clinical practice has given rise to the need for further research on the effects of SiHCL use on the ocular surface, and the use of *in vivo* confocal microscopy (IVCM) in this context has steadily increased.

IVCM is a non-invasive imaging method that allows *in vivo* visualization of the ocular surface structure and is used both in the imaging of healthy corneas and in the diagnosis and follow-up of many corneal diseases.[3] Dendritic cells are potent antigen-presenting cells that are considered an immune activation marker and have an important role in the regulation of the immune response.[4,5] IVCM also enables in vivo imaging of corneal dendritic cells, which are frequently seen throughout the subbasal nerve plexus layer.[6,7] Previous studies using IVCM have demonstrated changes in dendritic cell density in the corneal morphology in conditions that cause ocular surface pathology, such as dry eye, allergy, keratitis, keratoconus, and corneal dystrophies.[8,9] Anterior segment inflammation results in activation of Langerhans cells in the cornea and conjunctiva as part of the immune response.[10,11] In addition, dry eye-related symptoms can cause many patients to shorten the duration of soft CL use or completely stop using CLs altogether.[12] Previous studies reported reduced corneal sensitivity associated with CL use.[13,14] However, corneal sensitivity was shown to return to normal after discontinuing CL use.[15,16] Traditional CLs with low oxygen permeability (Dk) create a hypoxic environment in the cornea, resulting in decreased sensory nerve function.[17] Other factors contributing to this loss of sensitivity include sensory adaptation and acidosis-suppressed sensory nerve function.[18,19] Most published studies were conducted with earlier generation CLs made of low-Dk materials. With new-generation SiHCLs, lens-induced hypoxia is considerably reduced or even eliminated. Changes in ocular surface sensitivity that may occur in this low hypoxic environment after short- and long-term SiHCL use are not fully known.[20]

The use of SiHCLs is especially common in young adults, and investigating ocular surface changes in SiHCL users will provide guidance in solving the complications and problems caused by SiHCLs. The aim of this study was to evaluate dry eye findings, corneal subbasal nerve morphology, corneal sensitivity, and anterior segment changes after the short-term (1 month) use of SiHCLs.

Materials and Methods

Participants and Contact Lenses

Approval for this prospective study was obtained from the Medical Research Ethics Committee of Muğla Sıtkı Koçman University Faculty of Medicine on March 31, 2021 (decision number 7/XII). The study adhered to the principles of the Declaration of Helsinki. All participants signed an informed consent form after being informed in detail about the nature and purpose of the study.

Before the study, all participants underwent a complete ophthalmological examination including refraction, visual acuity examination with Snellen chart, intraocular pressure measurement with applanation tonometry, biomicroscopy, and indirect ophthalmoscopy. Twenty-five right eyes of 25 patients between the ages of 18 and 30 years who presented to the ophthalmology outpatient clinic of Muğla Sıtkı Koçman University Medical Faculty to obtain CL and had no previous history of CL use were included in the study. Only men were included in the study to avoid hormonal factors such as pregnancy and menstrual cycle that may affect the measurements. For standardization, all participants used lotrafilcon B (Air Optix, Alcon Laboratories, Fort Worth, USA) silicone hydrogel monthly CLs (lens DK/t ratio 138 @ -3.00 diopters [D]). Eyes with spherical values between -1 and -6 D and no astigmatism were included in the study. Users were asked to wear the CLs for at least 8 hours a day and no fewer than 5 days a week. Exclusion criteria of the study were determined as severe dry eye signs or symptoms, history of systemic disease, previous ocular surface surgery, systemic or ocular surface disease that may affect the cornea, and history of medication use. The participants' ocular surface disease index (OSDI), tear break-up time, Schirmer test, tear meniscus area, strip meniscometry tube (SMTube), corneal sensitivity, and IVCM were evaluated before and after using the SiHCLs for 1 month.

Ocular Surface Disease Index

The OSDI is a 12-item questionnaire that assesses dry eye-induced ocular irritation symptoms and associated visual functions. All participants were asked these questions in face-to-face interviews before and after 1 month of SiHCL use, and their answers were recorded in the system. Each item in the OSDI questionnaire is scored between 0 and 4. As in the original questionnaire, OSDI scores were calculated by summing the points from all 12 items, multiplying by 25, and dividing by the number of items answered to transform the results into a 0-100 scoring system. OSDI scores of 0-12 were regarded as normal, 13-22 as mild, 23-32 as moderate, and 33-100 as severe ocular surface disease.[21]

Schirmer Test, Tear Break-Up Time, Tear Meniscus Area, and SM Tube

The Schirmer test was performed by placing a sterile Schirmer paper (Tearflo; Alcon Laboratories, Inc., Fort Worth, TX, USA) in the outer third of the lower eyelid, waiting for 5 minutes, and recording the amount of strip wetting. Evaluation of tear break-up time was performed by touching a sterile fluorescein strip to the conjunctiva, asking the patient to blink once and then keep their eyes open, and recording the time (in seconds) when the first dark spot appeared under the biomicroscope with cobalt blue light. Tear meniscus area was measured using anterior-

segment optical coherence tomography (RTVue, Optovue Inc, USA) by delineating its borders and calculating the area in mm^2 (Figure 1a,b).[22] SMTube value is evaluated using meniscometry strips that measure the amount of tears accumulated in the tear meniscus. The strip was placed in the tear meniscus of the bottom eyelid without touching the ocular surface and the amount of wetting was measured in millimeters after 5 minutes using the scale on the strip.[22]

Corneal Sensitivity

To evaluate corneal sensitivity, we utilized a modified Cochet-Bonnet esthesiometer with 0.3 nylon filaments 0.09 mm in diameter (Unitika Ltd. Tokyo, Japan), as used previously in another study.[23] Seven filaments ranging in length from 0.5 cm to 4 cm were prepared. Starting from the longest (4 cm, lowest pressure), each length of nylon filament was used three times to stimulate the corneal nerves and elicit a corneal blinking response. The central cornea was touched with the filament held perpendicularly and avoiding the eyelashes and lid margins. The same procedure was repeated, reducing the length of the nylon filament by 0.5 cm each time, until a complete blink reflex was elicited. Three measurements were recorded for each eye and the average was used for analysis. The repeatability of this method for obtaining corneal sensitivity measurements was confirmed before performing any tests.

In Vivo Confocal Microscopy and Image Analysis

After all other assessments, topical anesthesia was provided with 0.5% proparacaine hydrochloride drops (Alcaine®, Alcon, Fort Worth, Texas, USA) and IVCM was performed with an HRT III (Heidelberg Engineering GmbH, Heidelberg, Germany) device using the Rostock cornea module. The internally mounted laser source in the HRT generates a 670-nm red diode laser. The high-resolution real-time images obtained in IVCM had a resolution of 1 µm/pixel and contained 384x384 pixels covering an area of 400x400 µm (horizontal x vertical). The images were recorded in a JPEG format with 8-bit data resolution and 128-bit binary floating-point format. Six to eight complete sequences were recorded, each containing 100 images from each cornea (each frame representing an area of 160.00 μm^2). For corneal morphological analysis, three non-overlapping representative images of each cornea were selected. Before IVCM was performed, a drop of Viscotears gel (Alcon Laboratories, Inc., Texas, USA) was placed in and on a TomoCap (Heidelberg Engineering) placed on the objective lens of the microscope. The tip of the TomoCap was brought in contact with the patient's cornea and the patient was asked to look at a fixed point while the scan was performed. Averages of the three best images obtained from the central cornea were obtained. Nerve number and density were measured using the NeuronJ add-on (National Institutes of Health, Bethesda, MD, USA) to the ImageJ software, which allows semi-automatic viewing of nerve fibers and enables their quantification. Distinguished by their bright cell bodies, dendritic cells in the subbasal nerve plexus were counted manually using the ImageJ software.[24] The degree of nerve tortuosity and reflectivity was assessed according to the scale (0-4) described by Oliveira-Soto and Efron.[25]

Figure 1. Representative image of tear meniscus area measurement using anterior-segment optical coherence tomography (OCT). Cross-sectional anterior-segment OCT image of tear meniscus before (a) and after (b) silicone hydrogel contact lens use. Patients with dry eye have significantly lower tear meniscus area than normal people. The black bar shows 250 µm

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Normality of data distributions was tested all parameters using Shapiro-Wilk test. Normally distributed data were analyzed using one-way analysis of variance (ANOVA). If the result of this test was significant, post-hoc Tukey's test was used for pairwise comparisons. Results were evaluated within 95% confidence intervals and a p value less than 5% was considered statistically significant.

Results

In this study, the OSDI score was found to be 10.6±1.1 before and 17.2±1.2 after 1 month of SiHCL use ($p<0.01$) (Figure 2). Schirmer test results at these two time points were 16.3±2.3 mm and 14.3±1.9 mm ($p>0.05$) (Figure 3a) and tear film break-up times were 7.1±0.4 s and 6.2±0.3 s, respectively ($p>0.05$) (Figure 3b). Tear meniscus area was 0.026±0.002 mm^2 before and 0.024±0.001 mm^2 after 1 month of SiHCL use ($p>0.05$) (Figure 4a), while SMTube values were 5.4±0.9 mm and 4.9±0.8 mm, respectively ($p>0.05$) (Figure 4b). Corneal sensitivity test values before and after 1 month of SiHCL use were 3.2±0.4 mm and 2.95±0.3 mm, respectively ($p>0.05$) (Figure 4c). On IVCM, dendritic cell density was determined to be 14.84±3.1 cells/mm^2 before and 32.57±4.2 cells/mm^2 after 1 month of SiHCL use ($p<0.01$) (Figure 5a). Subbasal nerve tortuosity was evaluated as stage 0.92±0.2 before and stage 1.03±0.2 after 1 month of SiHCL use (Figure 5b). Subbasal nerve density at the two time points was 4,726±310 pixels/frame and 4,570±272 pixels/frame ($p>0.05$) (Figure 5c) and subbasal nerve reflectivity was grade 1.73±0.3 and grade 1.66±0.2, respectively ($p>0.05$) (Figure 5d). A representative IVCM image of dendritic cells is shown in

Figure 6. In brief, there were no statistically significant changes in tear secretion, corneal sensitivity, or tear meniscus volume after 1 month of SiHCL use compared to before SiHCL use in our study, whereas there was a statistically significant increase in OSDI. IVCM revealed no change in subbasal corneal nerve density, reflectivity, or tortuosity, while the increase in dendritic cell activation was found to be statistically significant.

Discussion

IVCM is a new, noninvasive imaging method that allows examination of the cornea at the cellular level and is frequently used both in healthy corneas and in the differential diagnosis and follow-up of many diseases. IVCM can provide high-resolution images of the corneal subbasal nerves and immune/inflammatory (dendritic) cells.[26] With the increasing clinical use of IVCM, many studies evaluating the subbasal nerves in the healthy and pathological cornea have been published.

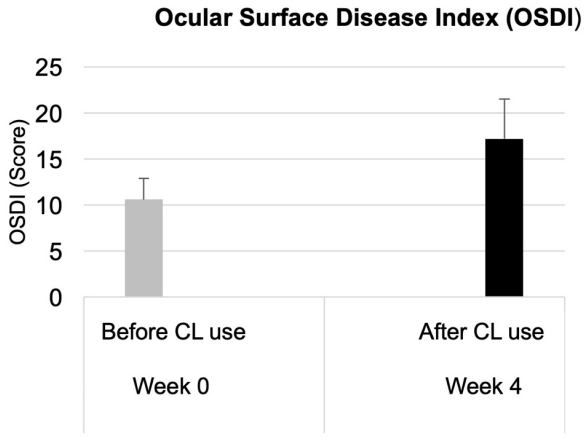

Figure 2. Ocular surface diseases index (OSDI) assessment. After short-term (1 month) use of silicone hydrogel contact lens, there was a statistically significant increase in OSDI compared to before use (*p<0.01)

In this study, we compared parameters such as OSDI score, tear break-up time, tear meniscus volume, Schirmer test results, corneal sensitivity, and corneal subbasal nerve morphology assessed before and after short-term (1 month) SiHCL use. Considering the previous literature, there is no study evaluating all of these parameters together in relation to short-term SiHCL use, thus the results of our study may be important. In our assessment after 1 month of SiHCL use, only the increases in dendritic cell activation and OSDI score were found to be statistically significant compared to before use. We observed no statistically significant changes in Schirmer's test, tear break-up time, corneal sensitivity, or corneal subbasal nerve density. Previous research on similar subjects includes studies demonstrating higher dendritic cell density in the central cornea in people using CLs. Zhivov et al.[27] observed a higher number of Langerhans cells in the corneal epithelium of CL users compared to non-users. These cells are thought to migrate centrally as a CL-induced inflammatory response.[28,29] This result is consistent with previous animal model studies demonstrating migration of Langerhans cells into the cornea in response to the mechanical effect of CL.[30,31] In their study, Zhang et al.[32] compared SiHCLs with low and high Dk value in a rat model and reported that the number of conjunctival dendritic cells increased more with the use of the low-Dk SiHCL. Similarly, two different studies led by Alzahrani et al.[33,34] showed that dendritic cell density was increased in people using soft CLs. These results may be an indicator of the inflammatory response in the cornea induced by the CL. Sindt et al.[35] proposed in their study that this dendritic cell activation could be due to CL-related ocular discomfort. Although we detected no statistically significant change in subbasal nerve density after short-term SiHCL use in this study, Liu et al.[36] reported lower nerve fiber density in CL users compared to non-users. However, they showed that there was no significant difference between CL users with and without dry eye. There are also studies in the literature showing increased dendritic cell activation in dry eye disease.[37] A report by Liu et al.[38] indicated that dendritic cell density gradually

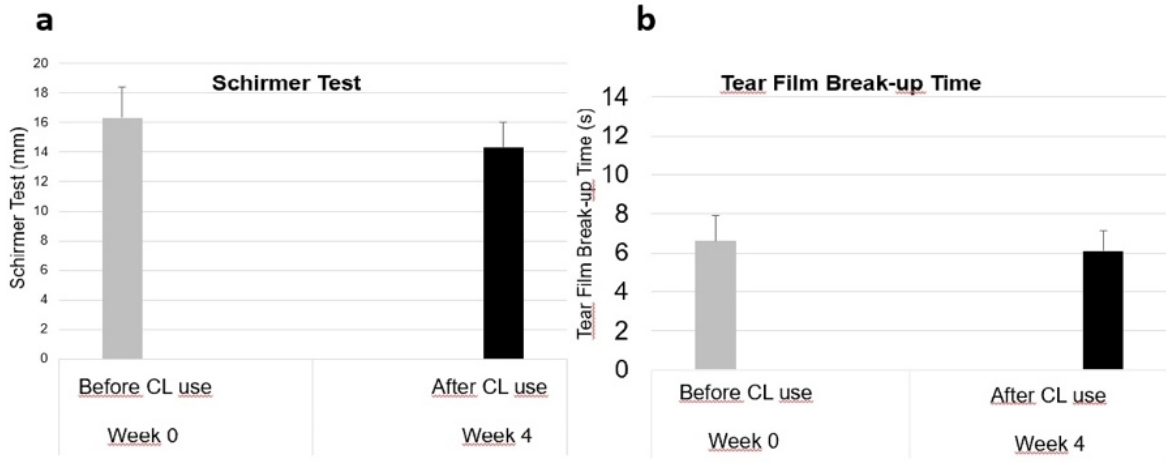

Figure 3. Comparison of Schirmer test and tear break-up time before and after silicone hydrogel contact lens (CL) use. Schirmer test (a) and tear break-up time (b) showed no statistically significant change after short-term use of a silicone hydrogel CL (p>0.05)

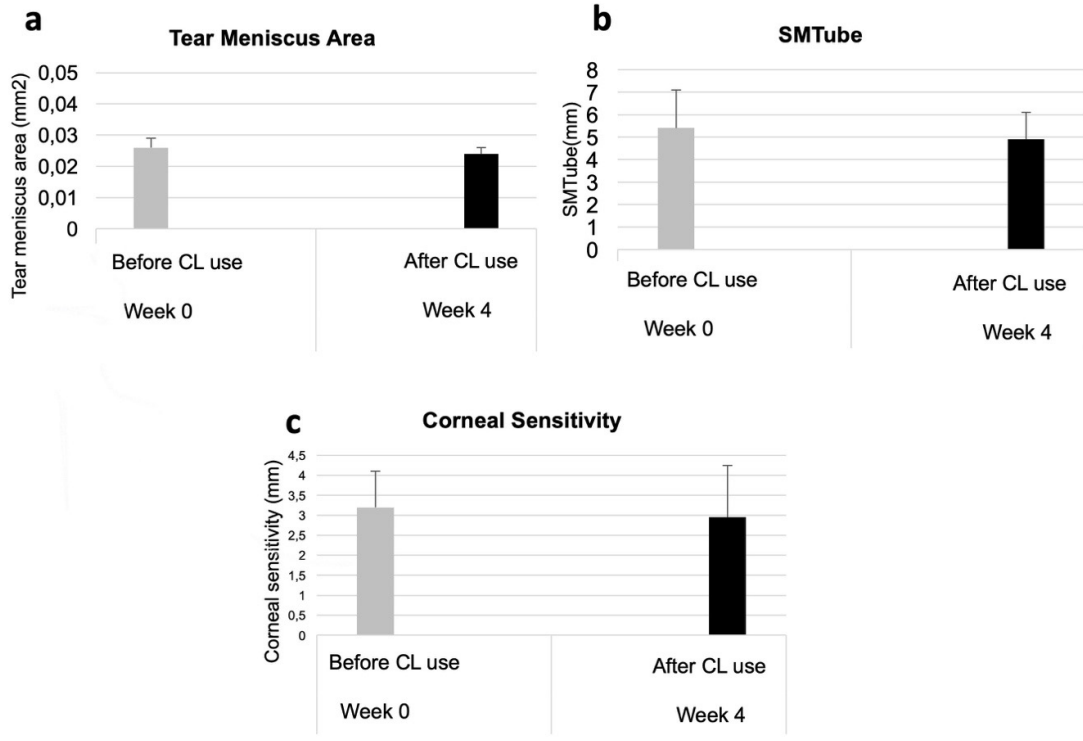

Figure 4. Comparison of tear meniscus area (a), strip meniscometry tube values (b), and corneal sensitivity (c) before and after silicone hydrogel contact lens use showed no statistically significant changes in any of the parameters (p>0.05)

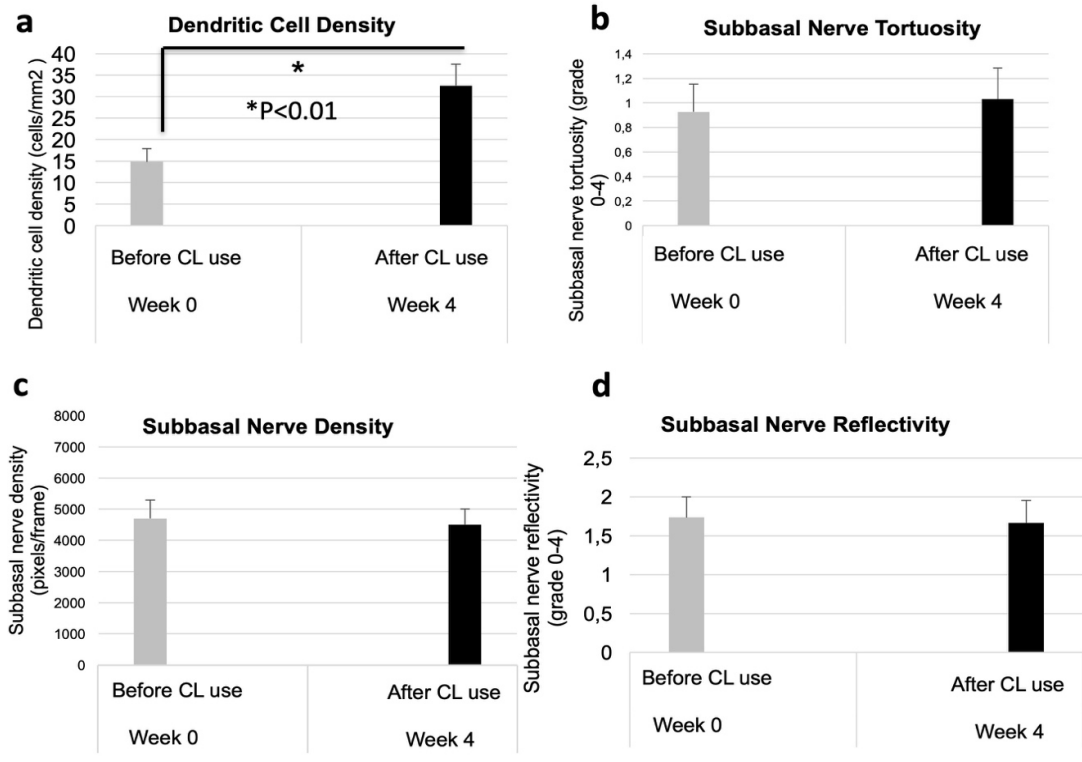

Figure 5. Before and after silicone hydrogel contact lens (CL) use. There was a statistically significant increase in dendritic cell density (a) (*p<0.01). There was no statistically significant change in subbasal nerve tortuosity (b), subbasal nerve density (c), or subbasal nerve reflectivity (d) (p>0.05)

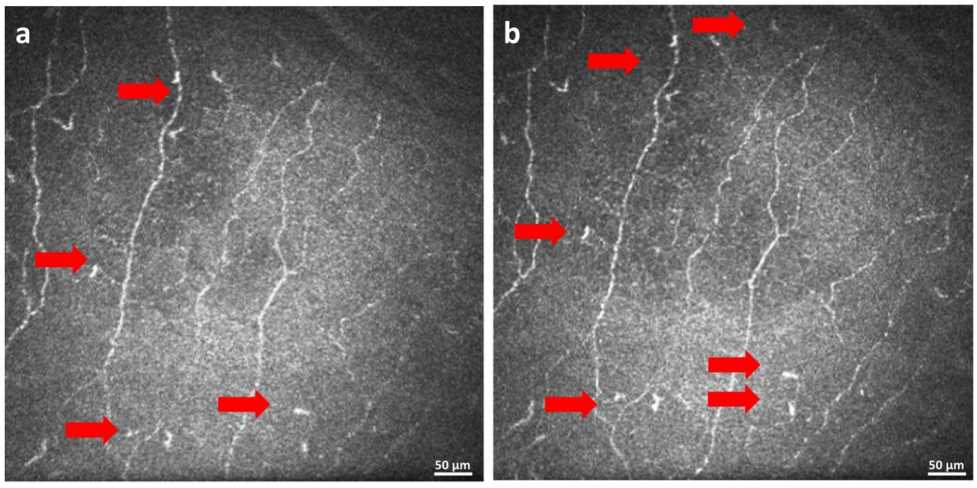

Figure 6. Representative in vivo confocal microscopy images showing dendritic cells (red arrows). Compared to before silicone hydrogel contact lens use (a), the same patient showed a marked and statistically significant increase in dendritic cell density after use (b). The white bar shows 50 µm

increased after starting CL use, reached a peak at week 4, and decreased after week 4. This suggests that ocular inflammation may be greatest at week 4. The decrease observed after week 4 may be associated with user adaptation and subsequent reduced CL-related discomfort.[39] Begley et al.[40] showed that most CL users had symptoms such as dry eye symptoms, itching, irritation, photosensitivity, pain, and blurred or variable vision. We believe the reason for the high OSDI scores after SiHCL use in our study was due to complaints that may occur with initial use, similar to the study by Begley et al.[40]

Previous studies have shown that the most important causes of CL-related dry eye are hypoxia, inflammation, infection, and mechanical effects.[41,42] CLs are foreign bodies that cause clinical or subclinical inflammation of the ocular surface.[43,44] This response may be due to mechanical irritation, hypoxia, and mediator release. Both the inflammation from CL-related dry eye and the inflammation induced by the CL itself may lead to increased dendritic cell density. At the same time, this situation may also be influenced by feelings of ocular discomfort caused by the CL, considering the increase in OSDI score. With long-term use, we believe this inflammation and dendritic cell activation will decrease due to adaptation.

Corneal sensitivity is very important to ensure the maintenance of a healthy ocular surface. The corneal epithelium becomes more susceptible to external factors if there is a decrease in the blink reflex or tear volume due for any reason. Excessive evaporation and cooling lead to increased tear osmolarity. The reduction in tear volume and this increase in osmolarity stress the ocular surface epithelium, resulting in local inflammation and peripheral nerve damage.[45] Local inflammation and nerve damage can cause short- and long-term genetic and molecular changes in primary sensory neurons.[46] Sensory nerve terminals are densely and superficially located between epithelial cells on the corneal surface. Therefore, corneal surface nerves are easily affected by environmental factors (air pollution, low humidity), trauma (cataract and refractive surgery), and ocular surface diseases (pterygium, conjunctivochalasis, keratoconus).[47,48] In this study, we observed no change in corneal sensitivity after short-term SiHCL use.

In addition to corneal subbasal nerve density, other morphological parameters most frequently evaluated include nerve tortuosity, reflectivity, and beading.[49,50] Our results showed no changes in these parameters, which may be because the mechanical exposure to the subbasal corneal nerves in the short 1-month period did not have any effect on neural degeneration and regeneration.

Study Limitations

Limitations of our study are that all participants were men, we used a single type of CL material, the study sample was small, and the results do not include longer term follow-up. Expanding the number of people in this study and creating a new group using a CL of a different material may allow a better comparison and lead to different results.

Conclusion

This study used objective procedures to investigate changes in ocular surface and corneal subbasal nerve structure variables related to the use of a SiHCL that is frequently used in daily practice. In conclusion, our study provides useful data on the anatomical effects of short-term SiHCL use on the ocular surface and corneal subbasal nerves, and may guide future studies designed to evaluate the long-term effects of CL use.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Muğla Sıtkı Koçman University Faculty of Medicine Medical Research Ethics Committee with the decision number 7/XII on 03/2021.

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ş., C.K., Concept: C.Ş., A.K., Design: C.Ş., Data Collection or Processing: C.Ş., C.K., Analysis or Interpretation: C.Ş., A.K., Literature Search: C.Ş., C.K., Writing: C.Ş., C.K.

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

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Original Article

Relationship Between Glycosylated Hemoglobin Levels and Contrast Sensitivity in People with Type 2 Diabetes Mellitus Without Diabetic Retinopathy

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Abstract

Objectives: This study aimed to investigate the relationship between glycosylated hemoglobin (HbA1c) value and contrast sensitivity (CS) in people with Type 2 diabetes mellitus (T2DM) and no diabetic retinopathy (DR) changes.

Materials and Methods: This cross-sectional study was conducted in the endocrinology department of a tertiary hospital and included 120 participants aged 30-40 years with T2DM without DR and with visual acuity of 6/6 in both eyes. Lea CS charts with one symbol size (10M) were used to measure CS. The relationship between HbA1c value and CS was calculated using linear regression analysis.

Results: Of 120 participants with T2DM without DR, 83 (69.2%) were female. Sixty-four participants (53.3%) were in the 36-40 years age group. Mean known duration of diabetes was 3.3±1.65 years. Mean HbA1c value was 10.46±1.48%, with three-fourths of participants having an HbA1c value greater than 8%. Mean CS measured at distances of 1 meter, 2 meters, 3 meters and 4 meters were 164.75±21.12, 122.0±45.08, 93.0±45.37, and 58.67±20.04, respectively. Most participants (n=113, 94.2%) had normal CS (170 at 0.6% contrast) tested at 1 meter. More than half (53.3%) of the participants had reduced CS (40 at 2.5% contrast) at 4 meters. CS measured at 3 meters showed a strong negative correlation with duration of diabetes ($r=-0.855$, $p<0.001$; $R^2=0.731$) and HbA1c values ($r=-0.865$; $p<0.001$; $R^2=0.747$).

Conclusion: CS was inversely associated with diabetes duration and HbA1c values in people with T2DM before any defect in visual acuity or clinical evidence of DR.

Keywords: Contrast sensitivity, HbA1c values, Type 2 diabetes mellitus, diabetic retinopathy

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Introduction

Diabetic retinopathy (DR) is an ocular complication of diabetes mellitus (DM) that causes retinal damage leading to vision impairment and blindness.[1] Vision loss can be prevented in more than 90% of people with diabetes if DR is diagnosed and managed at early stage.[2] Complications from diabetes are strongly related to the type and duration of diabetes and to glycemic control.[3,4] Though vision loss due to DR is preventable through better glycemic control, the prevalence of blindness and vision impairment due to DR is rising in developed and developing countries due to continuous increase in the number of people with diabetes.[5,6]

The prevalence of any type of DR among people with diabetes ranges from 17-22% in India, 17-26% in Pakistan, and 37% in Iran.[7,8,9,10,11] Up to 21% of people with type 2 DM (T2DM) develop DR before diabetes is diagnosed.[12] It is reported that in India, 45% of people with diabetes visit eye clinics for their first eye examination after loss of their vision.[13] Though it is evident that changes in the retinal neurons may be present in people with diabetes without any symptoms of DR, considerable delays in the early detection and treatment of DR are reported.[12,13,14] There is a need for cost-effective testing for people with diabetes to identify people with high risk of DR before the appearance of clinical signs of diabetic eye disease.

In people with DM, the normal function of the retinal neurons is affected by diabetes, and retinal neuronal damage is an early stage of the pathogenesis of DR.[15,16] Visual acuity may not be reduced until 55% of all neuro-retinal channels are affected.[17] One of the functions of the retina is contrast sensitivity (CS), the capacity of the neurological and optical processes to perceive dissimilarity between objects and their surroundings.[18] CS reflects the quality of central vision and may be decreased in people with diabetes despite having normal visual acuity and no signs of DR.[19]

As vision loss caused by DR is irreversible, predictive methods are important to prevent vision loss due to DR through timely intervention.[4] Early evaluation of changes in CS in people with diabetes could assist in the early detection of DR. An understanding of the relationships between glycosylated hemoglobin (HbA1c) values, diabetes duration, and CS may provide information about the usefulness of evaluating CS as a screening tool and predictive measures of retinal dysfunction in people with diabetes. This study aimed to investigate the correlation of HbA1c level and CS in people with T2DM without DR.

Materials and Methods

The study was approved by the Institutional Research and Ethics Committee. Signed inform consent was obtained from each participant. All procedures performed in the study were in accordance with the Declaration of Helsinki.

This cross-sectional prospective study was carried out on participants with T2DM, without DR changes, presenting to the Endocrinology out-patients department in Lady Reading Hospital (a tertiary care hospital) in Peshawar, Pakistan. Using a consecutive sampling method, a total of 120 participants examined from August 15 to November 15, 2019 were included in the study. Inclusion criteria were having T2DM with no signs of DR, age 30-40 years, and best corrected visual acuity of 6/6 in both eyes. Patients over the age of 40 were excluded to avoid age-related changes in CS.[20] Other exclusion criteria were a history of any other eye disease affecting visual acuity and/or CS (e.g., cataract, corneal opacities), refractive errors greater than -3.00 diopters sphere and/or more than ±1.00 diopter cylinder, and mental disability.

Duration of diabetes was determined based on the date of the first blood test that detected diabetes. People with fasting plasma glucose equal or higher than 7.0 mmol/L (126 mg/dL) or 2-h plasma glucose equal or higher than 11.1 mmol/L (200 mg/dL) were included in the study.[21] HbA1c level was measured for each participant at the same visit in the laboratory in the same hospital. HbA1c is a test for people with T2DM that can determine their average blood glucose levels over the previous 3 months.[21]

All participants underwent a detailed ophthalmological examination in the department of ophthalmology in the same hospital. Anterior segment and fundus examination was performed to exclude patients with DR, lens opacification, or any other ocular pathology which reduces visual acuity or CS. The visual acuity of each participant was recorded using a Snellen chart with standard illumination for each eye. Refraction and assessment of CS was performed on each participant by a senior optometrist. Each participant was required to wear their prescribed distance correction before measuring CS.

The contrast of the symbol was defined using the Michelson formula:[22]

$$Contrast = \frac{(Lmax - Lmin)}{(Lmax + Lmin)}$$

Where Lmax equals the luminance on the lighter surface, measured as candelas per square meter, and Lmin equals the luminance on the darker surface.

The ratio is multiplied by 100 and the contrast is expressed as a percentage. CS is expressed as inverse of the contrast. For instance, if the lowest contrast perceived by a person is 0.6%, their CS is 100/0.6=170. Similarly, if the lowest contrast discernable by a person is 1.25%, their CS is 100/1.25=80.

Lea contrast sensitivity charts with one symbol size, 10M, were used. Lea symbols were selected due to the low literacy rate in our society. As most of the participants were illiterate, it was easy for them to match symbols on Lea CS chart. The 10M size was considered appropriate for this study because at the most common testing distance of 1 meter, it corresponds to a visual acuity of 0.1 (20/200, 6/60); at 2 meters, it corresponds to a visual acuity of 0.2 (20/100, 6/30); at 4 meters, it corresponds to a visual acuity 0.4 (20/50, 6/15).[22] The test consists of four shapes: pentagon, square, circle, and apple. The contrast level of the test lines on the Lea contrast sensitivity test chart are 0.6%, 1.25%, 2.5%, 5%, 10%, and 25%. Details about CS on the Lea CS chart is as follows:[22]

Contrast 0.6% = CS 170 (normal CS)
Contrast 1.25% = CS 80 (reduced CS)
Contrast 2.5% = CS 40
Contrast 5% = CS 20
Contrast 10% = CS 10
Contrast 25% = CS 4

CS was measured at four different distances (1, 2, 3, and 4 meters) using standardized room lighting. Each participant was asked to match the shapes on each contrast level and was recorded for the specified four distances for each eye. Patients with CS 170 (who can discern all symbols at 0.6% contrast) were considered normal CS and the patients who could not discern at 0.6% contrast but at 1.25% or higher contrast were classified as having reduced CS.[22]

Statistical Analysis

Statistical analyses of the data were performed using the statistical software SPSS for Windows version 19 (IBM Corp, Armonk, NY, USA). Demographic characteristics were analyzed using descriptive statistics (frequency and percentage). Quantitative variables were expressed as mean ± standard deviation. The relationship between HbA1c value and CS was calculated using Pearson correlation. Taking CS as a dependent variable, linear regression analysis was conducted to measure the strength of the linear relationship between HbA1c values and CS. Statistical significance was accepted at $p<0.05$ within a 95% confident interval (CI).

Results

Of the total 120 participants with T2DM without any DR changes, 37 (30.83%) were male and 83 (69.17%) were female. The male-to-female ratio was 1:2.3. More than half of the participants (n=64, 53.33%) were in the 36-40 years age group. The mean known duration of diabetes was 3.3±1.65 years (range: 0.5-5 years). Most of the participants had a duration of 4-5 years. The mean HbA1c value was 10.46±1.48%, with three-fourths of participants having an HbA1c value greater than 8%. The demographic characteristics and disease profile of the participants are shown in Table 1.

In all participants, CS decreased at greater distance. Mean CS values measured at distances of 1 meter, 2 meters, 3 meters, and 4 meters were 164.75±21.12, 122.0±45.08, 93.0±45.37, and 58.67±20.04, respectively. At 1 meter, 113 participants (94.17%) had normal CS (170, 0.6% contrast) and 7 (5.83%) had reduced CS (80, 1.2% contrast). None of the participants had normal CS (170, 0.6% contrast) at 4 meters. In 64 participants (53.33%), CS fell to 40 (2.5% contrast) at 4 meters. Of 120 participants, none had CS lower than 40 (2.5.% contrast). The results of CS measurement at 1, 2, 3, and 4 meters are given in Table 2.

There was no significant association between the participants' gender and their CS assessed at 0.6% and 1.2% contrast at all distances. Table 3 shows details regarding the association of CS with gender.

Participants in the 36-40 years age group had a higher frequency of reduced CS than the younger age group at all distances. Participants in the 30-35 years age group had normal CS at 1 meter but their CS declined at increasing distances, as shown in Table 4. The difference in CS between the two age groups was statistically significant only at a distance of 1 meter (p=0.01). At longer distances, the difference in CS between the two age groups was not statistically significant, indicating that both groups had a decline in CS as the distance increased.

Pearson correlation analysis was conducted to examine the relationship of diabetes duration and HbA1c values with CS

Table 1. Demographic characteristics and disease profile (n=120)

	Characteristics	Frequency, n (%)
Gender	Male	37 (30.83)
	Female	83 (69.17)
Age	30-35 years	56 (46.67)
	36-40 years	64 (53.33)
Duration of diabetes	<1 year	16 (13.33)
	2-3 years	16 (13.33)
	4-5 years	48 (40.0)
	>5 years	40 (33.33)
HbA1c	<8%	28 (23.33)
	≥8%	92 (76.67)

Table 2. Contrast sensitivity measured at four different distances

Contrast sensitivity (% contrast)	1 meter n (%)	2 meters n (%)	3 meters n (%)	4 meters n (%)
170 (0.6% contrast)	113 (94.17)	56 (46.67)	28 (23.33)	0
80 (1.2% contrast)	7 (5.83)	64 (53.33)	68 (56.67)	56 (46.67)
40 (2.5% contrast)	0	0	24 (20)	64 (53.33)
Total	120	120	120	120

Table 3. Association between gender and contrast sensitivity (CS) measured at four different distances

Distance	Gender	Normal CS (170, 0.6% contrast) n (%)	Reduced CS (80, 1.2% contrast) n (%)	P value
1 meter	Male	35 (94.59)	2 (5.41)	0.89
	Female	78 (93.98)	5 (6.02)	
2 meters	Male	12 (32.43)	25 (67.57)	0.35
	Female	44 (53.01)	39 (46.99)	
3 meters	Male	7 (18.92)	30 (81.08)	0.45
	Female	21 (25.30)	62 (74.70)	
4 meters	Male	16 (43.24)	21 (56.76)	0.616
	Female	40 (48.19)	43 (51.81)	

at different distances. Considering CS of 170 (0.6% contrast) normal and CS of 80 (1.2% contrast) as reduced, the results showed that duration of diabetes and HbA1c values were strong negative correlates of CS in people with T2DM, as shown in Table 5. People who had diabetes for more than 5 years showed more reduction in CS. In addition, CS assessed at 3 meters was more strongly negative correlated with HbA1c values (r=-0.865, p<0.001) than CS measured at 1 meter (r=-0.287, p<0.001) and 2 meters (r=-0.768, p<0.001). Though mean CS assessed at 4 meters was significantly lower than mean CS assessed at 3 meters (58.67±20.04 vs. 93.0±45.37; p<0.001), the negative correlation of HbA1c with CS was slightly stronger when CS was assessed at 3 meters than at 4 meters (r=-0.865 vs. r=-0.813). These findings indicate that CS measured at 3 meters reveals much more about the relationship between HbA1c levels and CS than when measured at distances of 1 or 2 meters.

A bivariate regression analysis was conducted to examine how well HbA1c level could predict reduction in CS. Linear regression analysis showed that Hba1c level accounted for 74.9% of the variance in CS measured at a distance of 3 meters. There was a statistically significant relationship between HbA1c level and CS (p<0.001). The 95% confidence interval for the slope to predict decline in CS from HbA1c level ranged from -23.77 to -29.38. Therefore, for each unit of increase in HbA1c, CS decreased by 23.77 to 29.38 points. Similarly, linear regression indicated that diabetes duration was a strong negative correlate of CS at 3 meters (r=-0.855, p<0.001; R^2= 0.731; CI: -26.05 to -20.86).

Table 4. Association between age and contrast sensitivity (CS) measured at four different distances

Distance	Age (years)	Normal CS (170, 0.6% contrast) n (%)	Reduced CS (80, 1.2% contrast) n (%)	P-value
1 meter	30-35	56 (100)	0	0.01
	36-40	57 (89.06)	7 (10.94)	
2 meters	30-35	26 (46.43)	30 (53.57)	0.96
	36-40	30 (46.88)	34 (53.13)	
3 meters	30-35	16 (28.57)	40 (71.43)	0.20
	36-40	12 (18.75)	52 (81.25)	
4 meters	30-35	26 (46.43)	30 (53.57)	0.96
	36-40	30 (46.88)	34 (53.13)	

Table 5. Correlation of duration of diabetes and HbA1c values with contrast sensitivity

		Contrast sensitivity			
		1 meter	2 meters	3 meters	4 meters
Diabetes duration	rho	-0.257	-0.779	-0.855	-0.779
	p	0.002	<0.001	<0.001	<0.001
HbA1c value	rho	-0.287	-0.786	-0.865	-0.810
	p	<0.001	<0.001	<0.001	<0.001

Discussion

The results of this study demonstrated a statistically significant negative correlation between HbA1c values and CS (p<0.001). CS was affected earlier than any defect in visual acuity or manifestation of DR in people with diabetes. Our findings also indicated a significant association between CS and the duration of diabetes. People having diabetes for more than 5 years showed more reduction in CS. Additionally, reductions in CS were more pronounced when measured at a distance of 3 meters as compared to 1 meter.

We observed a decline in CS with increasing HbA1c values in this study. A similar association between HbA1c values and CS in people with diabetes has been reported in other studies.[23,24,25] Our study shows that people with diabetes who are able to read the 6/6 line on the Snellen chart may have reduced CS despite visual acuity in the normal range. These results are consistent with prior reports indicating that people with diabetes may experience a decline in CS even with no clinical signs of DR.[26,27] These findings suggest that higher HbA1c levels may affect retinal neuronal function in people with diabetes, and previous research has shown that damage to retinal neurons could precede DR.[16,28,29,30] Assessing CS in diabetic people with increased HbA1c values could aid in the monitoring of diabetes-related changes in retinal function.

Complications of diabetes are strongly associated with the duration of diabetes.[24] All 7 participants in this study who showed reduced CS even at a distance of 1 meter had diabetes for at least 5 years. Our results also indicated that participants with diabetes duration of less than 5 years but HbA1c level of 8% or greater had normal CS at 1 meter but reduced CS at longer distances. Similarly, participants aged 30 to 35 years had normal CS at 1 meter and reduced CS at increasing distance, indicating that CS at 3 meters may provide more information about the relationship between CS and HbA1c values than CS assessed at closer distances. These findings suggest that routine assessment of CS in people with a diabetes duration of 5 years or more and/or HbA1c level higher than 8% could be used to complement other diagnostic procedures when assessing the progression of retinal neuronal damage.

Reduced CS in the participants in this study indicates early impairment of retinal function in people with diabetes, as reported in the literature.[15,16,31] Detection of these early changes in retinal function can help in the regular monitoring of retinal function in people with diabetes. Researchers have suggested various types of diagnostic tests that can be used to identify signs of early retinal dysfunction in people with diabetes before anatomical changes appear. They used various types of tests such as retinal sensitivity, optical coherence tomography angiography, and electroretinogram.[20,29,30] These tests are expensive, whereas letter/symbol CS charts are inexpensive and simple to use for screening purposes.

Study Limitations

The limitation of the current study was that we only recruited people with T2DM and did not include a nondiabetic control group. The reason for this was that in the hospital where the study was conducted, laboratory tests are free of charge for people with diabetes but not for nondiabetic people (controls). Due to a lack of funding to cover the cost of laboratory investigations for a control group, we enrolled only people with T2DM.

Conclusion

CS is reduced in association with increased HbA1c values in people with T2DM before any defect in visual acuity or clinical evidence of DR. Findings from this study suggest that periodic evaluation of CS in people with a diabetes duration of 5 years or more and/or HbA1c value greater than 8% could help in the early detection of changes in visual function in people with diabetes.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Research and Ethics Committee.

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: M.S., A.F., Y.T., Design: M.S., A.F., Y.T., Data Collection or Processing: M.S., A.F., Y.T., Analysis or Interpretation: M.S., A.F., Y.T., Literature Search: M.S., A.F., Y.T., Writing: M.S., A.F., Y.T.

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Original Article

Bacillary Layer Detachment in Acute Vogt-Koyanagi-Harada Disease

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Abstract

Objectives: To evaluate the frequency and treatment response of eyes with bacillary layer detachment (BLD) in acute Vogt-Koyanagi-Harada (VKH) disease using spectral-domain optical coherence tomography (SD-OCT).

Materials and Methods: We retrospectively reviewed the medical records of 58 eyes of acute VKH patients with at least 6 months of follow-up between January 2009 and March 2021. SD-OCT, color fundus photographs, and fluorescein angiography images were analyzed in all patients.

Results: The study included 58 eyes of 29 patients. BLD was detected in 33 of the 58 eyes (56.9%) at baseline. Mean serous retinal detachment (SRD) height was 918.50±336.64 µm in the BLD group and 215.33±167.83 µm in the group without BLD ($p<0.05$). A positive correlation was found between SRD height and the presence of BLD ($r=0.783$, $p<0.05$). BLD was significantly more common in patients with a baseline SRD height greater than 500 µm ($p<0.05$). As subfoveal central choroidal thickness (CCT) could not be measured by enhanced depth imaging-OCT at baseline due to extreme choroidal thickness in all eyes, the earliest post-treatment CCT measurements were analyzed. At the completion of pulse steroid therapy, mean CCT was 425±82.87 µm in the BLD group and 385.58±82.87 µm in the group without BLD ($p=0.04$). The mean time to BLD resolution was 12.88±6.5 days (range: 2-26).

Conclusion: BLD is a common tomographic finding in eyes with acute VKH disease and can be differentiated from the associated SRD through careful SD-OCT analysis. Though it is mostly observed in patients with more serious disease, the presence of BLD has no negative effect on long-term visual function.

Keywords: Bacillary layer detachment, optical coherence tomography, serous retinal detachment, uveitis, Vogt-Koyanagi-Harada disease

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Introduction

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune disease involving bilateral granulomatous panuveitis characterized by exudative retinal detachment that may be accompanied by neurological, auditory, and cutaneous findings.[1,2] Ocular signs have been classified as occurring in the acute or late stages of the disease. Choroidal inflammation/thickening and multiple serous retinal detachment (SRD) in the posterior pole are typically observed in acute VKH.[3] Multimodal imaging, especially spectral-domain optical coherence tomography (SD-OCT), plays a key role in the diagnosis of VKH disease.

In acute VHD, SD-OCT findings are typical and diagnostic. The presence of SRD, subretinal fluid compartments separated by septa, and undulations in the retinal pigment epithelium (RPE) are important findings for the diagnosis of acute VHD.[4,5] With advances in OCT technology, these septa are generally thought to be hyperreflective membranous structures that separate from the retina anterior to the RPE-Bruch's membrane complex and form a bridge with the retina. This anatomical finding on SD-OCT is referred to using the term "bacillary layer detachment" (BLD).[6] The presence of BLD is not unique to acute VKH and has been reported in many conditions, including acute VKH disease,[7,8] toxoplasmosis retinochoroiditis,[6] peripapillary pachychoroid syndrome,[9] acute posterior multifocal plaque pigment epitheliopathy,[10,11] central serous retinopathy,[12] neovascular age-related macular degeneration,[13] macular telangiectasis type 2,[14] acute idiopathic maculopathy,[15,16] sympathetic ophthalmia,[17] and trauma.[18,19]

This study investigated the frequency of BLD in patients with acute VKH disease using SD-OCT and evaluated the relationship between SRD height and choroidal thickness and visual prognosis.

Materials and Methods

The records of 33 patients who were followed for at least 6 months for acute VKH disease between January 2009 and March 2021 were reviewed retrospectively. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and after obtaining approval from the Ethics Committee of Dokuz Eylül University.

The patients were diagnosed with VKH according to the revised diagnostic criteria defined at the First International Workshop on VKH Disease (2001).[2] Patients underwent systemic screening and an extensive ophthalmologic examination including best corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure measurement with Goldmann applanation tonometry, detailed fundus examination, colored fundus photography (Visucam® 500, Carl Zeiss Meditec AG, Germany and DRI OCT Triton Plus®; Topcon Corporation, Tokyo, Japan), fluorescein angiography (FA) (Heidelberg Retinal Angiography 2), SD-OCT and enhanced depth imaging-OCT (EDI-OCT) (Spectralis OCT®, Heidelberg Engineering, Heidelberg, Germany). Of the 33 patients whose records were examined, 3 patients were not included in the study because they did not have EDI-OCT images, and 1 patient was not followed up. In all eyes undergoing EDI-OCT imaging, subfoveal central choroidal thickness (CCT) was too high to be measured at baseline. Therefore, it was calculated based on the earliest post-treatment measurements that could be obtained. Patients with ocular conditions other than VKH disease and those with complications of VKH disease such as choroidal neovascularization were not included in the study.

All patients were treated with intravenous methylprednisolone (1 g/day) for a minimum of 3 and maximum of 10 days at the clinician's discretion based on improvement of the SRD, followed by oral corticosteroid (starting at 1 mg/kg, maximum 64 mg/day) tapering 8 mg/week and azathioprine (2 mg/day) or adalimumab (40 mg/2 weeks after an 80-mg loading dose).

Image Analysis

All patients' SD-OCT and EDI-OCT images were evaluated for SRD height, the presence of intraretinal septa, and CCT. The RPE-Bruch's membrane complex, cone interdigitation zone, photoreceptor ellipsoid zone (EZ), and external limiting membrane (ELM) were determined according to the International Nomenclature for OCT consensus guideline.[20] The hyporeflective band between the ELM and EZ was defined as the myoid zone (MZ). SRD height was measured as the vertical line from the upper border of the RPE layer through the fovea to the outer border of the anteriorly detached retina. In eyes with BLD, SRD height was measured from the lower border of the ELM in the anteriorly displaced retina. In EDI-OCT images, CCT was measured as the vertical line drawn through the foveal center from the outer border of the hyperreflective RPE-Bruch's membrane complex to the choroid-sclera junction. BLD was defined as separation of the photoreceptor layer at the level of the MZ (between the ELM and EZ inner segment), as described by Mehta et al.[6] (Figure 1). Time to resolution of BLD was calculated as the time from its first detection on OCT to the examination in which it was no longer observed. SD-OCT images were analyzed by retinal specialists (M.K., A.O.S.).

Statistical Analysis

Statistical analysis of all parameters was performed using IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY, USA) software. Mean, percentage, and standard deviation were used to analyze quantitative variables. BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) values. SRD height, presence of BLD, choroidal thickness, and BCVA data were analyzed. Wilcoxon's test was used to compare pre-treatment and post-treatment parameters. Groups with and without BLD were compared using the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

Results

A total of 58 eyes of 29 patients were included in the study. Of the patients, 23 (79.3%) were female and 6 (20.7%) were male. The mean age of all patients was 35.20±15.15 years (range: 8-66). The clinical characteristics of the patients are summarized in Table 1. All patients had bilateral SRD at the posterior pole.

In all eyes, multiple punctate hyperfluorescent leaks at the RPE level, pooling in the SRD regions, and hyperfluorescence of the disc were detected on FA. The mean follow-up time of the patients was 30±22 months (range: 8-132).

BLD was detected in 33 (56.9%) of the 58 eyes in the first examination. Involvement was bilateral in all patients found to have BLD. SRD height was 918.50±336.64 µm in the BLD group and 215.33±167.83 µm in the group without BLD (p<0.05). There was a positive correlation between SRD height and the presence of BLD (r=0.783, p<0.05). BLD was detected significantly more frequently in patients with an SRD height of 500 µm or greater at the time of diagnosis (p<0.05). Complete resolution of the SRD was first observed after 21.7±1.65 days in the BLD group and 17.66±1.26 days in the group without BLD. There was no significant difference between the two groups in terms of SRD resolution time (p=0.076) (Table 2).

At 1-month follow-up after complete SRD resolution, EZ disruption was detected in 6 eyes (18%) in the BLD group and 3 eyes (12%) in the group without BLD (p>0.05). RPE disruption was detected in 12 eyes (36%) in the group with BLD and 7 eyes (28%) in the group without BLD (p>0.05).

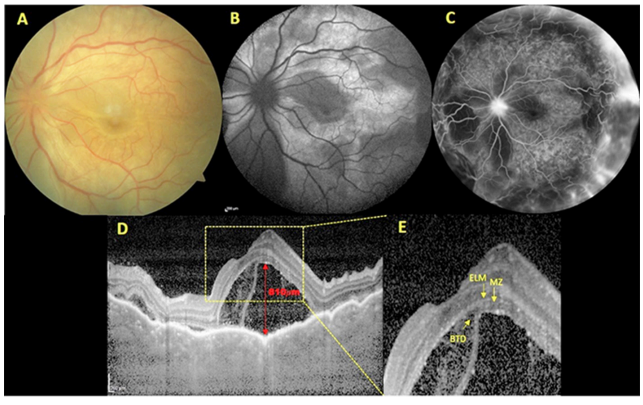

Figure 1. Left eye of a 45-year-old female patient. (A) Color fundus photograph showing multiple bullous serous retinal detachment (SRD) at the posterior pole. (B) Fundus autofluorescence imaging showing hypoautofluorescence in regions corresponding to the SRD and hyperautofluorescence in adjacent regions. (C) Fluorescein angiography shows numerous punctate hyperfluorescent leaks, pooling, and disc hyperfluorescence. (D) Spectral-domain optical coherence tomography (SD-OCT) shows high subretinal fluid (810 µm), septated fluid compartments within the subretinal detachment, and retinal pigment epithelium-choroidal folds. (E) An enlarged section from the SD-OCT image in panel D shows the bacillary layer detachment (yellow arrows) at the level of the inner myoid zone

ELM: External limiting membrane

The mean duration of pulse steroid therapy was 7.96±2.7 days (range: 3-10). After completion of pulse steroid therapy, CCT was measured as 425±82.87 µm in the BLD group and 385.58±82.87 µm in the group without BLD (p=0.04). Mean BCVA at baseline was 0.62±0.8 logMAR in the BLD group and 0.30±0.90 logMAR in the group without BLD (p<0.001). The final BCVA in the two groups was 0.08±1.0 and 0.07±0.90 logMAR, respectively (p=0.802). Final BCVA was significantly improved in both groups (p<0.001 for both). We detected no significant relationship between final BCVA and the presence of BLD. The mean time between first detection and resolution of BLD was 12.88±6.5 days (range: 2-26) (Table 2).

Discussion

The bacillary layer was first described by neuroanatomist Polyak[21] in 1941 as the inner and outer segments of the photoreceptors. In current studies, BLD is defined as the bacillary layer (MZ, EZ, and outer segments) adjacent to the RPE remaining to the posterior, with separation and anterior displacement of the ELM and other retinal layers.[6,7,8,9,10,11,12,13,14,15,16,18,19]

In studies conducted with time-domain OCT, hyperreflective septa that create cystoid spaces by dividing the fluid in SRD into compartments have been reported in acute VKH patients.[22,23]Authors have referred to these hyperreflective structures as subretinal fibrosis,[24] inflammatory fibrin,[5] fibrous strands,[25] or membranous structures.[4] In their study comparing the OCT features of VKH disease, central serous chorioretinopathy, and posterior scleritis, Liu et al.[26] reported that the presence of these membranous structures had over 95% specificity and 97% positive predictive value in the

Table 1. Clinical characteristics of patients with acute VHD

Clinical characteristic	Number of eyes, n (%)
SRD at posterior pole	58 (100)
Eyes with BLD Eyes without BLD	33 (56.9) 25 (43.1)
Anterior chamber cells	20 (34.4)
Vitritis	12 (20.6)
FA: Punctate hyperfluorescent spots and disc hyperfluorescence	58 (100)

SRD: Serous retinal detachment, BLD: Bacillary layer detachment, FA: Fundus fluorescein angiography

Table 2. Comparison of eyes with and without bacillary layer detachment

	Eyes with BLD	Eyes without BLD	*p* value
SRD height (µm), mean ± SD	918.50±336.64	215.33±167.8	**<0.05**
SRD resolution time (days), mean ± SD	21.7±1.65	17.66±1.26	0.076
CCT after pulse steroid (µm), mean ± SD	425±82.87	385.58±82.87	**0.04**
Initial BCVA (LogMAR), mean ± SD	0.62±0.8	0.30±0.90	**0.001**
Final BCVA (LogMAR), mean ± SD	0.08±1.0	0.07±0.90	0.802

SRD: Serous retinal detachment, CCT: Central choroidal thickness, SD: Standard deviation, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution

diagnosis of acute VKH disease. Mehta et al.[6] reported that in an eye with toxoplasma retinochoroiditis, the photoreceptor layer was detached from the inner segment myoid level, similar to the postmortem histological artifact seen in eyes with age-related macular degeneration, and their finding was the first tomographic definition of BLD. In this study, BLD was present in 56.9% of patients with acute VKH disease at initial presentation. BLD resolution on OCT was observed in a mean of 12.8 days with pulse steroid therapy. Agarwal et al.[8] reported the prevalence of BLD as 94.9% (n=112) in 118 eyes with acute VKH disease in their swept-source OCT study conducted between January 2015 and February 2019. Of the 112 eyes with BLD, focal defects in the ELM anterior to the BLD were observed in 8 (7.1%), disruption of the interdigitation zone at the base of the BLD was observed in 53 (47.3%), and the hyperreflective band representing the EZ could not be detected at the base of the BLD in 102 eyes (91.1%). In their study, the patients' mean CCT at the time of admission was 456.1 µm, and it was shown that BLD resolved with pulse steroid therapy in a mean of 3.4 days.[8] In all of the eyes in our study, CCT was too thick to be measured in the initial examination. Therefore, CCT measurements could only be obtained after pulse steroid therapy. The long BLD resolution time compared to the study by Agarwal et al.[8] suggests that the patients in our study were likely diagnosed later and had more severe disease. The difference in choroidal thickness at the time of diagnosis between the studies is consistent with this view.

The mechanism of BLD formation is still unknown. The most likely hypothesis is that decreased perfusion due to choroidal ischemia in the photoreceptor layer may cause BLD. After pulse steroid therapy, BLD regresses as inflammation resolves and choroidal perfusion improves.[4,16] In our study, both CCT and SRD height were significantly greater in eyes with BLD compared to those without BLD. These findings support the notion that increased choroidal thickness associated with intense inflammation may cause impaired photoreceptor perfusion and BLD formation. SRD height is believed to represent the degree of leakage in the choroid, which increases in thickness because of deterioration of the blood-RPE barrier and inflammation during the acute period of VKH disease.[27] It is also thought that in addition to the underlying inflammation, the sudden increase in hydrostatic pressure due to rapid fluid accumulation in the external retina may cause the development of BLD by splitting the photoreceptors.[14,28] In our study, SRD height in patients with acute VKH disease was significantly greater in eyes with BLD compared to the eyes without BLD. In addition, the prevalence of BLD increased to 94.2% among patients with SRD height of 500 µm or greater. These findings demonstrate the positive association between SRD height and the prevalence of BLD. Agarwal et al.[8] used swept source OCT to investigate the presence of BLD in acute VKH disease, whereas we used SD-OCT in our study. There are no studies in the literature comparing SS-OCT and SD-OCT devices for determining the frequency of BLD.

It is emphasized that the metabolic activity of the photoreceptor inner segment and its ability to renew the outer segment by producing new disc membranes persist in patients with VKH disease. As there is no permanent functional damage to the photoreceptors, improvement in visual acuity is reported to be rapid.[4] There are also studies indicating that the presence of SRD does not delay the functional recovery of photoreceptors in patients with VKH disease.[29] The results of histological and imaging studies suggest that rapid functional improvement can be expected in eyes with VKH disease. In our study, we observed that BLD resolved faster with pulse steroid therapy than SRD (mean 12.8 days vs. 21.7 days). In addition, rates of RPE and EZ disruption were 36% and 18%, respectively, in the eyes with BLD at 1-month follow-up after SRD resolution. In the eyes without BLD, these rates were 28% and 12%, respectively, with no significant differences between the groups. In addition, although BCVA was significantly lower at baseline in eyes with BLD compared to eyes without, both groups showed a significant increase in vision and there was no significant difference between them at final examination.

Study Limitations

The main limitations of this study are the small number of patients, its retrospective nature, and the fact that not all patients could be monitored daily. If postmortem histopathological studies could be performed, they may improve our understanding of these findings.

Conclusion

Although BLD is an OCT finding that has been described in many diseases in the literature, it is frequently observed in patients with acute VKH disease. BLD resolves quickly with treatment. The presence of BTD was not shown to have a favorable or unfavorable impact on visual prognosis in patients with acute VKH in this study.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and after obtaining approval from the Ethics Committee of Dokuz Eylül University.

Informed Consent: Obtained.

Peer-review: Externally peer revieved.

Authorship Contributions

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

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Original Article

Association Between Prognosis of Acute Retinal Necrosis and Retinal Involvement

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Abstract

Objectives: The aims of this study were to describe the clinical presentation and treatment modalities of acute retinal necrosis (ARN) and to evaluate complications and clinical outcomes according to the extent of retinal involvement at initial presentation.

Materials and Methods: The medical records of 52 patients diagnosed with ARN were reviewed and 48 were included in the study. Patients were categorized into two groups according to the extent of retinitis at presentation: retinal involvement of 1-2 quadrants (Group A) or 3-4 quadrants (Group B).

Results: The mean age of the 14 women and 34 men at presentation was 51.3±13.6 years (range: 27-78). There were 40 unilateral and 8 bilateral cases. There were 11 eyes (19.6%) in Group A and 45 eyes (80.4%) in Group B. Eleven patients (22.9%) had a history of herpes simplex virus/varicella-zoster virus infection. One patient in Group A and 11 patients in Group B had received local or systemic corticosteroid therapy without concomitant antiviral treatment before referral. The median follow-up period was 29 months (range: 1-209) in Group A and 8.5 months (range: 0.75-209) in Group B. Mean visual acuity (VA) at presentation was 0.42±0.55 LogMAR (range: 0-2.0) in Group A and 1.28±0.95 LogMAR (range: 0-2.9) in Group B ($p<0.05$). The presence of endothelial keratic precipitates at presentation was significantly different between two groups ($p=0.021$). Retinal detachment (RD) occurred in 1 eye (9.1%) in Group A and 30 eyes (66.7%) in Group B ($p<0.001$). Optic disc pallor was seen in 36.4% (4/11) of eyes in Group A and 71.1% (32/45) of eyes in Group B ($p=0.033$). Other ocular complications were not significantly different between two groups. Mean final visual acuity was 0.29±0.41 LogMAR in Group A and 1.61±0.90 LogMAR in Group B ($p<0.05$).

Conclusion: The extent of retinal involvement at presentation affects visual outcomes and this shows the importance of early diagnosis and early initiation of antiviral treatment.

Keywords: Acute retinal necrosis, viral retinitis, antiviral agents, varicella-zoster virus, herpes simplex virus, retinal detachment

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Introduction

Acute retinal necrosis (ARN) is a clinical syndrome characterized by foci of necrotizing retinitis that start in the peripheral retina and tend to spread rapidly to the posterior pole, with associated retinal arteritis, papillitis, vitritis, and anterior uveitis.[1] It is caused by herpes family viruses and can occur in immunocompetent individuals regardless of age or sex.[2,3,4]

ARN is diagnosed based on clinical examination findings. Polymerase chain reaction (PCR) analysis of anterior chamber fluid or vitreous samples can be used to confirm the diagnosis and identify the causative pathogen.[5,6,7] Systemic (intravenous [IV]/oral) and/or intravitreal antiviral agents are used in treatment.[8,9,10]

Despite effective antiviral therapy, patients may have poor final visual acuity (VA).[2,3] Areas of necrosis that regress with retinal atrophy often cause secondary retinal detachment (RD), a complication which negatively affects visual prognosis. However, Hillenkamp et al.[11] reported in their study that vision loss may be associated with retinal ischemia and optic atrophy rather than RD.

This study examined the clinical findings and treatment of patients diagnosed with ARN and aimed to evaluate the relationship between the extent of retinal involvement at initial presentation and the patients' complications and final VA.

Materials and Methods

We retrospectively analyzed the clinical records of 52 patients who presented to the Department of Ophthalmology of İstanbul University, İstanbul Faculty of Medicine between September 1998 and February 2018 and were diagnosed with ARN. The research followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of İstanbul Faculty of Medicine. Informed consent was obtained from all patients before the treatment.

The diagnosis of ARN was made clinically by a single clinician (İ.T.T.) according to the diagnostic criteria established by the American Uveitis Committee.[1]

The patients' clinical records were examined in terms of demographic characteristics, ocular and medical history, ocular findings at initial presentation and during follow-up, laboratory test results, treatments applied, and complications. Human immunodeficiency virus (HIV) and syphilis serology were investigated in all patients, and PCR analysis of intraocular fluid was performed in patients who presented after 2011.

In each examination, patients underwent complete ophthalmologic examination including best corrected VA (BCVA), biomicroscopic examination, intraocular pressure measurement by applanation tonometry, laser flare photometry (LFP) (KOWA FC-2000 or FM-700, Kowa Company, Ltd, Tokyo, Japan), and fundus examination, as well as spectral-domain optical coherence tomography. Statistical analysis was performed by converting BCVA assessed by Snellen chart to logarithm of the minimal angle of resolution (LogMAR) values. Patients with VA at the level of counting fingers, hand movements, light perception, and no light perception were assigned LogMAR values of 2.0, 2.3, 2.6, and 2.9, respectively.[12,13]

The infectious diseases department was consulted for the patients' IV antiviral therapy. All patients received IV acyclovir (10-15 mg/kg every 8 hours; Zovirax injection, GlaxoSmithKline SpA, Verona, Italy) or IV ganciclovir (5 mg/kg every 12 hours; Cymevene injection, F.Hoffmann-La Roche Ltd, Basel, Switzerland) plus topical corticosteroid (CS) (prednisolone; Pred forte 1% eye drops, Allergan Pharmaceuticals, Westport, Ireland) and mydriatic drops. Systemic CS (prednisolone; Prednol tablet, Gensenta Pharmaceuticals, Istanbul, Turkey) was added to treatment according to the patients' clinical findings. Intravitreal ganciclovir (Cymevene injection) or foscarnet (Foscavir injection, Pfizer, New York, USA) was administered to patients with severe involvement at the time of admission, insufficient improvement or progression of retinal necrosis under IV antiviral therapy. After IV therapy, treatment was continued with oral acyclovir (Aklovir tablet, Sandoz Pharmaceuticals, Kocaeli, Turkey) or valacyclovir (Valtrex tablet, GlaxoSmithKline SpA, Istanbul, Turkey). Antiviral prophylaxis was initiated in all patients.

The patients were divided into two groups according to the extent of necrotizing retinitis at initial presentation: 1-2 quadrants of necrotizing retinitis (Group A) or 3-4 quadrants of necrotizing retinitis (Group B). The extent of retinal involvement was assessed by a single clinician from a fundus photograph or detailed fundus drawings. The two groups were compared in terms of duration of complaints, initial VA, ocular findings at presentation, LFP values, disease progression, final VA, and ocular complications (RD, cataract, epiretinal membrane, cystoid macular edema, glaucoma, neovascularization, and optic disc pallor). The data were statistically analyzed using chi-square, Mann-Whitney U, Fisher's exact, and t tests, with p values <0.05 considered statistically significant.

Results

Of the 52 patients with ARN, we excluded 4 patients who were diagnosed with late-stage total RD at presentation or were not followed up. Fifty-six eyes of the remaining 48 ARN patients were included in the study.

Nine patients (18.8%) were referred to our clinic with the diagnosis of ARN and 9 patients (18.8%) were referred to our clinic with other diagnoses. Thirty patients (62.4%) presented to our clinic first. The mean age at presentation of the 14 women and 34 men in the study was 51.3±13.6 years (range: 27-78).

Presenting complaints were vision loss (89.6%), red eyes (47.9%), and ocular pain (33.3%). The mean time from symptom onset to presentation to our clinic was 15.4±11.8 days (range: 4-60). Eleven patients (22.9%) had a history of herpes simplex virus (HSV)/varicella-zoster virus (VZV) infection (herpes labialis in 2, herpetic encephalitis in 5, herpetic keratitis in 1, herpetic iridocyclitis in 1, and shingles in 2 patients). While 45 patients were immunocompetent, 2 patients with cancer and 1 patient with renal transplant were receiving immunosuppressive therapy. None of the patients had HIV infection.

Involvement was unilateral in 40 patients and bilateral in 8 patients. Five patients had involvement in both eyes at initial

presentation, whereas 3 patients developed involvement in the fellow eye during IV antiviral therapy (on days 4, 6, and 12). While 2 of the 3 patients with fellow eye involvement during antiviral therapy were not receiving steroid treatment, one patient developed fellow eye involvement 1 day after steroid treatment was added to the antiviral treatment.

Based on the extent of necrotizing retinitis at initial presentation, 11 eyes (19.6%) were included in Group A (Figure 1) and 45 eyes (80.4%) were included in Group B (Figure 2). Of the 8 patients with bilateral involvement, 5 had one eye in Group A and the other in Group B while 3 patients had both eyes in Group B. Therefore, Group B involvement was present in at least one eye of a total of 42 patients.

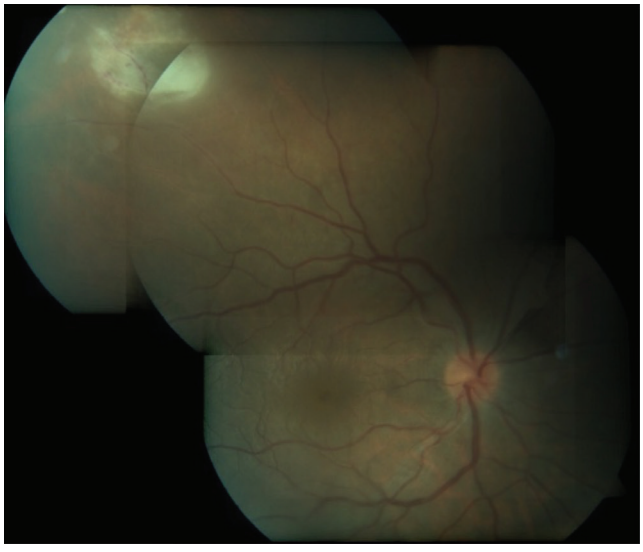

Figure 1. Color fundus photograph of a patients with retinal necrosis in one quadrant (Group A)

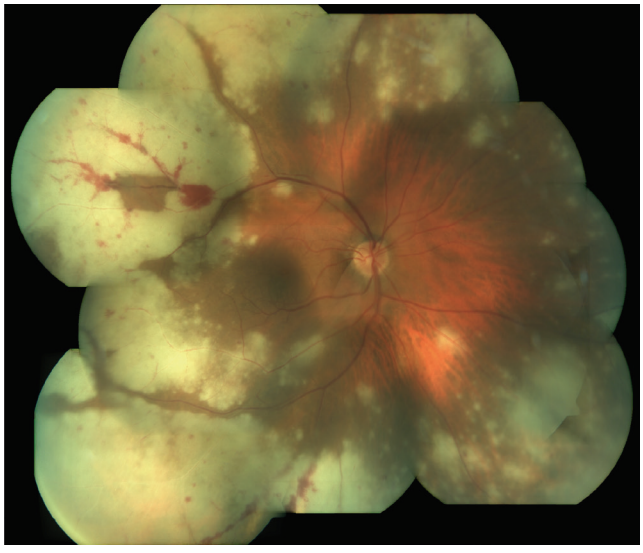

Figure 2. Color fundus photograph of the patient with retinal necrosis in four quadrants (Group B)

Nine patients who were referred with the diagnosis of ARN were receiving systemic antiviral treatment for 1-3 days at the time of presentation. Before presenting to our center, 11 patients (1 patient in Group A and 10 patients in Group B) received 16-1000 mg systemic CS for 3 to 90 days without antiviral therapy, and 3 patients in Group B also received a local depot CS injection. Of a total of 12 patients (1/6 patients in Group A, 16.6%; 11/42 patients in Group B, 26.2%; p>0.05) who received systemic and/or local CS therapy, CS was used for the treatment misdiagnosed noninfectious uveitis in 9 and accompanying systemic disease in 3 of the patients.

The mean duration of complaints was 15.3±13.5 days (range: 5-35) in Group A and 15.4±11.8 days (range: 4-60) in Group B (p>0.05).

Median follow-up time was 29 months (range: 1-209) in Group A and 8.5 months (range: 0.75-209) in Group B. Thirty-two patients (66.7%) were followed for at least 6 months and 24 patients (50%) for at least 1 year.

Mean BCVA at initial presentation was 0.42±0.55 LogMAR (range: 0-2.0) in Group A and 1.28±0.95 LogMAR (range: 0-2.9) in Group B (p<0.05). Mean LFP values at presentation were 73.5±83 photons/millisecond (ph/ms) (median: 46.3, range: 5.6-255) in Group A and 135.7±153 ph/ms (median: 79.9, range: 8.1-551) in Group B (p=0.409).

The patients' ocular findings at initial presentation are shown in Table 1. The only statistically significant difference between the two groups was in the prevalence of keratic precipitate (p=0.021).

PCR analysis of anterior chamber fluid was performed in 24 patients (50%). PCR was positive in a total of 17 patients, including 12 patients (50%) with VZV, 4 patients with HSV-1, and 1 patient with both HSV-2 and VZV. One patient who was positive for HSV-1 was in Group A and the other 16 patients with positive PCR were in Group B (2 VZV-positive patients with bilateral involvement had one eye in Group A and the other eye in Group B). PCR was negative in 7 patients (1 in Group A and 6 in Group B). In patients with negative PCR, diagnosis was confirmed by response to treatment; resampling was not performed.

In 38 patients, necrotizing retinitis was controlled with IV acyclovir in a median of 16.2 days (range: 4-28). Four patients with extensive retinal involvement who were immunosuppressed (2 patients with renal dysfunction receiving immunosuppression therapy by recommendation of the infectious diseases department and 2 patients who were immunosuppressed due to systemic disease) received IV ganciclovir treatment for a median of 22.5 days (range: 10-28) starting at presentation. Six patients who had extensive retinal involvement at initial presentation and persistent retinal necrosis after a median of 40.3 days (range: 22-43) of IV acyclovir treatment (even without progression) were switched to IV ganciclovir treatment. Of 4 patients who had elevated renal function tests (blood urea nitrogen and creatinine) while receiving IV acyclovir, the dose was reduced in 2 patients (10 mg/kg every 12 hours), while IV therapy was discontinued and oral valacyclovir was initiated in the other 2 patients. In

these 4 patients, renal function tests returned to normal with oral or reduced-dose IV antiviral therapy and good hydration, and no worsening of the retinal necrosis was observed. Intravitreal foscarnet and/or ganciclovir injections were administered in addition to IV antiviral therapy to 3 eyes (27.3%) in Group A and 26 eyes (57.8%) in Group B. A single intravitreal injection was performed in 10 eyes, while 19 eyes received multiple intravitreal injections (median: 4.6 injections). Forty-three patients (89.6%) received systemic CS therapy in addition to IV antiviral therapy. Prednisolone was initiated a mean of 12.6±8.4 days (range: 2-33) after IV antiviral therapy at a median dosage of 32 mg/day (range: 16-64 mg). One patient developed bilateral involvement the day after starting prednisolone 32 mg/day on day 5 of IV antiviral therapy, and the prednisolone was discontinued. Time to complete resolution of the retinal necrosis was 28.2±16.7 days (range: 13-58) in Group A and 32±15.2 days (range: 11-78) in Group B, with no statistically significant difference between the two groups (p>0.05).

At the end of IV antiviral therapy, mean LFP values were 32.2±21.7 ph/ms in Group A and 69.4±59.4 ph/ms in Group B (p=0.027).

Ocular complications developed by the patients are shown in Table 2. RD was detected in 55.4% (31/56) of all eyes, with a median time between diagnosis and RD development of 75.5 days (range: 13-330). One eye in Group A with a retinal tear and localized RD at the edge of the tear was treated with barrier retinal argon laser photocoagulation. Twenty-five eyes in Group B with RD were treated with vitreoretinal surgery and silicone injection, and anatomic success was achieved. Vitreoretinal surgery could not be performed in a total of 6 eyes (4 of which presented after developing advanced vitreoretinal proliferation and were deemed inoperable, and 2 because the patient refused the procedure), and phthisis bulbi developed in the 3 eyes that were followed. Silicone removal was performed in 6 patients (6 eyes) at a median of 16 months (range: 3-36). A second vitreoretinal surgery and silicone injection were performed in 1 patient who had silicone removal at 3 months and developed recurrent RD and in 2 eyes of 2 patients who developed fibrous

Table 1. Ocular findings at initial presentation

Ocular findings at presentation	All eyes (n=56) n (%)	Group A (n=11) n (%)	Group B (n=45) n (%)	p value
Conjunctival hyperemia	34 (60.7)	5 (45.5)	29 (64.4)	0.169
Keratic precipitates	52 (92.9)	8 (72.7)	44 (97.8)	**0.021**
Anterior chamber reaction	52 (92.9)	10 (91)	42 (93.3)	0.357
Iris nodule (Koeppe)	3 (5.4)	1 (9.1)	2 (4.4)	0.594
Iris transillumination	2 (3.6)	0	2 (4.4)	0.643
Posterior synechia	6 (10.7)	2 (18.2)	4 (8.9)	0.335
Vitritis	48 (85.7)	8 (72.7)	40 (88.9)	0.241
Vitreous haze	15 (26.8)	2 (18.2)	13 (28.9)	0.381
Elevated IOP	14 (25.0)	1 (9.1)	13 (28.9)	0.167
Optic disc inflammation	26 (46.4)	7 (63.6)	19 (42.2)	0.174
Retinal hemorrhage	43 (71.7)	6 (54.5)	37 (82.2)	0.065
Occlusive arteriolitis	33 (55)	4 (36.4)	29 (64.4)	0.088
Macular edema	12 (20)	4 (36.4)	8 (17.8)	0.162
Macular involvement	3 (5)	0	3 (6.7)	0.512
Retinal detachment	1 (1.8)	0	1 (2.2%)	0.804

IOP: Intraocular pressure

Table 2. Distribution and comparison of ocular complications by group

Ocular complications	Number of Group A eyes (%) (n=11)	Number of Group B eyes (%) (n=45)	p value
Retinal detachment	1 (9.1)	30 (66.7)	**0.001**
Cataract	2 (18.2)	16 (35.6)	0.273
Cystoid macular edema	3 (27.3)	18 (40.0)	0.726
Epiretinal membrane	8 (72.7)	19 (42.2)	0.072
Glaucoma	1 (9.1)	5 (11.1)	0.518
Optic disc pallor	4 (36.4)	32 (71.1)	**0.033**
Phthisis bulbi	0	4 (8.9)	0.309
Neovascularization (iris/retina)	0	4 (8.9)	0.309

Table 3. Mean best-corrected visual acuity (BCVA) values of the groups at initial admission and follow-up			
BCVA values (LogMAR), mean ± SD	**Group A**	**Group B**	**p value**
Initial	0.42±0.55	1.28±0.95	**0.001**
1 week	0.61±0.74	1.30±0.88	**0.015**
1 month	0.33±0.41	1.04±0.95	**0.001**
3 months	0.31±0.34	1.44±0.91	**<0.001**
Final	0.29±0.41	1.61±0.90	**<0.001**
SD: Standard deviation			

proliferation. One eye developed phthisis bulbi despite revision surgery and silicone reinjection. Prophylactic barrier retinal laser photocoagulation was performed in 1 eye of 1 patient.

Cataract developed in 18.2% (2/11) of the eyes in Group A and 40% (18/45) of the eyes in Group B. Cataract occurred after vitreoretinal surgery in 15 eyes in Group B.

Among the other complications, the only significant difference between the two groups was in the prevalence of optic disc pallor (p=0.033).

Comparison of the groups' mean BCVA values at initial presentation and during follow-up is shown in Table 3. The mean BCVA values of group A were significantly better than group B at all visits (p<0.05). The change in mean BCVA at week 1 and month 1 was statistically significant in Group A (p=0.029). In Group B, the change between 1 and 3 months and between values at initial presentation and final visit were found to be statistically significant (p=0.002 and p=0.003, respectively).

Compared to eyes with 1-2 quadrants of retinal involvement, eyes with 3-4 quadrants of retinal involvement at presentation had significantly higher prevalence of keratic precipitates and lower BCVA at initial presentation, and significantly higher rates of RD and optic disc pallor during follow-up, resulting in low VA and high LFP values.

Discussion

This retrospective study evaluated the clinical features, treatments, and outcomes of patients with ARN. Studies have reported that ARN is more common in the 20-60 age range and in the male sex.[14,15] In this study, the age range of the patients was 27-78 years, and involvement was found to be male-predominant (71.2%). It has been reported that patients present most frequently with complaints of vision loss.[16] Similarly, 89.6% of patients in our study complained of vision loss at presentation.

Takase et al.[17] reported a history of HSV/VZV infection in 5 (3.4%) of 149 patients diagnosed with ARN (herpes encephalitis in 1, herpes zoster infections in 4 patients), and the most common ocular finding at presentation was anterior chamber reaction and the presence of keratic precipitates (97%). We observed a higher rate of previous HSV/VZV infection in the present study (22.9%; herpes labialis in 2, herpetic encephalitis in 5, herpetic keratitis in 1, herpetic iridocyclitis in 1, and shingles in 2 cases). Sungur et al.[18] reported keratic precipitates, anterior chamber reaction, and vitritis at presentation in all 13 patients diagnosed with ARN. Similarly, in our study the most common ocular findings at initial presentation were anterior chamber reaction and keratic precipitates, which were detected in 92.9% of the eyes. When the ocular findings were evaluated according to the extent of retinal involvement, keratic precipitates were more common in the group with 3-4 quadrants of retinal involvement.

We divided the patients in this study into two groups according to the prevalence of necrotizing retinitis at presentation (1-2 quadrants or 3-4 quadrants of necrotizing retinitis) and compared their complication rates and outcomes. Meghpara et al.[19] divided 25 eyes with ARN into 3 groups (<25%, 25-50%, and >50% retinal involvement) and reported that 44% of the patients had <25% retinal involvement, 32% had 25-50% retinal involvement, and 24% had >50% retinal involvement. Khochtali et al.[20] detected <25% retinal involvement at presentation in 41.7%, 25-50% retinal involvement in 25%, and >50% retinal involvement in 33.3% of 12 eyes with ARN. In our study, extensive retinal involvement was detected in 80.4% of the eyes at initial presentation. We attribute the high prevalence of extensive retinal involvement with the higher rates of late diagnosis and delayed treatment in our patient group. Especially the fact that they received CS before antiviral treatment because of misdiagnosis may have contributed to the rapid spread of retinal necrosis. However, there was no significant difference between the two groups in terms of symptom duration before presentation. Therefore, extensive peripheral retinal involvement may be asymptomatic and not associated with symptom duration.

PCR analysis of anterior chamber fluid was performed in 25 patients (48.1%) and was positive for VZV in 13 patients (52%) in this study. Our results showed that VZV is the most common cause of ARN, similar to other studies.[11,21,22] Wong et al.[23] compared the clinical characteristics of patients with ARN caused by HSV and VZV, and although both groups had comparable initial VA, the group with VZV ARN was found to have lower final VA and a higher rate of RD. Of the 24 patients in our study who had PCR analysis of anterior chamber fluid, VZV was detected in 12, HSV-1 in 4, and both HSV-2 and VZV in 1 patient. One of the HSV-1-positive patients was in group A and 3 patients were in group B, whereas all VZV-positive patients were in group B.

Baltinas et al.[24] compared IV acyclovir and oral valacyclovir therapy in patients with ARN and reported a median IV treatment duration of 10 days (range: 7-12). Palay et al.[8] reported

treating ARN patients with IV acyclovir at a dose of 1500 mg/m^2/day for 7-10 days. In the present study, IV antiviral therapy was administered for longer than in other studies. Thirty-eight patients received IV acyclovir for a median of 16.2 days (range: 4-28), 4 patients received IV ganciclovir for a median of 20.8 days (range: 10-28), and 6 patients received IV acyclovir for a median of 40.3 days (range: 22-43) followed by IV ganciclovir due to persistent retinal necrosis. All patients continued with oral antiviral treatment after IV treatment. Retinal necrosis regressed completely after a mean of 31.3 days (range: 11-78) after the start of antiviral therapy. Our median duration of antiviral therapy may have been longer than in other studies because of the extent of retinal involvement at presentation.

Previous studies have reported the risk of RD development as 50-80%.[2,18,25,26] In their study, Meghpara et al.[19] found that eyes with >25% retinal involvement had a higher risk of developing RD, all eyes with >50% retinal involvement had optic nerve involvement at initial presentation, and greater extent of retinal involvement, which is also related to RD and optic nerve involvement, was associated with lower VA. Khochtali et al.[20] reported a high risk of RD development in eyes with >50% retinal involvement. In both studies, RD was not detected in any eye with <25% retinal involvement. Similarly, we observed that RD occurred at a higher frequency in the group with 3-4 quadrants of retinal involvement (66.7%). Unlike other studies, an eye in our study with 1 quadrant of retinal involvement developed RD, but unlike the group with extensive retinal involvement, the RD was localized and could be treated with retinal argon laser photocoagulation.

There was no significant difference between the two groups in terms of optic disc inflammation at the time of admission (Group A: 7/11, Group B: 19/45), and optic disc pallor was detected during follow-up in 36.4% (4/11) of the eyes in Group A and 71.1% (32/45) of the eyes in Group B ($p<0.05$). Unlike in the study by Meghpara et al.,[19] we found that eyes with 1-2 quadrants of retinal involvement also showed optic disc inflammation at initial presentation, but none had optic disc pallor. In the group with 3-4 quadrants of retinal involvement, eyes without optic disc inflammation at presentation also developed optic disc pallor over time. This suggests that the extent of retinal involvement at the time of admission is associated with the development of RD and optic disc pallor.

Studies have shown that VA worsens as the extent of retinal involvement increases.[19,20] Similarly, in this study, the group with 1-2 quadrants of retinal involvement had better mean BCVA than the other group at all visits, and 3-4 quadrants of retinal involvement was found to be associated with poor visual prognosis.

Study Limitations

PCR analysis of anterior chamber fluid could not be performed in all patients because it had not been widely adopted in our country early in the study period. Studies conducted with PCR analysis of anterior chamber fluid samples from all ARN patients may be useful in determining the relationship between widespread involvement of the pathogen and the prognosis of the disease and responses to treatment.

Conclusion

In conclusion, ARN is an ophthalmological emergency that requires immediate treatment after diagnosis. Delayed diagnosis and especially the administration of CS before starting antiviral therapy allow the retinal necrosis to spread. As greater extent of retinal involvement at presentation is associated with increased risk of complications and unfavorable visual prognosis, early diagnosis and prompt initiation of antiviral therapy are critical in terms of final vision.

Ethic

Ethics Committee Approval: İstanbul University, İstanbul Faculty of Medicine Ethics Committee, 2021/95-81693.

Informed Consent: Informed consent forms were obtained from all.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A.C., Z.C., M.O., N.K., İ.T.T., Concept: N.A.C., M.O., İ.T.T., Design: N.A.C., M.O., İ.T.T., Data Collection or Processing: N.A.C., M.E.G., Z.C., E.A., Analysis or Interpretation: N.A.C., M.E.G., Z.C., E.A., Literature Search: N.A.C., M.E.G., Writing: N.A.C., M.E.G., Z.C., E.A., M.O., N.K., İ.T.T.

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Original Article

Results of the School Children Ocular Biometry and Refractive Error Study in South India

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Abstract

Objectives: Axial length (AL) is an important contributor to refraction, and growth curves are gaining importance in the prediction of myopia. This study aimed to profile the distribution of ocular biometry parameters and to identify correlates of spherical equivalent refraction (SE) among school children in South India.

Materials and Methods: The School Children Ocular Biometry and Refractive Error study was conducted as part of a school screening program in southern India. The enrolled children underwent tests that included vison check, refraction, binocular vision assessment, and biometry measurements.

Results: The study included 1382 children whose mean (standard deviation [SD]) age was 10.18 (2.88) years (range: 5-16 years). The sample was divided into 4 groups (grades 1-2, grades 3-5, grades 6-9, and grade 10) based on significant differences in right AL ($p<0.001$). The mean (SD) AL (range: 20.33-27.27 mm) among the four groups was 22.50 (0.64) mm, 22.88 (0.69) mm, 23.30 (0.82) mm, and 23.58 (0.87) mm, respectively. The mean SE (range: +1.86 to -6.56 D) was 0.08 (0.65 D) in class 1 and decreased with increasing grade to -0.39 (1.20 D) in grade 10. There was a significant difference in all biometry parameters between boys and girls ($p<0.001$). Age, AL, and mean corneal curvature were the main predictors of SE.

Conclusion: This study provides a profile of ocular biometry parameters among school children in South India for comparison against profiles from other regions across the country. The study data will form a reference for future studies assessing myopia in this ethnicity.

Keywords: Myopia, ocular biometry, school children

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Introduction

Myopia is increasing in prevalence globally and is predicted to affect half the world's population by 2050.[1] Trends in myopia prevalence vary among different ethnicities and regions of the world, with East Asians being more susceptible.[1,2,3,4,6,7]

In India, the prevalence of myopia among school children has shown a steady increase in the past decade from 4-8% to 14-21%.[8,9,10,11,12] Accelerated eye growth is one of the key factors in the onset and progression of myopia. Hence, it is important to study the distribution of ocular biometry parameters among children to understand and predict myopia.[13,14] It is also important to have baseline ocular biometry data for individual ethnicity and race to understand the regional prevalence and patterns of myopia and to be able to correlate and compare with other regions and ethnicities.

There are large data sets on refraction and biometry measures available from various studies among children of various ethnicities.[5,6,7,15,16,17,18,19,20,21,22] In India, although ocular biometry data are available for adults, they are scarce for children.[23,24,25] This may be related to limitations in measurement techniques, as previously biometry measurements were largely obtained through ultrasound contact biometry. With the advent of non-contact biometry, it is now possible to assess ocular biometry parameters even in younger children.

Therefore, the aim of the School Children Ocular Biometry and Refractive Error study was to examine the distribution of ocular biometry parameters, identify correlates of spherical equivalent refraction, and create a database for ocular biometry measures among children aged 5 to 15 in South India.

Materials and Methods

Study Design and Location

This cross-sectional study was conducted from July 2017 to December 2018 in three private schools (one rural and two in urban locations) as part of the school vision screening camps conducted in Chennai, Tamil Nadu, India.

Consent and Ethics Approval

A written informed consent form explaining the purpose and procedures of the screening was distributed to the parents prior to the school vision screening. Consent was obtained from both the school authorities and parents. Oral assent was also obtained from the children prior to performing additional procedures apart from the regular vision screening. The study was approved by the institutional review board and ethics committee of the vision research foundation (approval number: 639-2017-P) and followed the tenets of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Children between aged 5-15 years with best corrected visual acuity of 20/30 or better were included in this study. Children with previous ocular morbidities and surgeries and children with special needs (e.g., cerebral palsy, mental retardation, and autism spectrum disorders) were excluded.

Vision Screening Process

The screening comprised three phases.

Phase 1: All the children underwent vision screening using a validated pocket vision screener with a 6/9 visual acuity cut-off, penlight examination, and basic binocular vision testing (a minimum test battery to diagnose non-strabismic binocular vision anomalies) in Phase 1 of the testing.[26,27] Children who passed Phase 1 were sent for objective refraction and axial length measurements.

Phase 2: If the children failed Phase 1 of testing, they were sent to Phase 2 for objective refraction, subjective refraction, and spectacle prescription. For children who were referred to Phase 2 and needed refractive correction or had a change in existing spectacle prescription, binocular vision assessment was done with subjective acceptance in trial frames followed by biometry.

Phase 3: Children whose visual acuity could not be improved with refraction were referred to Phase 3 for further assessment and referral. Children with ocular morbidities such as ptosis and strabismus were referred to the tertiary eye care center for further evaluation and management. These children were not included in the present study.

The school vision screening process is shown in Figure 1.

Definitions

Refractive errors were defined as follows based on refraction measurements obtained by open field autorefractor without cycloplegia:

- Myopia: Spherical equivalent refractive error of ≤-0.75 diopters (D) in either eye[28]
- Hyperopia: Spherical equivalent refractive error ≥+2.00 D in either eye[29]
- Astigmatism: Cylindrical correction of ≤-0.75 D in either eye
- Emmetropia: Spherical equivalent refraction of >-0.75 D to <+2.00 D

Refraction Measurements

Refraction measurements were obtained by open field autorefractor (WAM 5500™, Grand Seiko) without cycloplegia. Studies have found that open field autorefractors are reliable under non-cycloplegic conditions and have greater accuracy than closed field autorefractors because of the binocular open-field system.[30,31] Therefore, this was used as the preferred autorefractor for measuring refraction among children.

The average of five readings was taken as the final refraction measurement for each eye. A Maltese cross target was used at 6 m for distance. The open field autorefractor was calibrated once a week in accordance with the manufacturer's recommendations. Refractive error was converted to spherical equivalent for the purpose of statistical analysis.

Biometry Measurements

Ocular biometry parameters were measured using a non-contact swept source optical coherence tomography-based biometer (ARGOS™, Movu Inc.).[32,33] Measurements were done thrice and the average of the three readings was taken for

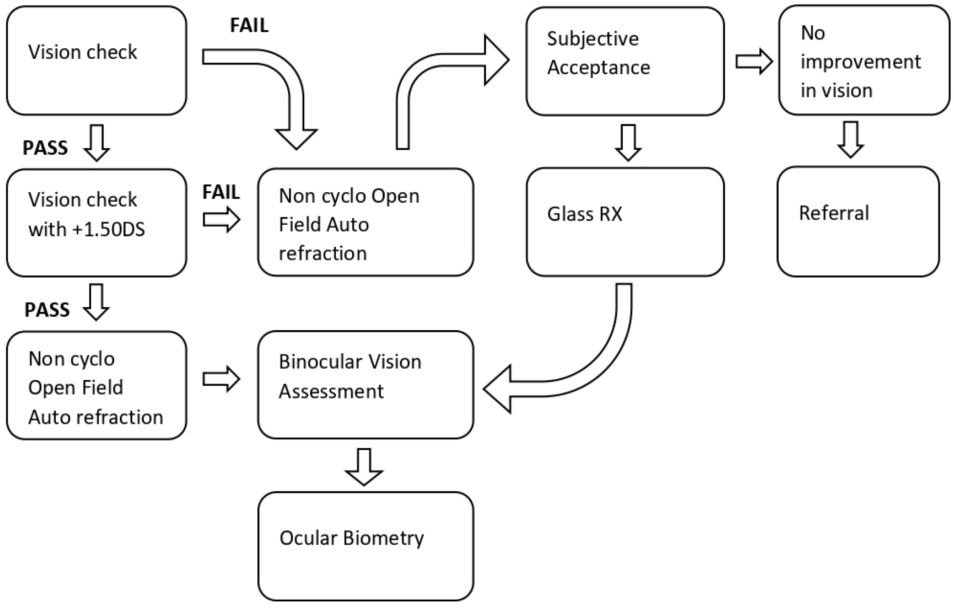

Figure 1. Flow chart of the school vision screening process

analysis. The outcome parameters of the ARGOS include axial length, anterior chamber depth, lens thickness, and corneal curvature along the flat and steep meridians.

All the tests were done at the schools by optometrists. One optometrist handled an instrument throughout the course of data collection. Calibration of the ARGOS is mandatory before beginning measurement and was performed by the optometrist as recommended by the manufacturer each day before use.

Data Entry and Data Quality Process

The data were entered by school and class into a Microsoft Excel spreadsheet. The entered data were re-checked twice by two of the investigators. The data were verified for completeness and scrutinized for errors.

Statistical Analysis and Outcome Measures

Statistical analysis was performed using SPSS Statistics for Windows, version 17.0 (SPSS Inc, Chicago, IL, USA). The mean, standard deviation, and 95% confidence intervals were obtained for all continuous measurements.

The primary outcome measures included spherical equivalent refraction and axial length measures. Other ocular biometry parameters, including anterior chamber depth, lens thickness, corneal curvature, and correlation between ocular biometry parameters and refraction, were considered as the secondary outcome measures.

There was no statistical difference between the two eyes in any refraction or biometry measures ($p>0.05$ in paired t-test; Pearson's correlation coefficient range: 0.60-0.97, $p<0.05$). Thus, only the right eye was taken for analysis. Spherical equivalent refraction and ocular biometry parameters were tested for normality using the Shapiro-Wilk test. Independent t-test was used to study the differences in ocular biometry parameters between genders.

Pearson's correlation analysis was used to understand the correlation between spherical equivalent refraction and biometry parameters. Linear regression was used to identify predictors of spherical equivalent refraction.

Results

In total, there were 1382 children included in the study, out of which 700 children were boys. The mean age of the children was 10.2 (2.9) years (range: 5-15). In the sample, based on the definition of refractive status described, 877 children were emmetropic (63.5%), 390 children had astigmatism (28.2%), and 229 children (16.6%) had myopia. Of the children with myopia (≤-0.75 D), 188 children had -0.75 D or less in both meridians whereas 41 children had -0.75 D or less in one of the meridians. Only 3 children (0.2%) had a hyperopic error greater than 2 D. Mean age, spherical equivalent, and ocular biometry parameters from grade 1 to grade 10 are summarized in Table 1.

There was a statistically significant difference across the grades for all ocular biometry measures (one-way ANOVA, $p<0.001$). The sample was then divided into four groups based on post-hoc analysis using Bonferroni correction with a conservative p value. These four groups represent grades 1-2 (mean age: 6.20 [0.75] years), grades 3-5 (mean age: 9 [1.04] years), grades 6-9 (mean age: 12.17 [1.30] years), and grade 10 (mean age: 14.71 [0.50] years).

Distribution of Ocular Biometry Parameters

The distribution of ocular biometry measures across the four groups is depicted in Figure 2. The axial length (range: 20.33-27.27 mm) showed an increasing trend with higher grade, with a corresponding increase in anterior chamber depth. There was progressive lens thinning with flattening of the corneal curvature across the four groups with age.

Table 1. Mean and standard deviation values of ocular biometry parameters, age, and spherical equivalent refraction in the right eyes of children from grades 1 to 10

School grade	n	Age (years)	SE (D)	AL (mm)	ACD (mm)	LT (mm)	Flat K (D)	Steep K (D)
1	150	5.67 (0.47)	0.11 (0.68)	22.46 (0.65)	3.32 (0.23)	3.82 (0.20)	43.71 (1.48)	44.86 (1.50)
2	126	6.84 (0.37)	0.05 (0.61)	22.55 (0.62)	3.37 (0.23)	3.75 (0.19)	43.71 (1.33)	44.74 (1.45)
3	153	7.94 (0.24)	0.07 (0.69)	22.86 (0.66)	3.45 (0.22)	3.69 (0.20)	43.45 (1.40)	44.53 (1.54)
4	149	9.02 (0.98)	0.26 (0.66)	22.90 (0.70)	3.45 (0.24)	3.67 (0.22)	43.48 (1.49)	44.40 (1.54)
5	154	10.05 (0.21)	0.21 (0.61)	22.96 (0.76)	3.50 (0.26)	3.61 (0.25)	43.66 (1.52)	44.61 (1.59)
6	138	10.70 (0.50)	0.07 (1.05)	23.27 (0.85)	3.56 (0.24)	3.60 (0.23)	43.42 (1.41)	44.44 (1.57)
7	129	11.68 (0.54)	-0.05 (0.93)	23.35 (0.79)	3.53 (0.25)	3.59 (0.21)	43.15 (1.45)	44.04 (1.55)
8	128	12.64 (0.59)	-0.27 (1.24)	23.39 (0.93)	3.57 (0.28)	3.62 (0.22)	43.39 (1.38)	44.41 (1.51)
9	115	13.97 (0.28)	-0.32 (1.24)	23.50 (0.89)	3.59 (0.26)	3.62 (0.21)	43.52 (1.65)	43.54 (1.60)
10	140	14.71 (0.50)	-0.39 (1.20)	23.58 (0.87)	3.56 (0.29)	3.60 (0.22)	43.14 (1.50)	44.15 (1.50)
Overall	1382	10.19 (2.88)	-0.03 (0.93)	23.07 (0.85)	3.49 (0.26)	3.66 (0.23)	43.47 (1.47)	44.46 (1.56)

SE: Spherical equivalent, AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, K: Corneal curvature

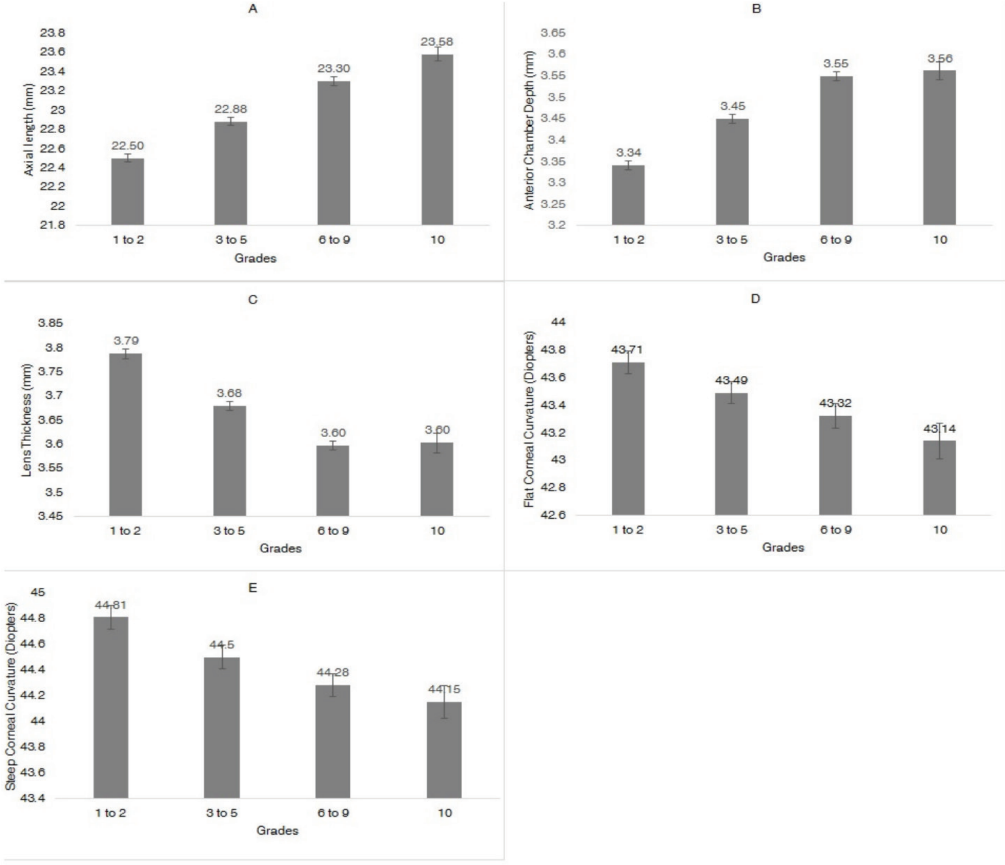

Figure 2. Ocular biometry distribution across the four groups from grades 1 to 10

Ocular Biometry and Spherical Equivalent Distribution by Sex

There were statistically significant differences in all biometry parameters between boys and girls (two sample t-test, p<0.001). Boys had longer axial lengths, deeper anterior chambers, thinner lenses, and flatter corneal curvatures compared to girls. However, there was no statistically significant difference in mean spherical equivalent refraction between the two groups. The mean ocular biometry parameters for the right eyes of the two groups are presented in Table 2.

Correlation of Age and Refractive Error with Ocular Biometry Parameters

Axial length and anterior chamber depth increased with age (r=0.43 and r=0.30, respectively; p<0.001), whereas lens thickness showed a decreasing trend with age (r=0.28) (Figure 3).

Similarly, an increase in axial length and anterior chamber depth was noted with increased spherical equivalent; i.e., negative spherical equivalent refraction or myopia was associated with longer axial length and deeper anterior chamber (r=0.50 and 0.22, respectively; p<0.001). A decreasing trend in lens thickness was noted with increased negative spherical equivalent refraction (r=0.15; p<0.001).

Multiple linear regression analysis was done to predict spherical equivalent refraction based on age and ocular biometry parameters (R^2=0.32; F(5,1376)=129.83, p<0.001). According to the model, axial length (β coefficient=-0.83, p<0.001), mean corneal curvature (β coefficient=-0.24, p<0.001), and age (β coefficient=0.02, p=0.003) were significant predictors of spherical equivalent refraction.

Refractive Error Profile

The distributions of spherical equivalent refraction in the right eye across the four age groups are illustrated in Figure 4 (SE range: +1.86 to -6.56 D). The mean spherical equivalent showed a leptokurtic distribution in grades 3-5, followed by a gradual skew towards negative refraction with increasing age/grade.

Discussion

The prevalence of myopia among Indian children has steadily increased in the past two decades. The present study reports a 16.6% prevalence, which is consistent with the recent Indian studies.[11,12] This is the first study to analyze the distribution of ocular biometry components and their correlation with refractive error distribution among children in India. We observed a significant increase in axial length and anterior chamber depth and a decrease in lens thickness and corneal curvature with increasing age among Indian children, consistent with previous studies.[5,6,7,13,14,15,16,17,18,19,20] A comparison of the findings of the present study with those of previous studies is shown in Table 3.

In recent years, growth percentile curves of axial length and refraction have gained importance for predicting the development of high myopia.[20,34] Given the differences in the prevalence of myopia among different ethnicities, it is important to develop region-specific growth percentiles to better predict ocular development. In this sense, the present study will be a reference point to develop similar percentile curves across various regions of India. The present study data when combined with other regional data can be a valuable tool for clinicians in myopia management.

Ocular Biometry Distribution

In the present study, children in grades 1 and 2 (mean age: 6.2 years) had a mean axial length of 22.50 mm, which was comparable with Australian children in grade 1 (age range: 5.5-8.4 years).[16] In a study of children in Singapore, the mean axial lengths at age 7, 8, and 9 years were 23.1, 23.4, and 23.8 mm, respectively, whereas in the present study the axial length was under 23 mm until the age of 9.[15] In a study among European children, the mean axial length was 22.36 mm at the age of 6, which is slightly lower than in the present study.[20] Chinese

Table 2. Comparison of ocular biometry parameters and spherical equivalent refraction between genders

Parameters	Sex	Mean ± SD	95% CI	P value*
AL (mm)	Boys (N=700)	23.35 (0.81)	23.29 to 23.41	<0.0001
	Girls (N=682)	22.77 (0.80)	22.71 to 22.84	
ACD (mm)	Boys	3.53 (0.26)	3.51 to 3.55	<0.001
	Girls	3.44 (0.26)	3.42 to 3.46	
LT (mm)	Boys	3.64 (0.22)	3.62 to 3.65	<0.001
	Girls	3.68 (0.23)	3.67 to 3.70	
Flat K (D)	Boys	43.09 (1.38)	42.99 to 43.19	<0.001
	Girls	43.86 (1.46)	43.75 to 43.97	
Steep K (D)	Boys	44.08 (1.49)	43.97 to 44.19	<0.001
	Girls	44.86 (1.53)	44.75 to 44.98	
SE (D)	Boys	-0.06 (0.95)	-0.13 to 0.01	0.204
	Girls	0.004 (0.92)	-0.06 to 0.07	

*Independent t test; AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, Flat K: Corneal curvature along the flatter meridian, Steep K: Corneal curvature along the steeper meridian, SE: Spherical equivalent

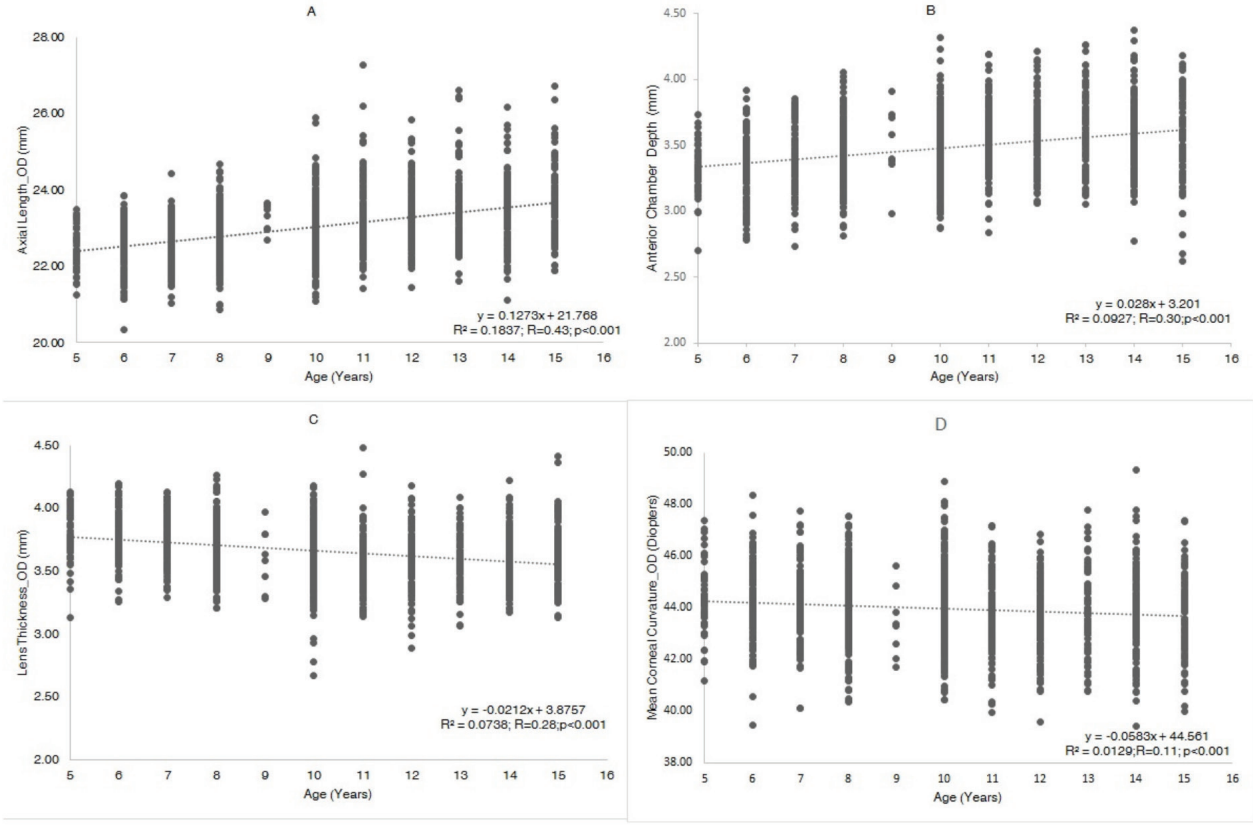

Figure 3. Correlation of ocular biometry parameters of the right eye with age. A) Age vs. axial length (in mm), B) Age vs. anterior chamber depth (in mm), C) Age vs. lens thickness (in mm), D) Age vs. mean corneal curvature (in diopters)

Table 3. Comparison of the present study findings with those in other ethnic groups

Study, year of publication	Location	Age (years)	SE (D)	AL (mm)	ACD (mm)	LT (mm)	MEAN K (mm)
Present study, 2019	South India	6.2 9.0 12.17 14.71	0.08 (0.65) 0.15 (0.70) -0.06 (0.99) -0.39 (1.20)	22.50 (0.64) 22.88 (0.69) 23.30 (0.82) 23.58 (0.87)	3.34 (0.23) 3.45 (0.23) 3.55 (0.25) 3.56 (0.29)	3.79 (0.20) 3.68 (0.20) 3.60 (0.22) 3.60 (0.22)	7.63 (0.24) 7.68 (0.26) 7.71 (0.26) 7.74 (0.26)
Saw et al.[15]	Singapore	7-9	-0.5 (1.7)	23.3	3.6	3.5	7.7
Ojaimi et al.[16]	Australia	6.7	1.26 (0.03)	22.61 (0.02)	3.34 (0.01)	-	-
Li et al.[17]	China	7 14	0.95 -2.06	22.72 24.39	2.89 3.18	3.61 3.42	7.89.7.70 7.89.7.71
Hashemi et al.[18]	Iran	6-18	-	23.13	3.01	3.58	7.77
Lira et al.[19]	Brazil	5-7 9-11 13-15	0.96 (0.95) 0.89 (1.07) 0.57 (1.23)	22.5 (0.66) 23.0 (0.81) 23.2 (0.78)	3.00 (0.26) 3.12 (0.28) 3.16 (0.28)	3.50 (0.20) 3.42 (0.20) 3.41 (0.20)	-
Tideman et al.[20]	Europe	6 9 15	- 0.74 (1.30) -	22.36 (0.75) 23.10 (0.84) 23.67 (1.26)			7.77 7.78
Harrington et al.[21]	Ireland	6-7 12-13	1.44 (1.25) 0.38 (1.61)	22.53 (0.79) 23.50 (0.89)	3.40 (0.21) 3.61 (0.25)		7.81 (0.27) 7.87 (0.26)
Yotsukura et al.[22]	Japan	6-11	-2.40 (2.23)	24.09 (1.30)	3.69 (0.27)	3.41 (0.19)	

SE: Spherical equivalent, D: Diopters, AL: Axial length, ACD: Anterior chamber depth, LT: Lens thickness, Mean K: Average corneal curvature (converted to mm to compare with other studies)

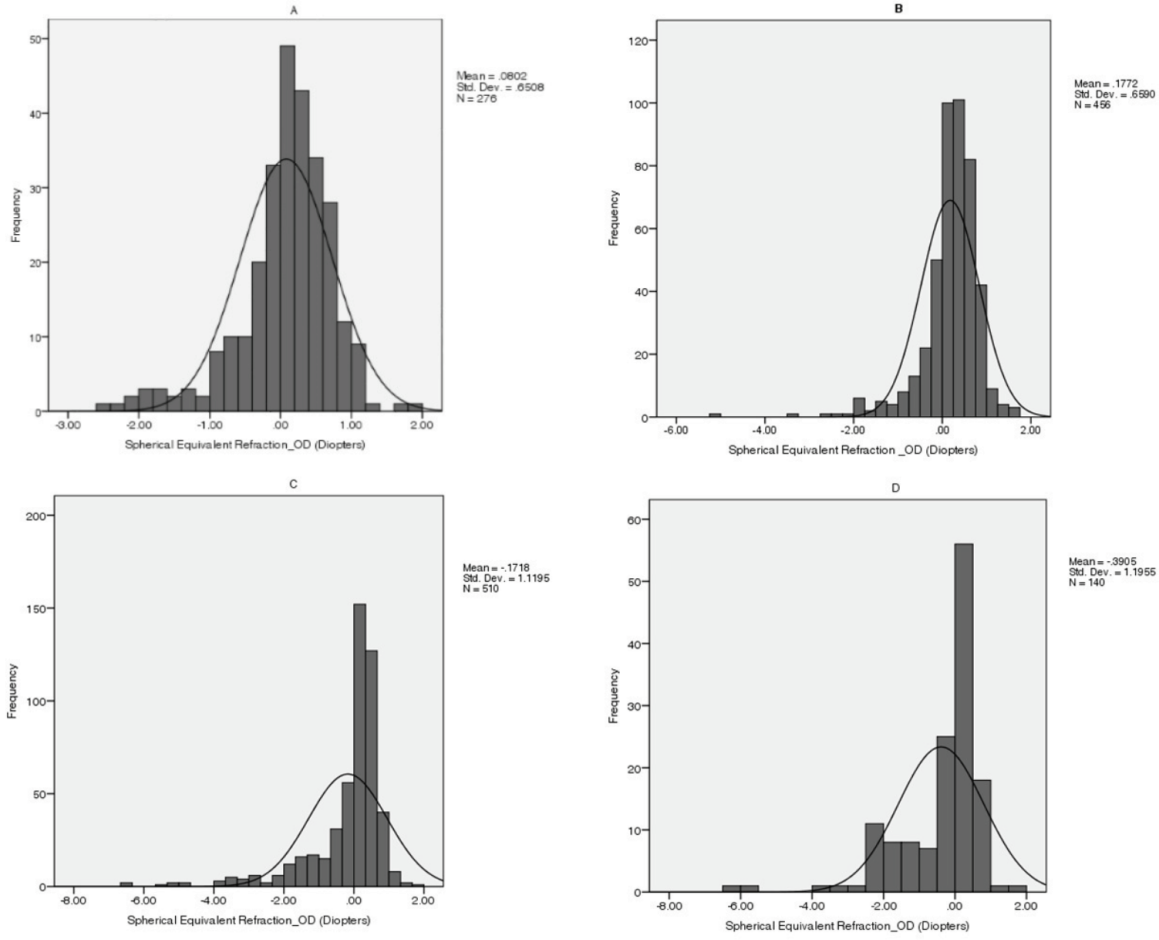

Figure 4. Distribution of spherical equivalent refraction across the four groups. A) Grades 1-2, B) Grades 3-5, C) Grades 6-9, D) Grade 10

children had a longer axial length at the age of 7 (22.72 mm) compared to Indian children in the present study (22.51 mm).[17]

Similarly, the mean anterior chamber depths of the children in the present study were comparable to children in Australia and Ireland.[16,21] Chinese children had a shallower anterior chamber compared to Indian children.[17] However, the data cannot be directly compared due to differences in measurement techniques, which ranged from ultrasound to partial coherence interferometry. The instrument used in the present study was comparable to and in agreement with the gold standard IOL master among children.[35]

The trend of increasing axial length with age is consistent with all previous studies on ocular biometry among various ethnicities. The increasing axial length with increasing anterior chamber depth, thinning of the lens, and flattening of corneal curvature is observed in all ethnicities. In addition, the significant difference found in all biometry parameters between boys and girls is consistent across all ethnicities.[5,7,16,17,18] Boys in the present study also had a significantly longer axial length, deeper anterior chamber depth, thinner lens, and flatter corneal curvature than girls. It is suggested that boys' taller stature could be a reason for longer axial lengths.[18] Although there was a difference in biometry parameters between genders, there was no significant difference in spherical equivalent refraction between the genders, indicating a compensatory mechanism of flattening of the corneal curvature with longer axial length among boys and vice versa among girls to keep the refraction in check.

Spherical Equivalent Refraction

The spherical equivalent refraction of children in the present study across all age groups was less myopic compared to children in Singapore and Japan.[15,22] Six-year-old children of Australia, China, Brazil, and Ireland had a more hyperopic refraction compared to the present study population, and remained more hyperopic than Indian children at 14 years of age, except in China.[16,17,19,21] Chinese children had a higher myopic refraction at 14 years (-2.06 D) compared to Indian children of the same age (-0.39 D).[14] This difference could be attributable to differences in genetic predilection and environmental factors, such as academic and near visual demands, gadget use, and outdoor activities. Compared to the current global myopia prevalence, the prevalence of myopia is still low in India (16.6% in this study)

compared to the rates reported in other urban Asian countries.[36] Since the aim of our study was to understand the distribution of ocular biometry parameters and their correlation with spherical equivalent refraction, we did not separately analyze astigmatism in this cohort of children.

The present study has a few limitations. The findings of the study are cross-sectional in nature, and a longitudinal study is warranted to understand the trends and risk factors that could give rise to myopia. Another limitation is that the refractive error distribution was non-cycloplegic in nature, thus there could be bias in the estimation of myopia prevalence in this study group. The use of cycloplegic drops on school premises is restricted by the government, thus it was not possible to obtain cycloplegic refraction estimates. The open field autorefractor has good agreement with cycloplegic refraction for myopia and also has a binocular viewing system.[7,30,31] Along with using an open field autorefractor, a higher cut-off for myopia (0.75 D or more) was used rather than 0.50 D as recommended by the International Myopia Institute (IMI).[28] However, the IMI also recommends using spherical equivalent refraction to identify myopia, thus the definition of myopia was based on SE refraction rather than sphere in both meridians.[28]

Study Limitations

The strength of this study is that there are no prior normative data available for Indian children in this age group, and the results of the study give an overall pattern of ocular biometry distribution among children in India. The study results will form a baseline reference for future studies on refractive errors and their associated risk factors, especially myopia among school-aged children, which is now being explored in a longitudinal study by the same study group. Further studies are required across different regions of the country to establish age-based norms for ocular biometry.

Conclusion

In conclusion, the present study is a valuable contribution to the literature in terms of profiling and establishing a database of ocular biometry parameters among school children in India. The findings of this study could be applied in future studies aimed at understanding risk factors for myopia among Indian children.

Ethics

Ethics Committee Approval: The study was approved by the institutional review board and ethics committee of the vision research foundation (approval number: 639-2017-P) and followed the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the children's parents and oral assent was obtained from the children.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N., Design: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N., Data Collection or Processing: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N., Analysis or Interpretation: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N., Literature Search: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N., Writing: A.G., J.R.H., R.C., B.R., S.A., A.C.B., D.S.J.S., M.S., R.S., V.M., V.S., A.N.

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Review

Hamartomas of the Retina and Optic Disc

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Abstract

Hamartomas are local malformation of cells that demonstrate abnormal proliferation in the area where they are normally present. Retinal and optic disc hamartomas include astrocytic hamartoma, congenital hypertrophy of the retinal pigment epithelium (CHRPE), simple congenital hamartoma of the retinal pigment epithelium (CSHRPE), combined hamartoma of the retina and retinal pigment epithelium (CHRRPE), retinal hemangioblastoma (retinal capillary hemangioma), and retinal cavernous hemangioma. Retinal and optic disc hamartomas can be observed sporadically as well as with systemic associations. Astrocytic hamartoma usually appears as a flat, transparent yellowish lesion. CHRPE is a round, pigmented, and flat lesion. CSHRPE usually presents as a dark black macular tumor. CHRRPE consists of vascular, glial, and pigment epithelial components, which can demonstrate peripapillary, macular, and peripheral localization. Retinal hemangioblastoma is a vascular tumor, red-pink in color with tortuous and dilated afferent and efferent vessels, typically located in the peripheral retina or optic disc. Retinal cavernous hemangioma is characterized by the formation of thin-walled saccular angiomatous structures in the retina or optic nerve head resembling concord grapes. Ultrasonography, fundus autofluorescence, optical coherence tomography, optical coherence tomography angiography, and fluorescein angiography methods are used in the diagnosis of retinal and optic disc hamartomas. Some retinal and optic disc hamartomas do not require treatment. However, complications including vitreous hemorrhage, macular exudation, retinal detachment, macular hole, epiretinal membrane, and choroidal neovascularization require treatment.

Keywords: Astrocytic hamartoma, congenital hypertrophy of the retinal pigment epithelium, simple congenital hamartoma of the retinal pigment epithelium, combined hamartoma of the retina and retinal pigment epithelium, retinal hemangioblastoma, retinal cavernous hemangioma

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Introduction

The term hamartoma is derived from the Greek word "hamartia," meaning error. Hamartomas are malformations formed by the abnormal proliferation of cells in the region where they are normally found.[1] Unlike neoplasms, which are caused by mutation in a single cell, multiple cells are affected in hamartomas. They are benign, slow-growing lesions that resemble normal tissue, but malignant transformation may occur. Hamartomas are usually associated with a genetic syndrome. They can occur in different parts of the body.[1] Most cases are asymptomatic and are detected incidentally during evaluation for other medical conditions.[2]

Retinal and optic disc hamartomas include astrocytic hamartoma, congenital hypertrophy of the retinal pigment epithelium (CHRPE), congenital simple hamartoma of the retinal pigment epithelium (CSHRPE), combined hamartoma of the retina and retinal pigment epithelium (CHRPE), retinal hemangioblastoma (retinal capillary hemangioma), and retinal cavernous hemangioma. Retinal and optic disc hamartomas can be observed sporadically or with systemic associations (Table 1). Possible syndromic associations include tuberous sclerosis complex (TSC), neurofibromatosis type 1, retinitis pigmentosa, Usher syndrome, and Stargardt disease for astrocytic hamartoma; familial adenomatous polyposis (FAP) syndrome for CHRPE; neurofibromatosis types 1 and 2, Gorlin-Goltz syndrome, Poland anomaly, and branchio-oculo-facial syndrome for CHRRPE; Von Hippel-Lindau (VHL) syndrome for retinal hemangioblastoma; and cerebral and dermal hemangiomas for retinal cavernous hemangioma.[3,4,5,6,7]

There has been no previous publication reviewing retinal and optic disc hamartomas in the literature. Our aim in this article was to collectively examine rare retinal and optic disc hamartomas.

Astrocytic Hamartomas of the Retina and Optic Disc

Clinical Features

Astrocytic hamartomas of the retina and optic disc are benign lesions. They are most commonly seen in patients with TSC. They can also occur in isolation or secondary to other diseases. Approximately 50% of patients with TSC have optic disc and retinal astrocytic hamartoma, and approximately 30% of TSC patients with astrocytic hamartoma develop bilateral tumors.[8] Astrocytic hamartoma is less commonly associated with neurofibromatosis type 1, retinitis pigmentosa, Usher syndrome, and Stargardt disease.[8]

Astrocytic hamartoma develops from glial cells. Tumorgenesis is caused by mutations in the *TSC1* and *TSC2* genes, which encode hamartin and tuberin, respectively.[9,10] Retinal astrocytic hamartoma, facial angiofibromas, and depigmented macules on the skin resembling vitiligo are the typical triad of patients with TSC.[8]

Astrocytic hamartoma usually presents as a flat, round, transparent lesion (Figure 1a). The lesion then grows into a nodular structure and becomes calcified.[11,12] Sometimes the central part of the lesion is calcific, while the peripheral part may be transparent. There may be hard exudates around astrocytic hamartomas.[13] Hard exudates are generally absent in untreated retinoblastoma/retinocytoma.[13,14] In contrast, changes in the retinal pigment epithelium (RPE) observed in retinoblastomas and retinocytomas do not usually occur in astrocytic hamartomas.[14] Calcification in astrocytic hamartomas is bright yellow with an appearance similar to fish eggs.[15] However, the calcification in retinoblastoma is chalky white.[15] Other diseases that should be considered in the differential diagnosis include optic nerve head drusen, acquired retinal astrocytomas, reactive gliosis, and conditions that cause optic disc edema.

Although astrocytic hamartomas generally have a stable course, giant cell astrocytomas can show progressive growth and cause secondary glaucoma and globe destruction.[15] These tumors are considered malignant but do not metastasize.[15]

Examination Methods

Astrocytic hamartomas appear on ultrasonographic examination as an acoustically solid mass and intralesional calcification is detected. On fundus autofluorescence (FAF) imaging, astrocytic hamartomas demonstrate

Table 1. Systemic diseases associated with retinal and optic disc hamartomas

Retinal and optic disc hamartomas	Associated systemic diseases
Astrocytic hamartoma	Tuberous sclerosis complex Neurofibromatosis type 1 Retinitis pigmentosa Usher syndrome Stargardt disease
Congenital hypertrophy of the retinal pigment epithelium	Familial adenomatous polyposis
Combined hamartoma of the retina and retinal pigment epithelium	Neurofibromatosis type 1 Neurofibromatosis type 2 Gorlin-Goltz syndrome Poland anomaly Branchio-oculo-facial syndrome
Retinal hemangioblastoma	Von Hippel-Lindau disease
Retinal cavernous hemangioma	Coexistence with cerebral and skin hemangiomas

hyperautofluorescence, depending on their calcium content (Figure 1b).[16] Optical coherence tomography (OCT) shows a dome- or plateau-shaped lesion with moderate to high reflectivity and choroidal shadowing (Figure 1c,d).[16] The choriocapillaris is preserved and "moth-eaten" cavities may be visible. OCT angiography (OCTA) reveals a well-defined, hyperreflective lesion and finely branching tumor vessels.[16,17] Retinal flow signals within the tumor can be detected on B-mode angiography (Figure 1e). The tumor vasculature is seen in the superficial and deep retina (Figure 1f,g). The outer retina and choriocapillaris show hyporeflective changes due to shadowing/masking caused by calcium or high blood flow within the lesion (Figure 1h,i). Because of the moth-eaten cavities within the lesion, areas of nonperfusion are seen in the deep retinal plexus and projection artifacts can be observed in the outer retina and choriocapillaris.[16] The lesion is hyporeflective in the full macular composite image (Figure 1j). Hyperreflective signals in the lesion center are due to the tumor vasculature in the deep capillary plexus. On fluorescein angiography (FA), early blockage can be seen in the choroidal phase, while the intrinsic tumor vessels begin filling and hyperfluorescence gradually increases during the arterial phase. There may be leakage in the late venous phase. The differential diagnosis of astrocytic hamartoma includes retinoblastoma, retinocytoma, myelinated nerve fibers, and massive retinal gliosis.[11,12,18]

Based on clinical and OCT findings, four types of retinal astrocytic hamartoma have been identified (Pichi classification).[19] Type 1 appears as a flat retinal lesion (<500 µm) on OCT, with no clinical signs of retinal traction. Type 2 appears as a mildly raised retinal lesion (>500 µm) on OCT, with clinical signs of retinal traction. Type 3 appears as a raised lesion (>500 µm) with calcification in the inner retina on OCT and "mulberry-like" calcification is observed clinically. Type 4 appears as a raised lesion with optically hollow cavities on OCT and the clinical

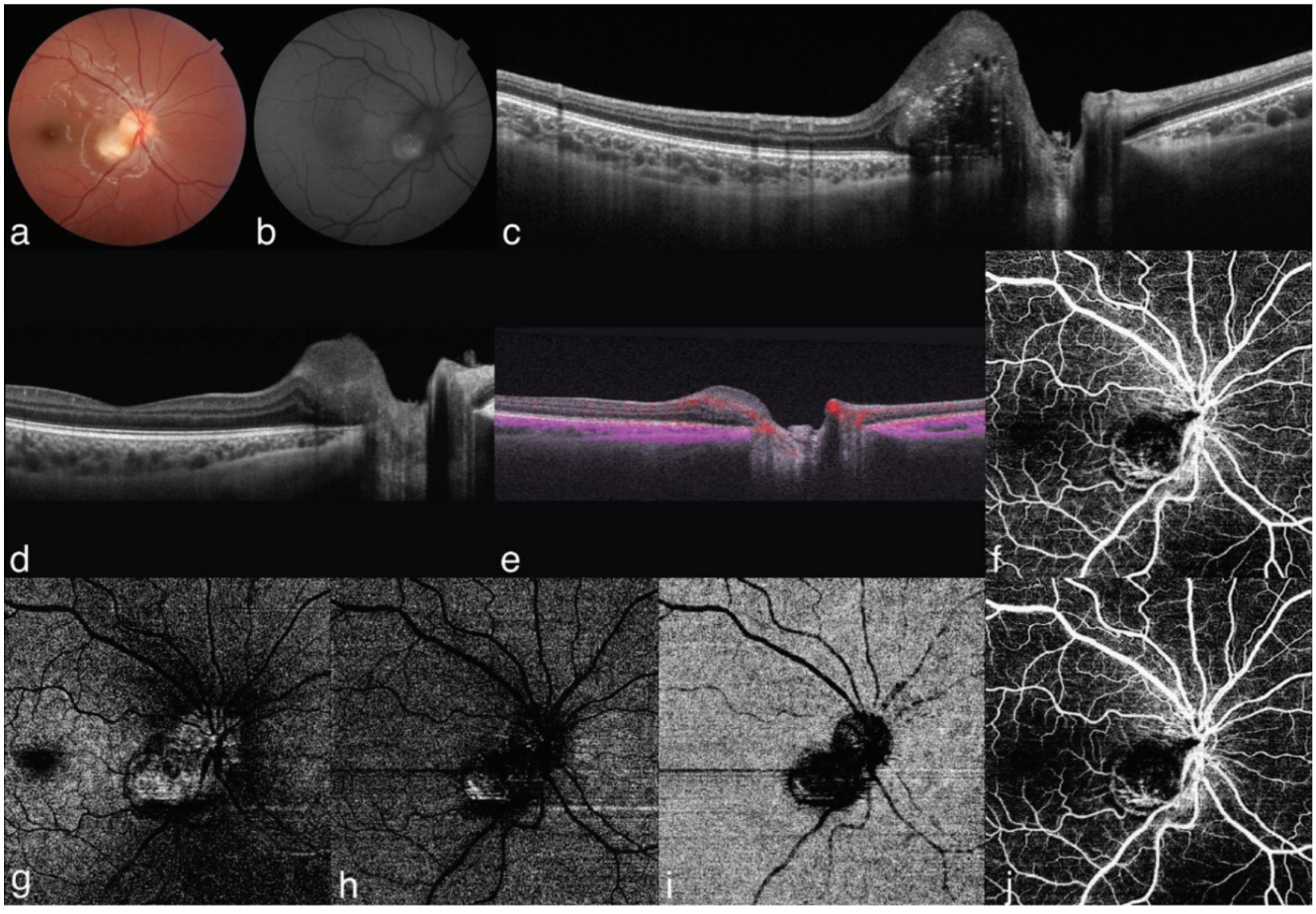

Figure 1. Fundus autofluorescence, optical coherence tomography, and optical coherence tomography angiography findings of a patient with retinal astrocytic hamartoma. a) Color fundus photograph shows a juxtapapillary astrocytic hamartoma in the lower temporal of the optic disc in the right eye. b) Fundus autofluorescence imaging demonstrates hyperautofluorescence due to the presence of calcium in the lesion. c-d) Swept-source optical coherence tomography depicts a moderately reflective, dome-shaped lesion with a base diameter of 1.0x1.0 mm and thickness of 1.1 mm, originating from the retinal nerve fiber layer and compressing the outer retina. Hyperreflective spots caused by the presence of calcium are observed (c). The lesion appears to be associated with the optic disc (d). e) B-mode angiography shows retinal flow signals within the tumor. f-j) Swept-source optical coherence tomography angiography demonstrates minimal hyperreflectivity related to the tumor in the superficial plexus (f). The tumor vascular network is visible in the deep retina (g). The outer retina (h) and choriocapillaris (i) demonstrate hyporeflective alterations due to shadowing/masking caused by intralesional calcium or high blood flow. The lower border of the lesion features a projection artifact from the retinal vessels (h,i). In the full macular composite image, the lesion appears hyporeflective, with hyperreflective signals centrally originating from the vascular network in the deep retinal plexus (j)

appearance is a flat, non-calcified lesion in the inner retina. Type 2 retinal astrocytic hamartoma is significantly more common in TSC patients with fibrous skin plaques, Type 3 in those with subependymal giant cell astrocytic hamartoma, and Type 4 in those with lung lymphangiomyomatosis.[19]

Treatment and Prognosis

Astrocytic hamartoma is generally stable and does not require treatment. Rarely, spontaneous regression may occur.[20] Periodic monitoring is important because of the risk of vitreous hemorrhage, retinal exudation, retinal detachment, and neovascular glaucoma. Laser photocoagulation can be applied to small lesions. Photodynamic therapy can be attempted for tumors that are larger and symptomatic (if exudates and fluid are present). Anti-vascular endothelial growth factor (anti-VEGF) injections can be administered in cases with secondary choroidal neovascularization. If vitreous hemorrhage from intratumoral fine vessels or neovascularization occurs, pars plana vitrectomy surgery may be required. Giant cell astrocytic hamartoma may show an aggressive course, and enucleation may be necessary due to tumor necrosis, vitreous hemorrhage, subretinal hemorrhage, massive exudation, and the development of neovascular glaucoma.[21] Neovascular glaucoma occurs as a result of intratumoral necrosis or chronic retinal detachment. TSC patients with subependymal giant cell astrocytoma and renal angiomyolipoma can be treated with m-TOR inhibitors (rapamycin, everolimus, sirolimus).[22]

Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)

Clinical Features

These are flat, round, and pigmented fundus lesions that are not raised from the surface. They are located at the RPE level. There are three variants: solitary, multifocal, and atypical (Figure 2a). Histopathologically, CHRPE lesions are composed of hypertrophic RPE cells containing excessive pigment granules. The choriocapillaris and choroid are normal. The photoreceptor layer over the RPE may be normal or atrophic. Photoreceptor atrophy fully manifests as the lesion becomes chronic.[23] Patients with photoreceptor atrophy exhibit absolute scotomas on visual field examination.[24]

The margins of CHRPE lesions are usually smooth but can occasionally be irregular. They often occur in the peripheral fundus; peripapillary localization is less common. There may be depigmented lacunae within the lesion and a hypopigmented halo around the lesion (Figure 2a). CHRPE lesions can show minimal growth, especially in myopic eyes.[23] Rarely, lesions such as RPE adenoma/adenocarcinoma may develop from CHRPE.[25]

CHRPEs are occasionally amelanotic.[26] These types of lesions are called amelanotic CHRPE. The retina and retinal vessels overlying the CHRPE are normal.[26] Focal intraretinal pigmentation may be present. In rare cases, neovascularization may occur at the edge of CHRPE.[27]

One type of CHRPE is associated with FAP. The gene responsible for FAP is called the *APC* (adenomatous polyposis coli) gene, located in the 5q21-q22 region. CHRPEs associated with FAP are generally oval-shaped and have tail-like extensions.[28] These lesions are called pigmented ocular fundus lesions (POFL) to distinguish them from other CHRPEs.[29] Their tails may be depigmented and they may contain lacunae. Histopathologically similar to CHRPE, they have pathological appearances of RPE hypertrophy, hyperplasia, and hamartoma.[29] POFLs usually have a base diameter smaller than 5 mm.[30]

POFL can be associated with Gardner syndrome and Turcot syndrome.[29] In Gardner syndrome, hundreds of polyps appear in the colon and give rise to adenocarcinoma of the colon. Prophylactic colectomy is recommended. Extracolonic cancers in Gardner syndrome occur in the thyroid, adrenal gland, and liver. Benign lesions include head and orbit osteomas, sebaceous cysts, lipomas, and fibromas. Opaque jaw lesions can also be observed. In general, detection of 4 or more POFLs is a strong indicator of FAP.[29] In Turcot syndrome, patients develop brain tumors in addition to POFL.[31]

Examination Methods

On ultrasonographic examination, CHRPE lesions appear as flat or minimally raised (<0.5 mm), acoustically solid lesions. FAF imaging typically shows hypoautofluorescence due to the lesions' high melanin content (Figure 2b).[16] Non-pigmented halos or cavities may show autofluorescence.[32] On OCT they are flat lesions at the RPE level that contain hyperreflective deposits and cause choroidal shadowing (Figure 2c,d).[16] The inner retinal layers are normal, but the outer retinal layers exhibit thinning.[16] On OCTA, CHRPEs are generally well-defined and hyperreflective in the superficial and deep retinal plexi.[16] B-mode angiography demonstrates flow signals in the retina overlying the tumor.[16] Masking of the outer retina and choriocapillaris causes the appearance of "signal void" areas.[16] On FA, leakage is not observed.[24] The underlying choroidal fluorescence is blocked in areas other than depigmented halos or cavities.[24]

Treatment and Prognosis

CHRPE lesions generally do not require treatment. However, long-term follow-up is essential. Rarely, RPE adenoma/adenocarcinoma may arise from CHRPE. This type of RPE tumor can be confused with choroidal malignant melanoma. RPE tumors are darker brown/near black in color. However, as they are indistinguishable from choroidal malignant melanoma, RPE adenoma/adenocarcinoma is usually treated by enucleation. The use of proton beam therapy for CHRPE-derived RPE adenocarcinoma was reported in one case.[33]

Congenital Simple Hamartoma of the Retinal Pigment Epithelium (CSHRPE)

Clinical Features

CSHRPE usually appears as a unilateral and dark black tumor with irregular margins. They are black nodules 0.5-1

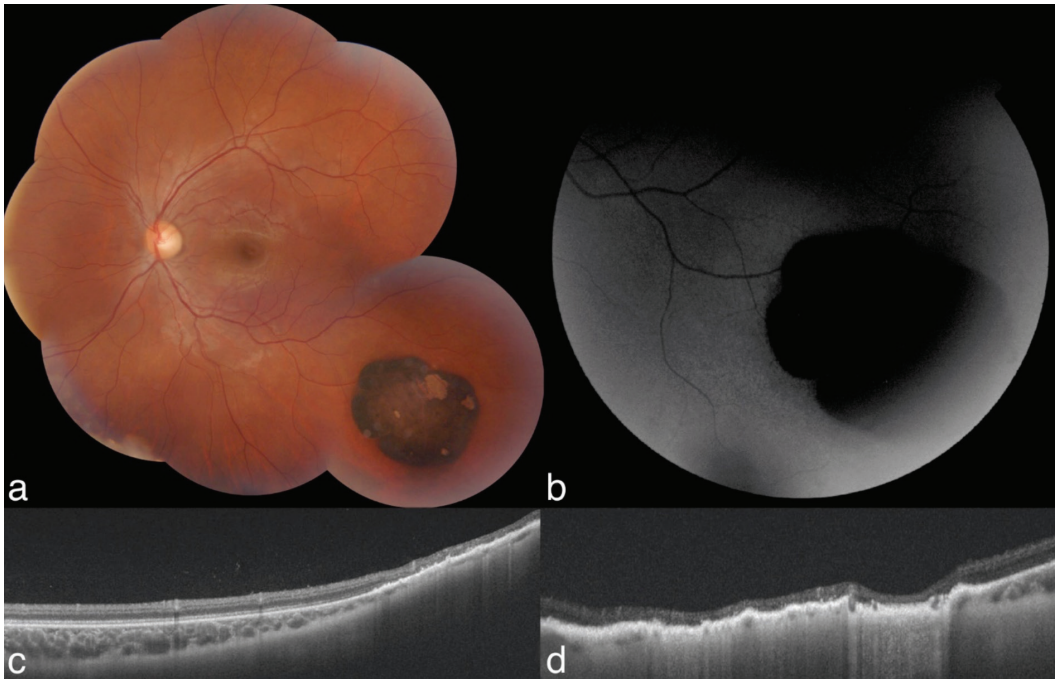

Figure 2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE). a) Composite colored fundus image reveals an inferotemporal CHRPE in the left eye. b) Fundus autofluorescence imaging shows a hypoautofluorescent lesion due to its high melanin content. c-d) Swept-source optical coherence tomography depicts a flat, highly reflective lesion causing choroidal shadowing. Proliferation and high reflectivity are noted at the level of the retina pigment epithelium. The outer retina is thinned. Increased optical transmission is observed in the lacunae within the lesion (d)

mm in size and involve the macula (Figure 3).[34,35] A slightly dilated afferent arteriole and efferent venule are present. Vision is generally preserved. There is retinal traction around the lesion in most cases (80%).[34,35] Pigmented cells may be detected in the vitreous (20%).[35] The development of full-thickness macular hole associated with CSHRPE has been reported.[36] Loss of vision occurs as a result of foveal traction and central foveal involvement.[35]

Examination Methods

On ultrasonographic examination, CSHRPE appears as a nodular lesion with moderate internal reflectivity.[35] The lesion is hypoautofluorescent on FAF.[37] OCT demonstrates a lesion with a hyperreflective surface that shows full-thickness retinal involvement and choroidal shadowing.[37,38] Intratumoral vessels can be detected on OCTA.[39,40] On FA, there is hypofluorescence starting in the early phase and continuing throughout the entire angiography, with no leakage.[35,38]

Treatment and Prognosis

As the lesion is not progressive, treatment is generally not necessary but periodic monitoring is recommended. Vision loss is inevitable with lesions involving the macula. Vitreoretinal surgery can be performed if macular hole or tractional epiretinal membrane develop.[36]

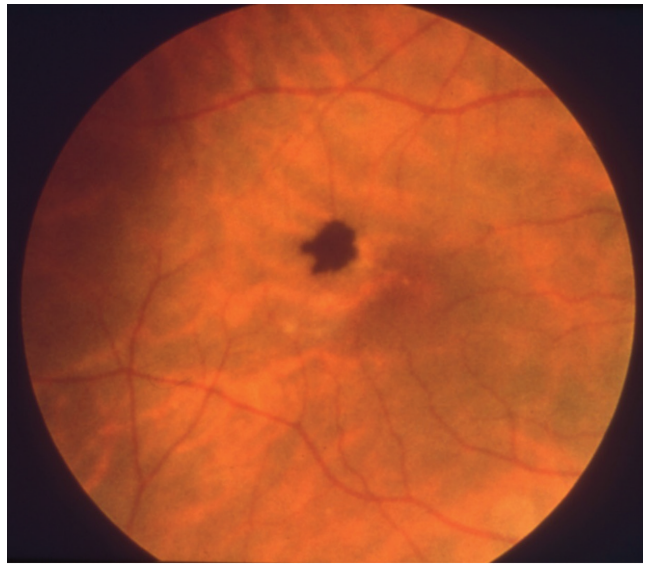

Figure 3. Congenital simple hamartoma of the retinal pigment epithelium. Fundus photograph shows a congenital simple hamartoma of the retinal pigment epithelium located in the macula

Combined Hamartoma of the Retina and Retinal Pigment Epithelium (CHRRPE)

Clinical Features

CHRRPE is a rare benign lesion.[41,42,43,43] It presents between the ages of 1 and 74 years and the mean age at diagnosis is 23 years.[44] Combined hamartoma is usually unilateral and most cases are sporadic.[24] It has been reported to occur more frequently in patients with neurofibromatosis type 2. Less common associations include neurofibromatosis type 1, Poland syndrome, Gorlin syndrome, and branchio-oculo-facial syndrome.[24] Combined hamartoma consists of vascular, glial, and pigment epithelial components.

It can occur in the optic disc or other areas of the fundus (Figure 4a). CHRRPE is classified into three groups according to location: peripapillary, macular, and peripheral. CHRRPE is believed to originate from the inner retina and progress towards the outer retina over time, and an increase in macular thickness may occur regardless of tumor location.[44] Young patients exhibit partial involvement, mainly of the inner retina, and full-thickness retinal involvement is more often seen in older patients. Preretinal fibrosis is more common in young patients, while pigmentary changes are more frequently detected in older patients. An increase in average macular thickness is more common in macular lesions than with those in other locations.[44] There are three stages of CHRRPE according to the anatomical condition of the retina: 1) no retinal traction, 2) retinal traction or retinoschisis is present, and 3) retinal detachment is present.[45] Pigmentation, full-thickness retinal involvement, intraretinal cystic cavities, ellipsoid zone/RPE disruption, and choroidal neovascularization are more common in peripapillary CHRRPE lesions compared to macular CHRRPE lesions.[46] Vision loss varies depending on optic disc, papillomacular bundle, and foveal involvement.[41,42] Tractional distortion occurs in the macula due to epiretinal membrane formation. They usually do not show malignant transformation. Choroidal neovascularization may cause vitreous hemorrhage, retinoschisis, and macular hole.[47]

Examination Methods

Combined hamartoma is diagnosed by indirect ophthalmoscopy. On ultrasonographic examination, CHRRPE lesions appear as slightly raised, acoustically solid lesions with moderate to high internal reflectivity. Peripapillary pigmented lesions exhibit hyperautofluorescence on FAF.[46] On OCT, CHRRPE is divided into three groups according to lesion anatomy: A) epiretinal component only, B) partial retinal involvement, and C) full retinal and RPE involvement.[45] The pathogenesis involves focal vitreoretinal traction. The inner retina exhibits a "sawtooth" pattern (mini-peak) and "omega sign" (maxi-peak).[48,49] The sawtooth and omega signs are usually detected in young patients (Figure 4c).[44] OCTA demonstrates retinal vascular alterations and a "filigree" pattern in the intratumoral vessels.[50,51] On FA, the lesion is hyperfluorescent (Figure 4b). Despite increased pigmentation in the RPE, early

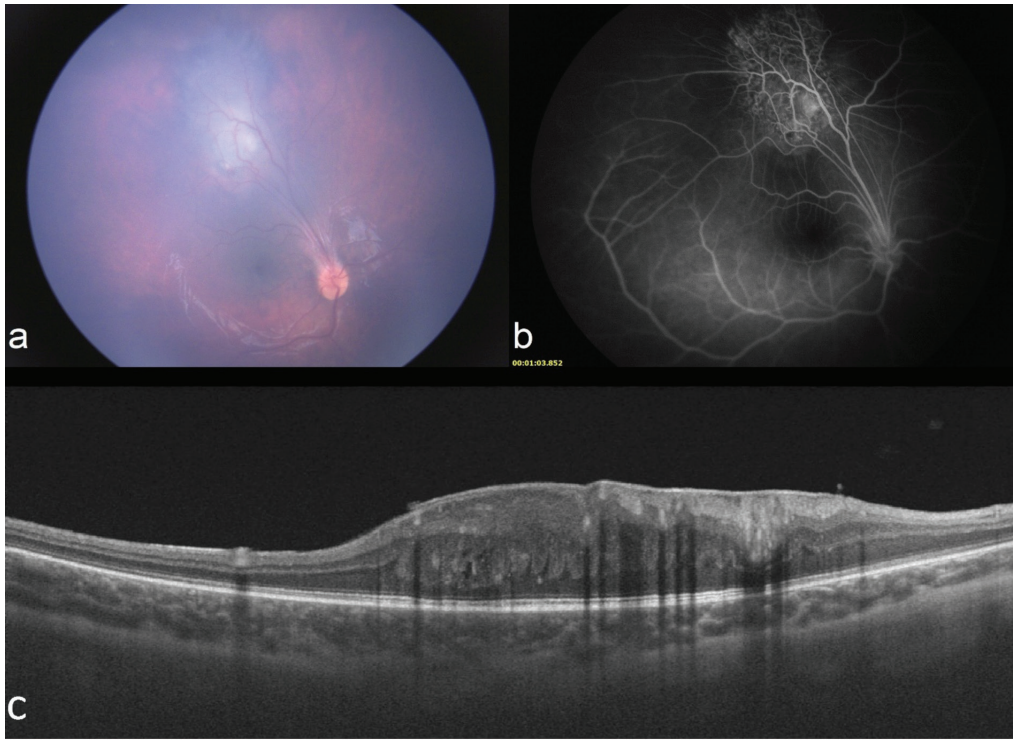

Figure 4. Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE). a) Retcam 3 fundus photograph of a superotemporal amelanotic CHRRPE. b) Retcam 3 fluorescein angiography shows that the lesion is hyperfluorescent. Microaneurysms and non-leaking telangiectatic vessels are observed. c) Swept-source optical coherence tomography demonstrates retinal thickening, intraretinal hyperreflective foci, epiretinal membrane, and the CHRRPE-specific "omega sign" and "sawtooth" pattern

and late hyperfluorescence is observed because of RPE atrophy and cell migration. Microaneurysms and telangiectatic vessels are observed. Although there is usually no leakage from the telangiectatic vessels, minimal leakage from the tortuous vessels may be seen in the late phase.[51,52]

Treatment and Prognosis

Periodic monitoring is recommended for treatment. The role of epiretinal membrane peeling surgery is controversial. In some cases, visual improvement has been reported with vitrectomy and membrane peeling.[53,54] Intravitreal anti-VEGF injection can be administered in eyes with secondary choroidal neovascularization.[55] Amblyopia treatment should also be provided.[24] However, visual improvement is rarely achieved. Vision loss occurs in most cases.[24]

Retinal Hemangioblastoma (Retinal Capillary Hemangioma)

Clinical Features

Retinal hemangioblastomas are benign vascular tumors.[56] They are red-pink tumors typically located in the peripheral retina or optic disc (Figure 5a). Their afferent and efferent vessels are tortuous and dilated.[56] They may be single or multiple. The disease has two types, exudative and tractional.[56] The exudative type is characterized by intraretinal and subretinal exudation, the tractional type by retinal gliosis, vitreoretinal traction, vitreous hemorrhage, and tractional retinal detachment. They may exhibit exophytic and endophytic growth.[56]

Retinal hemangioblastomas may be isolated or occur as part of VHL syndrome. Patients presenting with solitary retinal hemangioblastoma before the age of 10 years have a 45% risk of developing VHL syndrome, while the risk is <1% in those over 60 years of age.[57] Pheochromocytoma, renal cell carcinoma, central nervous system hemangioblastomas, pancreatic cysts, and neuroendocrine tumors may be seen in VHL syndrome. The VHL Alliance recommends dilated fundus examination every 6-12 months until the age of 30 and annually after the age of 30 for patients with VHL syndrome (https://www.vhl.org/patients/clinical-care/screening). Retinal hemangioblastoma is often the initial sign of VHL syndrome (50%) and is seen in VHL patients at an average age of 25 years.[58] Approximately 58% of cases are bilateral.[59] Central nervous system hemangioblastoma is seen in patients aged >20 years, pheochromocytoma in patients aged >40 years, and renal cell carcinoma in patients aged >50 years.[58] Renal cell carcinoma is the most common cause of death.[58]

Examination Methods

FAF shows a hypoautofluorescent lesion (Figure 5b). On OCT, a hyperreflective lesion originating from the retina with compression of the outer retina, retinal edema, and localized retinal detachment is observed (Figure 5c,d). On ultrasonographic examination, retinal hemangioblastoma appears as a raised lesion with moderate to high internal reflectivity (Figure 5e). On FA, the lesion shows hyperfluorescence in the arterial phase that increases in the late phase, with dye leakage into the vitreous (Figure 5f). The afferent and efferent vessels are better detected with OCTA than with FA, because leakage and pooling are not seen on OCTA.[60] However, peripheral tumors cannot be imaged with OCTA.[60,61]

Treatment and Prognosis

For some small, asymptomatic masses, periodic monitoring can be sufficient and spontaneous regression may be observed in some cases.[62] Tumors with limited retinal exudation or retinal detachment can be treated with laser photocoagulation (Figure 5g,i), cryotherapy, transpupillary thermotherapy, and photodynamic therapy and advanced tumors may be treated with plaque radiotherapy or external beam therapy.[63] Successful treatment results in shrinkage of the lesion, narrowing of the afferent vessels, and regression of exudative symptoms in the macula (Figure 5h,j). If vitreous traction and retinal detachment occur, pars plana vitrectomy can also be performed. Endoresection may also be attempted for some tumors.[64] The United States Food and Drug Administration (FDA) recently approved the use of belzutifan, a hypoxia-inducible factor inhibitor, in patients with VHL-associated renal cell carcinomas, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease).

Retinal Cavernous Hemangioma

Clinical Features

Retinal cavernous hemangioma is a unilateral, benign vascular hamartomatous lesion. Ninety percent of cases are unifocal.[65] The lesions are characterized by the formation of thin-walled saccular angiomatous structures in the retina or optic nerve head that resemble a bunch of concord grapes (Figure 6). Malignant transformation has not been reported. It is usually sporadic but can also show autosomal dominant inheritance. In this syndromic association, it may co-exist with cerebral and skin hemangiomas.[66] *KRIT1/CCM1, CCM2/MGC4607, CCM3/PDCD10,* and 7q mutations may be present.[67] The *CCM3* mutation is associated with intracranial hemorrhage.[68]

Examination Methods

On ultrasonographic examination, retinal cavernous hemangioma appears as a raised lesion with high internal reflectivity. On FA, the tumor exhibits hypofluorescence in the early phase and slow filling in the late venous phase. Dye accumulation in the upper half of the saccule and the presence of hypofluorescence underneath give the appearance of a "fluorescein cap."[69] This pattern is the result of hypofluorescence caused by erythrocyte sedimentation at the bottom of the saccule and hyperfluorescence caused by free fluorescein in the plasma at the top.[69]

Treatment and Prognosis

Most cases do not require treatment. Recurrent vitreous hemorrhage can be treated with pars plana vitrectomy.[70] Membrane peeling can be performed in cases with severe traction and vision loss.[71]

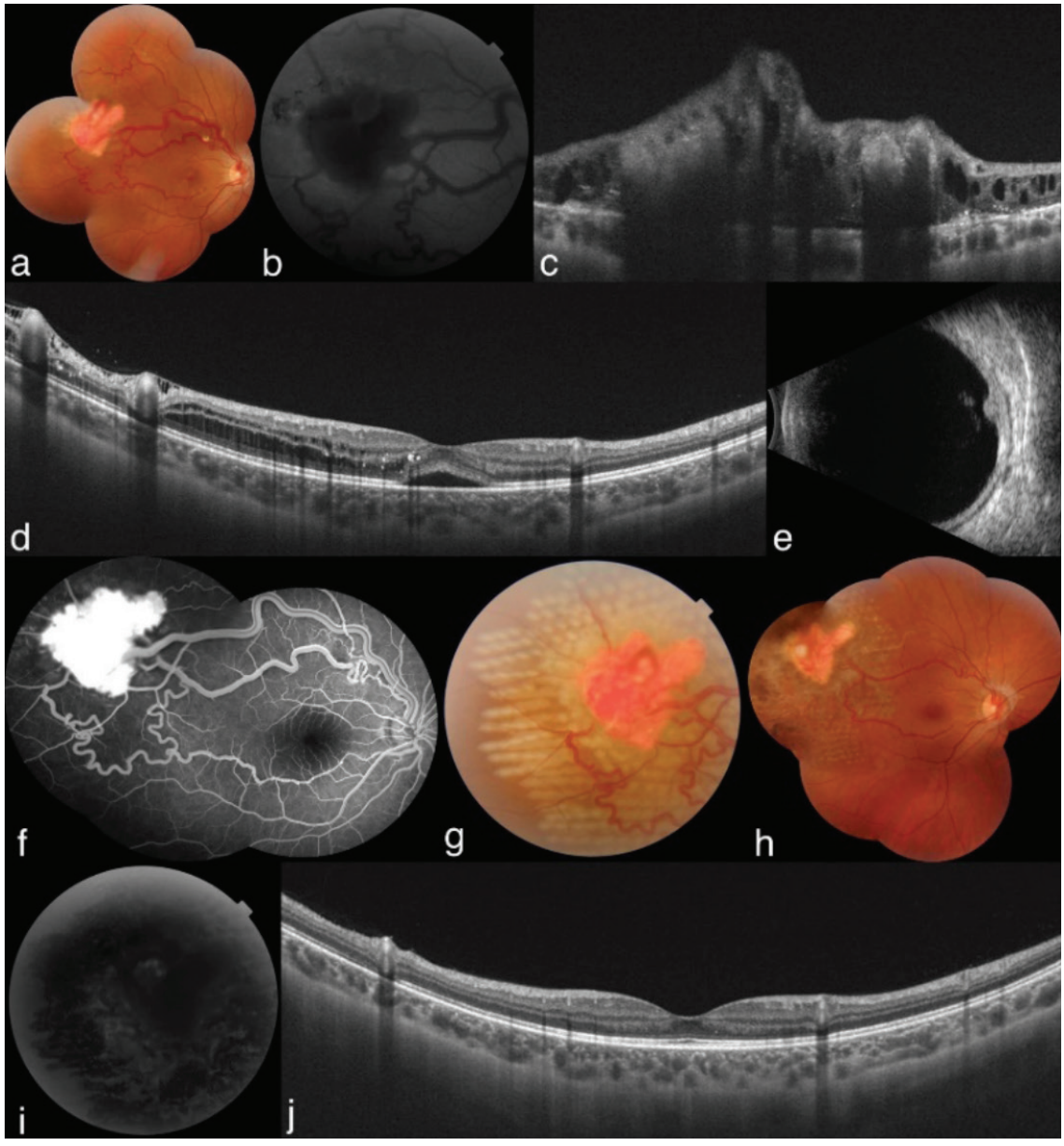

Figure 5. Retinal hemangioblastoma. a) Composite colored fundus photograph shows a temporally located retinal hemangioblastoma with tortuous and dilated afferent and efferent vessels. b) The lesion is hypoautofluorescent on fundus autofluorescence (FAF) imaging. c) Swept-source optic coherence tomography (SS-OCT) through the tumor demonstrates moderate reflectivity causing choroidal shadowing and intraretinal edema. d) In the SS-OCT section passing through the macula, subretinal fluid, retinal schisis, and choroidal shadowing from dilated tumor vessels are observed. e) B-mode ultrasonogram shows that tumor has acoustic solidity, basal diameter of 4.5x4.5 mm, and thickness of 1.9 mm. f) Fluorescein angiography demonstrates an intensely hyperfluorescent lesion with dilated vessels and vascular beading. g) After performing scatter laser photocoagulation to the tumor and surrounding tissue, pattern laser spots are observed on fundus photography. h) Composite color fundus photograph 2 months after 3 sessions of laser photocoagulation therapy demonstrates narrowing of the afferent vessels and areas of fibrosis over the tumor. i) FAF imaging 2 months after 3 sessions of laser photocoagulation shows the hypoautofluorescent lesion as well as hypoautofluorescent areas corresponding to the laser photocoagulation spots. j) Two months after 3 laser photocoagulation sessions, the subretinal fluid has resolved and the retinal schisis is almost completely regressed on SS-OCT

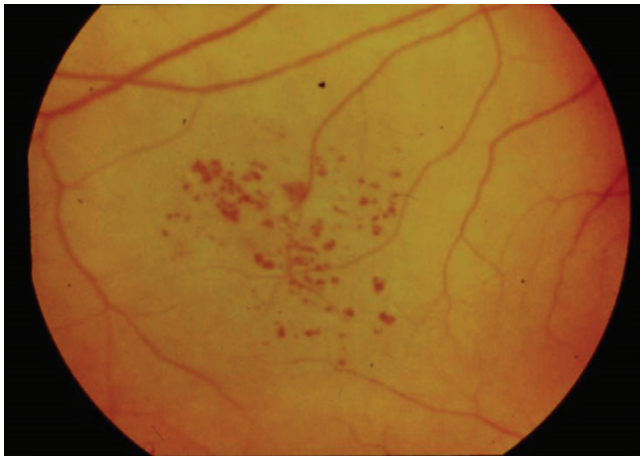

Figure 6. Retinal cavernous hemangioma. Color fundus photograph shows a retinal cavernous hemangioma resembling clusters of red grapes

Conclusions

Hamartomas of the retina and optic disc include astrocytic hamartoma arising from glial cells; CHRPE, CSHRPE, and CHRRPE arising from the RPE and retina; and the vascular tumors retinal hemangioblastoma and retinal cavernous hemangioma. Most of these lesions are asymptomatic and detected incidentally in patients presenting for routine eye examination. Macular lesions may cause findings such as reduced visual acuity and visual field loss.

Retinal and optic disc hamartomas may be isolated or associated with systemic diseases As they may be the initial sign of systemic diseases, the ophthalmologist must know the syndrome/diseases associated with these hamartomas.

Most retinal and optic disc hamartomas do not require treatment but should be monitored periodically. While they are generally benign and slow-growing lesions, malignant transformation can occur in rare cases. Treatment can be provided for complications secondary to the tumors.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Case Report

Multimodal Imaging of Pigmented Paravenous Retinochoroidal Atrophy in a Pediatric Patient with Cystoid Macular Edema

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Abstract

The aim of this case report is to present the multimodal imaging characteristics of pigmented paravenous retinochoroidal atrophy (PPRCA) in a pediatric patient with cystoid macular edema (CME). A 7-year-old girl was admitted to our clinic with complaints of mild blurred vision and poor night vision. Best corrected visual acuity was 10/10 in both eyes. Fundus examination showed atrophic areas around the optic nerve and along the retinal vessels in both eyes. A few small dot-shaped paravenous pigmentations were observed in the mid-peripheral retina. Fundus autofluorescence was consistent with PPRCA. Spectral-domain optical coherence tomography (OCT) revealed the presence of CME and loss of the outer retinal layers outside the macula, with intact retinal layers in the macula. OCT angiography revealed normal choriocapillaris vasculature and flow. The patient was followed up for 6 months but showed no change in CME or clinical appearance. CME without ocular inflammation is an unusual finding of PPRCA and may suggest the involvement of chronic or latent inflammation in the etiology of PPRCA.

Keywords: Cystoid macular edema, optical coherence tomography angiography, pigmented paravenous retinochoroidal atrophy

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Introduction

Pigmented paravenous retinochoroidal atrophy (PPRCA) is characterized by pigment accumulation along the retinal vessels and retinal pigment epithelium (RPE) as well as atrophy of the choriocapillaris bilaterally. The diagnosis is usually based on a typical and characteristic appearance of the fundus. The etiology of PPRCA is unknown, but it is believed to be hereditary or associated with an initial inflammatory cause.[1,2,3,4,5]

PPRCA is a non-progressive or slowly progressive ocular disease and the visual prognosis is generally good. Macular involvement is rare, but macular changes such as macular RPE atrophy, choroidal thinning, pigmentary macular degeneration, epiretinal membrane, and lamellar holes can be seen.[1,2] To date, the presence of cystoid macular edema (CME) in PPRCA with accompanying active inflammation has been reported in only one case.[3] Herein, we present the multimodal imaging characteristics of PPRCA in a pediatric patient with CME but no signs of ocular inflammation.

Case Report

A 7-year-old girl was admitted to our clinic with complaints of mild blurred vision and poor night vision. There was no family history of hereditary retinal disease. The patient had a medical history of hospitalization for an unidentified viral illness at 15 months of age. Written informed consent was obtained from the patient's parents.

Best corrected visual acuity was 10/10 and intraocular pressure was 12 mmHg in both eyes. Slit-lamp examination of the anterior segment was unremarkable and there were no cells or flare in the vitreous. Fundus examination showed the presence of atrophic RPE areas around the optic nerve and along the retinal vessels in both eyes. A few small, dot-shaped paravenous pigmentations were observed in the mid-peripheral retina.

Color fundus photography (Visucam 524 Fundus Camera, Carl Zeiss Meditec AG, Jena, Germany), fundus autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA) (Heidelberg Spectralis HRA + OCT, Heidelberg, Germany), and OCT angiography (OCTA) (RTVue-XR Avanti AngioVue OCTA, Optovue Inc., Fremont, CA) were performed.

Color photographs clearly showed multiple areas of changes in the RPE along the retinal vessels and the spots of paravenous pigmentation in the mid-peripheral retina. FAF demonstrated areas of hypoautofluorescence along the retinal vessels consistent with the observed RPE changes in both the central and peripheral retina. SD-OCT showed significant retinal thinning with loss of all outer retinal layers including the outer nuclear layer and external limiting membrane outside of the macula, as well as the presence of CME in both eyes. However, all retinal layers were intact within the macula. Subfoveal choroidal thickness and choriocapillaris were normal on enhanced depth imaging (EDI) with SD-OCT. FA revealed areas of hyperfluorescence along the vessels in both the central and peripheral retina, with no leakage in any of the phases. En face OCTA showed normal flow of superficial and deep retinal layers and choriocapillaris (Figures 1 and 2). The clinical examination was consistent with PPRCA.

The patient was referred to a pediatric infectious disease specialist for etiological investigation that included both clinical examination and laboratory tests. However, no clinical or serological evidence of bacterial, viral, or parasitic disease such as tuberculosis, syphilis, toxoplasmosis, herpes simplex virus, herpes zoster virus, cytomegalovirus, rubella, or measles could be identified. The patient was given topical nonsteroidal anti-inflammatory eye drops and followed up 6 months later. No change in the CME or clinical findings were detected.

Discussion

In this study, we demonstrated PPRCA in a pediatric patient with CME but no signs of ocular inflammation, and documented its characteristics in multimodal imaging including color fundus photography, FAF, SD-OCT, FA, and OCTA.

The diagnosis of PPRCA is usually based on a typical and characteristic fundus appearance such as paravenous pigment accumulation and areas of RPE atrophy around the optic disc and along the vessels. However, it has been reported that the fundus appearance may vary and retinal changes can be mild, moderate,

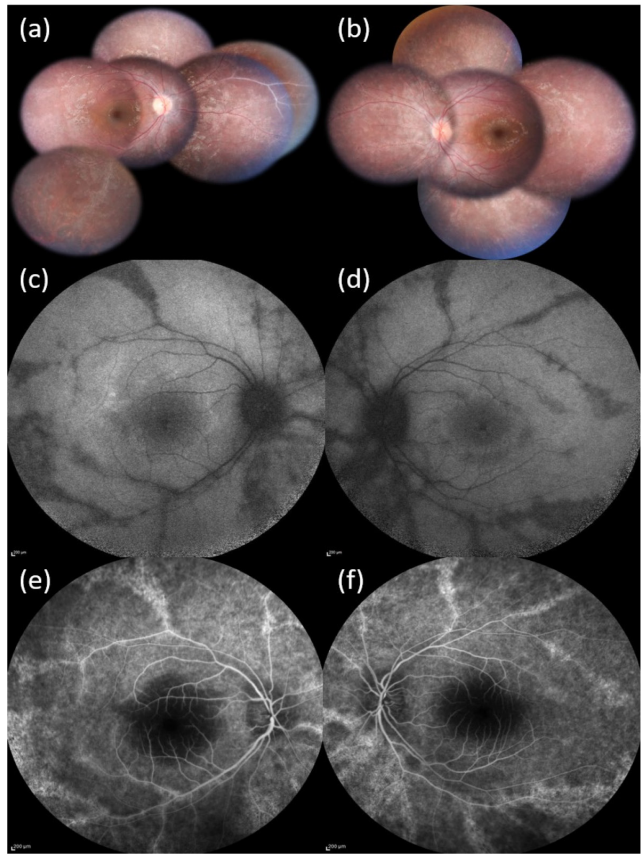

Figure 1. Multimodal imaging of the patient. a,b) Composite color fundus photography shows areas of retinochoroidal atrophy along the retinal veins without pigmentation. c,d) Fundus autofluorescence reveals perivenous hypoautofluorescence and cystoid macular edema. e,f) Fundus fluorescein angiography shows perivenous hyperfluorescence

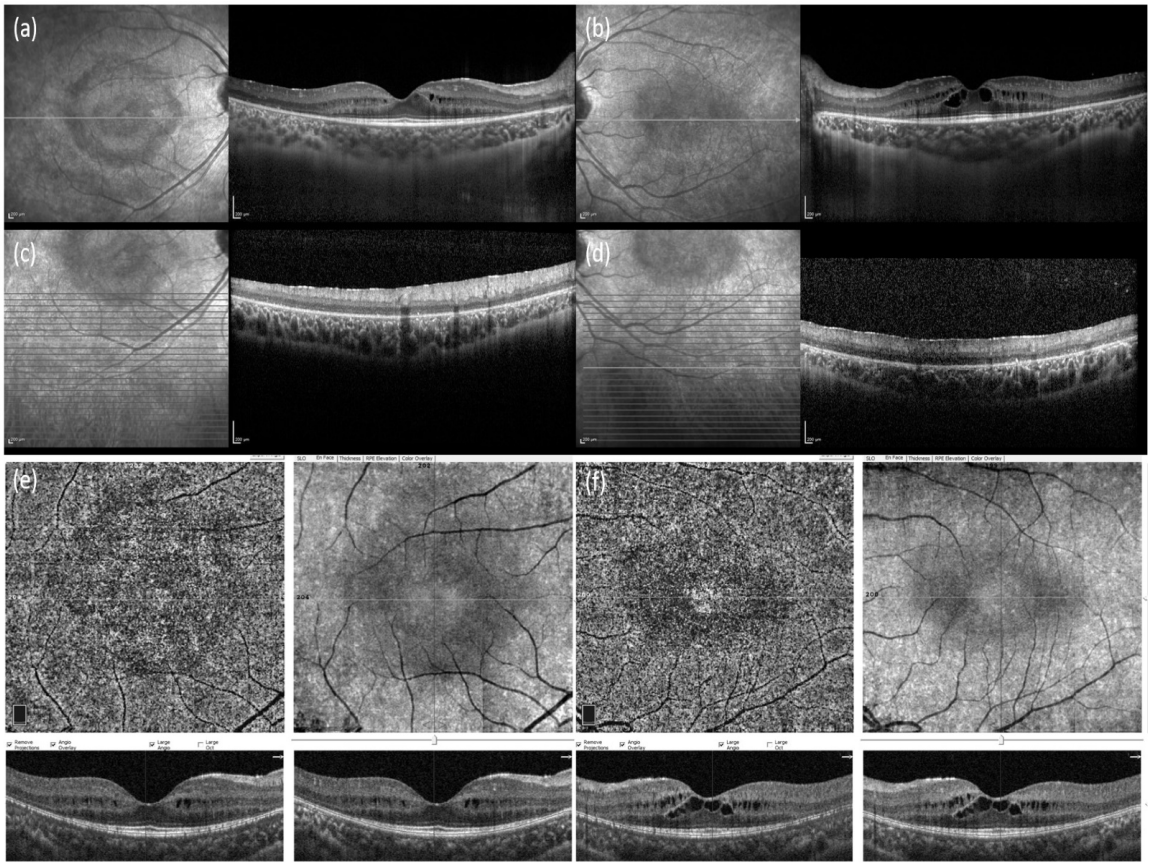

Figure 2. Optical coherence tomography (OCT) and OCT angiography images. a,b) Macular OCT shows cystoid macular edema. c,d) OCT of the perivenous atrophic areas reveals outer retinal layer loss. e,f) OCT angiography images of the macula

or very severe in PPRCA. FAF, SD-OCT, and FA are helpful tools to confirm the diagnosis of PPRCA.[2] The pediatric patient described in this case report had minimal paravenous pigment deposition and large areas of RPE atrophy around the optic disc and along the vessels. FAF, SD-OCT, and FA findings were also consistent with the diagnosis of PPRCA.

Visual acuity is generally good and minimally adversely affected in PPRCA patients without macular involvement. Only a small number of PPRCA cases with macular involvement have been reported in the literature.[3,5] Shona et al.[1] reported in a series of 23 cases that two-thirds of the patients were asymptomatic and the most common macular changes were mild or severe disruption of the outer retina and RPE, and/or choroidal thinning. They found mild macular intraretinal cysts in only one patient with extensive PPRCA. Batioglu et al.[3] reported the case of a 54-year-old woman with the typical fundus appearance of PPRCA accompanied by active inflammation with CME. To the best of our knowledge, the current case is the first reported case of PPRCA with CME but without obvious signs of ocular inflammation.

PPRCA is defined as a non-progressive or slowly progressive disease with an unknown etiology. Several infectious diseases that cause inflammation have been associated with PPRCA, including tuberculosis, sarcoidosis, syphilis, measles, rubella, and Behçet's disease. However, no systemic disease has yet been identified as the cause of PPRCA.[2] We could not find any clinical or serological evidence of disease in our etiological investigations of the patient in the current study. However, the presence of CME and a history of an unidentified viral illness at 15 months of age may support the contribution of chronic or latent inflammation in the etiology of PPRCA.

Shen et al.[6] described areas of choriocapillaris hypoperfusion on OCTA and suggested that it may also result from RPE/outer retinal loss. Recently, Ranjan et al.[4] reported that swept-source OCTA may show a relatively normal choriocapillaris structure, which they noted may be due to a milder form of the disease in their young patient. We demonstrated significant retinal thinning with loss of all outer retinal layers in the patient in the current study, although subfoveal choroidal thickness and choriocapillaris were normal on EDI SD-OCT. The flow in the superficial and deep retinal layers and choriocapillaris was also normal in the 6x6 mm^2 central macular area on OCTA.

PPCRA seems to be an acquired rather than inherited retinal disorder that is generally non-progressive. The underlying

basis of PPCRA is controversial and may include genetic and postinflammatory etiologies. In the literature, PPCRA was reported to be associated with a heterozygous CRB1 variant of uncertain significance identified in a family with apparently dominantly inherited PPCRA with variable expressivity. Others have proposed degenerative, developmental, vascular, or congenital etiologies. Differential diagnoses include chorioretinal degeneration in addition to inflammatory diseases that cause chorioretinal atrophy, including retinitis pigmentosa (pericentral, sector, and typical), helicoid peripapillary chorioretinal atrophy, serpiginous choroidopathy, angioid streaks, cone dystrophy or degeneration, Stickler syndrome, gyrate atrophy choroideremia, and Wagner's dominant vitreoretinal degeneration, and these aspects should be discussed including the patient's family history.[1,7,8,9,10]

In conclusion, by describing the multimodal imaging characteristics of an early/mild form of PPRCA in a pediatric patient with CME, we provide helpful insights into the stages and etiology of the disease.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: J.M., C.D., Concept: J.M., C.D., Design: J.M., C.D., Data Collection or Processing: J.M., C.D., Analysis or Interpretation: J.M., C.D., Literature Search: J.M., C.D., Writing: J.M., C.D.

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

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Case Report

A Rare Orbital Pathology: A Large Orbital Dermatofibrosarcoma Protuberans

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Abstract

Dermatofibrosarcoma protuberans (DFSP) is a rare sarcoma of the dermis. It is a malignant, locally aggressive, and infiltrative tumor with frequent recurrence. In this case, a 44-year-old woman presented with a 15-year history of a swelling in the medial canthus of the right eye that caused tearing. Imaging revealed a septated mass isodense to soft tissue that had eroded the medial wall of the orbit. Macroscopic examination showed an elastic, gray-brown, encapsulated, irregular mass measuring 45x35x22 mm. The surgical margins were positive, so adjuvant radiotherapy was started. The patient was followed for 2 years without recurrence. According to the literature, this mass is the largest orbital DFSP treated by globe-sparing primary resection.

Keywords: Dermatofibrosarcoma protuberans, orbital tumor, orbital radiotherapy, medial canthus tumor, eye tearing

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a primary, well-differentiated mesenchymal tumor of the dermis with an incidence of 0.8-5 per million. It constitutes 0.1% of malignancies in the head and neck region and 1% of soft tissue sarcomas.[1] It is a locally aggressive tumor with a high rate of local recurrence and low metastasis rate.[2] Treatment consists of excision with a wide safety margin. In the presence of recurrence and metastases or in cases where surgical treatment cannot be performed, radiotherapy and chemotherapy are alternative methods. According to the literature, 14 cases of orbital DFSP have been reported, and the mass presented here is the largest DFSP treated by globe-sparing primary resection. It is also the first case of orbital DFSP reported in Turkey.

Case Report

A 44-year-old woman presented to our clinic with complaints of progressive swelling over the right medial canthus region for 15 years that was causing eye tearing. She had a history of a previously excised mass at the same location 20 years ago, with no pathology report. On ophthalmologic examination, best corrected visual acuities were 20/25 in the right eye and 20/20 in the left eye. A non-tender, rubbery, immobile mass was palpated over her right medial canthus (Figure 1A). The right globe was displaced laterally without any motility restriction. Anterior

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and posterior segment findings were unremarkable except for prominent tearing on the right.

The mass was visualized preoperatively with magnetic resonance imaging (MRI). A hypodense mass (isodense to soft tissue) was detected on T1-weighted MRI (Figure 2A). MRI showed heterogeneous contrast enhancement in T2-weighted and short tau inversion recovery sequences. There were septa inside the mass and the bones showed erosion and remodeling. It was observed that the mass originated from the extraconal space (Figure 2B), reached the ethmoidal cells, and breached the medial orbital wall (Figure 2C). There was destruction of the lamina papyracea and ethmoidal septa, with a 3.5-mm defect in the fovea ethmoidalis and a millimetric defect in the lateral lamina of the cribriform plate. The mass obliterated the nasolacrimal groove, displaced the globe laterally, and grew posteriorly, nearly reaching the brain (Figure 2D).

Excisional biopsy under general anesthesia was planned. Following a right Lynch incision (Figure 3A) and orbicularis dissection, the mass was visualized, carefully dissected (Figure 3B), and removed en-bloc (Figure 3C). Intraoperatively, a small orbital wall defect measuring 3x2 mm was seen in the lamina papyracea, but the underlying mucosa was intact. No tissue representing the lacrimal sac was detected in the orbit. After removing the mass, we inspected for cerebrospinal fluid leakage but did not perform any additional tests.

Macroscopic inspection of the specimen revealed an elastic, gray-brown, encapsulated, irregularly surfaced mass measuring 4.5x3.5x2.2 cm in size (Figure 3D). In the sections, the inner tissues were tan-pink colored with a softer consistency. The tumor cells were positive for vimentin (Figure 4A) and CD34 (Figure 4B) and negative for CD31, Factor 8, EMA, CD68, desmin, and S-100. The proliferation index was 5% (Ki-67) (Figure 4C). The tissue margins were positive at multiple locations because the tumor's proximity to the brain and globe made a wide margin excision impossible.

Due to the positive surgical margins, the patient was treated postoperatively with 5400 Gy (180 Gy/fraction/day) intensity-modulated radiation therapy applied using helical tomotherapy. The patient was followed for 2 years with no recurrence and no distant metastasis (Figure 1B). However, she did not come to follow-up visits after 2 years.

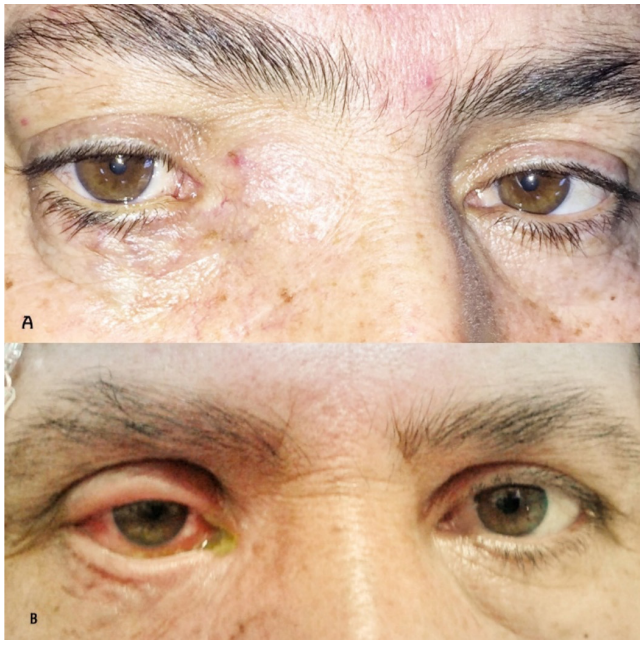

Figure 1. A) Preoperatively, swelling due to a mass completely under the skin is seen in the medial canthus region. B) Postoperative photo showing eyelash loss, eyelid edema, and conjunctival hyperemia due to radiation treatment. Persistent tearing is also seen, which is the result of both surgery and radiotherapy

Discussion

DFSP is seen most frequently between the ages of 20-50 years, with male predominance. DFSP occurs most often on the trunk and least commonly in the head and neck. Only 3.5% of DFSPs of the head and neck involve the periocular region.[1] Among orbital cases, half of patients are over 60 years of age and the gender ratio is equal. Orbital cases are most frequently in the medial canthus area, followed by the lower and upper eyelids.[3]

The tumor usually appears initially at a single focus, in the form of a mobile, pink, fibrotic skin nodule that does not adhere to deep tissues. Apart from the solitary nodule, there are also flat sclerotic and atrophic plaque forms.[4] It was named protuberans because of its protruding structure. It may occur in scar areas secondary to trauma or vaccination, in areas exposed to ionizing radiation, or spontaneously.

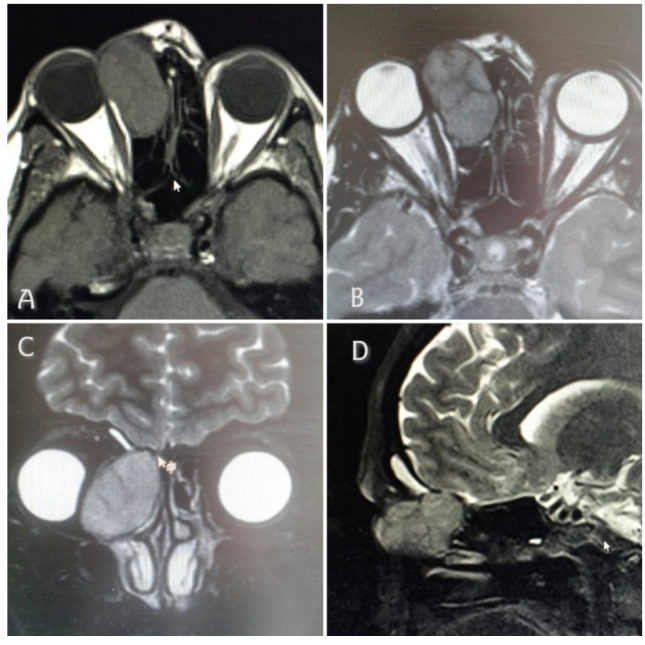

Figure 2. A) A hypodense mass (isodense to soft tissue) was detected on T1-weighted magnetic resonance imaging (MRI). B) In the axial section of the MRI, a septated mass originating from the extraconal space and causing destruction of the bones was observed. C) The coronal section of the MRI showed that the mass reached the ethmoid cells and pushed the medial orbital wall. D) The sagittal section of the MRI showed a 3.5-mm defect in the fovea ethmoidalis and the mass extending posteriorly and approaching the brain

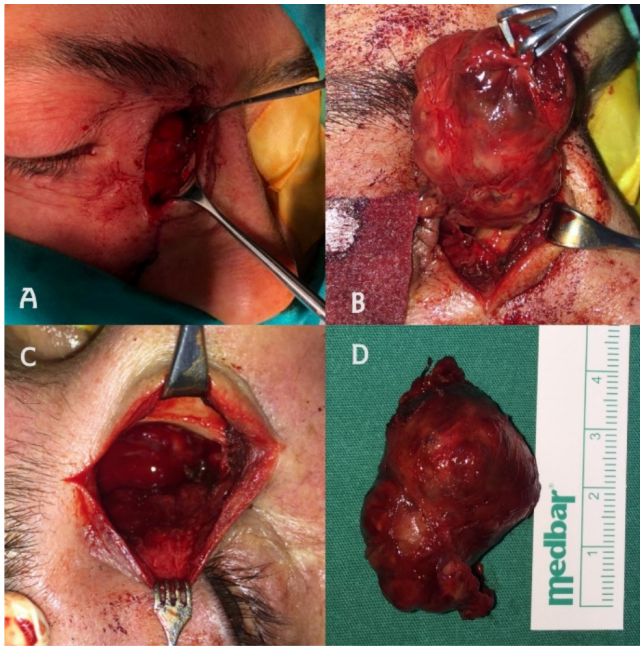

Figure 3. Intraoperative images of the right Lynch incision (A), the dissection (B), the mass removed en-bloc (C), and the irregularly surfaced mass measuring 4.5x3.5x2.2 cm in size (D)

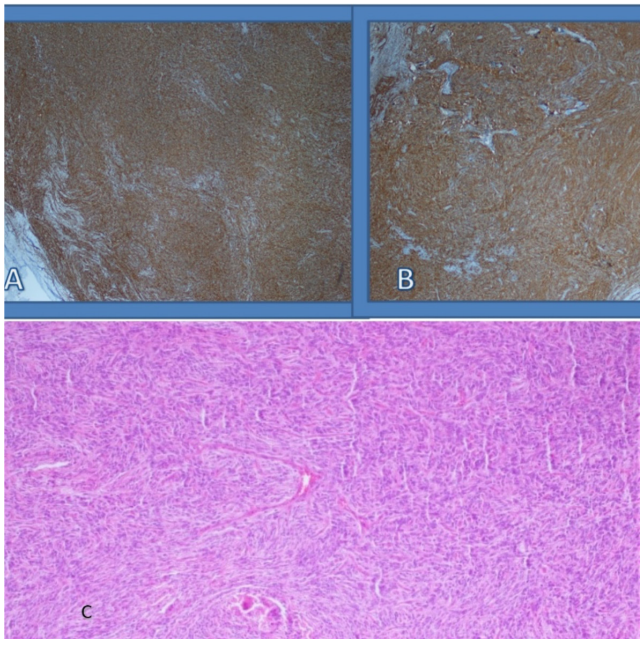

Figure 4. Diffuse strong vimentin (A) and CD34 (B) staining (x40) and vortex-like array of monotonous spindle tumor cells (C) (hematoxylin and eosin, x100)

It tends to grow by infiltrating the surrounding skin, subcutaneous, muscle, and bone tissues. Therefore, MRI and computed tomography are very useful in demonstrating local involvement during diagnosis, follow-up, and treatment.

The tumorigenesis of DFSP involves the t(17;22)(q22:13) reciprocal translocation.[5] The expression of CD34 and vimentin strongly supports the diagnosis of DFSP. Some tumors may be SMA-positive in focal areas, but S100 positivity is not observed. In our case, CD34 and vimentin were positive, while SMA and S100 were negative.

The main principle in the treatment of DFSP is excision with a wide margin of safety. Frozen section analysis and Mohs surgery are controversial because of the high likelihood of local recurrence.[6] Low-grade, cutaneous sarcoma with autocrine overproduction of the platelet-derived growth factor (PDGF The dense connective tissue found at the periphery of the tumor appears as a pseudocapsule that has irregular finger-like cellular protrusions invading surrounding tissues. As this tumor is mostly seen in the trunk and extremities, removing 3-5 cm with normal tissue is recommended in those exposed areas to prevent recurrences. However, this is impossible in the orbital area. Local recurrence is around 20-50% and mostly occurs within three years. The earliest local recurrence reported for orbital DFSPs was observed 1 week after excision.[7] In a previous case of orbital DFSP, exenteration was performed in addition to tumor excision due to the detection of positive surgical margins.[8] The 5-year survival rate is reported to be 93-100% for excisions made with adequate safety margins.[2]

Radiotherapy and transforming growth factor-beta inhibitors are other promising treatment options for DFSP, but their routine use is still controversial.[9] Adjuvant radiotherapy was reported to improve 10-year local control and survival rates in cases with positive surgical margins, local invasion, and recurrence.[9] Therefore, adjuvant radiotherapy and chemotherapy should also be kept in mind to avoid exenteration. These patients should be followed up for life, as local recurrence can be seen after many years.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A.K., Z.G.Ö., A.G., M.N., Concept: Z.G.Ö., Design: Z.G.Ö., Data Collection or Processing: A.A.K., Z.G.Ö., A.G., M.N., Analysis or Interpretation: Z.G.Ö., A.G., Literature Search: A.A.K., M.N., Writing: A.A.K., Z.G.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

Filtering Pseudo-Bleb Secondary to Sutured Posterior Chamber Intraocular Lens with Implications for Ocular Surgery in Marfan Syndrome

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Abstract

A 51-year-old female Caucasian patient with a history of Marfan syndrome and multiple previous bilateral ocular surgeries presented with increasing discomfort, epiphora, and blurred vision in her right eye for a few months. On examination, we found an overhanging cystic Seidel-positive filtering pseudo-bleb with hypotony in her right eye and a smaller Seidel-negative filtering pseudo-bleb in the left eye secondary to sutured intraocular lens (IOL) in both eyes. Intraoperatively, two full-thickness scleral defects were found close to the limbus, suggesting a melting flap in the location of the previous sutured IOL implant in the right eye. The defects were plugged with two pieces of donor sclera and covered with a larger donor scleral patch, the ischemic conjunctiva was excised, and the remaining healthy conjunctiva was advanced and sutured along the limbus. At last follow-up, intraocular pressure and vision in the right eye increased to preoperative levels, and no pseudo-bleb or leak was detected.

Keywords: Marfan syndrome, pseudo-bleb, bleb leak, sutured intraocular lens

Introduction

Marfan syndrome is a congenital connective tissue abnormality caused by mutations in the fibrillin *(FBN1)* gene and affecting cardiovascular, musculoskeletal, and ocular structures.[1] Weakening of the sclera in Marfan syndrome poses a risk of primary (spontaneous scleral rupture) or secondary (following scleral incisions) pseudo-bleb.

Herein, we report a rare case of leaking pseudo-bleb secondary to sutured posterior chamber intraocular lens (IOL) in a patient with Marfan syndrome.

Case Report

A 51-year-old Caucasian woman presented with increasing discomfort, epiphora, and reduced vision in her right eye for a few months. She had a history of Marfan syndrome with multiple previous ocular surgeries. Twenty-six years ago, she underwent bilateral lens extractions and sutured posterior chamber IOL implantation. Seventeen years ago, her right IOL subluxated after eye rubbing and was treated with IOL removal and insertion of an iris-clip IOL. Eight years ago, the right eye developed corneal endothelial decompensation with secondary bullous keratopathy. As a result, the iris-clip IOL was removed and replaced with

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another sutured IOL. Six years ago, a right retinal detachment was detected and treated with pars plana vitrectomy and gas tamponade. Three years ago, bilateral superonasal filtering pseudo-blebs were noted with the right more prominent than the left. At that time, mild right bleb dysesthesia was present but both blebs were Seidel-negative.

At presentation to our clinic, her vision was 6/36 right and 6/6 left with intraocular pressures of 5 mmHg and 9 mmHg, respectively. The right eye displayed an overhanging cystic Seidel-positive filtering pseudo-bleb, corneal edema with Descemet's folds and endothelial decompensation. There were no clinical signs of blebitis or endophthalmitis. The sutured IOL was centered and the retina flat. On the left, a smaller Seidel-negative filtering pseudo-bleb was noted with clear cornea, quiet anterior chamber, centered IOL, and flat retina (Figure 1A-C). Ultrasound biomicroscopy (UBM) showed a suspected scleral fistula connecting the anterior chamber and subconjunctival space in both eyes (Figure 1D-F). Posterior segment optical coherence tomography revealed macular subretinal fluid in the right eye (Figure 3A).

The patient underwent surgery to the right eye to i) identify the source of aqueous flow into the subconjunctival space, ii) to close the defect allowing aqueous flow to the subconjunctival space, and iii) excise the ischemic leaking conjunctiva and reconstruct the ocular surface tissues. During surgery, two full-thickness scleral defects were identified close to the limbus, suggesting a melting flap in the location of the previous sutured IOL implant and matching the UBM findings (Figure 2A). The defects were plugged with two pieces of donor sclera and covered with a larger donor scleral patch, the ischemic conjunctiva was excised, and the remaining healthy conjunctiva was advanced and sutured along the limbus (Figure 2B). At last follow up, IOP and visual acuity in the right eye were 20 mmHg and 6/36, respectively, and no pseudo-bleb or aqueous leak was detected. Corneal edema persisted, but the macular subretinal fluid had significantly reduced (Figure 3B).

Discussion

The first filtering bleb cases secondary to sutured IOL in Marfan patients were reported by Rees et al.[2] Time to onset of the pseudo-blebs was 2 months in one of their cases and 2 years in the other. In our case, the time to onset appeared significantly longer (somewhere between 5 and 26 years prior to presentation). Our observation together with that of Rees et al.[2] suggests this complication may occur early or late after sutured IOL surgery when performed in individuals with Marfan syndrome. Additionally, our patient presented with a leaking bleb requiring surgical intervention, and her scleral wounds were thoroughly assessed by UBM, which was not reported in Rees' patients.[2] Other similar cases are rare in the literature. Turaga et al.[3] reported a spontaneous pseudo-bleb due to scleral rupture in Marfan syndrome. Conjunctival cyst was also documented to masquerade as a pseudo-bleb after sclera-fixated IOL implantation in Marfan syndrome.[1] Shanmugam et al.[4] described a case of pseudo-bleb secondary to vitrectomy, but that patient was diagnosed with Traboulsi syndrome. UBM has also been employed to describe the anterior segment findings of this syndrome.[5]

Pseudo-blebs may be problematic for several reasons, several of which were present in our case. An elevated pseudo-bleb can lead to dysesthesia and in turn reduce the patient's quality of life. The eye may develop structural changes related to hypotony, such as the maculopathy present in our patient, and this can adversely affect vision and contribute to ocular discomfort. Furthermore, an ischemic and/or leaking pseudo-bleb may predispose to blebitis or endophthalmitis, which is potentially blinding.

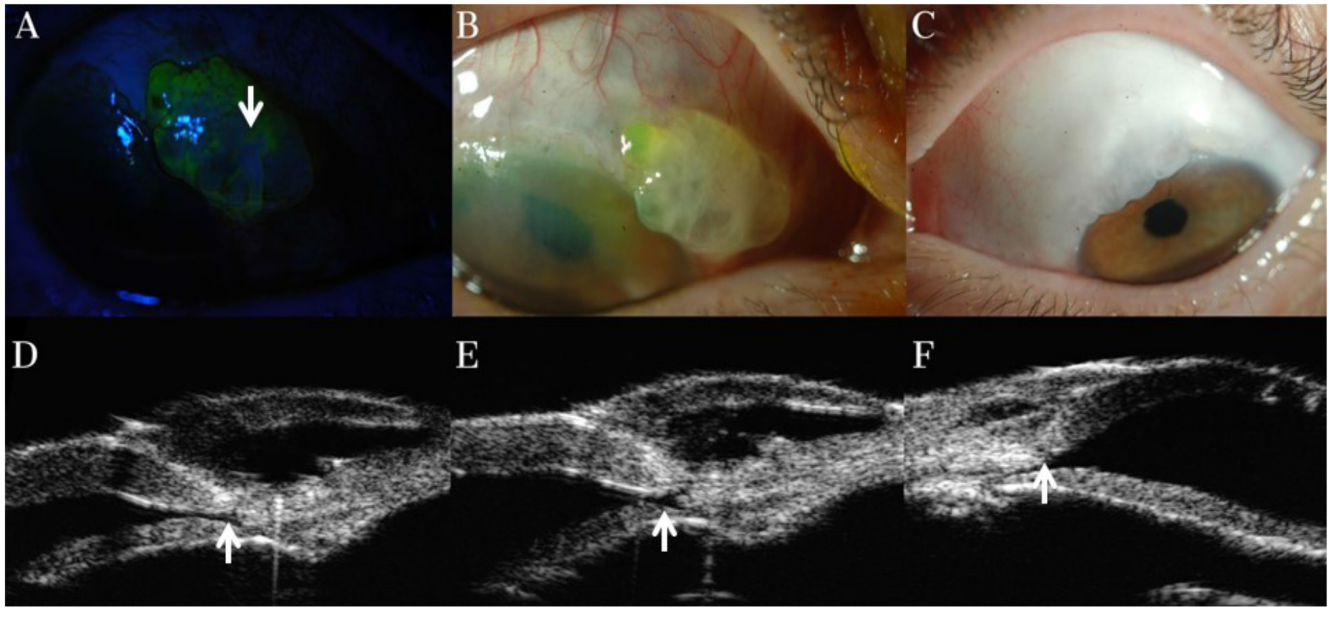

Figure 1. A-B) Right leaking filtering bleb. C) Left filtering bleb. D-F) Scleral defects in ultrasound biomicroscopy

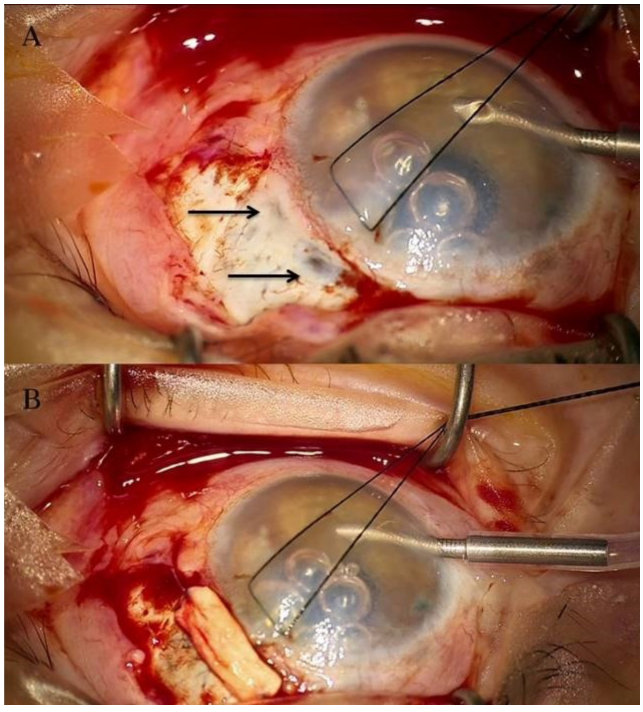

Figure 2. A) Intraoperative investigation of scleral wounds. B) Scleral patch graft

Both eyes of our patient presented with pseudo-blebs despite the fact that most surgeries had occurred on the right. This suggests the sutured IOL surgery was the likely contributing factor to scleral fistula development and subsequent pseudo-bleb formation. Therefore, scleral-fixated IOL surgery should be performed with caution. Alternative IOL choices may be preferable such as an iris-claw lens or three-piece IOL sutured to the iris.

It is interesting to note that both eyes in our patient, and those of other reported cases, developed cystic ischemic pseudo-blebs despite no exposure to anti-metabolites such as mitomycin C or 5-fluorouracil.[1-5] This suggests aqueous dynamics in the subconjunctival space plays a role in bleb morphology. This has been reported as a risk factor for bleb leak after trabeculectomy.[6] Hence, our case highlights the importance of directing aqueous flow posteriorly and over a broad area in bleb survival after filtration surgery.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Sidney Eye Hospital, Concept: T.H., Design: T.H., Data Collection or Processing: T.H., C.C., Analysis or Interpretation: T.H., C.C., Literature Search: T.H., C.C., Writing: T.H., C.C.

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

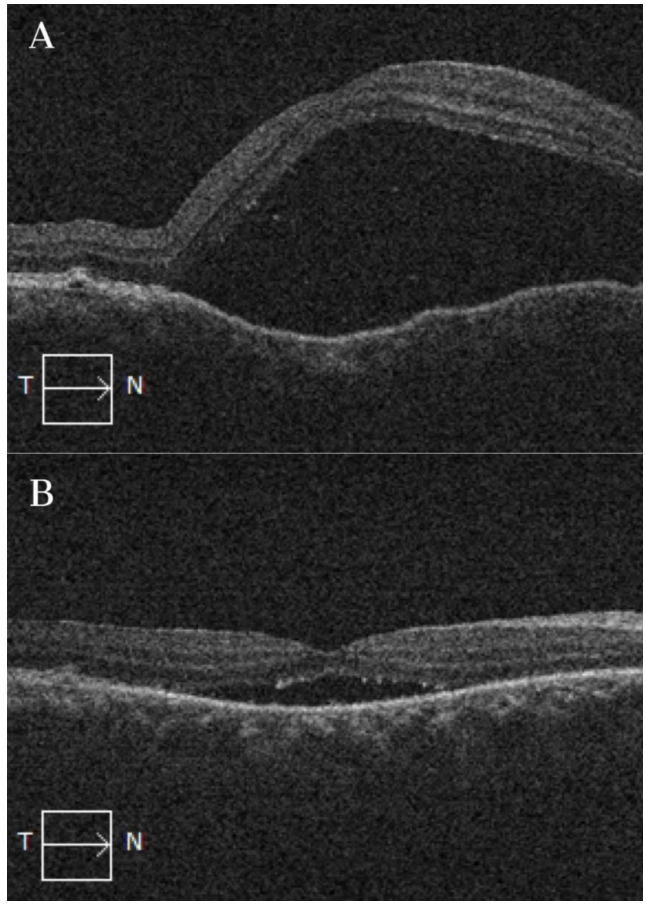

Figure 3. Subretinal fluid before (A) and after (B) the surgery

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2022 Referee Index

Ahmet Akman
Ahmet Dirican
Ahmet Kaan Gündüz
Ahmet Murat Sarıcı
Ahmet Özer
Akın Çakır
Ali Bülent Çankaya
Ali Hakan Durukan
Ali Osman Saatci
Ali Rıza Cenk Çelebi
Alp Alaluf
Altan Atakan Özcan
Argun Sertaç Kıvanç
Arif İbrahim Koytak
Arzu Taşkıran Çömez
Atilla Bayer
Ayça Yılmaz
Ayşe Ayça Sarı
Ayşe Gül Altıntaş
Ayşe Öner
Ayşegül Mavi Yıldız
Aysel Pelit
Aysun Şefay İdil
Banu Coşar
Banu Öncel Açıkalın
Banu Solmaz
Banu Turgut Öztürk
Barış Yeniad
Başak Bostancı
Bengü Ekinci Köktekir
Berna Akova
Betül Çakmak Tuğcu
Bülent Yazıcı
Burak Bilgin
Çağatay Çağlar
Canan Aslı Utine
Canan Gürdal
Cem Yıldırım
Cemal Özsaygılı
Cengiz Aras
Ceyhun Arıcı
Cezmi Doğan
Çiğdem Altan
Deniz Altınbay
Didar Uçar
Dilaver Ersanlı
Dilek Dursun Altınörs
Dilek Güven
Doğan Ceyhan
Ebru Nevin Çetin
Elif Demirkılınç Biler
Elif Erdem
Erdal Yüzbaşıoğlu
Erdem Dinç
Esat Çınar
Esin Başer
Fatih Özcura
Ferda Çiftçi
Feyza Önder
Figen Şermet
Filiz Afrashi
Furkan Kırık
Gamze Öztürk Karabulut
Giray Ersöz
Gölge Acaroğlu
Gül Arıkan
Gürsel Yılmaz
Hakan Özdemir
Halil Özgür Artunay
Halit Oğuz
Hande Çeliker
Harun Çakmak
Hatice Elvin Yıldız
Haydar Erdoğan
Hikmet Başmak
Hilal Eser Öztürk
Huban Atilla
Hülya Gökmen
Hürkan Kerimoğlu
Ilgaz Yalvaç
İmren Akkoyun
Işıl Sayman Muslubaş
Jale Menteş
Kadriye Ufuk Elgin
Kazım Hilmi Or
Kıvanç Güngör
Lale Közer Bilgin
Leyla Asena
M Sinan Sarıcaoğlu
Mehmet Ali Şekeroğlu
Mehmet Baykara
Mehmet Kemal Gündüz
Melda Nursal Yenerel
Melih Hamdi Ünal
Melis Palamar Onay
Meltem Söylev Bajin
Meltem Yağmur
Merih Soylu
Mümin Hocaoğlu
Murat Karaçorlu
Murat Tunç
Mustafa Doğan
Nazmiye Erol
Necip Kara
Nihal Demircan
Nihat Sayın
Nilgün Yıldırım
Nilüfer Berker
Nilüfer Koçak
Nilüfer Yalçındağ
Nur Kır
Nuray Akyol
Nurşen Yüksel
Nurten Ünlü
Öner Gelişken
Özay Öz
Özcan Kayıkçıoğlu
Özcan Ocakoğlu
Özge Saraç
Özgür Yalçınbayır
Özlem Barut Selver
Özlem Evren Kemer
Özlem Gürbüz Köz
Özlem Şahin
Özlem Yıldırım
Pelin Kaynak
Pınar Çakar Özdal
Raciha Beril Küçümen
Rana Altan Yaycıoğlu
Remzi Avcı
Şaban Gönül
Şafak Karslıoğlu
Sait Eğrilmez
Samuray Tuncer
Şansal Gedik
Selçuk Sızmaz
Şerife Bayraktar
Sevda Aydın Kurna
Şeyda Karadeniz Uğurlu
Sezin Akça Bayar
Sibel Çalışkan Kadayıfçılar
Sibel Demirel
Sibel Doğuizi
Sibel Kocabeyoğlu
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Zeliha Yazar
Zeynep Aktaş
Zühal Özen Tunay
Züleyha Yalnız Akkaya

2022 Author Index

2022 Author Index

2022 Author Index

2022 Subject Index

2022 Subject Index

2022 Subject Index