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AT A GLANCE

2024 Issue 1 at a Glance:

Esteemed colleagues,

The Turkish Journal of Ophthalmology, to which many valuable researchers have made scientific contributions over the years, features in its first issue of 2024 six original studies, one review, two case reports, one letter to the editor, and one authors' response.

In a clinical study by Değirmenci et al. titled "Impression Cytologic Evaluation of the Conjunctiva in Patients Treated with Topical 1% Voriconazole", the conjunctivas of 26 patients with culture-positive severe fungal keratitis who received 1% topical voriconazole for at least 3 months were evaluated by impression cytology. The study did not include patients with previous ocular surface disease or users of contact lenses or any topical drugs, and the fellow eyes of the patients constituted the control group. Impression cytology samples taken from the nasal, temporal, superior, and inferior conjunctiva at least 3 months after the discontinuation of topical voriconazole treatment were evaluated according to the Nelson staging system. Impression cytology grade in the inferior and temporal quadrants of the conjunctiva differed between treated and control eyes (p=0.03 and 0.02, respectively). The authors pointed out that voriconazole, a broad-spectrum antifungal, can cause metaplastic changes and emphasized that the conjunctiva should be checked at each examination in these patients (See pages 1-4).

Özdemir Yalçınsoy et al. investigated tubulointerstitial nephritis and uveitis syndrome (TINU), a multisystemic autoimmune disease that increased in frequency during the COVID-19 pandemic, in their study evaluating the clinical findings, laboratory results, and treatment of 10 pediatric TINU patients seen during a 2-year period during the pandemic. They concluded that among patients with TINU, which is normally rare, the rate of SARS-CoV-2 antibody positivity was 70%, suggesting that SARS-CoV-2 infection may have a triggering role in the development of the disease (See pages 5-10).

In their prospective study titled "Using the Amsler Grid Test for Age-Related Macular Degeneration Screening", Kuzucu Üşümüş et al. investigated the effectiveness of the Amsler grid test (AGT) in detecting age-related macular degeneration (AMD). The study included 355 people over the age of 50 who presented to a family health center but had no eye complaints. The AGT was performed in 700 eyes and was considered positive if the person saw broken or curved lines, differences in square shape or size, and color changes or blurring in any area. The AGT was positive in 97 (13.9%) of the 700 eyes tested. In the second stage, a total of 184 eyes (79 with positive AGT and 105 negative but considered at risk for AMD) were examined by an ophthalmologist, and optical coherence tomography (OCT) imaging was performed as deemed appropriate by the physician. At this stage, AMD was detected in 42 of the 79 AGT-positive eyes and 25 of 105 AGT-negative eyes, for a total of 67 eyes. The authors stated that AGT has moderate sensitivity (62.7%) and specificity (68.4%) in AMD screening and reported that more studies on the use of this cheap and easy-to-apply method as a screening test in primary health care are needed (See pages 11-16).

A retrospective study by Doğan et al. titled "Demographic, Etiological, and Clinical Characteristics of Eyelid Lacerations" evaluated data from 135 cases between 2018 and 2022. Twenty-nine of the patients were female and 21.4% were aged 18 or younger, while 68.8% were between the ages of 19 and 64 years. The leading causes of injury were sharp objects and blunt trauma. Foreign bodies were present at the wound site in 11.1% of the cases, and 22.2% had canalicular lacerations. The authors reported that eyelid injuries are frequently seen in young men and are often accompanied by findings such as conjunctival lacerations, open-globe injury, corneal epithelial damage, and hyphema, with serious pathologies more common in blunt trauma and traffic accidents (See pages 17-22).

Öner and Sinim Kahraman conducted a prospective clinical study titled "Evaluation of Full-Field Stimulus Threshold Test Results in Retinitis Pigmentosa: Relationship with Full-Field Electroretinography, Multifocal Electroretinography, Optical Coherence Tomography, and Visual Field" to evaluate the results of the full-field stimulus threshold (FST) test, which was developed to evaluate the efficacy and safety of treatment in low-vision hereditary retinal diseases, in patients with retinitis pigmentosa (RP) and compare them with the results of other ophthalmological tests. The study included 51 intermediate and advanced RP patients and 21 healthy individuals in a similar age range, all of whom were examined with the FST test, as well as visual field, OCT, and full-field and multifocal electroretinography (mfERG) tests. No full-field ERG response was obtained in any of the RP patients, but all were able to perform the FST test. Compared to the control group, the RP group had lower visual acuity and central macular thickness and significantly higher mean visual field defect. On mfERG, mean P1 wave amplitudes were found to be

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significantly lower and mean P1 wave latencies were longer in all rings in the RP group. The results of the FST test corresponded to those of other functional and anatomical tests, with significantly lower results in the RP group compared to the control group. The authors stated that the FST test is an easy-to-perform, reliable, and rapid test in cases with low vision and narrowed visual field and can measure retinal sensitivity in advanced RP cases with flat ERG (See pages 23-31).

In a study titled "The Effects of Lens Extraction Surgery on Intraocular Pressure and Anterior Segment Parameters in Primary Angle-Closure Glaucoma", Bayraktar et al. evaluated the effect of lens extraction with intraocular lens (IOL) implantation on intraocular pressure (IOP) and anterior segment parameters in 55 patients with cataract and primary angle-closure glaucoma (PACG) and compared the results with data from 34 control subjects with no problems other than cataract. Best corrected visual acuity, IOP, anterior chamber depth (ACD), aqueous depth (AD), and lens thickness were evaluated before and 6 months after surgery. It was found that all parameters changed postoperatively in PACG patients ($p<0.001$) and that these changes were greater than in the control group ($p<0.0001$). The authors reported that lens extraction+IOL surgery significantly increased the anterior segment depth in PACG patients and allowed better IOP control with fewer antiglaucomatous drugs after surgery (See pages 32-37).

A review penned by our esteemed colleague Faik Gelişken examines in detail the general features and clinical uses of indocyanine green angiography (ICGA), which is an important component of multimodal imaging that enables angiographic examination of the choroidal structure and is used in the evaluation of various pathologies of the choroid and retina (See pages 38-45).

In the case reports section, Özbek et al. presented the case of foreign body embedded in the episclera mimicking nodular scleritis and emphasized that considering a history of trauma and the possibility of a foreign body is important to guide clinical diagnosis and treatment in cases of anterior scleritis (See pages 46-48).

Bayraktar et al. presented a rare case of anterior chamber synchysis scintillans with concurrent neovascular glaucoma. Synchysis scintillans, also known as cholesterolosis bulbi, is described as a degenerative ocular pathology that is usually bilateral and characterized by the accumulation of cholesterol crystals in the vitreous. The authors examined the factors involved in cholesterol crystal accumulation in the anterior chamber in addition to the vitreous and discussed the pathologies that should be considered in the differential diagnosis (See pages 49-51).

In a letter to the editor, Fikret Uçar expressed his views and posed some questions regarding Dericioğlu et al.'s article titled "Predictive Factors of Complications and Visual Outcomes after Pediatric Cataract Surgery: A Single Referral Center Study from Türkiye." Uçar stated that IOL insertion is more beneficial in terms of visual acuity in cataract surgery for children older than 12 months and that scleral IOL fixation may be considered in cases where capsule integrity is impaired during surgery. He also emphasized that due to the problems of postoperative inflammation, pupillary membrane, and capsule opacification in pediatric patients, it is important to administer intraoperative triamcinolone to the anterior chamber and use more intensive anti-inflammatory treatment, and he discussed the techniques of posterior capsulorhexis, anterior vitrectomy, and IOL optic capture in pediatric cataract surgery (See pages 52-53).

In their response letter, Dericioğlu et al. stated that in accordance with clinical protocols, aphakic contact lenses were primarily recommended for pediatric cataract patients and IOLs were implanted situations where it would be more appropriate for socio-economic reasons or the use of contact lenses was not feasible, and the authors noted that this issue is still controversial. They also pointed out that in their study, there were no patients requiring IOL implantation with scleral fixation and stated that their treatment approaches for inflammation control were similar. The authors concurred that there is a need for comprehensive randomized studies in which different techniques are applied in pediatric cataract surgery (See pages 54-55).

We hope that the valuable articles in the first 2024 issue of the Turkish Journal of Ophthalmology will contribute to your knowledge and experience.

Respectfully on behalf of the Editorial Board,

Nilgün Yıldırım, MD

Original Article

Impression Cytologic Evaluation of the Conjunctiva in Patients Treated with Topical 1% Voriconazole

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Abstract

Objectives: The aim of the present study was to evaluate any conjunctival metaplastic changes by impression cytology in patients who underwent topical 1% voriconazole treatment for severe fungal keratitis.

Materials and Methods: The study was conducted at Ege University Faculty of Medicine, Departments of Ophthalmology and Medical Pathology. Patients who were treated with 1% topical voriconazole for fungal keratitis for at least 3 months were included. The used topical voriconazole treatment was initiated as one drop every hour and was tapered according to clinical improvement in all patients. Treatment was continued 4 times a day for at least 3 months. Impression cytology samples were collected at least 3 months after cessation of topical voriconazole from the affected eyes and from the fellow eyes as a control group. Collected specimens were transferred to the pathology department for evaluation and grading (Nelson's grading system).

Results: The mean age of the patients was 57.68±17.32 years (range, 22-87 years). The impression cytology grade of the inferior bulbar conjunctiva was 1.73±0.77 (range, 0-3) in the study group and 1.19±0.98 (range, 0-3) in the control group (p=0.03). The impression cytology grade of the temporal bulbar conjunctiva was 1.69±0.73 (range, 0-3) in the study group and 1.15±0.88 (range, 0-3) in the control group (p=0.02). The impression cytology grades of the nasal and superior bulbar conjunctiva did not differ statistically (p values 0.13 and 0.17, respectively).

Conclusion: Topical voriconazole is an effective broad-spectrum antifungal drug, but it induces conjunctival squamous metaplasia. Clinicians should be aware of this possible side effect of topical voriconazole and should carefully evaluate the conjunctiva of treated patients at each visit to detect possible metaplastic changes.

Keywords: Fungal keratitis, voriconazole, impression cytology, metaplasia

Introduction

Voriconazole is a broad-spectrum antifungal agent which is derived from fluconazole to improve its potency and spectrum. The mechanism of the drug is to inhibit the cytochrome P450 enzyme lanosterol 14α-demethylase. Inhibition of this enzyme prevents ergosterol synthesis and results in the accumulation of toxic sterols in the cell, leading to membrane disruption. Voriconazole was approved for the treatment of invasive aspergillosis, invasive *Candida* infections, and other fungal infections including *Scedosporium apiospermum* and *Fusarium* spp. It can be used for the treatment of patients who are intolerant or refractory to other treatment options as well. There are also reports of its off-label use for the treatment of histoplasmosis and coccidioidomycosis and for prophylaxis against *Aspergillus* spp. and fungal infections in patients with hematopoietic cell transplant, solid organ transplant, febrile neutropenia, and HIV.[1,2,3,4]

Voriconazole has high oral bioavailability and is available as oral suspensions, tablets, and an intravenous formulation. Almost 98% of voriconazole is metabolized in the liver, primarily by cytochrome P450 enzymes. Its primary metabolite is voriconazole N-oxide (VNO), which accounts for 72% of voriconazole metabolites in the plasma. VNO is not an antifungal metabolite, but it may be responsible for some adverse effects of the drug, such as skin reactions.[5,6]

Voriconazole is effective in the treatment of invasive aspergillosis and refractory fungal infections with other species.

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In ophthalmology practice, it can be used via topical, intrastromal, intracameral, or intravitreal routes for fungal infections. Topical voriconazole reaches therapeutic concentration in the aqueous humor in 24 minutes. However, in some recent articles it was reported to cause conjunctival squamous metaplasia.[6,7,8]

Conjunctival impression cytology is a relatively simple, practical, and non-invasive or minimally invasive technique that allows the collection of one to three layers of cells from the bulbar conjunctival surface. This technique is rapid, convenient, and widely performed to confirm a variety of ocular surface diseases and to monitor changes in the ocular surface.[9,10]

The aim of the present study was to use impression cytology to evaluate any conjunctival metaplastic changes in patients who underwent voriconazole treatment for severe culture-proven fungal keratitis for at least 3 months.

Materials and Methods

The study was conducted at the Ege University Faculty of Medicine, Departments of Ophthalmology and Pathology. It was approved by the Ege University Ethic Committee of the hospital and followed the Declaration of Helsinki ethical principles for medical research involving human subjects (decision no: 22-12T/45, date: 01.12.2022). The study was funded by the Ege University Scientific Research Project Foundation (project number: 18-TIP-005). Written informed consent was obtained from all participants.

Patients who were treated with 1% topical voriconazole for fungal keratitis for at least 3 months were included. Topical voriconazole treatment was initiated as one drop every hour and was tapered according to clinical improvement in all patients. The treatment was maintained as one drop 4 times a day for at least 3 months and maximum 8 months. Patients with any previously known ocular diseases including keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, pterygium, pinguecula, and glaucoma were excluded from the study. Also, patients who wore contact lenses or were taking any type of ocular medications were excluded. Samples for impression cytology were collected at least 3 months after cessation of topical voriconazole from the affected eye (study group) and from the contralateral eye (control group).

All eyes underwent a routine ophthalmological examination including best corrected visual acuity, intraocular pressure measurement (Tonopen AVIA, Reichert Technologies, Depew, NY), and anterior and posterior segment evaluations.

Impression cytology was performed at least 2 hours after ophthalmologic evaluation in order to prevent any interference. Cellulose acetate filter paper trimmed into four equal pieces was used to collect samples. After instilling one drop of local anesthetic into the inferior fornix, the impression cytology papers were applied to the superior, inferior, nasal, and temporal bulbar quadrants of the conjunctiva for approximately 5-10 seconds while the patient was looking in the opposite direction. Afterwards, the cellulose acetate filter paper was transferred to the fixative medium containing acetic acid, formaldehyde, and 70% ethyl alcohol in a 1:1:20 volume ratio. After staining with periodic acid-Schiff, the samples were examined under a light microscope. Conjunctival specimens were graded according to Nelson's[11] grading system (Table 1).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 20; IBM Corp., Armonk, NY) and a significance level of 5% (95% confidence interval) was accepted. A p value 0.05 was accepted as statistically significant. Results were given as mean ± standard deviation. Data were compared with t-test for parametric variables and Mann-Whitney U test for non-parametric variables.

Results

After obtaining ethical approval, 26 patients with culture-proven keratitis were included in the study. The median visual acuity of the patients was 1/10 (range, hand motion to 6/10) with Snellen chart at the time of sampling. The median intraocular pressure was 11 mmHg (range, 4-26 mmHg). The mean age of the patients was 57.68±17.32 years (range, 22-87 years). Seventeen patients were male (65%) and 9 patients were female (35%). After scraping the cornea for culture, topical voriconazole treatment was started and continued at least 3 months. The maximum duration, which was not limited at the beginning of the study, was 8 months. The mean duration of topical voriconazole use was 124.57±34.12 days (93-198 days). The mean impression cytology grade of the inferior bulbar conjunctiva was 1.73±0.77 (range, 0-3) in the study eyes and 1.19±0.98 (range, 0-3) in the control eyes (p=0.03). The impression cytology grade of the temporal bulbar conjunctiva was 1.69±073 (range, 0-3) in the study eyes and 1.15±0.88

Table 1. Nelson classification of squamous dysplasia

	Grade 0	Grade 1	Grade 2	Grade 3
Cell size	Small	Small	Large	Large
Nucleus	Large	Small	Small	Pyknotic
Cytoplasm	Eosinophilic	Eosinophilic	Variable	Basophilic
Nucleus/cytoplasm	1:2	1:3	1:4-1:5	1:6
Goblet cell	>500	350-500	100-350	<100
Goblet cell cytoplasm (periodic acid-Schiff staining)	+++	+++	++	-

+++: High, ++: Moderate, -: None

(range, 0-3) in the control eyes (p=0.02). The impression cytology grades in the nasal and superior bulbar conjunctiva did not show statistically significant differences between the groups (p values 0.13 and 0.172, respectively) (Table 2). There was no relationship between duration of drug use and grade (p=0.11).

Discussion

This study evaluated the relationship between topical 1% voriconazole use and conjunctival metaplastic changes as demonstrated with impression cytology in patients with severe fungal keratitis. To the best of our knowledge, this the first study to demonstrate these metaplastic changes by impression cytology after topical voriconazole use.

Voriconazole is a broad-spectrum antifungal agent and is effective against fungi that are resistant to other antifungal drugs. It is commercially available in oral and intravenous forms. It is also effective in refractory fungal keratitis when applied topically, which can be prepared by diluting intravenous 200 mg voriconazole lyophilized powder to a concentration of 1% as described previously.[12] Vemulakonda et al.[13] stated that topically administered voriconazole reached the minimum concentration to inhibit 90% of isolates for pathogens in the aqueous and vitreous. Edwar et al.[14] investigated topical 1% voriconazole combined with single-dose intrastromal 0.05% voriconazole versus topical 5% natamycin monotherapy in an experimental *Fusarium* keratitis model in rabbits. They concluded that topical 1% voriconazole combined with single-dose intrastromal 0.05% voriconazole was as effective as topical 5% natamycin monotherapy for the treatment of *Fusarium* keratitis. The efficacy of the topical voriconazole was also determined in other studies.[12,15]

Voriconazole has adverse effects including visual disturbances, skin rashes, photosensitivity, and squamous cell neoplasia.[16,17,18] VNO absorbs ultraviolet (UV)-A and -B radiation, causing skin photosensitivity and resulting in severe sunburns. Skin squamous cell neoplasia may arise from these sunburned areas. In 2015, Palamar et al.[7] reported ocular surface neoplastic changes demonstrated with confocal microscopy in a patient who received topical 1% voriconazole treatment for 4 months. This was the first report in the literature regarding a possible effect of topical voriconazole to induce conjunctival squamous cell neoplasia, which was subsequently investigated in two animal studies. Arikan et al.[19] observed histological changes in rabbits with topical 1% voriconazole application. Degirmenci et al.[20] also detected immunohistochemical changes in rats with 2% voriconazole eye drops. The most striking finding from the latter study was that rats exposed to sunlight had more prominent conjunctival metaplastic changes, demonstrating the additive effect of sunlight exposure.

Table 2. The impression cytology grades of the patients (n=26)

	Treated eyes Mean ± SD (range)	Fellow eyes Mean ± SD (range)	p value
Inferior	1.73±0.77 (0-3)	1.19±0.98 (0-3)	0.03
Temporal	1.69±073 (0-3)	1.15±0.88 (0-3)	0.02
Nasal	1.26±0.87 (0-3)	0.96±0.72 (0-2)	0.13
Superior	1.19±0.63 (0-2)	0.92±0.62 (0-2)	0.17

SD: Standard deviation

In the current study, the inferior and temporal quadrants of the bulbar conjunctiva were the areas most affected according to impression cytology findings. The temporal bulbar conjunctiva was probably the quadrant most exposed to direct sunlight, which enhanced metaplastic changes. Although the nasal bulbar conjunctiva also is exposed to sunlight, it is more likely to be indirect reflection from the nose.[21] The superior bulbar conjunctiva is covered by the upper eyelid and thus not exposed to enough sunlight to induce metaplastic changes. As mentioned earlier, VNO absorbs UV-A and UV-B but does not emit UV-B. This leads to accumulation of free oxygen radicals and causes oxidative stress.[22,23] Waste products of the ocular surface are eliminated after accumulating in the inferior fornix. Kojima et al.[24] detected conjunctival epithelial alterations from normal epithelium to metaplastic epithelia by increased oxidative stress. The current study revealed that the most affected area was the inferior bulbar conjunctiva, which has the most interaction with the tear film and its contents. Although the inferior bulbar conjunctiva is not exposed to direct sunlight, all waste products accumulate in the inferior fornix and are in contact with inferior bulbar conjunctiva. Moreover, the inferior conjunctiva has the most exposure to topical voriconazole. These factors may explain the greater conjunctival metaplastic changes in the inferior conjunctival quadrant.

Study Limitations

The main limitation of the study is the small sample size. Moreover, as these were resistant keratitis cases, the possibility of multiple topical agent use affecting the impression cytology results cannot be ruled out. It would be better to set up a prospective study to exclude the possible effects of multidrug use.

Conclusion

Although voriconazole is an indispensable agent in fungal infections including fungal keratitis, it may trigger conjunctival metaplastic changes that can lead to conjunctival squamous cell carcinoma. Clinicians should be aware of this serious adverse effect and be cautious even in topical use. Further studies correlating this side effect with the duration of the topical voriconazole use are needed.

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Ethics

Ethics Committee Approval: It was approved by the Ege University Ethic Committee of the hospital and followed the Declaration of Helsinki ethical principles for medical research involving human subjects (decision no: 22-12T/45, date: 01.12.2022).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: C.D., Concept: C.D., M.P., Ö.B.S., Design: M.P., Ö.B.S., Data Collection or Processing: C.D., Z.E., Analysis or Interpretation: M.P., A.V., A.Y., Literature Search: C.D., Z.E., Writing: C.D., M.P.

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Original Article

Tubulointerstitial Nephritis and Uveitis Syndrome During the COVID-19 Pandemic: A Case Series

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Abstract

Objectives: To report the ocular findings, laboratory results, and management of patients with tubulointerstitial nephritis and uveitis syndrome (TINU), whose numbers increased during the 2019 coronavirus disease (COVID-19) pandemic.

Materials and Methods: Demographic characteristics, ophthalmic examination findings, laboratory results including polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), serum SARS-CoV-2 immunoglobulin G (IgG) antibody, and treatment of patients diagnosed with TINU between March 2020 and March 2022 were evaluated retrospectively.

Results: The study included 19 eyes of 10 patients (6 female/4 male). The mean age was 13.5±2.4 years (range: 8-16 years). The mean follow-up duration was 13.5±6.1 months (range: 6-24 months). All patients presented with anterior uveitis. Anterior uveitis was bilateral in 9 patients (90%) and unilateral in 1 patient (10%). Posterior segment findings were normal in 8 patients (80%), and bilateral optic disc edema was observed in only 2 patients (20%). None of the patients had a previous SARS-CoV-2 infection and/or vaccination history. The SARS-CoV-2 PCR test was negative in all patients at presentation. The SARS-CoV-2 IgG antibody test was reactive in 7 patients (70%). Recurrent uveitis developed in 8 patients (80%) during follow-up. Systemic immunomodulatory therapy was required for the control of ocular inflammation in 7 patients (70%) with severe uveitis flare-ups.

Conclusion: TINU is a multisystemic autoimmune disease, especially in response to environmental triggering factors such as viral infections. Although TINU is a rare disease, the number of cases increased during the COVID-19 pandemic. SARS-CoV-2 antibodies were detected at a significant rate of 70% in these patients, who did not have a history of SARS-CoV-2 infection and vaccination. Previous asymptomatic SARS-CoV-2 infection in children may be a triggering factor in the development of TINU.

Keywords: COVID-19, pediatric uveitis, SARS-CoV-2, TINU, tubulointerstitial nephritis, uveitis

Introduction

Tubulointerstitial nephritis and uveitis syndrome (TINU), which was first reported in 1975 by Dobrin et al.[1], is a rare autoimmune disease. TINU is characterized by acute kidney inflammation and uveitis without any underlying systemic disease and it appears more frequently in children.[2] Uveitis in TINU is typically bilateral non-granulomatous anterior uveitis, but unilateral involvement, granulomatous uveitis, intermediate uveitis, and various posterior segment presentations may also occur.[3,4] While ocular findings usually follow tubulointerstitial nephritis (TIN), they may also occur concurrently or before TIN.[3] The etiopathogenesis of TINU is still unknown, but it is clear that TINU is an autoimmune inflammatory disease that develops with multifactorial environmental triggers such as viral, bacterial, and parasitic infections or pharmacological agents.[2,3,4]

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The 2019 coronavirus disease (COVID-19) caused by the severe acute respiratory distress syndrome-coronavirus 2 (SARS-CoV-2) became a pandemic that has affected the whole world.[5] In addition to the severe pulmonary effects of COVID-19, the multisystemic effects of COVID-19 began to emerge over time.[5,6,7,8] Several case reports of acute TIN and TINU that may be associated with SARS-CoV-2 infection have been described in the literature. [9,10,11,12,13,14,15,16,17] Recently, an increase in the incidence of acute TIN and TINU was reported in France in the first wave of the COVID-19 pandemic.[12] Another study reported a significant increase in TINU cases during the COVID-19 pandemic compared to the pre-pandemic period.[13] These studies suggested that SARS-CoV-2 infection may be among the infectious agents responsible for the development of acute TIN and TINU in children.[12,15,16,17]

TINU is known to account for less than 2% of all uveitis patients in ophthalmology clinics.[3,18] Although TINU is a relatively rare disease, an increase in the number of TINU cases has been observed in our clinic during the COVID-19 pandemic. Therefore, we think that the SARS-CoV-2 virus may be a triggering viral infection for TINU. In this study, we aimed to present the ophthalmic examination findings, laboratory results, and treatment approaches of patients diagnosed with TINU during the COVID-19 pandemic.

Materials and Methods

The records of patients diagnosed with TINU were evaluated retrospectively between March 2020 and March 2022 in the uvea clinic of a tertiary eye hospital. The study was carried out according to the principles of the Helsinki Declaration, and the study was approved by the University of Health Sciences Türkiye, Ankara City Hospital Ethics Committee (number: E1-22-2979).

All patients were diagnosed by the same uveitis specialists and pediatric nephrologists according to the diagnostic criteria of TINU.[19] Typical uveitis findings of TINU were described as bilateral acute anterior uveitis that started within 2 months before or 12 months after acute TIN, while atypical uveitis findings of TINU were described as unilateral anterior uveitis, intermediate uveitis, posterior uveitis, or a combination of these.[19] TINU was categorized as definite (histopathologically or clinically diagnosed acute TIN with all criteria and typical uveitis), probable (histopathologically diagnosed acute TIN and atypical uveitis or clinically diagnosed acute TIN with incomplete criteria and typical uveitis), and possible (clinically diagnosed acute TIN with incomplete criteria and atypical uveitis).[19] Since the clinical findings of acute TIN were considered sufficient, a kidney biopsy was not performed in all patients.

Patients' demographic data, detailed ocular examination findings (Snellen visual acuity, tonometry, anterior and posterior segment slit-lamp examination), follow-up duration, and treatment approaches were evaluated. Best-corrected visual acuities (BCVA) at presentation and last visit, recurrent uveitis flare-up, and development of ocular complications such as cataracts, glaucoma, and posterior synechia were recorded. Ocular inflammation was defined based on the Standardization of Uveitis Nomenclature Working Group Guidelines.[20]

All patients underwent routine complete blood counts, liver and kidney function tests, acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein), and urinalysis. Extensive laboratory workup was performed to rule out other diseases. Laboratory tests included serology tests for syphilis; ELISA tests for hepatitis viruses and HIV; serum angiotensin-converting enzyme (ACE) and lysozyme values; antinuclear antibody (ANA), anti-Sjögren's syndrome-related (SS)-A antibody, antiSS-B antibody, proteinase 3-antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase-ANCA tests; and additional tests if needed. The interferon-gamma release assay test and tuberculin skin test were done to exclude tuberculosis. X-ray and/or chest computed tomography were performed. All patients had polymerase chain reaction (PCR) tests for SARS-CoV-2 from oral and nasal swabs obtained at presentation. To evaluate the relationship between TINU cases and COVID-19, these patients were retrospectively tested for serum SARS-CoV-2 immunoglobulin G (IgG). Patients with at least 6 months of regular follow-up were included.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp, Armonk, NY, USA). Qualitative data were expressed as number and percentages, and quantitative data as mean ± standard deviation and range.

Results

There were 3 patients with TINU in our clinic between 2010 and 2020, whereas TINU was diagnosed in 10 patients who presented with anterior uveitis in the following two years (2020-2022). This study included 19 eyes of 10 patients diagnosed with TINU between March 2020 and March 2022. Nine patients (90%) had bilateral and 1 patient (10%) had unilateral anterior uveitis. Six patients (60%) were female and 4 (40%) were male. The mean age of the patients at presentation was 13.5±2.4 years (range: 8-16 years). The mean follow-up duration was 13.5±6.1 months (range: 6-24 months). The onset of uveitis followed TIN in 2 patients (20%) and occurred concurrently with TIN in 8 patients (80%). The demographic characteristics, clinical findings, and laboratory results of the patients are summarized in Table 1.

All patients had abnormal kidney function at presentation and the mean serum creatinine level was 1.4±1.4 mg/dL (range: 0.98-3.38 mg/dL). Urine β2 microglobulin level was elevated in 8 patients (80%), and the mean urine β2 microglobulin level was 3.5±1.1 mg/L (range: 1.76-5.42 mg/L). Liver function tests were within normal limits in all patients. ESR was high in 8 patients (80%), and the mean ESR was 40.6±26.3 mm/h (range: 10.0-98.0 mm/h). C-reactive protein was elevated in all patients (100%) and the median C-reactive protein level was 9.2 g/L (range: 3.0-78.7 g/L). ANA autoantibody was positive in 3 patients (30%), but no systemic disease was detected in any

patient. Kidney biopsy was performed in only 3 patients (30%), and the results were consistent with TIN (Table 1).

None of the patients had a previous SARS-CoV-2 infection or vaccination history. Only 2 patients (20%) had family contact with SARS-CoV-2 infection within the last month. The SARS-CoV-2 PCR test was negative in all patients. The SARS-CoV-2 IgG antibody test was reactive in 7 patients (70%), and the mean SARS-CoV-2 IgG antibody level was 9.3±7.3 S/co (range: 1.26-22.79) (Table 1). Furthermore, the patients did not have a history of any medication use.

The ocular findings at presentation and treatment approaches are summarized in Table 2. All patients presented with symptoms of acute anterior uveitis; 8 patients (80%) had redness and 3 patients (30%) had blurred vision. BCVA at presentation was 20/100 in 2 eyes (10.5%), 20/40 in 1 eye (5.3%), and 20/25 or better in the remaining eyes (84.2%). Nine patients (90%) had non-granulomatous anterior uveitis and only 1 patient (10%) had granulomatous anterior uveitis (Figure 1). While fundus examination was normal in 8 patients (80%), bilateral optic disc edema was observed in 2 patients (20%). Fluorescein angiography (FA) was performed only in 2 patients (20%) with optic disc edema and showed bilateral optic disc hyperfluorescence and no vascular leakage. Considering all the above findings, 7 patients (70%) were categorized as definite TINU and 3 patients (30%) as probable TINU syndrome.

Topical 1% prednisolone acetate (Allergan, Dublin, Ireland) (4 to 8 times daily), 1% cyclopentolate HCl (Abdi İbrahim, İstanbul, Türkiye) (1 to 3 times daily) and oral prednisolone (Gensenta, İstanbul, Türkiye) (0.5-1 mg/kg/day) treatment was given to all patients (100%). Topical and oral corticosteroid treatments were tapered weekly according to the patient's clinical response. Recurrent bilateral anterior uveitis was observed in 8 patients (80%) when topical

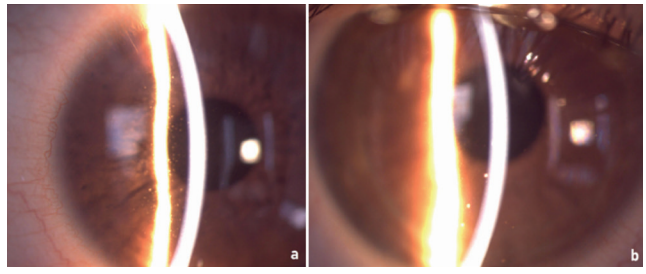

Figure 1. Anterior segment images of two different patients with TINU. Anterior segment imaging showed diffuse non-granulomatous keratic precipitates (a) and several paracentrally located granulomatous keratic precipitates (b)

TINU: Tubulointerstitial nephritis and uveitis syndrome

Table 1. Demographic characteristics, clinical findings, and laboratory work-up of the patients

Case no	1	2	3	4	5	6	7	8	9	10
Age/gender	13/F	15/F	14/F	14/F	8/F	15/M	12/F	12/M	16/M	16/M
Follow-up duration (months)	10	11	24	9	6	12	12	6	6	6
Clinical findings	AAU, muscle pain and malaise	AAU	AAU	AAU	AAU, muscle pain and malaise	Fever and body rash	AAU, weight loss	AAU	Muscle pain and malaise	AAU
Laboratory work-up										
Serum creatinine (mg/dL)	1.21	1.10	1.05	0.98	0.94	3.38	1.54	1.01	1.98	1.04
Urine β2 microglobulin (mg/L)	3.10	5.42	N/A	2.64	3.72	4.34	4.76	N/A	3.50	3.90
Urine analysis	Proteinuria	Proteinuria, pyuria	Proteinuria	Pyuria	Glucosuria	Proteinuria	Normal	Pyuria	Normal	Normal
CBC	Normal	Anemia	Anemia	Normal	Anemia	Anemia	Anemia	Normal	Normal	Normal
Erythrocyte sedimentation rate (mm/h)	29	40	98	48	12	69	29	39	32	10
C reactive protein (g/L)	20	8.5	39.9	25.2	3.0	78.7	3.0	10.0	6.0	3.0
ANA	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Kidney biopsy	N/A	TIN	TIN	N/A	N/A	TIN	N/A	N/A	N/A	N/A
SARS-CoV-2 PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
SARS-CoV-2 IgG antibody (S/co)	Non-reactive	Reactive 22.79	Reactive 1.26	Non-reactive	Reactive 12.97	Non-reactive	Reactive 10.59	Reactive 3.69	Reactive 9.98	Reactive 4.05

F: Female, M: Male, AAU: Acute anterior uveitis, CBC: Complete blood count, ANA: Antinuclear antibodies, TIN: Tubulointerstitial nephritis, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, PCR: Polymerase chain reaction, IgG: Immunoglobulin G

Table 2. Ocular findings at presentation and treatment approaches

Case no	1	2	3	4	5	6	7	8	9	10
Ocular involvement	Bilateral AU	Bilateral AU	Bilateral AU	Bilateral AU	Bilateral AU	Bilateral AU	Bilateral AU	Bilateral AU	Unilateral AU (left)	Bilateral AU
Anterior segment (right/left)	3+/4+ cells PS	1+/2+ cells	1+/2+ cells	2+/3+ cells	1+/2+ cells	2+/1+ cells	1+/2+ cells, PS	2+/3+ cells granulomatous KP	/4+ cells, PS	2+/2+ cells
Posterior segment	Bilateral OD edema	Normal	Normal	Normal	Bilateral OD edema	Normal	Normal	Normal	Normal	Normal
Recurrence	+	+	+	+	-	+	+	+	-	+
Treatment approach										
Topical and systemic corticosteroid	+	+	+	+	+	+	+	+	+	+
Immunosuppressive	MTX	MTX	MTX	-	-	MTX, MMF	MTX	MTX	-	AZA
Biological agent	ADA	ADA	ADA	-	-	ADA	ADA	-	-	-
Ocular complications	Steroid-induced IOP elevation, persistent PS	Steroid-induced IOP elevation, PSC	PSC			Steroid-induced IOP elevation	Persistent PS			

AU: Anterior uveitis, PS: Posterior synechia, KP: Keratic precipitates, OD: Optic disc, MTX: Methotrexate, MMF: Mycophenolate mofetil, AZA: Azothioprine, ADA: Adalimumab, IOP: Intraocular pressure, PSC: Posterior subcapsular cataract

and systemic corticosteroid therapy was reduced. Systemic immunomodulatory therapy was given to 7 patients (70%). In 2 patients (20%) (case 6, case 10), immunomodulatory therapy was also recommended for renal disease. Six patients (60%) used methotrexate (MTX, Koçak Farma, Ankara, Türkiye) (7.5-15 mg/week) and 1 patient (10%) used azathioprine (Aspen Pharmacare, Durban, South Africa) (100 mg/day). MTX therapy was switched to mycophenolate mofetil (Roche, Basel, Switzerland) in 1 patient (10%) (case 6) due to an elevation of liver function tests. The anti-tumor necrosis factor-a (TNF-a) agent adalimumab (Abbvie, Chicago, Illinois, USA) (40 mg every 2 weeks), was added to systemic immunosuppressive therapy in 5 patients (50%) to control intraocular inflammation. Triple topical agents (brimonidine [Bilim İlaç, İstanbul, Türkiye] with a combination of non-selective beta-blocker and topical carbonic anhydrase inhibitor) were used for a mean of 2.3±0.5 months (range: 2-3 months) in 3 patients (30%) with steroid-induced intraocular pressure (IOP) elevation. IOP could be controlled, and no patient had glaucoma.

BCVA at the last visit was 20/25 or better in all eyes except 1 eye (5.3%) with 20/100 vision due to cataracts. Intraocular inflammation was controlled, and all patients had normal renal function at the last visit. The patients remain under follow-up, and systemic immunomodulatory treatment has not been discontinued in any patient yet.

Discussion

This study evaluated the increased cases of TINU in a tertiary uvea clinic during the COVID-19 pandemic and detected reactive SARS-CoV2 IgG antibodies in 70% of these patients. TINU syndrome, an oculorenal disease, is more commonly diagnosed in children aged 10-15 years, especially in female patients, but may also occur in adults.[2,3,19,21,22] All of our patients were in the pediatric age group and the majority were females. Although the etiopathogenesis of TINU is still unknown, studies have provided evidence for the involvement of cellular and humoral immunity in susceptible individuals.[3,4] Pharmacological and infectious agents have been suggested as two important triggering factors in the etiopathogenesis of TINU, yet active infection at the tissue level has not been demonstrated.[2,3,4,12] It is clear that TINU is an autoimmune inflammatory disease that develops with multifactorial environmental triggers. In our series, none of the patients had a history of drug use or previous infection, and ANA positivity was detected at a rate of 30%.

Avramescu et al.[12] recently evaluated 48 patients aged 9.4-17.6 years who were diagnosed with acute TIN (25 cases) and TINU (23 cases) during the COVID-19 pandemic. In addition to the increase in the incidence of acute TIN and TINU during the pandemic, the authors reported that the obtained positive serological and histopathological findings support a causal association between SARS-CoV-2 infection and the development of acute TIN/TINU in children.[12] SARS-CoV-2 uses ACE2 receptors to infect the cells, and these receptors are commonly in the renal tubules and the eye.[5,8] Studies suggest that SARS-CoV-2 damages kidney cells using this receptor pathway and initiates the inflammatory response.[10,16] García-Fernández et al.[16] reported an adolescent patient diagnosed with TINU in whom SARS-CoV-2 spike protein was detected in kidney tissue. The authors argued that SARS-CoV-2 played a potential role,

both directly and indirectly, in the development of TINU in these patients. There is currently no conclusive evidence in the literature on how acute TINU occurs after COVID-19, but it is hypothesized that the humoral and cellular autoimmune response triggered after SARS-CoV-2 infection may be the cause.[8,10,12] In our study, the increase in the number of pediatric patients with TINU during the COVID-19 pandemic and the detection of SARS-CoV-2 IgG antibodies in most of these patients suggest that previous asymptomatic SARS-CoV-2 infection in children may be a trigger in the development of TINU. Publications and reported cases on this subject are increasing day by day, and future multicenter studies with large sample sizes may help elucidate the pathogenesis.

Ocular involvement of TINU is typically bilateral anterior uveitis, but inflammatory manifestations of the posterior segment, such as optic disc edema, vascular sheathing, and chorioretinal lesions, may also occur.[22,23,24,25] There are currently few reports in the literature reporting uveitis findings in patients diagnosed with TINU during COVID-19.[11,13,14,15,16,17] In some of these, ocular involvement was reported as bilateral anterior uveitis in cases of TINU associated with SARS-CoV2 infection.[14,16,17] Although various posterior segment findings such as disc edema, chorioretinal scar, disc leakage, and peripheral vascular leakage were reported more frequently in TINU patients (87%) during the pandemic period than in pre-pandemic patients (67%), no significant difference was found.[13] Eser-Ozturk et al.[11] reported 4 patients with TINU aged 8-17 years with bilateral granulomatous panuveitis and choroidal inflammation possibly associated with COVID-19. In our series, 90% of the patients presented with bilateral anterior uveitis, and only 1 patient (10%) had granulomatous uveitis. Moreover, optic disc edema (20%) was the only posterior segment finding detected; no clinical signs of choroidal inflammation were observed in any patient. As we did not perform indocyanine green angiography and/or FA in patients without posterior segment findings, we cannot comment on the subclinical choroidal and retinal involvement.

In addition to SARS-CoV-2 infection, cases of uveitis or nephritis developing after COVID-19 vaccination have been reported in the literature.[26,27,28] Chen et al.[26] recently reported a case of TINU with bilateral anterior uveitis after receiving the COVID-19 mRNA vaccine. In a report of TINU cases during the COVID-19 pandemic, 2 out of 18 patients were reported to have received the COVID-19 vaccine before the onset of ocular symptoms.[13] Therefore, not only infection itself but also COVID-19 vaccines may cause autoimmune diseases such as TINU.[26,29] However, none of the cases in our series had a history of COVID-19 vaccination.

Renal involvement of TINU is usually self-limited, but uveitis may be chronic and recurrent, especially in children.[3,4] Topical and systemic corticosteroids are the first-line treatment for uveitis in TINU. However, steroid-sparing systemic immunomodulatory therapy is generally required to control intraocular inflammation.[25,30,31,32] A study evaluating the long-term treatment results in TINU showed that early systemic immunomodulatory treatment was effective in achieving permanent remission.[31] Tirelli et al.[32] reported that anti-TNF agents are effective in the treatment of TINU cases with uveitis resistant to conventional immunomodulatory therapy. Good outcomes have been recently reported with antimetabolites and adalimumab therapy in patients with TINU associated with SARS-CoV2.[11,13,15] Even though Huang et al.[13] used TNF-α inhibitors only in TINU patients during the COVID-19 pandemic, they found no significant difference in the number of patients requiring biologic therapy before and during the COVID-19 pandemic. Maggio et al.[15] achieved complete uveitis remission after adalimumab treatment in a 7-year-old girl with recurrent uveitis who developed TINU after SARS-CoV-2 infection. Recurrent uveitis occurred in 80% of our patients when corticosteroid therapy was tapered. Therefore, 70% of patients required systemic immunomodulatory therapy, and adalimumab was used in 71% of these patients.

Mandeville et al.[19] reported an ocular complication rate of 21% in TINU, and the most common ocular complications were posterior synechia and optic disc edema. Furthermore, steroid-induced IOP elevation was found in 5% of patients aged 9-74 years.[19] In our series, ocular complications developed in 50% of the patients, and the most common complication was steroid-induced IOP elevation, followed by cataracts and posterior synechia. Steroid-induced IOP elevation is more common in pediatric uveitis patients compared to adults.[33] The high rate of steroid-induced IOP elevation in our series can be explained by the fact that all cases were in the pediatric age group.

Study Limitations

The study's main limitations are the retrospective design and the small sample size. Another limitation is that SARS-CoV-2 serological testing was performed only on patients diagnosed with TINU during the pandemic, and a control group of other uveitis could not be established, which may indicate a potential bias in the sample. However, the present study may be useful to draw attention to patients with TINU during the COVID-19 pandemic and to share experiences in the management of intraocular inflammation in TINU.

Conclusion

TINU should be considered in the differential diagnosis of bilateral anterior uveitis, especially in pediatric patients. SARS-CoV-2 infection may be among the environmental factors triggering TINU. Steroid-sparing treatments may be needed to control recurrent uveitis and prevent ocular complications in TINU.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Ankara City Hospital Ethics Committee (number: E1-22-2979).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: K.Ö.Y., P.Ç.Ö., Y.Ö.E., M.K., D.K., Concept: K.Ö.Y., P.Ç.Ö., Design: K.Ö.Y., P.Ç.Ö., Data Collection or Processing: K.Ö.Y., A.G., P.Ç.Ö., Y.Ö.E., M.K., D.K., L.Ö., Analysis or Interpretation: K.Ö.Y., P.Ç.Ö., Literature Search: K.Ö.Y., A.G., P.Ç.Ö., Writing: K.Ö.Y., P.Ç.Ö.

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Original Article

Using the Amsler Grid Test for Age-Related Macular Degeneration Screening

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Abstract

Objectives: To evaluate the use of the Amsler grid test (AGT) in screening for age-related macular degeneration (AMD), one of the most common causes of blindness, in primary healthcare settings.

Materials and Methods: The AGT was applied to 700 eyes of 355 people aged 50 and over who applied to a family health center in Ankara and had no eye complaints. The test was considered positive if the lines on the AGT card were seen as broken or curved, there was a difference in shape or size between the squares, or a color change or blurring was described in any area. An ophthalmologist was consulted if the AGT was positive in one or both eyes. Patients considered suitable by ophthalmologists were evaluated with optical coherence tomography. AGT results were compared with ophthalmologist examination and tomography findings in terms of AMD detection.

Results: The AGT was positive in 97 (13.9%) and negative in 603 (86.1%) out of 700 eyes included in the study. A total of 184 eyes, 79 with a positive AGT and 105 eyes with a negative test, were evaluated by an ophthalmologist. As a result of examinations and tests performed by ophthalmologists, AMD was detected in a total of 67 eyes: 42 of 79 eyes with positive AGT and 25 of 105 eyes with negative AGT but referred to an ophthalmologist for different reasons. In our study, the AGT had 62.7% sensitivity and 68.4% specificity.

Conclusion: The AGT is an inexpensive and easily applicable test. Although moderate sensitivity and specificity were found in our study; further studies are needed to evaluate the suitability of its use for AMD screening in primary care with limited facilities.

Keywords: Amsler grid test, macular degeneration, scanning, specificity, sensitivity

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Introduction

Age-related macular degeneration (AMD) is a disease that damages the central part of the retina responsible for visual acuity, leading to dark spots and shadows in the central visual field, object distortion, and impaired central vision.[1] With the aging global population, AMD is the third most common cause of age-related blindness after cataracts and glaucoma.[1]

AMD is usually asymptomatic in the early stages but can cause irreversible vision loss in the advanced stages. With preventive measures and treatment, it is possible to avoid permanent damage or slow disease progression. By the time visual changes occur, the patient most likely has intermediate or late AMD.[2] Therefore, identifying the risk factors and early findings of AMD, especially in primary health care centers, is important for early diagnosis and slowing the course of the disease.[3]

Metamorphopsia, the most typical symptom of AMD, can be detected by the Amsler grid test (AGT). The traditional AGT, developed by Swiss ophthalmologist Marc Amsler, is a handheld test for identifying areas of scotoma or metamorphopsia.[4] The test is an inexpensive, self-administered, practical method for detecting signs of macular disease and monitoring its progression.[5]

Despite the increasing frequency of AMD, there is insufficient data on screening methods that can be implemented in daily practice, especially in primary health care settings where resources are limited. The aim of this study was to investigate the utility of the AGT for AMD screening in primary health care settings.

Materials and Methods

Our study was carried out in a family health center (FHC) in Ankara with people aged 50 years or older who were all registered with the same family physician. Of the 1222 people

who met this description, the AGT was performed on 700 eyes of 355 volunteers who presented to the FHC for outpatient examination during a period of approximately 1 year and met the inclusion criteria (Figure 1). The family physician obtained the participants' medical history and their electronic health records. After reviewing their past medical records and drugs used, systemic examination and external eye examinations were performed. Individuals having any of the following criteria (including the findings observed by the ophthalmologist for those referred) were excluded from the study:

- Diagnosis of diabetes mellitus (all types)
- History of previous ocular surgery other than cataract (e.g., cornea, vitreoretinal surgery)
- History of cataract surgery in the last 6 months
- Advanced glaucoma
- Impaired central or paracentral vision due to ocular or systemic disease
- History of surgery for ocular trauma
- Presence of corneal structural disorders or scars such as nebula
- Uveitis
- Pathologic myopia
- Optic neuropathy
- Vascular occlusion
- Solar retinopathy
- Poor cooperation during the test

The demographic information of all participants and possible risk factors and exposures related to AMD were recorded.[3] Distance visual acuity was evaluated with the Snellen test in an examination room of the FHC that was illuminated by natural sunlight. For participants with glasses, the Snellen test was repeated with and without their glasses.

For all participants, each eye was tested individually with the AGT by the same physician under the same lighting conditions with the fellow eye covered. The AGT consists of 20 horizontal and 20 vertical white lines arranged in parallel on a black background to form a grid of 400 squares 5x5 mm in size. For the test, the card was shown at a reading distance of 30 cm. Participants with presbyopia were tested while wearing presbyopic glasses. Each participant was asked to fixate on the white spot in the middle of the card with the eye being tested and was asked whether the surrounding lines appeared straight and the squares equal in size, as Amsler[6] described. Describing the lines on the card as interrupted or curved, squares appearing different in shape or size, and discoloration or blurring in any area (presence of metamorphopsia, micropsia, macropsia, or scotoma) was accepted as a positive AGT result.

An ophthalmologist was consulted for participants with a positive AGT result in one or both eyes. Participants with negative AGT were also referred to an ophthalmologist if they had any of the following AMD risk factors: family history of AMD, especially in a sibling; history of parental vision loss (even if this could not be confirmed because most participants' parents were deceased); long smoking history; and history of prolonged ultraviolet exposure, especially outdoor work.[7] In addition, we also referred participants observed to have difficulty focusing in distance vision measurements in their FHC examinations, participants with problems suggesting an ocular pathology, such as decreased reading speed or inability to see relatives clearly, and those who had no ocular signs and symptoms but had not been examined by an ophthalmologist within the last 2 years.

The ophthalmological examination included visual acuity measurement, slit-lamp anterior segment examination, and dilated fundus examination. Participants with findings of drusen, pigmentation suggestive of retinal pigment epithelium anomalies, areas of retinal atrophy, exudate, or hemorrhage on fundus examination underwent further testing. In the literature, drusen smaller than 63 µm (also called druplets) are considered signs of normal aging and not associated with risk of developing AMD. However, eyes with medium-sized drusen (63-125 µm in diameter) and without pigmentary changes are classified as early AMD, eyes with drusen larger than 125 µm or medium-sized drusen with pigmentary changes are classified as intermediate AMD, and the development of geographic atrophy or the neovascular form characterized by hemorrhage and/or exudation is classified as late AMD.[7] In our study, eyes with findings from any stage were accepted as having an AMD diagnosis, and no further staging was performed.

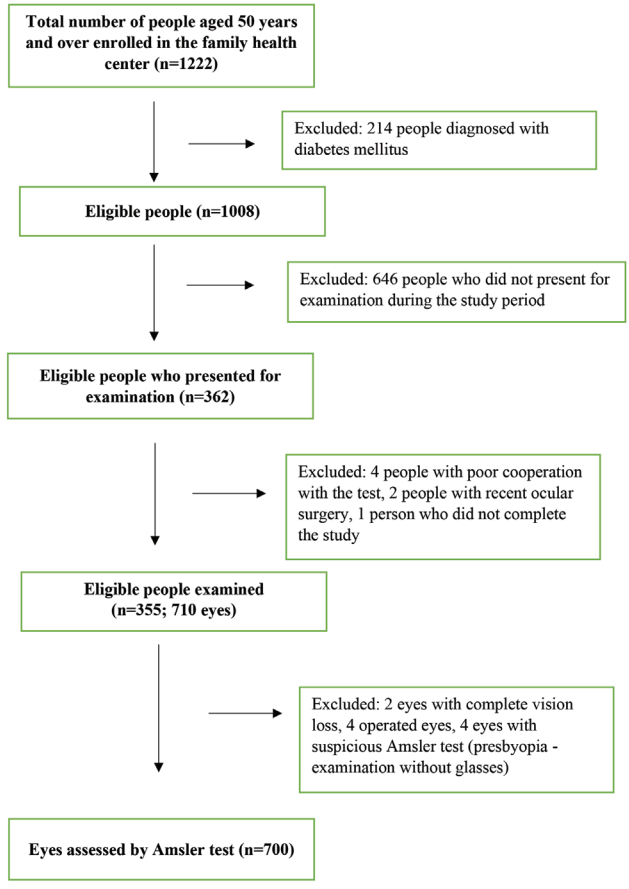

Figure 1. Study sample selection

Selected participants with positive AGT and others for whom it was deemed necessary were referred by the ophthalmologist for optical coherence tomography (OCT) imaging.

In our study, the results of the ophthalmologist examination were used as a reference for the accuracy of AMD diagnosis, and the results of the AGT applied in the FHC were compared with the ophthalmologist's conclusion regarding the presence or absence of AMD. To evaluate the diagnostic performance of the AGT, sensitivity and specificity values, as well as positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR) were calculated with 95% confidence intervals (CI). Approval for the study was obtained from the Ethics Committee of University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital (date: 10.09.2018, decision no: 54/06), and the Research Commission of Ankara Provincial Health Directorate.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics software, version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 700 eyes of 355 subjects were included in the study. Of the participants, 222 (62.5%) were women. The median age of the participants was 62 years (range: 51-92 years). Of the 93 people referred to and examined by an ophthalmologist, 62 (66.7%) were women and 31 (33.3%) were men. The AGT performed in primary care was positive in 52 (55.9%) and negative in 41 (44.1%) of these 93 patients evaluated by an ophthalmologist.

Overall, the AGT was positive in 97 (13.9%) and negative in 603 (86.1%) of the 700 eyes. Although all individuals with positive AGT were referred to the ophthalmologist, 9 of them were unable to go to the ophthalmologist during the study period for personal reasons (e.g., emergence of other health problems).

Of the total 700 eyes tested in primary care, 184 eyes of a total of 93 people (79 eyes with positive AGT and 105 eyes with negative AGT) were examined by an ophthalmologist (Figure 2). AMD was detected in 67 (36.4%) of the 184 eyes evaluated by an ophthalmologist.

According to the medical data obtained in the ophthalmologist examination (Figure 2, Table 1), AMD was detected in 42 of the 79 eyes with positive AGT. Of the 105 eyes that had negative AGT but were referred to an ophthalmologist for other reasons, 25 had AMD. As a result, the AGT detected AMD of different forms and stages in a total of 67 eyes of 41 people (unilateral in 15 and bilateral in 26).

When the diagnostic accuracy of the AGT was analyzed, its sensitivity was 62.7% (0.51-0.73; 95% CI) and specificity was 68.4% (0.59-0.76; 95% CI). The PPV was 53.2% and NPV was 76.2%. The positive and negative LRs (+LR/-LR) were 1.98 (1.44-2.77; 95% CI) and 0.55 (0.38-0.74; 95% CI), respectively. Thus, the accuracy rate (sum of true positives and true negatives) of the AGT in detecting AMD was 66.3%.

Other pathologies that can cause a positive AGT (e.g., epiretinal membrane, vitreous detachment, vitreomacular traction) were reported by ophthalmologists in a total of 21 eyes. The values obtained upon recalculation after excluding these pathologies were: sensitivity 62.7% (0.51-0.73; 95% CI), specificity 81.3% (0.72-0.88; 95% CI), PPV 70%, NPV 75.7%, +LR 3.34 (2.17-5.43; 95% CI), and -LR 0.46 (0.32-0.62; 95% CI) (Table 2). The accuracy rate increased to 73.7% (0.51-0.83; 95% CI).

Of the participants examined by ophthalmologists, 147 eyes of 74 participants (79.6%) were also evaluated by OCT imaging. OCT was not performed on 37 eyes of 19 people. Only 3 of these eyes had positive AGT (3 eyes of 2 older people could not adapt to OCT). In these eyes, a diagnosis of AMD was not considered in the expert examination. In the other 34 eyes without OCT, AGT was negative. OCT, which is an advanced test, was not performed in these eyes due to both the negative AGT and the absence of AMD findings in the ophthalmologist's examination.

In the analysis using OCT as the gold standard, the accuracy rate of the AGT was 59.9% for the 147 eyes that underwent OCT. The calculated values were: sensitivity 62.7% (0.51-0.73; 95% CI), specificity 57.5% (0.47-0.68; 95% CI); PPV 55.3%, NPV 64.8%; +LR 1.47 (1.08-2.05; 95% CI), and -LR 0.65 (0.44-0.92; 95% CI) (Table 3).

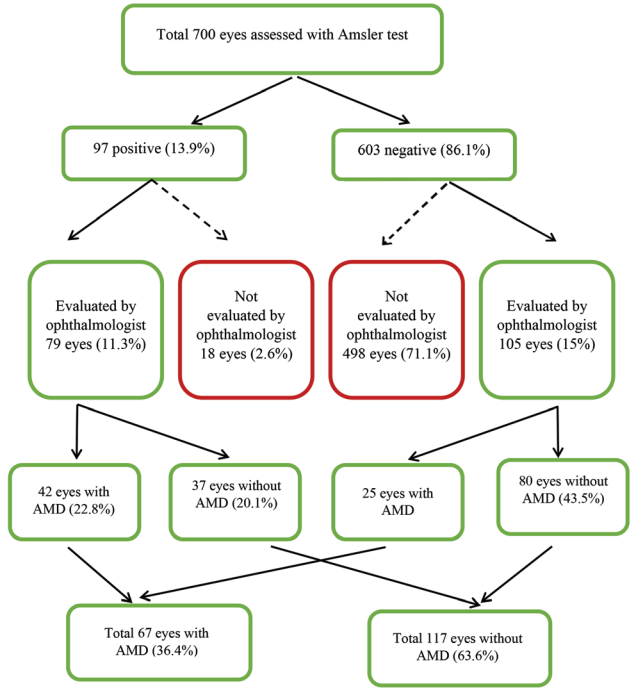

Figure 2. Results of the Amsler grid test and ophthalmologist examination
AMD: Age-related macular degeneration

Table 1. Comparison of Amsler grid test results with ophthalmologist examination results in the diagnosis of age-related macular degeneration

Amsler grid test result	Ophthalmologist evaluation	
	AMD+ n (%)	AMD- n (%)
Positive	42 (22.8)	37 (20.1)
Negative	25 (13.6)	80 (43.5)
Total eyes	67 (36.4)	117 (63.6)

AMD: Age-related macular degeneration

Table 2. Reanalysis of Amsler grid test results in the diagnosis of age-related macular degeneration compared to the results of ophthalmologist examination after excluding eyes diagnosed with other pathologies (n=21 eyes)

Amsler grid test result	Ophthalmologist evaluation	
	AMD+ n (%)	AMD- n (%)
Positive	42 (25.8)	18 (11.0)
Negative	25 (15.3)	78 (47.9)
Total eyes	67 (41.1)	96 (58.9)

AMD: Age-related macular degeneration

Table 3. Diagnostic values of the Amsler grid test in the diagnosis of age-related macular degeneration using optical coherence tomography as a reference

Amsler grid test result	OCT findings	
	AMD+ n (%)	AMD- n (%)
Positive	42 (28.6)	34 (23.1)
Negative	25 (17.0)	46 (31.3)
Total eyes	67 (45.6)	80 (54.4)

OCT: Optical coherence tomography, AMD: Age-related macular degeneration

Discussion

This prospective study investigated the diagnostic value of the AGT for AMD screening in primary health care services and family practice routine examinations. Most of the studies on this subject have been conducted by ophthalmology clinics among people diagnosed with macular disease. To our knowledge, there is no similar study in the literature in primary care and the general population.

Findings of various stages of AMD were detected in 67 (36.4%) of 184 eyes evaluated by ophthalmologists. Our aim was not to classify AMD stages but to enable the early diagnosis and timely treatment of people with suspected AMD using only a screening method that can be implemented in primary health care centers. Therefore, the cases were evaluated as a whole without further staging. Although our study is not an AMD prevalence study, 67 (9.57%) of the 700 eyes screened in primary care received a first-time diagnosis of AMD. Considering that not all eyes with negative AGT were evaluated by an ophthalmologist, this high rate obtained in a relatively young group for the diagnosis of AMD is noteworthy in terms of the need to screen for AMD, given the conditions' prevalence and potential consequences for society.

A previous study showed that a delay of 21 weeks or more in the treatment of AMD increased the risk of visual impairment five-fold compared to a delay of 7 weeks or less.[8] The fact that a delay in treatment increases the risk of irreversible damage is an issue that should be brought to the attention of primary care physicians, especially regarding the importance of AMD screening.

In our study, the AGT had sensitivity of 62.7%, specificity of 68.4%, PPV of 53.2%, and NPV of 76.2% in diagnosing AMD. These data include all results of ophthalmologist-performed fundus examinations and tests in which AMD lesions were observed, without differentiation of AMD type.

Excluding eyes with different pathologies reduced the AGT's number of false positives in recognizing only AMD, thereby increasing its specificity to 81.3%, PPV (rate of catching true positives) to 70%, and accuracy rate (sum of true positives and true negatives) to 73.6%. The possibility that AGT results may be affected by these pathologies, which cannot be diagnosed in primary care, cannot be eliminated. However, this is not a disadvantage in our opinion and suggests that the AGT may also be beneficial in the early diagnosis of other such pathologies.

In a meta-analysis evaluating the diagnostic accuracy of the AGT in AMD screening based on the results of 903 individuals, it was found that the sensitivity of the test ranged from 0.34 to 1.0 and the specificity from 0.85 to 1.0, with a pooled sensitivity of 0.78 (95% CI 0.64-0.87) and a pooled specificity of 0.97 (95% CI 0.91-0.99).[9] The AGT performance values obtained in our study conducted in the primary care setting are consistent with these data.

In their study including a total of 317 patients (mean age: 44±7 years) mainly of Hispanic origin (77%) presenting to an ophthalmology outpatient clinic, Ariyasu et al.[10] screened visual function with 4 different measurements (contrast sensitivity test, AGT, distance and near visual acuity) and detected macular degeneration at a rate of 4.1%. In their patient group, which was younger than in our study, they reported the AGT had 19% sensitivity and 92% specificity but showed poorer performance in patients younger than 40 years of age. Our results support this finding, and because our study group consisted of older individuals, both the rate of macular degeneration and the sensitivity of the AGT were higher. In addition, it can be said that repeating the test over time is important for the diagnosis of AMD due to the increase in AGT positivity with increasing age.

Do et al.[11] evaluate the performance of the AGT compared to fluorescein angiography as a secondary objective in their study investigating OCT sensitivity in detecting conversion to neovascular AMD. For the AGT, they reported low to moderate sensitivity for the detection of new-onset choroidal neovascular membrane (CNVM), with values of 0.42 (95% CI: 0.15-0.72) and 0.50 (95% CI: 0.19-0.81). The AGT was reported to have lower specificity than OCT in the detection of new CNVM due

to the high false positivity rate. In our study, when we reanalyzed the performance of the AGT using OCT as a reference for the 147 eyes evaluated with OCT, we determined its specificity to be 57.5% and NPV as 64.8%. As 34 of the 37 patients who did not undergo OCT were in the AGT-negative group, the statistical values of the AGT in diagnosing this group seem to be low.

Miller and Fortun[12] reported that the traditional AGT was useful for monitoring patients' vision but had limited specificity and sensitivity as a screening tool for neovascular macular degeneration. However, when community screening for AMD is considered, a test that is cost-effective, practical, and repeatable, with the highest diagnostic performance possible is the priority. The sensitivity of the AGT in detecting new CNVM development has been reported be limited to 42% when patients perform the test themselves and increases to 52.6% when the test is applied by a professional.[13] Some researchers who think the AGT is a difficult subjective test for patients argue that it requires patients to describe their perception of their visual defects in other areas of the grid while fixating elsewhere.[14] In our study, we repeatedly warned the participants to keep their eye fixed on the center during the AGT, which we believed improved their adaptation to the test and contributed to the higher specificity and sensitivity of the AGT in this study.

Study Limitations

Being the first study on AMD screening in primary care, our study has various limitations. Testing people with symptoms of disease when investigating the accuracy of a screening test is a common but flawed practice. In contrast, applying these tests in the asymptomatic population enables many people to be tested while identifying those with the disease and allows follow-up to identify actual patients.[15] In our study, 18 eyes with positive AGT and 498 eyes with negative AGT were not examined by an ophthalmologist. However, the proportion of participants who tested positive and did not undergo ophthalmologist examination was low (2.6%). Considering the unwillingness of older people with no ocular complaints to undergo examination for a routine check-up, the study included a considerable number of people evaluated by an ophthalmologist despite a negative AGT.

Although in this kind of study it is preferred to perform one-stop examinations and testing of participants, we gave participants the freedom to choose a physician and a center. However, the examination and AGT performed in the FHC were carried out by a single physician, and the ophthalmologists were informed via the consultation request made by that physician. For all participants, anterior segment and dilated posterior segment examination were performed by ophthalmologists, and all those with positive AGT as well as those deemed necessary by the ophthalmologist were referred for OCT. The same researcher received feedback regarding the procedures conducted by the specialist and the results. OCT was not performed on all eyes of the participants referred to an ophthalmologist. However, OCT was performed in 96.2% (76/79) of eyes that had positive AGT and were referred; only 3 eyes of 2 people could not be examined by OCT. Likewise, OCT was deemed necessary and performed in 67.6% (71/105) of the eyes with negative AGT results. The ophthalmologist did not consider further OCT evaluation necessary for the remaining 34 eyes with negative AGT. In our study, the diagnosis of AMD was taken as a whole, ignoring the prognostic differences between AMD types. Identifying patients with wet AMD and high risk of transformation to wet AMD transformation is of utmost importance to ensure early diagnosis and treatment. This point should be taken into consideration in other studies on the subject.

Conclusion

AMD is one of the most common causes of age-related blindness, and its importance is increasing as the older population grows. Our study was conducted among the general patient population in primary care, and AMD was detected for the first time at a high rate of 9.57% (67 of the 700 eyes tested). Therefore, our findings in terms of the diagnosis of new cases differed from those of studies conducted by evaluating patients diagnosed in eye clinics.

In our study, the AGT had 62.7% sensitivity, 81.3% specificity, and 73.7% accuracy in the detection of AMD when the ophthalmologist examination was taken as a reference. When we reanalyzed the performance of the AGT using OCT as a reference, its specificity was 57.5%.

Although alternative tests are being developed, the AGT appears to be a test that can easily be applied for the detection of AMD. Therefore, although we observed moderate sensitivity and specificity in this study, the utility of the AGT in AMD screening in primary care settings with limited facilities must be evaluated in similar community-based studies designed in reference to OCT, which has been proven to have a high diagnostic value for AMD.

We think that our study will increase awareness of AMD, which is a serious eye disease, both among physicians working in primary health care centers and in the general population, thereby increasing the chance of early diagnosis and treatment.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital (date: 10.09.2018, decision no: 54/06), and the Research Commission of Ankara Provincial Health Directorate.

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

Demographic, Etiological, and Clinical Characteristics of Eyelid Lacerations

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Abstract

Objectives: To evaluate the demographic, etiological, and accompanying clinical factors in eyelid lacerations (EL).

Materials and Methods: The records of patients who presented to our clinic between 2018 and 2022 with eyelid trauma were retrospectively reviewed. Age, gender, cause of injury, clinical findings, accompanying ocular findings, and additional complications were analyzed.

Results: The study included 135 patients (106 male, 29 female) with a mean age of 37.0±18.6 years. Among the patients, 29 (21.4%) were 18 years old or younger, 93 (68.8%) were between 19 and 64 years old, and 13 (9.6%) were 65 years old or older. EL were most caused by various sharp objects in 44 patients (33%), blunt trauma in 40 patients (30%), falls in 30 patients (22%), and traffic accidents in 21 patients (15%). Fifteen eyes (11.1%) had foreign bodies at the wound site. Thirty patients (22.2%) (20 lower eyelid, 10 upper eyelid) had accompanying canalicular lacerations. Twenty-three (17%) patients had accompanying conjunctival lacerations, 14 (10.3%) had open-globe injury, 10 (7.4%) had corneal epithelial defects, 9 (6.6%) had intravitreal hemorrhage, 6 (4.4%) had hyphema, and 5 (3.7%) had retinal detachment. Four patients had lid notching and 1 patient (0.7%) had ectropion. Five patients (3.7%) required suturing. No additional complications were observed.

Conclusion: EL are more commonly seen in young adulthood and in males. The most common mechanism of injury is impact by various objects. Eyelash margin and canalicular lacerations frequently accompany these injuries. Serious ocular pathologies such as hyphema and open-globe injury can accompany eyelid trauma.

Keywords: Eyelid trauma, epidemiology, complications

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Introduction

The eyelids, which protect the globe against external factors, are frequently affected by orbital and periorbital trauma. Eyelid traumas encompass a wide spectrum, ranging from simple lacerations to more severe injuries that can lead to deeper tissue damage and vision-threatening globe injuries. Eyelid injuries account for approximately 10% of all ocular injuries, with an incidence of 185.9 per million reported in a study conducted in the United States (US).[1] The causes of eyelid trauma are often preventable, vary in frequency according to age group, socio-economic status, and geographical region, and include workplace-related injuries, falls, traffic accidents, sports injuries, and assaults.[2]

Eyelid lacerations (EL) present with various findings, such as partial- or full-thickness lid defects, canalicular damage, and accompanying ocular damage.[3,4] If not promptly and appropriately treated, these injuries can result in serious anatomic and functional problems, including lid deformities, ocular surface disorders, and associated ocular damage.[5] Incomplete or inadequate repair of the eyelids may lead to complications such as entropion, ectropion, trichiasis, and epiphora, significantly affecting the patient's quality of life.[5,6]

Understanding the factors that contribute to eyelid trauma and having knowledge of the epidemiological features are crucial in the prevention of such injuries. While there are numerous publications on ocular trauma in the literature, studies specifically focusing on eyelid injuries are relatively limited, often being included within the broader category of ocular trauma.

The aim of this study was to determine the demographics, epidemiological factors, and clinical characteristics of EL.

Materials and Methods

The data of patients who presented to the emergency department due to eyelid trauma and were subsequently referred to the ophthalmology department for EL between 2018 and

2022 were retrospectively analyzed. Approval for this study was received from the Sakarya University Faculty of Medicine Ethics Committee (decision no: E-71522473-050.01.04-241666-111) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

The medical records of 135 patients who were followed up for at least 3 months were reviewed and the following information was collected: demographic data (age, gender, laterality), the cause and nature of the trauma, the presence of eyelid margin and canalicular injuries, the presence of foreign bodies, and accompanying clinical findings such as conjunctival laceration, corneal abrasion, hyphema, and open-globe injury. Based on the involvement of the eyelid margin or canaliculus, trauma type was classified as eyelid margin involvement, canalicular involvement, or only periocular involvement. Details of the surgical procedures performed (primary and additional) and findings from follow-up examinations, including any ocular complications, were also reviewed.

EL were ideally repaired within 12 to 24 hours of the injury to minimize future complications. In patients with life-threatening injuries, EL repair was delayed until an appropriate time, after the wound had been cleaned and adequate corneal lubrication had been achieved.

In cooperative adults, most EL were managed using local anesthesia, while in cases involving small children or EL with canalicular or open-globe injury, general anesthesia was typically employed.

In simple superficial EL affecting only the anterior lamella, the wound was first irrigated with saline solution to remove all foreign bodies and debris. Then subcutaneous suturing with 6-0 or 7-0 polyglactin (Vicryl, Ethicon, Ohio, USA) was done, followed by reapproximating the wound edges using simple interrupted sutures using 6-0 or 7-0 nylon or polypropylene (Prolene, Ethicon, Ohio, USA) for non-absorbable sutures, or 6-0 polyglactin absorbable sutures. Non-absorbable sutures were avoided in patients who were unlikely to be compliant with follow-up (such as children and patients with dementia).

In cases of EL involving the eyelid margin, the process began with suturing the edges of eyelid margin using one simple interrupted 6-0 polyglactin suture from gray line to gray line. Then, the tarsus was reapproximated using several additional interrupted lamellar 6-0 polyglactin sutures. Subsequently, one or two additional 6-0 polyglactin sutures were applied at the eyelid margin parallel to the first but closer to the lash line in an interrupted vertical mattress or buried interrupted fashion. The wound edges in the skin were then sutured with absorbable polyglactin sutures. If there was a canalicular injury, the procedure involved reuniting the two edges of the canaliculus using bicanalicular intubation with a pigtail probe or monocanalicular stent, after which the EL was repaired.

After EL repair, topical antibiotic or a combination of antibiotic and steroid ointment was applied to the wound. Oral antibiotics were prescribed if the wound was contaminated, such as a bite wound, or if the patient was at high risk of infection. Patients were typically examined 5-14 days later for any complications and the removal of any non-absorbable sutures.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 15 (SPSS Inc, Chicago, IL, USA) and descriptive variables were reported as number and percentage.

Results

The mean age of the 135 patients (106 male, 29 female) was 37.0±18.6 years. The male to female ratio was 3.9:1. Most of the patients were between the ages of 19 and 64 years. The right and left eyes were similarly affected (p=0.942). Of the EL, 54 involved the lower eyelid, 70 involved the upper eyelid, and 11 included both eyelids (Table 1, Figure 1).

The most frequent causes of EL were various sharp objects (glass, scissors, iron, twig, wire, cat scratch, drill, nails, umbrella, hook) in 44 patients (33%), blunt trauma (assault, horn) in 40 patients (30%), falls in 30 patients (22%), and traffic accidents in 21 patients (15%) (Figure 2). When examined by age group, the most common cause of EL was trauma with sharp objects in patients aged 18 and under, blunt trauma in patients between the ages of 19 and 64, and falls in patients 65 and over (Table 2).

In the classification of trauma types, it was determined that of the 135 patients, 37 (27.4%) had full-thickness EL, 30 (22.2%) had full-thickness laceration involving the lacrimal passage, and 68 (50.3%) had laceration limited to the periocular area (Figure 3). Among the patients with lacrimal passage injury, 20 (66.6%) had lower canalicular injury and 10 (33.3%) had upper canalicular injury. Falls were found to be the most common cause of injury in these patients.

Fifteen patients (11.1%) had a foreign body present in the trauma region (Figure 4). The most common clinical findings accompanying the EL were conjunctival laceration in 23 patients (17%) and open-globe injury in 14 patients (10.3%). Other accompanying clinical findings are listed in Table 3. Among patients with additional ocular findings, the 19-64 age group was the most frequently affected, with traffic accidents and injuries with blunt objects being the most common causes.

Primary suturing was performed in all patients, and in most cases, the tissues could be approximated to their normal anatomical position. Lateral canthotomy was performed in 3 patients who had tissue loss. Conjunctival suturing was performed in 16 patients, while repair of penetrating eye injuries was performed in 14 patients. Lens extraction and anterior vitrectomy were performed in 1 patient (Figure 5).

For patients with open-globe injury, reparation was performed prior to eyelid repair to prevent further damage due to increased intraocular pressure. In cases of canalicular lacerations, monocanalicular silicone intubation was performed in 20 patients and annular intubation in 10 patients. Among patients who underwent canalicular repair, anatomical success was achieved in 96.6% and functional success was achieved in 86%.

During follow-up, most of the patients had acceptable aesthetic outcomes. Only 4 patients showed lid notching, and 1 patient developed ectropion. In the early period, 5 patients underwent re-suturing due to wound dehiscence caused by tension at the wound site or improper wound configuration leading to lid malposition. In 2 patients who had irregularity at the wound site, fusiform excisions or Z-plasty was used to improve the appearance of scars and eliminate contracture, after the scar tissue was removed. The patient with ectropion was followed until scar maturation, and spontaneous resolution was observed after a period of 3-6 months. Of the patients with canalicular injury, 4 had epiphora. In 2 of these patients, the silicone stents spontaneously detached from their lacrimal passages, while the other 2 patients had their silicone stents removed early due to foreign body sensation and pain.

Discussion

EL are common ophthalmic injuries that require prompt assessment and appropriate management to minimize the risk of complications. The incidence of EL in the US has been reported as approximately 1.7 million cases per year, while in the UK this rate has been reported as 8.3 to 13.2 cases per 100,000 population per year.[1] In a study conducted in our country, this rate was reported as 5.9%.[7]

Consistent with other studies, our results showed that EL are more common in men, with a ratio of 3.9:1.[2,3] In a publication conducted in Türkiye, similar to our results, the reported ratio was 3.75:1.[7] This may be related to the more frequent participation of men in activities that can increase the risk of eye injury, such as occupational or industrial

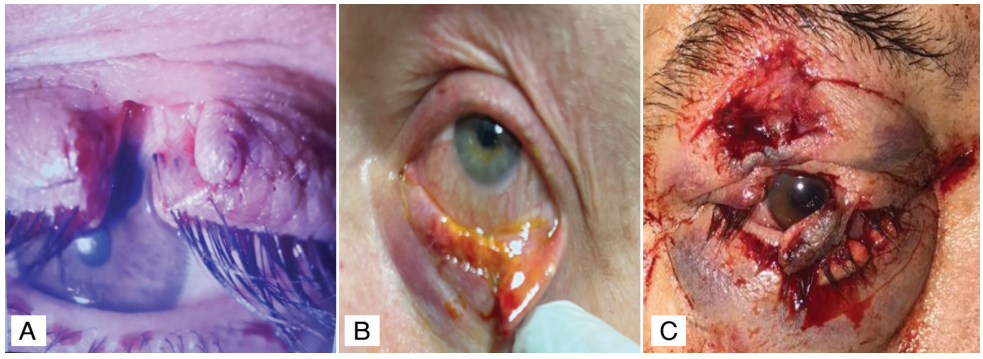

Figure 1. Preoperative photos of patients. (A) Patient with upper eyelid laceration. (B) Patient with lower eyelid laceration. (C) Patient with both upper and lower eyelid laceration

Table 1. Demographic characteristics of eyelid lacerations

	n	%
Age (years), mean ± SD	37.0±18.6	
≤18 19-64 ≥65	29 93 65	21.4 68.8 9.6
Gender		
Female Male	29 106	21.4 78.5
Laterality		
Right Left	68 67	50.3 49.6
Eyelid		
Lower Upper Both	54 70 11	40 51.8 8.1
Trauma type		
Periocular Full-thickness Canalicular	68 37 30	50.3 27.4 22.2

SD: Standard deviation

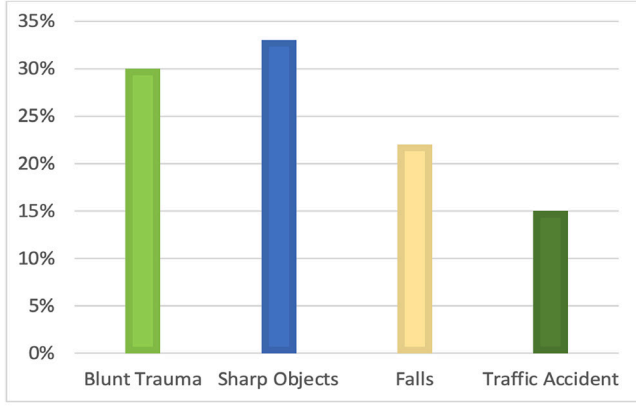

Figure 2. Causes of eyelid lacerations

Table 2. Causes of eyelid lacerations by age group

Age (years)	Sharp objects		Blunt trauma		Falls		Trafic accidents	
	n	%	n	%	n	%	n	%
≤18	14	73.6	6	20.6	5	17.2	4	13.7
19-64	30	32.2	33	35.4	13	13.9	17	18.2
≥65			1	7.6	12	92.3		

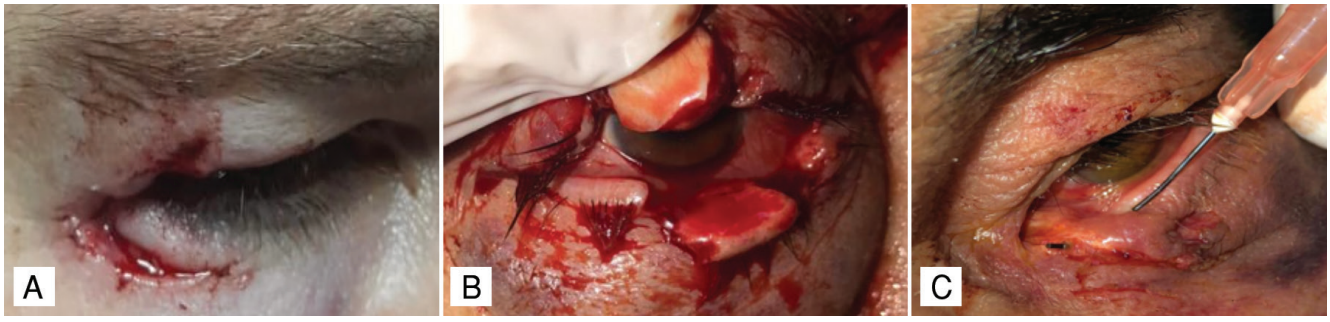

Figure 3. Preoperative photos of patients. (A) Patient with periocular laceration. (B) Patient with full-thickness laceration with lid margin involvement on both lower and upper eyelids. (C) Patient with lower canalicular tear

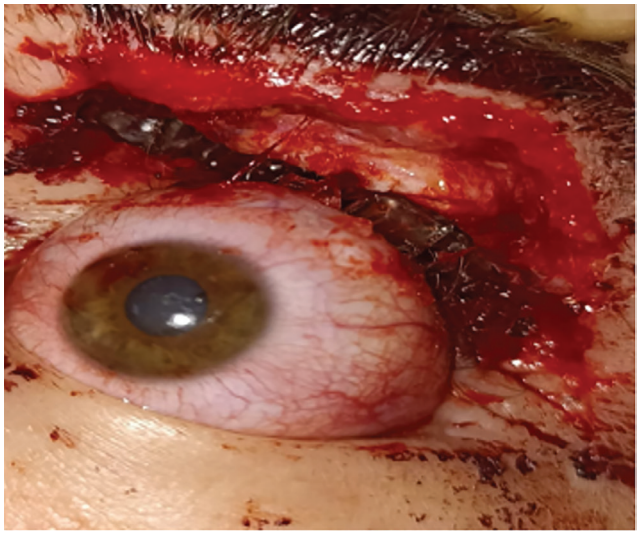

Figure 4. Patient with periocular laceration with multiple foreign bodies (glass) in the upper bulbar space

activities (construction, manufacturing), sports or recreational activities (contact sports, shooting, hunting), and certain hobbies (woodworking, metalworking).[8]

Considering the distribution of EL by age group in the literature, most injuries were reported in adolescence and the average age was around 30 years. Of the total, 23% of patients were between the ages of 0-9 years, 18% were between the ages of 9-18 years, and 6% were aged 60 and over.[9] These results may be attributed to a higher level of active work participation among individuals aged 20-50. The results of our study are consistent with the literature. Most of the patients (68.8%) were between the ages of 19-64, the mean age was 37.0±18.6 years, 21.4% all patients were aged 18 years or younger, and 9.6% were aged 65 and over.

Considering the etiology of injury in the literature, the prevalence in different countries may vary due to differences in geographical location and socio-economic status. Regional variations in lifestyle, occupational hazards, and cultural practices may also influence the etiology of EL. In a study conducted in the US, object-related injuries were reported to be the most common cause of EL overall and the most common cause among children.[1]

Figure 5. Preoperative and postoperative photos of patients. (A) Preoperative photo of a patient with periocular and full-thickness laceration with lower canalicular tear. (B) Postoperative photo of the same patient. (C) Preoperative photo of a patient with lower and upper canalicular tear with full-thickness laceration. (D) Postoperative photo of the same patient

Table 3. Accompaying ocular findings in eyelid lacerations

	n	%
Conjunctival laceration	23	17
Open-globe injury	14	10.3
Corneal abrasion	10	7.4
Vitreous hemorrhage	9	6.6
Hyphema	6	4.4
Retinal detachment	5	3.7
Commotio retina	3	2.2
Lens subluxation	1	0.7

In a study from Iran, Tabatabaei et al.[10] reported that 62.5% of patients had blunt ocular trauma, while 37.5% had trauma with sharp objects. They reported that blunt moving objects, motor vehicle accidents, falls, and fighting were the other main causes of EL. In another study conducted in India, 59.9% of EL were caused by road accidents, followed by assault (13.6%), animal attacks (12.7%), and falls (9%).[3]

Considering the age disruption, common causes of EL in children and adolescents include falls, accidents during play, sports-related injuries, and animal bites.[11,12] In our study, trauma with sharp objects (73.6%) was the most common cause in children, followed by trauma with blunt objects and falls. In young adults and adults, EL are mostly due to occupational hazards, accidents, and trauma. Our study results showed that trauma with blunt objects (35.4%) and sharp objects (32.2%) occurred at similar proportions. In older adults, it especially occurs as a result of falls or accidental injuries associated with age-related changes like decreased vision, impaired balance, and frailty.[13,14] Cade et al.[1] reported that falls were the most common factor for older patients, accounting for 74% of cases. Consistent with the literature, patients 65 and over in our study were usually injured in falls (92.3%).

Considering EL types, the incidence of periocular, full-thickness, and lacrimal passage-involving EL represented 91%, 6.5%, and 2.6% of cases, respectively, in a study conducted in the US.[1] Zhao et al.[15] reported that out of 303 EL cases, 56% were periocular, followed by 24% with canalicular involvement and 20% crossing the eyelid margin. Similar to these results, our study showed that 50.3% of the patients had periocular, 27.4% had full-thickness, and 22.2% had full-thickness laceration involving the lacrimal passage.

Foreign bodies frequently accompany eyelid trauma, especially when due to mechanisms such as high-speed trauma, occupational hazards, or outdoor activities. Studies have reported foreign body prevalence rates ranging from 18% to 30%.[16,17] In our study, 11.1% of the patients had a foreign body in the trauma region.

EL are often accompanied by canalicular trauma, and the prevalence ranges from about 10% to 30%.[7,9] With a rate of 22.2%, our study results were compatible with the literature, and falls was the most common etiologic factor in these cases. Zhao et al.[15] reported that animal bite or scratch was the most common etiology of canalicular-involving lacerations (29%). In another study conducted in Türkiye, this rate was reported as 30.2% and the most common causes were traffic accidents, assault, and animal bites.[8] Similar to our study, Adıbelli and Cakmak[18] reported the incidence of lower canaliculus injury as 65.6%. In the literature, the anatomical success rate of canalicular laceration repair ranges between 75% and 100%, while the functional success rate is in the range of 58-96%.[19,20] Our study results were compatible with the literature, with rates of 96.6% and 86%, respectively. Qin et al.[6] reported that epiphora following canalicular trauma might be associated with the time elapsed from injury to repair, duration of stent placement, structural abnormities in the medial canthus, and distance between the distal cut end and the lacrimal punctum.

The incidence of accompanying ocular injuries has been reported as 17-24% in various studies. Kumar and Batham[3] reported that the most common accompanying finding was subconjunctival hemorrhage, followed by hyphema, conjunctival laceration, traumatic lens injury, and corneal laceration. Tabatabaei et al.[10] reported that globe injury was present in 6.1% of the cases. In a study conducted in our country, open-globe injuries accompanied 15.7% of cases.[8] However, Chaudhary et al.[21] reported globe perforation in about 50% of cases. In our study, the most common accompanying ocular findings were conjunctival laceration (17%), open-globe injury (10.3%), corneal abrasion (7.4%), vitreous hemorrhage (6.6%), and hyphema (4.4%). Patients with additional ocular findings were most frequently in the 19-64 age group, and traffic accidents and injuries with blunt objects were more common etiologic factors. Zhao et al.[15] reported that assaults were more likely to present with concomitant ophthalmic injuries. Schmidt et al.[22] reported that EL following blunt trauma such as falls or blows are frequently accompanied by corneoscleral perforations extending to the posterior pole. Therefore, they stated that the visual prognosis is worse in these cases.

Similar to our results, the most commonly reported late complication of EL is lid notching, which usually results from improper approximation or development of a wound gap.[9] Kumar and Batham[3] also reported lid notching (6.3%), hypertrophic scars (1.8%), ptosis (2.7%), tearing (2.7%), and lagophthalmos (0.9%) as other complications. Most complications can be prevented through careful and effective primary closure. Complications tend to arise when closure is delayed or when tissue approximation is poorly executed.

Study Limitations

The limitations of our study include the small sample size and the fact that it was conducted at a single center, which may limit the generalizability of the findings. Another reason for the small sample size was the exclusion of patients who were being treated in the intensive care unit for systemic reasons. Additionally, the study had a relatively short follow-up period, which limited our ability to observe long-term outcomes and complications.

Conclusion

Like other types of trauma, EL are more commonly observed in young adults and men. Considering this, it is crucial to provide preventive advice and implement safety measures in workplaces to reduce the incidence of preventable injuries. The most frequent mechanisms of injury involve trauma with sharp objects, while falling is the leading cause among older adults. Notably, EL involving the lacrimal passage are predominantly associated with falls. It is important to note that eyelid traumas are often accompanied by severe ocular pathologies such as conjunctival laceration, hyphema, corneal abrasion, and corneoscleral perforation. In particular, traffic accidents and injuries caused by blunt objects were the most commonly reported etiologic factors in patients presenting with these ocular pathologies.

Overall, a comprehensive understanding of EL, their etiologic factors, associated ocular injuries, and appropriate management strategies is crucial to achieving optimal outcomes and preserving both the functional and aesthetic aspects of the eyelids.

Ethics

Ethics Committee Approval: Approval for this study was received from the Sakarya University Faculty of Medicine Ethics Committee (decision no: E-71522473-050.01.04-241666-111).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: E.D., Ş.B.C., G.A., Concept: E.D., B.G.S., Design: E.D., Data Collection or Processing: E.D., B.G.S., Ş.B.C., G.A., Analysis or Interpretation: E.D., B.G.S., Literature Search: E.D., B.G.S., Writing: E.D.

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

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Original Article

Evaluation of Full-Field Stimulus Threshold Test Results in Retinitis Pigmentosa: Relationship with Full-Field Electroretinography, Multifocal Electroretinography, Optical Coherence Tomography, and Visual Field

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Abstract

Objectives: The full-field stimulus threshold (FST) test was developed to evaluate the efficacy and safety of treatments of hereditary retinal diseases. In this study we performed the FST test in patients with retinitis pigmentosa (RP) and compared the results with findings from other ophthalmological tests.

Materials and Methods: The study included 51 intermediate and advanced RP patients and 21 normal subjects. All patients and controls underwent routine examination and ophthalmological tests including visual field, optical coherence tomography, full-field and multifocal electroretinography (mfERG), and FST tests. During FST testing, the perception thresholds of retina to the white, blue, and red FST were determined in decibels.

Results: The mean age of the patients and the controls were 35.2 and 33.5 years, respectively. For all RP patients, no response was obtained on full-field ERG. All subjects were able to perform reliable FST tests. The mean values of visual acuity and central macular thickness were significantly lower and visual field mean deviation values were significantly higher in the RP group than the controls. When we evaluated the mfERG findings, the mean P1 wave amplitudes in all rings were significantly lower and the mean peak times were significantly longer in RP patients than controls. In comparisons of FST test results, the mean values for white, blue, red and the difference between blue-red thresholds were significantly lower in the RP group than the control group.

Conclusion: The FST test is a fast and a reliable exam which can be done in subjects with poor visual acuity and reduced visual field. The results of this study confirm that the FST test can measure retinal sensitivity in severely affected RP subjects with flat flash ERG.

Keywords: Full-field electroretinography, full-field stimulus threshold test, visual field, multifocal electroretinography, optical coherence tomography, retinitis pigmentosa

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Introduction

Retinitis pigmentosa (RP) is a progressive, hereditary retinal disease that causes damage to the retinal photoreceptors. The condition first manifests with impaired night vision, followed by visual impairment during the day, narrowing of the visual field, and total vision loss in the end stage.[1] Although there is not yet an accepted effective treatment option, successful results have been reported in recent years with gene and stem cell therapies and electrical stimulation interventions aiming to halt disease progression and regenerate the retinal cells.[2,3,4,5,6,7,8,9] Many of these clinical studies have included patients with advanced RP, and reliable results cannot be obtained with standard tests of visual function in such cases.

Standard full-field electroretinography (ERG) testing is often used in the clinic to evaluate photoreceptor function in patients with RP. Full-field ERG demonstrates total rod and cone responses from the entire retina. As there is more retinal damage in advanced RP, amplitudes may be very low and reliable data may not be attainable. In addition, full-field ERG cannot aid in regional assessment of the retina and is therefore insufficient for evaluation of the central retina, which is spared until the final stages of RP.[10] Previous studies have indicated that multifocal

ERG (mfERG), which is a cone-derived electrophysiological test, can be used to monitor disease progression in cases where full-field ERG readings cannot be obtained, there is advanced damage to the rod cells, and the cone cells have also begun to be affected. These publications have shown that reliable mfERG responses can be obtained in a large majority of advanced RP cases.[11,12,13] Therefore, performing mfERG in addition to full-field ERG in advanced RP cases will aid in evaluating the condition of the retina. However, it should be kept in mind that the visual field and mfERG tests used in the follow-up of RP are dependent on patient cooperation and fixation.[10,11]

The full-field stimulus threshold (FST) test is an electrophysiological test developed to evaluate the level of light perception after dark adaptation, especially in cases of advanced retinal dystrophy. This easy and rapid test is based on whether the patient perceives a light shown using a full-field stimulation system, with no need for fixation. At the end of the test, the level of light sensitivity of the retina is determined in decibels (dB). The biggest advantage is that it can be performed easily even in cases with very low vision or nystagmus. The FST test allows the determination of dark-adapted light and color perception levels as dB. Chromatic tests give us information about the condition of the rods and cones affected by the disease. Rods are more sensitive to blue light than red light, whereas cones are equally sensitive to blue and red light. A difference in sensitivity between the two color tests indicates that the rods are affected, while a similar decrease in sensitivity indicates that the cones are affected. In exclusively rod-derived responses, blue light sensitivity is approximately 25 dB higher than red. In cone-derived responses, blue and red light sensitivities are very similar. In previous studies, the blue-red sensitivity threshold difference has been calculated to determine from which cells the responses originate. It was reported that in cases where this difference is less than 10 dB, the rod cells made no contribution to the FST test.[14,15]

The present study aimed to use the FST test to evaluate white and color light sensitivity levels of the retina in RP patients. In addition, we planned to compare FST test results with optical coherence tomography (OCT) findings and visual field results to evaluate their relationship with anatomical and functional damage to the retina. As the study would include intermediate and advanced cases, we considered that it may not be possible to obtain rod-based electrophysiological responses. Therefore, we also planned to compare the results of the FST test and mfERG, which is a cone-based test.

Materials and Methods

Patient Selection and Evaluation

Patients over 18 years of age who presented to our clinic, were diagnosed with RP clinically and electrophysiologically, and whose disease was in the intermediate to advanced stage were included in this study. Approval for the study was received from Acıbadem University Medical Research Ethics Committee (ethics committee no: 2023-05/160, date: 24.03.2023) and adhered to the tenets of the Declaration of Helsinki. All patients were informed about the study and signed an informed consent form.

Criteria for inclusion in the study were:

1. Being over 18 years of age,
2. Having a clinical diagnosis of RP, confirmed with the tests performed,
3. Having the mental capacity to perform the tests,
4. Having undergone any ocular surgery other than cataract surgery.

Exclusion criteria were:

1. Having any retinal diseases other than RP (e.g., cataract, glaucoma, diabetic retinopathy) or vitreous opacity that may affect the test results,
2. Having any systemic or neurological disease that may affect the test results,
3. Having RP associated with a diagnosed syndrome such as Usher or Bardet-Biedl (due to the coexisting problems).

In addition to routine ophthalmological examinations of the patients, visual field results were recorded with the Humphrey 30-2 program (Carl Zeiss Meditec AG, Germany), and central macular thickness (CMT) and ellipsoid zone (EZ) band width were evaluated with OCT (Figure 1). CMT and EZ band width were measured independently by two separate evaluators and the values were averaged. Measurements were made using a horizontal OCT section passing through the foveal center. CMT was manually measured as the distance between the inner limiting membrane in the center of the fovea and the retinal pigment epithelium. EZ band width was determined by manually measuring the EZ band line between the nasal and temporal ends in the same horizontal OCT section (Figure 1C).

All patients in the study underwent electrophysiological testing with full-field ERG, mfERG, and FST test (Metrovision, France) performed in accordance with international standards. Full-field ERG aimed to assess rod and cone responses in the whole retina, while mfERG aimed to locally assess cone responses in the central retina. In the mfERG test, a stimulus consisting of 61 hexagons and 5 concentric rings (<2°, 2-5°, 5-10°, 10-15°, and >15°) was used, and the mean amplitude and latency of the P1 wave were recorded for all rings.

Patient evaluations started with routine examination, OCT, and visual field tests. The pupil was then dilated by instilling 1% tropicamide 3 times at intervals of 5 minutes, after which the electrophysiological tests were started. After completing the full-field ERG and mfERG tests in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards, the patient was taken for dark adaptation for the FST test.[16,17] As the FST test is relatively new, the procedure is explained in detail below.

FST Test Procedure

The patients with dilated pupils were taken into a dark room where their eyes were covered with a bandage for 40 minutes to allow dark adaptation. During the test, recordings were obtained from each eye separately while the other eye remained covered.

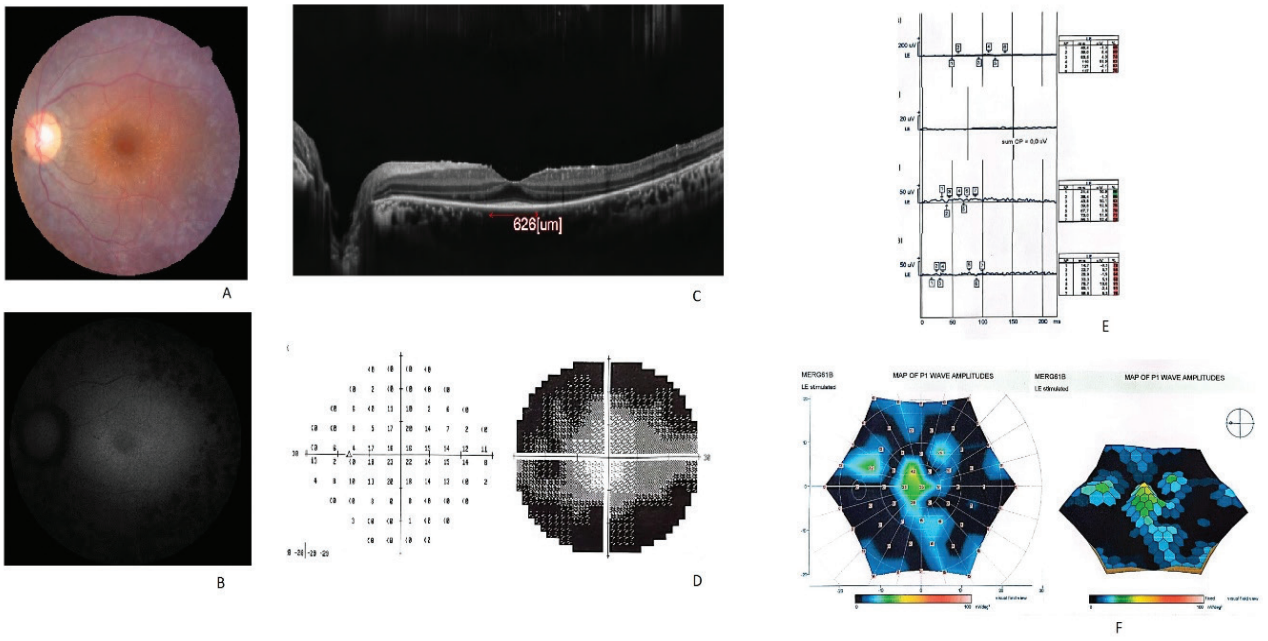

Figure 1. Fundus photograph (A), fundus autofluorescence (FAF) (B), optical coherence tomography (OCT) (C), visual field (D), full-field electroretinogram (ERG) (E), and multifocal ERG (F) images from the left eye of a patient with retinitis pigmentosa and visual acuity of 0.8 Snellen decimal. The fundus photograph shows peripheral pigmentary changes, FAF shows a central hyperautofluorescent ring, and OCT shows a decrease in retinal thickness, narrowing of EZ band, and the measurement of the EZ band. The visual field test indicates peripheral field loss. Full-field ERG responses are completely flat, while multifocal ERG shows depressed peripheral responses and attenuated central responses

The FST test was performed with the MonCvONE-CR system produced by Metrovision using full-field light as the stimulus. The device uses an LED light source for white light, a 500 nm filter for blue, and a 647 nm filter for red. During the test, patients were shown light stimuli of different colors every 3 seconds, and the patient was asked to press a button held in their hand when they saw the light. Sensitivity thresholds were determined using the 8-4-2-1 step method, in which the luminance (light value) is first increased by intervals of 8 dB. When the patient saw the light, the luminance was decreased and increased by 4 dB, then 2 dB, and finally by 1 dB to determine the threshold value. To ensure the reliability of the test, checks were made at regular intervals to ensure the patient was not responding without presenting the stimulus.[18]

The control group included patients in the same age group who presented to our outpatient clinic for examination and had no pathology detected in the ophthalmological examination. After obtaining consent, the control subjects underwent visual field, OCT, mfERG, and FST tests in addition to routine examination.

Due to the very low amplitudes in the full-field ERG test in the RP group and the inability to obtain reliable records, full-field ERG was not performed in the control group.

Statistical Analysis

The study data were statistically analyzed using SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test for normal distribution, descriptive statistics (mean, standard deviation) were used to evaluate the data, analysis of variance (ANOVA) was used for comparisons of paired groups, and Pearson correlation analysis was used for correlation analysis. The results were considered statistically significant at p values less than 0.05.

Results

A total of 101 eyes of 51 RP patients and 42 eyes of 21 control subjects were included in the study. Both groups conformed to normal distribution. The mean age was 35.2 years (range: 18-70 years) in the RP group and 33.5 years (range: 18-50 years) in the control group. The mean disease duration in RP patients was 16.9 years (range: 4-49 years). The mean visual acuity in the eyes with RP was 0.19 (range: 0.03-0.7) Snellen decimal, compared 1.0 in the control group. To examine the findings in more detail, the RP group was divided into two subgroups based on visual acuity: ≤0.05 and >0.05 Snellen decimal. The demographic data of the patients are given in Table 1. As patient age and disease duration increase, vision level decreases. Due to the very low full-field ERG amplitudes in all of the RP patients included in the study, no measurable response could be obtained. Of the 101 eyes, 91 had visual field and 89 had mfERG data. The visual acuity of eyes that could not be assessed with these tests was found to be lower than 0.05 Snellen decimal. All patients were able to perform the FST test easily. Meaningful FST test results could be obtained in 46 eyes of 23 patients with a vision level of 0.05 Snellen decimal or lower.

The patients' visual acuity, visual field, and OCT findings are shown in Table 2. When OCT findings were evaluated, the mean CMT was 132.2 µm in the RP group and 221.5 µm in the control group, which was a statistically significant difference ($p<0.05$). When the RP subgroups were examined, we observed that mean CMT value was significantly lower (121.5 µm) in the group with low visual acuity ($p<0.05$). The mean EZ band width was 1018.8 µm in the RP group. According to the RP subgroups, the EZ bands were significantly narrower (629.3 µm) in the group with low visual acuity ($p<0.05$). The control group exhibited no deterioration in EZ band integrity. These findings show that as the disease progresses, vision level decreases and the anatomical findings on OCT also worsen due to cell loss.

When the visual field results were evaluated, we observed that the mean MD value was -4.38 dB in the control group versus -30.91 dB in the RP group, and this difference is statistically significant ($p<0.05$). When evaluated by RP subgroup, we determined that visual field defects were more severe in the group with lower visual acuity (mean deviation: -32.53). These findings indicate that functional loss in the visual field increases as the disease progresses.

On mfERG, mean P1 wave amplitudes were significantly lower and mean P1 wave latency was significantly longer in all rings in eyes with RP compared to the control group, with a more prominent difference in the peripheral rings ($p<0.05$) (Tables 3, 4). These data demonstrate that mfERG recordings can be obtained even in advanced cases of RP, and the cone cell damage detected in mfERG progressed from the periphery toward the center.

When the FST test results were evaluated, the white, blue, and red light thresholds and the blue-red threshold difference were found to be significantly lower in the RP group than in the control group ($p<0.05$) (Table 5). The mean blue-red FST difference was 11.1 dB, and this difference was below 10 dB in 51 eyes. In these cases, the rod response was minimal or absent. In 13 eyes, this difference was found to be 0 dB, indicating that there is no rod response. When the RP subgroups were evaluated, all FST test values were found to be significantly lower in the group with low visual acuity. In addition, the mean blue-red threshold difference in this group was 9.2 dB, which is below 10 dB. Therefore, it can be said that there is very little to no

Table 1. Demographic characteristics of all subjects

Characteristic	RP group total (n=51)	RP group VA ≤0.05 (n=23)	RP group VA >0.05 (n=28)	Control (n=21)	p value
Age (years), mean	35.2	39.2	32.5	33.5	0.08
Sex (male), n (%)	27 (53)	11 (47)	16 (57)	11 (52)	0.31
Disease duration (years), mean	16.9	19.8	12.5		0.001*

*Mean disease duration was statistically longer in the group with VA ≤0.05 Snellen decimal. RP: Retinitis pigmentosa, VA: Visual acuity (in Snellen decimal), n: Number of patients

Table 2. Comparison of visual acuity, visual field, and OCT data of RP patients and the control group

	RP group total (n=101 eyes)	RP group VA ≤0.05 (n=46 eyes)	RP group VA >0.05 (n=55 eyes)	Control (n=42 eyes)	p value
VA (Snellen decimal)	0.19±4.4	0.04±0.03	0.31±5.2	1.0	0.008*
Visual field MD (dB)	-30.91±9.52	-32.53±5.52	-28.05±7.52	-4.38±2.63	0.020*
OCT CMT (µm)	132.2±47.4	121.5±37.4	145.7±42.6	221.5±19.3	0.023*
OCT EZ band width (µm)	1018.8±761.8	629.3±642.6	1363.6±833.6		0.010**

*There was a statistically significant difference between all groups. **There was a statistically significant difference between all groups, with lowest EZ band width on OCT in the RP group with visual acuity of 0.05 Snellen decimal. RP: Retinitis pigmentosa, OCT: Optical coherence tomography, VA: Visual acuity (in Snellen decimal), dB: Decibel, MD: Mean deviation, CMT: Central macular thickness, EZ: Ellipsoid zone

Table 3. Comparison of P1 wave amplitudes on multifocal electroretinography

Ring	RP group Mean ± SD (nV)	Control group Mean ± SD (nV)	p value
<2°	349.3±86.0	1412.3±162.2*	0.001*
2-5°	192.2±96.9	1192.5±163.4*	0.001*
5-10°	141.5±63.5	1112.5±141.3*	0.001*
10-15°	137.8±65.6	1054.5±132.4*	0.001*
>15°	95.1±58.1	1008.2±144.6*	0.001*

*P1 wave amplitudes were significantly lower in all rings in the RP group than in the control group. RP: Retinitis pigmentosa, SD: Standard deviation, nV: Nanovolt

rod response in eyes with a vision level of 0.05 Snellen decimal or lower. The blue-red threshold difference was greater than 20 dB in 17 eyes, all of which had visual acuity higher than 0.05 Snellen decimal. In our study, the mean test duration was 199 seconds (3.3 minutes) after dark adaptation.

Correlation analyses showed that older age, longer disease duration, and lower CMT and EZ band width were associated with lower visual acuity and increased visual field loss. All FST test results were negatively correlated with age, disease duration, and visual field MD values ($p<0.05$), indicating that FST test values decreased as age, disease duration, and visual field defects increased. All FST test results were positively correlated with mfERG amplitudes in all rings, with stronger correlation in the peripheral fourth and fifth rings. In addition, all FST test results showed a strong positive correlation with CMT and EZ band width ($p<0.05$).

Figure 1 shows the full-field ERG, mfERG, visual field, and OCT results of a patient with a visual acuity of 0.8 Snellen decimal, and Figure 2 shows the FST test results of the same patient and a subject in the control group.

Discussion

Developments in gene and stem cell therapies in recent years have required the inclusion of patients with low vision in clinical trials. Unfortunately, available tests were not sufficient to understand whether patients with low vision, especially the legally blind, benefitted from any of the treatment options applied. Visual field testing cannot always be performed reliably in this patient group, and existing electrophysiological tests do not yield meaningful responses due to the severe retinal damage. This demonstrated the need for a new test for use in the low vision patient group. As a result, the FST test was developed to be used in clinical trials for hereditary retinal diseases. As the FST test enables the light sensitivity threshold of the retina to be determined in dB even in patients with only light perception, it is expected to enable the collection of objective data in studies conducted in patients with low vision.[19,20]

Since FST is a new test, there are few studies on this subject in the literature. To date, this test has been used in studies involving low vision patient groups such as Leber congenital amaurosis (LCA), RP, Usher syndrome, and Stargardt's macular dystrophy.[21,22,23]

Klein and Birch[24] evaluated the accuracy, sensitivity, and repeatability of the FST test in 53 eyes of 42 advanced RP patients. The patients included in the study could not perform static perimetry and had no response on full-field ERG. Seven control subjects were also included in the study. In 51 of the 53 eyes, a light sensitivity threshold could be determined in the FST test. Of the 2 eyes with no result, one had no light perception and the other had only slight light perception. A threshold value could be obtained in the FST test in 14 eyes of 13 patients with light perception only. All patients who could count fingers were able to perform the test easily. The test was repeated at different times in 24 patients and yielded similar results. The authors concluded that the FST test is an easily reproducible and useful test that can be used to evaluate retinal light sensitivity and light perception level in patients with low vision.[24] In our study, none of the patients had a measurable response in the full-field ERG but all were able to perform the FST test easily. Our study group did not include any patients whose vision was at the level of light perception. The lowest level of visual acuity was hand

Table 4. Comparison of P1 wave latencies on multifocal electroretinography

Ring	RP group Mean ± SD (ms)	Control group Mean ± SD (ms)	p value
<2°	51.8±6.4	47.5±6.4*	0.020*
2-5°	52.9±8.0	46.3±5.4*	0.023*
5-10°	56.2±8.3	46.3±6.5*	0.010*
10-15°	54.5±8.4	49.4±5.7*	0.030*
>15°	55.7±12.4	48.4±6.3*	0.026*

*P1 wave latencies were significantly longer in all rings in the RP group than in the control group. RP: Retinitis pigmentosa, SD: Standard deviation, ms: Millisecond

Table 5. Comparison of full-field stimulus threshold test values

FST	RP group	RP group VA ≤0.05	RP group VA >0.05	Control group	p value
White FST	43.9±13.9	36.8±11.6	48.2±14.6	81.8±18.4	0.001*
Red FST	41.5±12.5	34.7±9.8	45.7±12.9	67.3±17.6	0.001*
Blue FST	52.6±16.2	43.2±10.6	58.3±15.7	92.8±18.3	0.001*
Blue-red FST	11.1±10.3	9.2±7.8	12.6±11.9	27.4±11.8	0.001*

*All FST test results and the blue-red threshold difference were significantly lower in the RP group than in the control group. All test results were significantly lower in the group with visual acuity of ≤0.05 Snellen decimal than in the other groups. FST: Full-field Stimulus Threshold, RP: Retinitis pigmentosa, VA: Visual acuity (in Snellen decimal), SD: Standard deviation

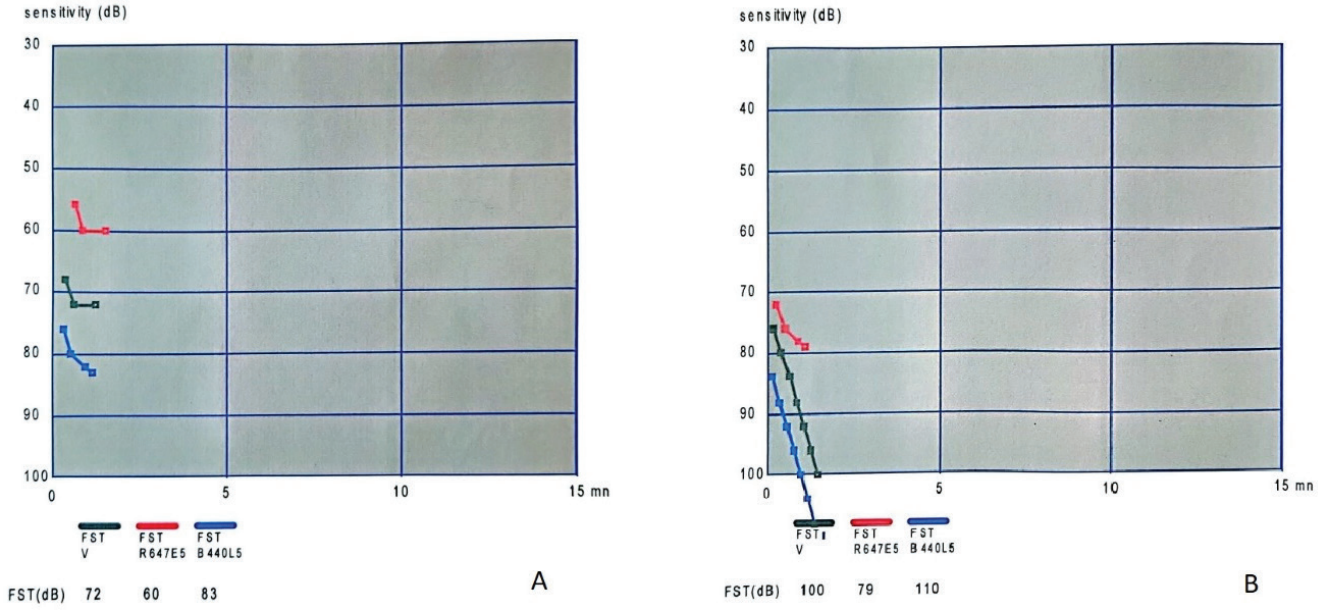

Figure 2. The full-field stimulus threshold (FST) test results of the patient shown in Figure 1 (A) and a control subject (B). White, blue, and red FST values were 72, 60, and 83 decibels (dB) in the patient with retinitis pigmentosa compared to 100, 79, and 110 dB in the control subject, respectively

movements at a distance of 1 meter. Significant FST test results could be obtained in all 46 eyes of the 23 patients with visual acuity lower than 0.05 Snellen decimal. Therefore, it can be said that the FST test is reliable in all patients whose vision level is better than light perception. However, all FST test results also decreased in correlation with the decrease in visual acuity.

Another clinical trial including 42 eyes of 21 RP patients compared FST results with flicker ERG, fundus autofluorescence (FAF), and OCT findings. White, blue, and red FST results were found to correlate with 3.0 flicker ERG amplitude, EZ band length on OCT, and the vertical and horizontal diameter of the hyperautofluorescent ring detected on FAF.[25] In two similar studies examining the relationship between the central retinal cell layers and visual field in RP patients, retinal sensitivity detected within the visual field decreased linearly as the outer nuclear layer thinned. It was also noted in these studies that the outer segment length (EZ band width) was proportional to photoreceptor cell density and correlated with visual field.[26,27] In our study, the retinal layers were not evaluated separately on OCT, but CMT and EZ band width (which indicates photoreceptor cell integrity) were examined. Similar to previous studies, we observed that as the retina thins and the EZ band narrows, visual field loss increases and the level of vision decreases. Our correlation analyses demonstrated that anatomical losses detected on OCT were strongly correlated with visual field and visual acuity loss. When other correlation data obtained from our study were evaluated, both white FST and chromatic (blue and red) FST values were positively correlated with the wave amplitudes in all rings on mfERG and with EZ band width and CMT values on OCT. This indicates that FST values decreased with increased retinal cell damage, narrowing of the EZ band, and thinning of the macula. Similarly, FST values decreased as mfERG wave amplitudes decreased (i.e., as cone cell function deteriorated). These results show that the FST test reflects functional and anatomical findings and can be used reliably in the clinical evaluation of patients with retinal disease.

The multicenter RUSH2A study published by Birch et al.[28] included 127 patients with Usher syndrome type 2A (*USH2A*)-associated retinal degeneration or biallelic *USH2A* mutation from 16 centers in the United States and Europe. The patients were aged 8 years and older with visual field less than 10° and were assessed with full-field ERG and FST tests during follow-up. As all patients in this study had severe retinal damage, full-field ERG results could not be obtained in 47% of the study group. All patients with unmeasurable ERG responses were able to perform the FST test. Therefore, the authors stated that the FST test complements ERG and may be more useful in follow-up. The results of their study showed that white FST and the blue-red FST difference were correlated with duration of vision loss. In eyes with a blue-red FST difference of less than 10 dB, the responses were assumed to be cone-derived. Rod function was found to be absent in 43% of all patients. In these cases, the white FST was below 30 dB and the blue-red difference was approximately 0 dB, suggesting that the response was entirely from cones. In eyes with a blue-red FST difference greater than 20 dB, the responses were presumed to be mostly rod-derived.

Eyes with rod-driven responses mostly had disease durations of less than 20 years, while most patients with a disease duration longer than 20 years had no rod response and cone-mediated FST. In that study, visual acuity was very weakly correlated with scotopic ERG results and weakly correlated with photopic ERG results, but a strong correlation was found with FST results. The FST test was strongly correlated with disease duration, and thus with disease severity. White FST values were found to be 18 dB higher in eyes with a disease duration of less than 10 years versus more than 20 years.[28]

In our study, all FST test values showed a strong negative correlation with patient age and disease duration. To better evaluate the results, we divided the RP patients into subgroups based on visual acuity. The mean age was 6.7 years older and the mean disease duration was 7.3 years longer in patients with visual acuity of 0.05 Snellen decimal or lower compared to RP patients with higher visual acuity. In cases with low vision, CMT and EZ band widths were found to be more significantly decreased, indicating greater anatomical damage to the retina. Consistent with these findings, visual field defects were more advanced in the subgroup with low visual acuity. Considering the FST results, there was a similar decrease in both white and chromatic FST results in the RP patients in our study. This indicates damage not only to rod cells but also cone cells. The mean blue-red FST difference was 11.1 dB, with values lower than 10 dB in 51 eyes. When visual acuity decreased to below 0.05 Snellen decimal, the mean blue-red FST difference decreased to less than 10 dB (9.2 dB). In 13 eyes, this difference was found to be 0 dB. These findings indicate that rod cells contribute little to the FST results in advanced disease and even make no contribution in some cases. The continued ability to obtain FST responses in patients with very low vision is due to the fact that cone cell function continues until the end stage. This also supports the mfERG results reported in the literature. The blue-red threshold difference on the FST test was greater than 20 dB in 17 eyes, all of which had visual acuity better than 0.05 Snellen decimal. It can be concluded that rod cells contributed to the FST results in these eyes. Based on the FST results, rod responses were absent in approximately half of the eyes in our study and were very low overall, leading to the conclusion that cones contribute more to light perception in advanced RP.

The FST is a fairly quick test. In previous studies, the average test duration per eye was 3.6 minutes, with a range of 2.9 to 4.8 minutes. In addition, it has high repeatability. The average difference between repeat tests in the same patients was reported to be 1.51 dB.[14,22] In our study, the mean duration of the test was 199 seconds (3.3 minutes) after dark adaptation.

As mentioned earlier, the FST test was developed to evaluate the effectiveness of treatment in clinical studies of gene and stem cell therapies in which low vision patients are included. The FST test was first used in clinical studies investigating the active substance in voretigene neparvovec, which received U.S. Food and Drug Administration approval for use in patients with LCA and RP associated with homozygous *RPE65* gene mutation. The open-label randomized controlled phase 3 trial by Russell et al.[29] included patients over 3 years of age with visual acuity 20/60 or worse, visual field less than 20 degrees, and biallelic *RPE65* mutation. All patients were able to perform the FST test and 90% of them exhibited improvements in the FST test at 1-year follow-up.[30] In studies presenting the 4-year results of treated patients, the FST test was repeated during follow-up and the improvements in the FST test achieved at 1 year were found to be maintained at 4 years.[30,31]

In another study, patients with CEP290-associated LCA type 10 were treated with sepofarsen, an RNA antisense oligonucleotide targeting CEP290. In this phase 1b/2 trial, intravitreal sepofarsen was administered to 11 patients, 5 of which were children, up to 4 times and the 12-month follow-up results were examined. FST was the only electrophysiological test used in the study. It was a dose determination study and 5 patients had light perception only. In such a low-vision group, responses could not be obtained with other electrophysiological tests. However, FST could be performed by all patients. Improved light perception was detected in both white and chromatic (blue/red) FST tests in the treated eyes of all patients.[32] It is clear that there is no test other than FST that can be used to evaluate treatment outcomes in patients with light perception only.

Study Limitations

Our patient group consisted of intermediate to advanced cases. There were no patients with early RP in the study. Therefore, it was not possible to evaluate how FST tests would be affected at an early stage. In addition, the RP cases were only subdivided according to visual acuity. In a larger patient group, the interpretation of FST tests will be more informative by grouping according to inheritance patterns, genetic test results, or clinical findings. Finally, there is no database of FST test results in normal individuals in the literature, and we have not yet created a normative database in our own laboratory. It would be more useful to determine normal data by age group and compare them with disease groups.

Conclusion

In summary, FST is an easy, rapid, non-interventional test that can be performed reliably in all patients who have low vision, nystagmus, and unmeasurable ERG responses. Clinical studies conducted in recent years, especially in patients with low vision, have revealed the importance of this test. Therefore, it is necessary to know and evaluate FST test results in different patient groups. This study presents a detailed analysis of FST test results and their relationship with other ophthalmological tests in patients with RP.

Ethics

Ethics Committee Approval: Approval for the study was received from Acıbadem University Medical Research Ethics Committee (ethics committee no: 2023-05/160, date: 24.03.2023).

Informed Consent: Obtained.

Authorship Contributions

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

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

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Original Article

The Effects of Lens Extraction Surgery on Intraocular Pressure and Anterior Segment Parameters in Primary Angle-Closure Glaucoma

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Abstract

Objectives: To investigate the effects of phacoemulsification with intraocular lens implantation (phaco+IOL) surgery on intraocular pressure (IOP) and anterior segment parameters in patients with cataract and primary angle-closure glaucoma (PACG).

Materials and Methods: Fifty-five patients with PACG undergoing phaco+IOL surgery were evaluated in terms of best corrected visual acuity (BCVA), IOP, anterior chamber depth (ACD), aqueous depth (AD), and lens thickness (LT) measured by optical biometry preoperatively and at the 6-month postoperative visit. They were compared with 34 healthy age- and gender-matched cataract patients who underwent phaco+IOL surgery.

Results: Preoperative evaluation revealed higher IOP, shorter axial length, shallower ACD and AD, and greater LT in the PACG group ($p<0.001$ for all). Postoperative evaluation in the PACG group showed an increase in BCVA, a significant decrease in IOP, an increase in ACD and AD, and a decrease in LT ($p<0.001$ for all). Additionally, a reduction in the average number of antiglaucomatous medications used postoperatively was observed in the PACG group ($p<0.001$). The changes in IOP, ACD, AD, and LT between preoperative and postoperative assessments were significantly greater in the PACG group compared to the control group ($p<0.0001$ for all).

Conclusion: Phaco+IOL surgery in PACG patients leads to a significant increase in ACD compared to the control group and allows better control of IOP with fewer antiglaucomatous medications after surgery.

Keywords: Primary angle-closure glaucoma, lens extraction, intraocular pressure, anterior segment parameters

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Introduction

Glaucoma is a progressive optic neuropathy characterized by damage to retinal ganglion cells and their axons.[1] Early diagnosis and treatment of glaucoma, which is one of the leading causes of irreversible blindness worldwide, are crucial in preventing vision loss.[1,2] Primary angle-closure glaucoma (PACG), an important subtype of glaucoma, is less common than primary open-angle glaucoma (POAG) but tends to have a more aggressive course.[2,3] PACG affects around 20 million people globally, particularly in East Asia.[3] It is estimated that this number will exceed 34 million by the year 2040, with an estimated risk of blindness for 5.3 million people.[3] While most patients do not experience complete vision loss, their quality of life is reduced by peripheral visual field narrowing and the need for long-term treatment.[2]

Angle closure occurs due to anatomical features that lead to the narrowing or closure of the iridocorneal angle.[4,5] This closure can occur through either synechial or appositional mechanisms, both of which obstruct the flow of aqueous humor. PACG is defined as the presence of glaucomatous optic nerve damage with more than 180° of the iridocorneal angle blocked due to apposition between the iris and the trabecular meshwork, accompanied by elevated intraocular pressure (IOP).[4]

It is known that various factors, including an increase in lens thickness (LT) or curvature, narrow anterior chamber depth (ACD), hyperopic eyes, zonular dialysis leading to anterior displacement of the lens, pupillary block triggered by the lens, and iris configuration play important roles in the pathogenesis of PACG.[2,4,5,6,7,8]

In the treatment of PACG, the traditional method known as laser peripheral iridotomy (LPI) is effective in preventing acute angle-closure attacks. However, it may not open the angle in up to 58% of eyes with PACG.[4] Phacoemulsification with intraocular lens implantation (phaco+IOL) surgery not only enhances visual acuity but also effectively lowers IOP, diminishes reliance on antiglaucoma medications, and can potentially

decrease the necessity for subsequent glaucoma surgeries in these patients.[1,2,5,6,7,9] Compared to LPI, initial phaco+IOL is 10 times more likely to help patients with PACG maintain good IOP control without the need for antiglaucomatous medication.[9] Furthermore, lens extraction can correct the commonly encountered hyperopic refractive error in these patients, reducing the need for glasses or contact lenses and improving their quality of life.[10] In recent years, the Effectiveness of Early Lens Extraction for the treatment of primary angle closure glaucoma (EAGLE) study also evaluated clear lens extraction (CLE) surgery in PACG patients without cataract.[2,9] However, the potential risks of complications associated with phaco+IOL surgery in PACG patients should not be disregarded.[2,5,6,7] This is because these eyes have risk factors such as elevated IOP, decreased endothelial cell count and function, narrow anterior chamber space, floppy iris due to previous iris ischemia, posterior synechiae, increased LT, and loose lens zonules.[2,4,6,11,12] These factors increase the difficulty of intra- and postoperative management, and inexperienced surgeons performing lens surgery in such eyes can lead to potentially devastating complications such as posterior capsule rupture, lens drop, suprachoroidal hemorrhage and potential complications such as malignant glaucoma.[2,4,12]

The present study aims to investigate the visual outcomes, changes in IOP, and the need for postoperative antiglaucoma treatment in PACG patients undergoing phaco+IOL surgery for cataract. Additionally, the differences in preoperative and postoperative anterior segment parameters were compared between the PACG group and a control group consisting of patients with no condition other than cataract who underwent phaco+IOL surgery.

Materials and Methods

This prospective cross-sectional study was conducted in the glaucoma unit of a tertiary referral eye hospital. Fifty-five eyes of 55 patients who received medical treatment for PACG and underwent phaco+IOL surgery for cataract were compared to a control group consisting of 34 eyes of 34 age- and gender-matched patients with no health conditions other than cataract who also underwent phaco+IOL surgery. All participants were provided with detailed information about the nature of the study and their written informed consent was obtained. The study protocol was approved by the Ankara Training and Research Hospital Ethics Committee (number: 15.09.2021 E-21/661). All study procedures were planned in accordance with the ethical principles of the Helsinki Declaration and Good Clinical Practice Guidelines.

A thorough ophthalmological examination was performed on all participants after obtaining a detailed ocular and systemic medical history. This examination included best-corrected visual acuity (BCVA) with Snellen chart, IOP measurement with Goldmann applanation tonometry, gonioscopy with a Goldmann three-mirror lens, slit-lamp biomicroscopy of the anterior segment and fundus examination, visual field assessment using the Humphrey Visual Field Analyzer with the standard 24-2 Swedish Interactive Threshold Algorithm strategy, and measurement of anterior segment parameters including central corneal thickness (µm), ACD (mm), aqueous depth (AD) (mm), and LT (mm) using the Lenstar 900 optical biometry device (Haag-Streit AG, Koeniz, Switzerland). Within the scope of the study, all measurements were obtained both before cataract surgery and at the 6-month postoperative visit.

The diagnosis of PACG was made according to the criteria of the European Glaucoma Society Guidelines.[13] The criteria for the diagnosis of PACG included untreated IOP >21 mmHg, iridotrabecular contact of 180° or more on gonioscopy (peripheral iris pushed forward and in appositional or synechial contact with Schwalbe's line), glaucomatous appearance of the optic nerve head (e.g., neuroretinal rim thinning, notching, cup-to-disc ratio asymmetry, focal hemorrhages), and the presence of glaucomatous visual field defects. Patients with primary angle closure without glaucomatous findings and primary angle closure suspects were excluded from the study.

Participants with nuclear lens opacities higher than grade 2 were included in the study with the dual aim of enhancing visual quality by addressing cataracts that reduce vision and providing more effective glaucoma control in the PACG group after cataract surgery. All participants in the PACG group had a patent LPI prior to phaco+IOL surgery. All surgical procedures were performed by the same experienced surgeon (E.Ş.) using the same device (Centurion Systems Alcon Surgical, Fort Worth, Texas, USA) and similar torsional phaco, vacuum, and aspiration flow parameters. In all surgeries, an Alcon SA60AT single-piece, aspheric, hydrophobic acrylic, monofocal, foldable IOL (Alcon Laboratories, Inc.) was implanted according to the measurements obtained from Lenstar 900 (Haag-Streit AG, Koeniz, Switzerland) optical biometry, and 0.1 mL/1 mg of intracameral cefuroxime (Aprokam, Thea Pharma İlaç, İstanbul, Türkiye) was administered at the end of the surgery. No complications occurred during or after the surgeries. An anterior chamber biomicroscopy image of a patient from the PACG group before and after surgery can be seen in Figure 1.

Participants with a history of glaucoma other than PACG, non-glaucomatous optic neuropathy, previous ocular surgery, trauma or laser procedures, vitreoretinal diseases (e.g., such as diabetic retinopathy, hypertensive retinopathy, retinal vascular occlusions), active intraocular infections or inflammation, eyes with intraocular conditions that may affect anterior segment findings (e.g., corneal scars, pseudoexfoliation, uveitis), over 3D of myopia, hyperopia, or astigmatism, and patients diagnosed with systemic diseases (e.g., diabetes mellitus, arterial hypertension, coronary artery disease, history of malignancy) were excluded. Additionally, patients who did not attend regular follow-up or could not cooperate with the measurements were also excluded from the study.

Statistical Analysis

The statistical analyses were conducted using IBM® SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The normality of continuous variables was examined using the

Kolmogorov-Smirnov test. Comparisons between the study groups was performed using the independent-samples t-test. The paired-samples t-test was used to compare preoperative and postoperative findings within the groups. The presence of correlation between numerical variables was evaluated using the Pearson correlation test. A significance level of 0.05 was established for statistical significance.

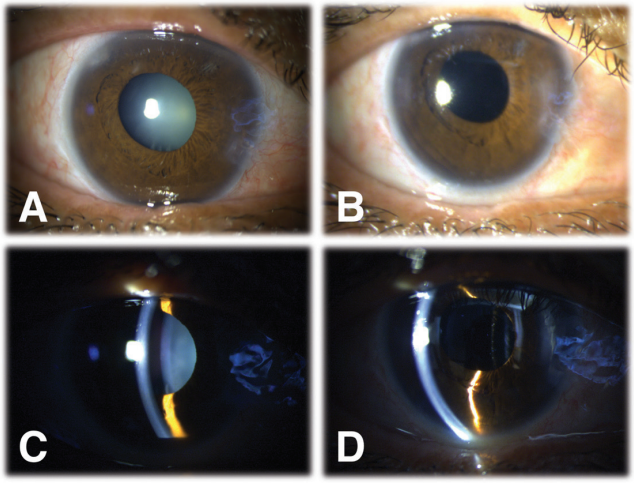

Figure 1. An anterior chamber biomicroscopy image of a patient from the primary angle-closure glaucoma group before (A, C) and after surgery (B, D). The anterior chamber depth in the slit-lamp biomicroscopic image is shallow before (C) and deep after surgery (D)

Results

There was no significant difference in demographic data between the PACG group and the control group (Table 1). Before surgery, BCVA was better in the control group, while the PACG group had significantly higher IOP and LT values and significantly lower AL, AD, and ACD values than the control group ($p<0.001$ for all). There was no significant difference in central corneal thickness between the two groups ($p=0.05$). The preoperative BCVA, IOP, and anterior segment parameters of the study groups are summarized in Table 1, and the postoperative findings are presented in Table 2.

After surgery, the PACG group showed a significant decrease in IOP, an increase in ACD and AD, and a decrease in LT ($p<0.001$ for all). Additionally, the number of antiglaucoma eye drops used significantly decreased compared to the preoperative period ($p<0.001$). The preoperative and postoperative findings of the PACG group are compared in Table 3.

When compared to the control group, the PACG group showed statistically significantly greater changes in IOP, ACD, AD, and LT between the pre- and postoperative measurements ($p<0.0001$ for all) (Table 4).

Table 1. Demographic data, preoperative visual acuity, intraocular pressure measurements, and anterior chamber parameters of the study groups

	PACG (n=55) Mean ± SD (range)	Control (n=34) Mean ± SD (range)	p[a]
Age (years)	63.7±10.7 (36-83)	61.4±9.9 (40-82)	0.31
Best corrected visual acuity (Snellen decimal)	0.45±0.30 (0.05-0.8)	0.14±0.12 (0.05-0.5)	**<0.001**
Intraocular pressure (mmHg)	20.1±6.41 (10-30)	15.5±3.39 (9-21)	**<0.001**
Axial length (mm)	22.08±0.7 (20.61-23.27)	23.60±0.9 (21.77-24.79)	**<0.001**
Central corneal thickness (µm)	539.8±38.2 (449-619)	523.9±33.4 (464-587)	0.05
Aqueous depth (mm)	1.86±0.16 (1.52-2.38)	2.78±0.4 (2.08-3.91)	**<0.001**
Anterior chamber depth (mm)	2.4±0.17 (1.99-2.68)	3.3±0.37 (2.63-4.06)	**<0.001**
Lens thickness (mm)	4.86±0.34 (4.20-5.61)	4.25±0.41 (3.20-4.90)	**<0.001**

[a]Independent samples t-test, SD: Standard deviation, PACG: Primary angle-closure glaucoma

Table 2. Postoperative visual acuity, intraocular pressure measurements, and anterior chamber parameters of the study groups

	PACG (n=55) Mean ± SD (range)	Control (n=34) Mean ± SD (range)	p[a]
Best corrected visual acuity (Snellen decimal)	0.78±0.19 (0.6-1)	0.81±0.12 (0.6-1)	0.27
Intraocular pressure (mmHg)	15.1±2.83 (10-24)	14.5±3.1 (9-20)	**<0.05**
Axial length (mm)	22.02±0.7 (20.57-23.20)	23.5±0.9 (21.69-24.65)	**<0.001**
Central corneal thickness (µm)	539.7±39.8 (456-627)	532.1±32.6 (466-590)	0.35
Aqueous depth (mm)	3.5±0.26 (2.65-4.51)	4.0±0.31 (3.36-4.82)	**<0.001**
Anterior chamber depth (mm)	4.02±0.26 (3.24-4.46)	4.5±0.3 (3.38-5.27)	**<0.001**
Lens thickness (mm)	0.75±0.02 (0.68-0.80)	0.68±0.08 (0.52-0.90)	**<0.001**

[a]Independent samples t-test, SD: Standard deviation, PACG: Primary angle-closure glaucoma

Table 3. Comparison of preoperative and postoperative findings in the primary angle-closure glaucoma group			
	Preoperative Mean ± SD (range)	**Postoperative Mean ± SD (range)**	**p[a]**
Best corrected visual acuity (Snellen decimal)	0.45±0.30 (0.05-0.8)	0.78±0.19 (0.6-1)	**<0.001**
Intraocular pressure (mmHg)	20.1±6.41 (10-30)	15.1±2.83 (10-24)	**<0.001**
Aqueous depth (mm)	1.86±0.16 (1.52-2.38)	3.5±0.26 (2.65-3.96)	**<0.001**
Anterior chamber depth (mm)	2.4±0.17 (1.99-2.68)	4.02±0.26 (3.24-4.46)	**<0.001**
Lens thickness (mm)	4.86±0.34 (4.20-5.61)	0.75±0.02 (0.68-0.80)	**<0.001**
Antiglaucomatous medications	2.9±1.16 (1-4)	1.7±1.2 (0-3)	**<0.001**
[a]Paired samples t-test, SD: Standard deviation			

Table 4. Comparison of preoperative and postoperative differences in anterior chamber parameters between the two groups			
	PACG Mean ± SD (range)	**Control Mean ± SD (range)**	**p***
Intraocular pressure (mmHg)	5.04±6.44 (-3-27)	0.94±3.03 (-5-8)	**<0.0001**
Aqueous depth (mm)	1.64±0.25 (0.75-2.05)	1.25±0.30 (0.74-2.36)	**<0.0001**
Anterior chamber depth (mm)	1.62±0.25 (0.79-2.00)	1.19±0.29 (0.39-1.77)	**<0.0001**
Lens thickness (mm)	4.05±0.45 (1.82-4.89)	3.6±0.41 (2.52-4.31)	**<0.0001**
*Independent samples t-test, SD: Standard deviation, PACG: Primary angle-closure glaucoma			

Mean deviation values on the visual field test were -3.43±1.95 decibels (dB) and pattern standard deviation values were 3.06±1.74 dB in the PACG group. Preoperative and postoperative mean gonioscopic grades were 0.64±0.32 (range: 0-1) and 2.04±0.68 (range: 1-3) in the PACG group, and 2.89±0.74 (range: 2-4) and 3.26±0.56 (range: 2-4) in the control group, respectively.

Postoperative IOP reduction was correlated with preoperative AD (r=-0.28, p=0.008) and preoperative ACD (r=-0.27, p=0.009) but not with preoperative LT (r=0.19, p=0.064).

Discussion

The standard treatment for PACG involves LPI to open the aqueous outflow pathway and medical treatment with topical antiglaucoma eye drops to reduce IOP.[2,6,7,8] Surgical intervention should be considered for patients who are not adequately controlled with these methods.[6,7] Phaco+IOL surgery has shown promising results for PACG and can serve as a stand-alone treatment or be performed in combination with the aforementioned modalities.[5,6,7] Studies comparing phaco+IOL and trabeculectomy surgeries in PACG patients have shown similar long-term IOP control between the methods, with trabeculectomy patients requiring fewer postoperative glaucoma medications.[11,14] However, despite the significant IOP-lowering effect of trabeculectomy, authors have highlighted the increased risk of complications such as postoperative anterior chamber shallowing and even malignant glaucoma.[2,5,6,7,8,11,14] They also recommended phaco+IOL as a viable alternative for initial surgical treatment instead of trabeculectomy in PACG management. A meta-analysis comparing phacotrabeculectomy and phaco+IOL surgeries in PACG patients also yielded similar results.[15] Additionally, the risk of trabeculectomy failure is higher in PACG compared to POAG.[7,11,15]

The position and thickness of the lens, volume of the anterior chamber, and iris position play a significant role in the pathogenesis of PACG.[1,2,4,7,8,11,15] Therefore, phaco+IOL surgery is highly effective in achieving glaucoma control, especially in cases where coexisting cataracts are present.[1,2,6,12,16] Phaco+IOL also leads to a clinically significant reduction in IOP in PACG cases when compared to normal eyes and cases of POAG.[16] When considering PACG cases for lens extraction, a detailed evaluation of the angle, determination of whether the angle closure is appositional, and assessment of the presence of peripheral anterior synechiae are crucial for the success of the surgery.[6] Appositional angle closure occurs when factors such as pupillary block or a thick peripheral iris roll are present. Lens extraction allows the iris to assume a more posterior position within the eye, leading to widening of the anterior chamber angle and resolution of appositional angle closure.[12] However, the decision and timing of lens surgery when cataract is not significant remain controversial.[2,7] In the EAGLE study,[2] CLE was performed on 208 patients with PAC and PACG at the time of initial diagnosis, while 211 patients received LPI and medical treatment. After a 3-year follow-up, the group that underwent CLE showed better IOP control, improvement in visual quality and daily activity skills, and reduced need for additional glaucoma surgery. The long-term results of the EAGLE study also support the initial findings.[9] This study demonstrated the potential benefit of performing early lens surgery in eyes where the lens is a significant component of angle closure, without waiting for the development of cataract.[2,9] However, these patients were over 50 years old, with lost accommodative ability and without

significant advanced glaucoma. It should be noted that young individuals may experience accommodative loss following CLE.[12] Furthermore, it should be considered that due to the structural characteristics of PACG eyes, they may be more prone to complications during and after phaco+IOL surgery.[2,6,11,12]

Cases where phaco+IOL surgery is more successful in angle closure are those with shallow anterior chambers, where peripheral anterior synechiae have not yet developed, and with more stable preoperative IOP in appositional angle closure.[8,17] In cases of peripheral anterior synechial closure, phaco+IOL surgery alone does not definitively resolve the issues with the anterior chamber angle.[6,8,12,18] Combining phaco+IOL with goniosynechialysis show promising results in this situation.[6,8,17,18] Recent studies conversely found that both interventions significantly reduced IOP, but there was no significant difference between phaco+IOL with and without goniosynechialysis.[19,20] Additionally, both groups exhibited similarly low rates of complications. Since a significant portion of our participants had appositional PACG, goniosynechialysis was not performed in any case in order to standardize the surgical procedure of study.

Tarongoy et al.[7] analyzed 22 studies investigating the impact of phaco+IOL surgery on suspected angle closure, angle closure, and PACG. These studies primarily focused on eyes with cataracts that were affecting vision. The analysis showed that more than 65% of patients who underwent phaco+IOL surgery returned to normal IOP without the need for glaucoma medication. Another report by Chen et al.[5] evaluated 12 studies involving a total of 495 PACG patients. The mean preoperative IOP value was 20.2 mmHg, and patients were using an average of 1.9 medications. After phaco+IOL surgery, during an average follow-up period of 15.7 months, the mean IOP decreased to 14.2 mmHg and average number of medications used fell to 0.8. This corresponds to a 30% reduction in IOP and a 58% reduction in medication use.[5] A meta-analysis conducted by Masis et al.[21] also discovered that in patients with PACG, CLE led to a mean IOP reduction of 6.4 mmHg (range: -9.4 to -3.4). Shams and Foster[22] reported an average IOP reduction of 3 mmHg in PACG patients after phaco+IOL surgery and emphasized the significant impact of lens surgery for advanced-stage glaucoma patients. However, the authors have also pointed out the high rate of complications in this patient group. Liu et al.[14] noted a decrease in the need for glaucoma medications initially, but an increase over the subsequent 4 years. The long-term results of the EAGLE study also indicated that patients with PACG who undergo CLE have a 10-fold higher rate of achieving IOP control without using antiglaucoma eye drops compared to the group that underwent LPI.[9] In the present study, the PACG group had a mean preoperative IOP of 20.1 mmHg and used an average of 2.9 medications, which decreased to 15.1 mmHg and 1.7 medications after surgery. The decrease in IOP was significantly greater in the PACG group compared to the control group.

In various studies, the degree of IOP reduction after phaco+IOL surgery for PACG has been associated with several factors, such as the difference in ACD measurements before and after surgery, as well as a reduction in LT.[4,14,22,23,24,25,26] Helmy[23] also indicated that ACD and LT are related to postoperative IOP and the number of medications used by PACG patients. In the present study, we observed that postoperative IOP reduction was correlated with preoperative AD and ACD but not preoperative LT. There is only one report in the literature that argues that changes in ACD or LT after surgery are not associated with IOP reduction.[27] Additionally, while a reduction in LT was certainly expected after cataract surgery, we believed that quantitatively reporting these data would be valuable in enhancing the comprehensibility of the study.

Although the LT of the PACG group was greater than that of the control group, the preoperative BCVA was lower in the control group. Nevertheless, the significant difference in BCVA between the two groups suggests that cataracts may be at a more advanced stage in the control group. Unfortunately, our inability to quantitatively measure lens densities prevents us from providing objective data to assess nuclear lens opacities. Additionally, the structurally thick lens in PACG patients may indicate the importance of LT in the pathogenesis of the disease.

In cases of mild to moderate glaucoma, multifocal lenses are occasionally used. However, their use is contraindicated in cases with advanced glaucomatous damage because of reported reductions in contrast sensitivity and potential impact on visual field.[8] Evidence suggests that the best IOL option is aspheric monofocal IOLs, which have been shown to provide a 4-dB improvement in perifoveal threshold values compared to the standard IOL for glaucoma patients.[8,28] Therefore, single-piece, aspheric, hydrophobic acrylic, monofocal, foldable IOL (Alcon SA60AT, Alcon Laboratories, Inc.) was implanted in all participants in our study to standardize the surgery.

In the present study, the PACG group exhibited an increase in BCVA, a significant decrease in IOP, an increase in ACD, a decrease in LT, and a significant reduction in the number of antiglaucoma medications used after phaco+IOL surgery. Furthermore, when comparing the preoperative and postoperative differences in these parameters between the PACG and control groups, statistically significant differences were observed. To the best of our knowledge, there is no similar study comparing preoperative and postoperative anterior chamber parameters using the Lenstar in patients with PACG and a control group among Caucasian people. However, the presence of certain limitations should not be overlooked when interpreting the results of the study.

Study Limitations

One limitation of the study was the relatively small sample size and short follow-up duration. A larger sample size and longer follow-up period involving a more diverse participant group would provide more generalizable information about the effects of phaco+IOL surgery in patients with PACG. Another limiting factor that affected the results of our study is the absence of quantitative measurements of iridocorneal angle. Although the presence of generalized peripheral anterior synechiae was ruled out by a skilled clinician through gonioscopic examination, evaluating the iridocorneal angle with objective measurements

and comparing it with other parameters would yield more reliable results. As ACD is low in PACG, the probability of endothelial damage during phaco surgery is higher than in open-angle eyes. Therefore, it would be appropriate to compare the preoperative and postoperative endothelial cell counts of the patients in the study design.

Conclusion

In PACG patients, phaco+IOL surgery leads to significant widening of the widening of anterior chamber compared to the control group and allows better control of IOP with fewer antiglaucomatous medications after surgery. Further long-term studies conducted with larger patient series will provide more guidance in this regard.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara Training and Research Hospital Ethics Committee (number: 15.09.2021, E-21/661).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: E.Ş., S.B., Concept: E.Ş., S.B., Design: S.B., B.D.Y.E., F.B.A., Data Collection or Processing: M.T., F.B.A., S.B., Analysis or Interpretation: E.Ş., Literature Search: S.B., B.D.Y.E., F.B.A., Writing: S.B.

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Invited Review

Indocyanine Green Angiography

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Abstract

The choroid plays an important role in the pathophysiology of the eye. Multimodal imaging offers different techniques to examine the choroid. Fundus fluorescein angiography offers limited visualization of the deep layers of the fundus due to the barrier property of the retinal pigment epithelium. Therefore, indocyanine green angiography (ICGA) is widely used in the angiographic examination of the choroidal structure. ICGA is an important component of multimodal imaging in the diagnosis and treatment of many degenerative, tumoral, and inflammatory diseases of the choroid and retina. This review presents the general characteristics of ICGA and a practical approach to its clinical use.

Keywords: Indocyanine green, angiography, choroid, retina, diagnosis, treatment, imaging

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Introduction

While indocyanine green (ICG) dye has long been used in heart and liver function tests, its introduction into ophthalmology as an angiography dye dates back to approximately 40 years ago.[1,2,3]

Its limited leakage from the choroidal vessels and ability to penetrate into the deep layers with little absorption by xanthophyll pigment and the retinal pigment epithelium (RPE) when exposed with infrared light make ICG angiography (ICGA) advantageous in the examination of the choroidal circulation. However, difficulty obtaining quality images because of the low-intensity fluorescence of ICG dye delayed the adoption of this method in ophthalmic diagnosis.

Thanks to the combination of this method with infrared-sensitive high-resolution fundus cameras and scanning laser ophthalmoscopy (SLO), ICGA has taken its place in the diagnosis and monitoring of pathophysiological processes involving the choroidal vasculature.[3,4,5,6] The introduction of wide-angle lenses has also expanded ICGA's area of use.

ICGA is an important component of multimodal imaging in centers performing the diagnosis and treatment of posterior segment diseases. This article aims to provide information about the basic features of ICGA and its role in clinical use.

History

ICG infrared absorption angiography was first used by Kogure and Choromokos[7] in 1969 to examine the pial circulation in dogs. The same study group introduced the fundus infrared absorption angiography technique into ophthalmology by administering the dye intraarterially in monkeys.[8] Using this method, David[9] performed intraarterial ICG infrared absorption choroid angiography in humans for the first time in 1971. Hochheimer[10] obtained a better quality image by administering intravenous ICG to cats and using black and white film instead of infrared-sensitive color film.

As the infrared absorption technique did not provide sufficient choroidal detail, Flower and Hochheimer[2] took advantage of the fluorescent property of ICG and described choroidal ICG fluorescence angiography in 1973. Tokoro et al.[11] enhanced ICG choroid angiography with an infrared-sensitive modified camera and the video angiography technique in 1984. In the following years, Hayashi et al.[12,13,14,15] used this method to detect choroidal blood flow and examine central serous chorioretinopathy (CSCR) and subretinal choroidal neovascular membranes (CNV). In 1989, Scheider and Schroedel[5] performed ICG videoangiography with SLO. The ICG digital videoangiography technique was used in patients with CNV in 1991.[16] Thereafter, ICGA was widely used in the evaluation of retinal and posterior segment diseases, especially cases of occult CNV.[17]

In the following years, ICGA was also used to visualize tumors and inflammatory diseases in the fundus, and images specific to many diseases were published.[18,19,20,21]

Physical and Chemical Properties of ICG

ICG is a tricarbocyanine dye with a molecular weight of 775 g/mol and chemical formula of $C_{43}H_{47}N_2NaO_6S_2$. It differs from sodium fluorescein (NaFl) in two main ways. First is its high rate of plasma protein bonding, which is 98% for ICG compared to 70-90% for NaFl.[22,23] The second important difference is that its maximum absorption is at 805 nm and its maximum fluorescence is at 835 nm, which is in the near-infrared part of the electromagnetic spectrum. For NaFl, these wavelengths are 465 nm and 525 nm, respectively (Table 1).[4]

Unlike NaFl, ICG shows very little leakage from choroidal and pathological vessels due to its high plasma protein binding. Light at its maximum fluorescence wavelength of 835 nm is not absorbed by macular xanthophyll pigments and only 10% is absorbed by the RPE.[24] These features of ICG together with its ability to penetrate into the deep tissues enable visualization of the choroidal vascular structures, especially the submacular area where NaFl is insufficient.

ICG Metabolism

ICG is excreted from the body exclusively by the liver. In people with normal liver function, the half-life of ICG in the circulation is approximately 2.6 minutes. Its rapid elimination from the circulation allows angiography to be repeated after a short time when needed.[25]

ICGA Procedure

After dissolving crystallized ICG in 5 mL of solvent, a bolus of 25-50 mg or 1-2 mg/kg is administered via the antecubital vein. Some researchers follow this with an injection of 5 mL of sterile saline solution.

The early phase is very short, so even if no dye is observed in the fundus at 10 seconds after ICG administration, serial images should be obtained and the light level should be kept as low as possible during imaging. This reduces the "blooming artifact" (i.e., a white field that obscures detail) which occurs due to choroidal fluorescence in the first few seconds after the dye reaches the choroid. Dark images can be improved by adjusting the light and contrast during the angiography analysis phase. Immediately after the first early phase images are obtained in one eye, imaging of the fellow eye should be started. Afterwards, ICGA images should be acquired at 1-minute intervals until minute 5 and then typically at 5-minute intervals from minute 10 to 20. These intervals can be adjusted according to the characteristics of each case. Pseudostereoscopic imaging may be helpful in the analysis.

Some devices allow fluorescein angiography (FA) and ICGA to be performed simultaneously. Although this may be advantageous when interpreting the angiograms, it is rarely done in practice. A disadvantage of this method is the difficulty of revealing the exact cause of a side effect after injecting two different dyes at the same time.

ICGA recordings can also be obtained as video, which enables the determination of circulation times and a dynamic examination of the vasculature.[25] This allows the feeding vessels of vascular anomalies to be identified more easily, and can also demonstrate the pulsation feature of lesions such as polypoidal choroidal vasculopathy (PCV).

Side Effects of ICGA

ICGA has a safer side effect profile compared to FA. Moderate side effects have been reported at a rate of 1:63, serious side effects at a rate of 1:1900, and death at a rate of 1:222000 after FA.[26]

Adverse effects after the use of ICG are rare. Rates of mild, moderate, and severe reactions have been reported as 0.15%, 0.02%, and 0.05-0.07%, respectively.[27,28]

ICG dye contains up to 5% sodium iodide as an additive to prevent recrystallization. Therefore, caution should be exercised considering the potential side effects in patients with thyroid hyperfunction. Thyroid function tests performed after ICGA give inaccurate results. On the other hand, it is argued that since iodine is naturally found in the human body, there can be no risk of antibody formation or the development of an immune-mediated allergic reaction against it.[29] The allergies that develop after consuming shellfish and other seafood are attributed to the proteins in the food, not the iodine.[30]

The cause of side effects following ICGA has not been fully explained. Non-allergic histamine release due to iodine or ICG, IgE-mediated hypersensitivity, complement system activation, or the release of other inflammation mediators are suggested mechanisms.[31]

Moreover, although very rare, adequate preparation is necessary in the event of anaphylactic shock after ICG injection.[32]

Table 1. Absorption, fluorescence, and protein binding properties of indocyanine green and sodium fluorescein

	ICG	NaFl
Maximum absorption (nm)	805	465
Maximum fluorescence (nm)	835	525
Protein binding (%)	98	70-90

ICG: Indocyanine green, NaFl: Sodium fluorescein

ICG dye can also be prepared without the addition of iodine, but severe side effects have also been reported after iodine-free ICGA.[33]

As ICG separates bilirubin from protein in *in vitro* studies, it should not be administered to preterm infants and neonates who require transfusion due to hyperbilirubinemia. The indication should also be reviewed in patients with uremia, severe liver failure, or a history of severe multiple allergy (Table 2).[3]

It has been reported that ICG shows minimal passage across the placenta and that the placenta has a protective effect against its passage to the fetus.[34] Although there is no proven teratogenic effect, its indication for use in pregnancy should be carefully discussed.

Non-specific side effects following angiographic dye delivery are usually recorded as allergic reactions. This leads to the restriction of new angiographic examinations needed in the future. For this reason, it is important to reevaluate a patient's history of post-angiography side effects and other possible factors in detail.

ICGA Phases

Early phase: Filling of the choroidal arteries, choriocapillaris, and choroidal veins. It includes the few seconds after the ICG dye reaches the choroidal circulation.

Middle phase: Late venous phase, lasting up to minute 10. In this phase, contrast differences between the choroidal vessels and background fluorescence decrease slowly.

Late phase: Between 10 and 20 minutes. The fundus is dominated by homogeneous fluorescence (i.e., isofluorescence). Hypofluorescent silhouettes of the large choroidal veins are observed on this background. This phase is also called the inversion phase due to the reversal of the contrast pattern.[35]

ICGA Interpretation

The logic of ICGA and FA interpretation is similar. However, because the infrared excitation light used in ICGA penetrates beneath the RPE and ICG shows less leakage due to high plasma protein binding, the images appear more "whitish" in the early phase compared to FA in normal eyes. The contrast between the vascular structures and the background is low. ICGA interpretation should be made in conjunction with color fundus photographs and FA images from the same eye. In eyes that have undergone multimodal imaging, these data should also be considered when interpreting ICGA.

Hypofluorescence: Appears as dark or black areas caused by filling defects and blockage. Filling defects (i.e., failure of the ICG dye to reach the vessel) is mostly seen in pathologies that directly affect the circulation of the choriocapillaris. Blocked hypofluorescence is the result of a formation that prevents tissue fluorescence from reaching the imaging device. A pigmented lesion in the fundus (e.g., choroidal nevus), thick subretinal hemorrhage, or infiltrations in the choroidal stroma are the most common causes.

Hyperfluorescence: Appears as a white area. Window defect often causes the underlying vascular structures to appear brighter after thinning or atrophy of the RPE or choriocapillaris. The best example of this is that in age-related macular degeneration (AMD), large choroidal veins in atrophic areas show more hyperfluorescence than the choroidal vessels observed in other areas of the macula. Leakage can be observed in severe stromal choroiditis, although it is considerably less with ICG compared to FA. Another cause of hyperfluorescence is abnormal vessel formations, such as choroidal hemangioma or nodular formations in PCV.

Table 2. Contraindications of indocyanine green angiography

1. Thyroid gland hyperfunction
2. History of previous or suspected severe allergy
3. Severe liver failure, uremia
4. Hyperbilirubinemia
5. Pregnancy and breastfeeding

ICGA in Clinical Practice

1. Neovascular Age-Related Macular Degeneration

ICGA was used extensively in the mid-90s to visualize occult CNVs. Hyperfluorescent lesions (generally referred to as "hot spots") that appear in the middle phase and are smaller than one disc diameter were considered to be the active part of occult CNV. A larger "plaque" type lesion seen in the late phase was considered the silent or less active component of the occult CNV.[36,37] Another application area, dynamic ICGA, enabled visualization of CNV feeder vessels.[38] However, after the results of laser photocoagulation to both hot spots and feeder vessels demonstrated its limited effectiveness and the superiority of photodynamic therapy to laser photocoagulation, the use of ICGA in neovascular AMD declined.

ICGA has an important place in the differential diagnosis of neovascular AMD subgroups. ICGA can demonstrate nodular hyperfluorescent lesions in PCV and the accompanying abnormal vascular network (Figure 1).[39]

In type 3 CNV or retinal angiomatous proliferation lesions, the retinochoroidal vascular anomaly can be visualized more clearly with ICGA than FA due to the low leakage.[40]

In recent years, the causal relationship between pachychoroid (thick choroid) and neovascular AMD has been intensively studied. ICGA plays an important role in visualizing the choroidal vasculature in the macula.[41]

2. Central Serous Chorioretinopathy

Although the pathogenesis is not completely understood, exudation resulting from permeability of the choroidal vasculature in CSCR causes RPE detachment and serous retinal detachment. Areas of leakage in the choroid can be visualized in more detail with ICGA compared to FA (Figure 2). The hyperfluorescent areas detected on ICGA reveal targets for the application of photodynamic therapy. Due to their choroidal thickening, ICGA plays a central role in the differentiation of CSCR, PCV, and other pachychoroidal entities.[41,42]

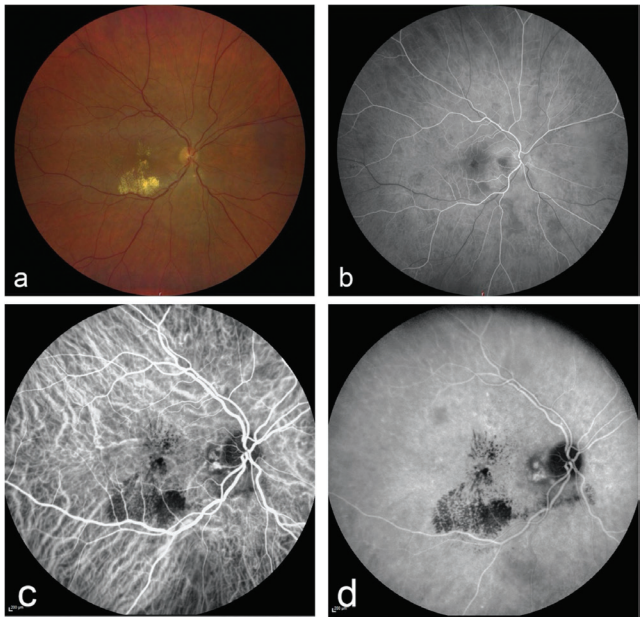

Figure 1. Polypoidal choroidal vasculopathy. (a) Color fundus photograph of the right eye posterior pole shows perifoveal lipid deposition. (b) Early-phase fluorescein shows hypofluorescence temporal to the optic disc and an arc of hyperfluorescence temporal to this lesion. (c) Mid-phase indocyanine green angiography (ICGA) (1.5 minutes) shows hyperfluorescent lesions with a nodular appearance (polypoidal lesions) temporal to the optic disc and perifoveal hypofluorescence (masking due to lipid deposition). (d) Late-phase ICGA (18 minutes) shows persistence of the temporal juxtapapillary hyperfluorescence and macular hypofluorescence

In cases of neovascular AMD that do not respond to treatment with anti-vascular endothelial growth factors, ICGA imaging is also used for the differential diagnosis of possible PCV, CSCR, or secondary CNV associated with CSCR.

3. Choroidal Inflammation

Due to the limited blocking effect of the RPE layer, ICGA plays an important role in the evaluation of inflammatory events in the choroid.[43] Diseases affecting the choriocapillary structure, such as acute posterior multifocal posterior pigment epitheliopathy (APMPPE) or multiple evanescent white dot syndrome (MEWDS), cause reduced choriocapillaris perfusion that manifests as filling defect and hypofluorescence (Figures 3, 4). Diseases that cause infiltration and granuloma formation in the choroidal stroma, such as birdshot retinochoroidopathy (Figure 5) and Vogt-Koyanagi-Harada disease (VKH), also present with hypofluorescent lesions due to blocked fluorescence. The number, shape, size, location, and laterality of hypofluorescence lesions are important in the evaluation of ICGA. Inflammations that involve the choroidal stroma and follow an aggressive course (e.g., VKH disease) may cause leakage from the large choroidal veins, resulting in diffuse hyperfluorescence and vessel staining in the choroid. If in cases of multiple white dot diseases ICGA does not yield pathognomonic features, then findings in other organ systems, retinal involvement, multimodal imaging methods (especially FA, optical coherence tomography, and autofluorescence) and demographic characteristics should also be evaluated.

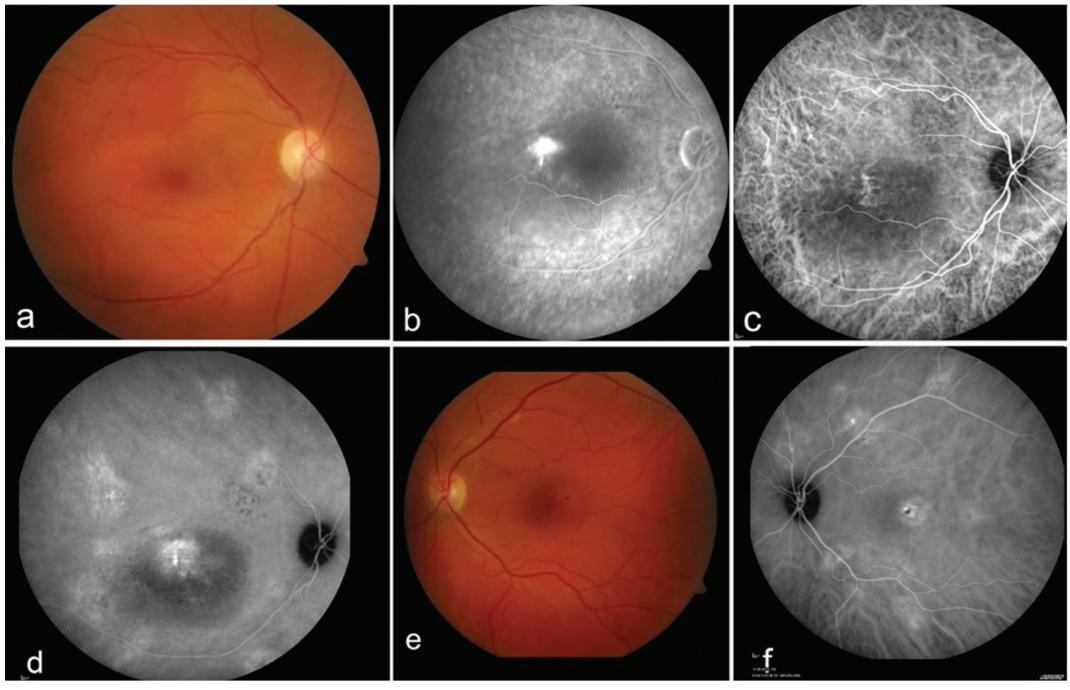

Figure 2. Central serous chorioretinopathy. (a) Color fundus image of the right eye posterior pole shows altered reflex temporal and inferior to the fovea. (b) Late-phase fluorescein angiography shows hyperfluorescence temporal to the fovea (consistent with the umbrella-like leakage of central serous chorioretinopathy). (c) Mid-phase indocyanine green angiography (ICGA) (2 minutes) shows a thick, hyperfluorescent choroidal vascular structure temporal to the fovea and an arc of hypofluorescence inferior to the macula (consistent with a possible neurosensory retinal detachment). (d) Late-phase ICGA (12 minutes) reveals multiple hyperfluorescent lesions in the posterior pole. (e) Color fundus photograph of the left eye posterior pole. (f) Mid-phase ICGA (6 minutes) reveals multiple hyperfluorescent lesions around the fovea and the major vascular arcades. This case is a good example of ICGA revealing occult lesions in an asymptomatic eye

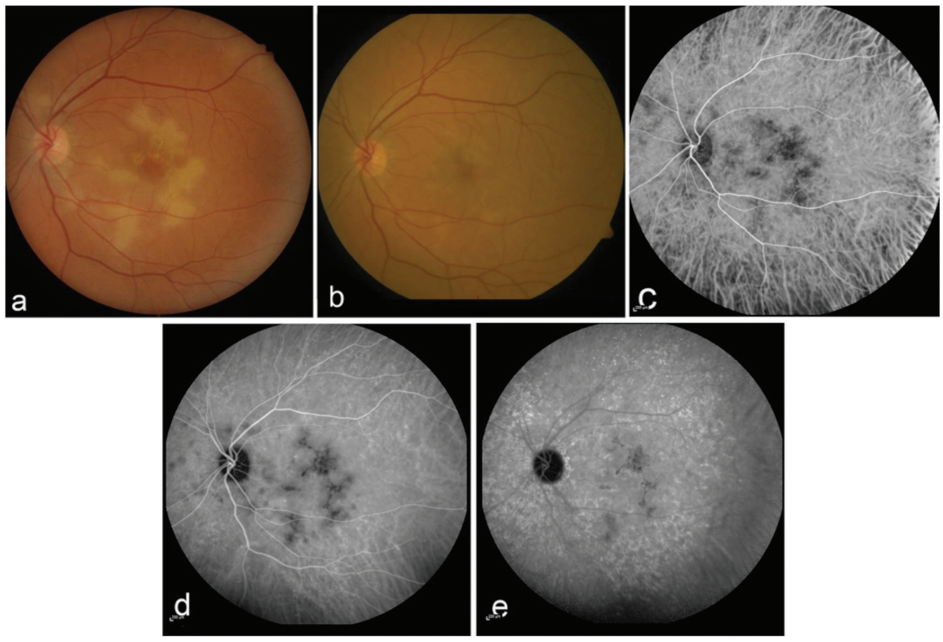

Figure 3. Acute posterior multifocal placoid pigment epitheliopathy. (a) At initial presentation, color fundus photograph of the posterior pole (left eye) showed granular pigment epithelial changes in the fovea and multiple white/cream-colored lesions in the deeper retinal layers in the perimacular and parapapillary areas. (b) After 6 weeks, color fundus photograph of the posterior pole demonstrated changes in the fovea and perifoveal granular pigment epithelium. The cream-colored lesions were not observed. (c) Early-phase indocyanine green angiography (ICGA) (11 seconds) performed at 6 weeks showed multiple macular and peripapillary hypofluorescent lesions (hypofluorescence consistent with filling defects due to choriocapillary ischemia). (d) In mid-phase ICGA (4 minutes), an increased number of hypofluorescent lesions were observed as a result of the difference in contrast from the background isofluorescence. (e) In late-phase ICGA (14 minutes), the hypofluorescent lesions decreased in number and size (likely due to reperfusion from the intact choriocapillary tissue surrounding the lesions)

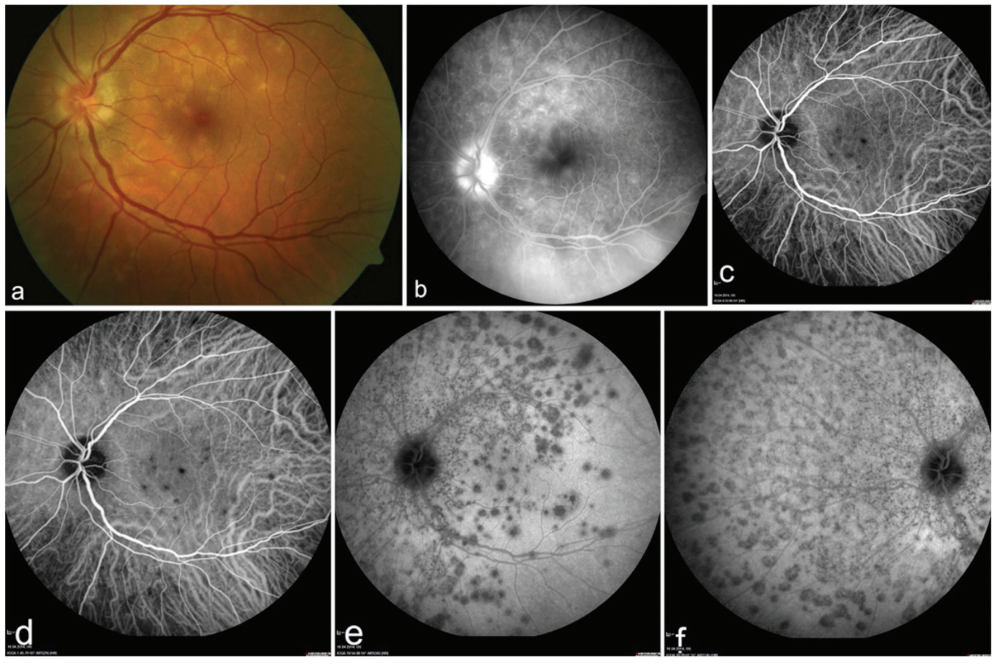

Figure 4. Multiple evanescent white dot syndrome (MEWDS). (a) Color fundus photograph of the posterior pole (left eye) shows numerous hypopigmented lesions. The optic disc margin is ill-defined. (b) Late-phase fluorescein angiography shows optic nerve head staining and diffuse hyperfluorescence in the posterior pole. (c) Early/mid-phase indocyanine green angiography (ICGA) (1 minute) shows small, barely visible hypofluorescent lesions. (d) In mid-phase ICGA (4 minutes), the hypofluorescent lesions in the macula become more evident as a result of increased contrast difference. (e) Late-phase ICGA (14 minutes) reveals numerous small hypofluorescent lesions in the posterior pole that did not appear in previous phases. (f) Late-phase ICGA (14 minutes) also shows numerous small hypofluorescent lesions nasal to the papilla. This case example of MEWDS demonstrates phase-specific differences in findings and the importance of imaging nasal to the papilla (and also in all fundus quadrants)

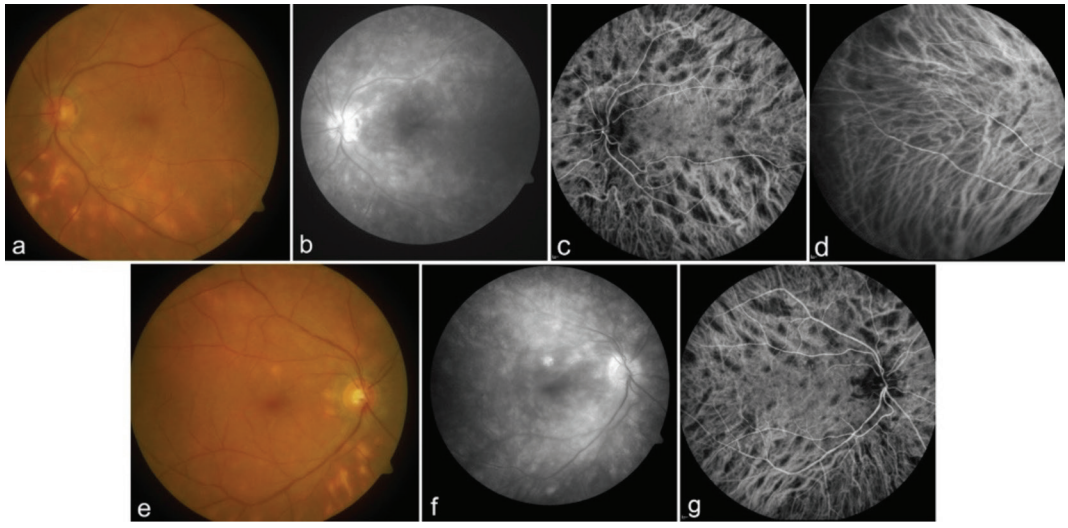

Figure 5. Birdshot chorioretinopathy. (a) Color fundus photograph of the posterior pole (left eye) shows numerous hypopigmented subretinal lesions around the inferior major arcade. (b) Late-phase fluorescein angiography (FA) shows diffuse hyperfluorescence due to leakage in the optic nerve head and posterior pole. (c) Early/mid-phase indocyanine green angiography indocyanine green angiography (ICGA) (30 seconds) reveals numerous oval hypofluorescent lesions resembling rice grains in the macula. (d) Mid-phase ICGA (4 minutes) shows scattered hypofluorescent lesions in the nasal middle periphery. (e) Color fundus photograph of the posterior pole (right eye) shows hypopigmented lesions in the macula and along the major arcades. (f) Late-phase FA shows diffuse hyperfluorescence due to leakage at the optic nerve head margin and the posterior pole. (g) Early/mid-phase ICGA (35 seconds) showed numerous oval hypofluorescent lesions resembling rice grains in the macula. The similarity of ICGA images in both eyes is important for the diagnosis of birdshot chorioretinopathy

4. Intraocular Tumors

The most important contribution of ICGA is in the diagnosis of choroidal hemangiomas. ICGA particularly helpful in the differential diagnosis of thin, amelanotic fundus tumors and choroidal metastases from choroidal hemangioma.[19,44] In the choroidal filling phase, the tumor shows rapid, bright hyperfluorescence. In the late phase, the intensity of hyperfluorescence decreases as the ICG dye leaves the vessels ("wash-out phenomenon"). This feature enables the differentiation of choroidal hemangioma from amelanotic malignant melanoma of the choroid (Figure 6).

In cases where FA is insufficient or cannot be applied, ICGA also facilitates the examination of vascular tumors of the fundus. Due to rapid leakage and masking, FA has limited ability to determine the topographic location and vascular structure of pathologies that present with intense exudation at the papillary margin and retinal thickening. ICGA is advantageous in recognizing lesions because of the deep penetration and low leakage of ICG. Thus, it aids in the differential diagnosis of masses and pathologies around the optic disc, such as juxtapapillary retinal capillary angioma, PCV, and CNV.

5. Hemorrhagic Diseases of the Fundus

Retinal arterial macroaneurysms may cause bleeding in the posterior segment. They may be located in the inferior or superior temporal arcade and can usually be recognized as white-yellowish round formations along the arteries. However, in cases where intense hemorrhage covers the lesion or blocks FA, ICGA can be used to visualize the vascular anomaly despite bleeding. Distinguishing retinal artery macroaneurysms from CNV and PCV in hemorrhages localized to the macula is an important area of use of ICGA.

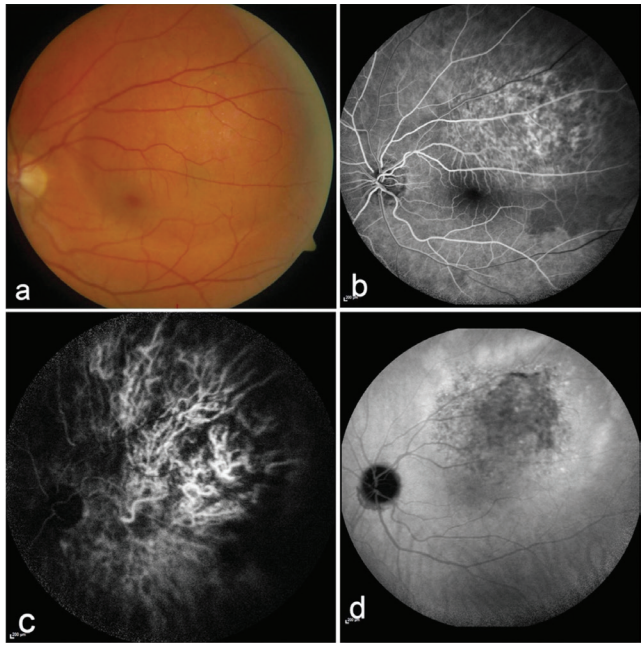

Figure 6. Choroidal hemangioma. (a) Color fundus photograph of the posterior pole (left eye) shows a subretinal red-orange colored lesion in the superior half of the macula. (b) Early-phase fluorescein angiography shows a large number of linear hyperfluorescent lesions in the upper half of the macula and above the superior major arcade (pathological tumor vasculature is observed because of reduced masking due to retinal pigment epithelium atrophy. These lesions could not be observed with a healthy retinal pigment epithelium). c) Early-phase indocyanine green angiography (ICGA) (12 seconds) demonstrates early hyperfluorescence of the pathological tumor vasculature in the superior part of the macula. (d) In late-phase ICGA (15 minutes), the lesion superior to the macula appears as a hypofluorescent area due to the dye leaving the eye (wash-out phenomenon). ICGA is an important diagnostic tool for choroidal hemangioma because of its hyperfluorescent vasculature in the very early phase and wash-out phenomenon in the late phase

ICGA is also used as a diagnostic tool for the differentiation of CNV, PCV, and vasoproliferative retinal tumors in eyes with large hemorrhagic lesions in the peripheral fundus (Figure 7).

6. Unexplained Vision Loss

In patients with unexplained vision loss, ICGA can be performed if choroidal involvement is suspected and other multimodal diagnostic methods are inconclusive.

Conclusion

Despite the important role in the physiopathology of the eye, diagnostic methods that examine the choroidal circulation have not been incorporated in routine ophthalmological diagnosis with the same intensity. This deficiency arose more from limitations of the techniques used rather than a disregard for their function. Although ICGA was introduced to ophthalmology in the 1970s, technical challenges delayed its development. Recently developed devices with high time and space resolution capacity have provided excellent image quality. The need for sophisticated and expensive imaging devices and experienced practitioners constitutes the main barriers to the wider adoption of ICGA in clinical practice. Despite all of these difficulties, the information it provides has made ICGA an important component of multimodal imaging in the examination of the fundus.

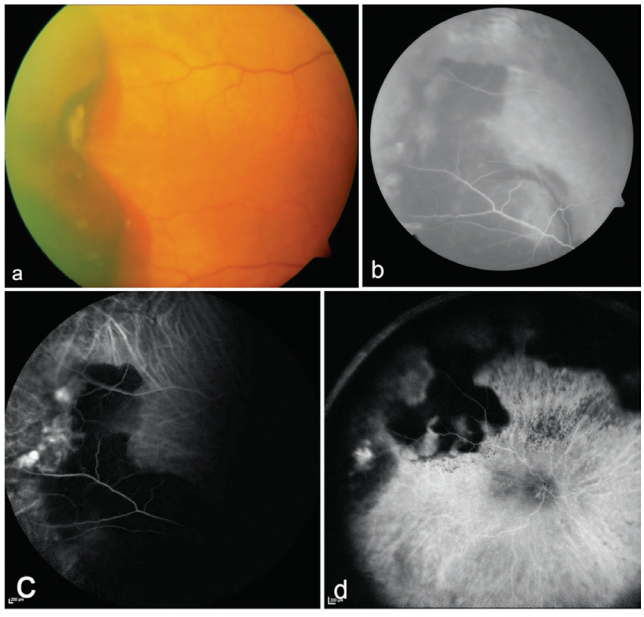

Figure 7. A peripheral hemorrhagic lesion. (a) Color fundus photograph of the temporal mid-periphery (right eye) shows a subretinal hemorrhagic lesion. (b) Late-phase fluorescein angiography shows hypofluorescence due to the hemorrhage and hyperfluorescence with indistinct borders at its periphery. (c) Mid-phase indocyanine green angiography (ICGA) (3 minutes) shows nodular hyperfluorescent lesions at the periphery of the hemorrhagic masking and branching vessels between them. This appearance is consistent with peripheral polypoidal choroidal vasculopathy. (d) A wide-angle image of late-phase ICGA (13 minutes) shows leakage from the temporal lesion and large areas of hypofluorescence due to hemorrhage in the upper peripheral quadrants

Ethics

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Embedded Episcleral Foreign Body Mimicking Nodular Anterior Scleritis

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Abstract

A 56-year-old man was referred to our clinic for unilateral nodular scleritis unresponsive to systemic corticosteroids. A localized, nodular hyperemia on the nasal bulbar conjunctiva surrounding a central cyst-like lesion together with vascular engorgement was observed on slit-lamp examination of the left eye. No abnormal fundoscopic findings were noted. Surgical exploration revealed an embedded episcleral brown colored, soft to touch, splinter-like organic foreign body (FB) which was confirmed by the histopathological examination. Nodular hyperemia resolved during the postoperative follow-up period, and mild scar tissue accompanied by scleral thinning developed in the left nasal bulbar conjunctiva. Ocular injury associated with FBs may cause significant ocular morbidity depending on the nature and location of the FB. Severe visual disability may occur if left untreated. Subconjunctival FBs are rare and may present with a clinical picture mimicking episcleritis or scleritis. History of trauma involving a FB should always be assessed for an accurate differential diagnosis and appropriate management of patients with anterior scleritis.

Keywords: Foreign body, nodular scleritis, ocular trauma

Introduction

Ocular injury involving a foreign body (FB) may impose significant ocular morbidity and visual disability depending on the extent of the injury as well as the nature and location of the FB.[1] A superficial FB in the conjunctiva or cornea can be easily detected and removed, and thus may not cause much harm if treated appropriately without delay.[2] Subconjunctival FBs are relatively rare, commonly missed, and may present as FB granuloma.[3] Even if they are visible, their extent in deeper tissue is difficult to assess.[4]

Scleritis is an inflammatory condition usually associated with systemic immunological disorders.[5] Anterior scleritis may be diffuse or nodular and is characterized by pain and hyperemia. Nodular scleritis is the second most common clinical presentation of anterior scleritis, accounting for approximately 20% of cases.[6] The differential diagnosis of anterior scleritis includes episcleritis and severe microbial conjunctivitis. Rarely, FB-induced episcleral granulomas can mimic nodular anterior scleritis.[7]

We hereby report a patient who was referred for nodular anterior scleritis unresponsive to systemic corticosteroids for 2 months who was found to have an embedded episcleral organic FB.

Case Report

A 56-year-old male agricultural worker was referred for unilateral nodular scleritis unresponsive to systemic corticosteroids. He was suffering from pain and hyperemia in his left eye for nearly 2 months. His history did not reveal any trauma or systemic disease. Systemic workup done before referral was unremarkable.

Best corrected visual acuity was 20/20 in both eyes on Snellen chart. There was localized nodular hyperemia on the nasal bulbar conjunctiva surrounding a central cyst-like lesion and moderate vascular engorgement in the left eye (Figure 1). The rest of the slit-lamp examination was unremarkable for both eyes. No suppuration or necrosis was noted. Conjunctival

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hyperemia did not resolve following the instillation of 2.5% topical phenylephrine (Mydfrin®, Alcon, Geneva, Switzerland). Intraocular pressures were 12 mmHg in the right and 13 mmHg in the left eye. Fundoscopy revealed no abnormal findings.

The patient was already receiving 15 mg/day systemic steroids (Deltacortril®, Pfizer, New York, United States). Topical moxifloxacin (Vigamox®, Novartis, Basel, Switzerland) 5 times a day and dexamethasone (Maxidex®, Alcon, Geneva, Switzerland) twice a day were added. Systemic work-up to rule out any systemic infectious or inflammatory background was negative. Since there was no response to topical and systemic therapy after 10 days, surgical examination and exploration of the inflamed area under local anesthesia was planned. The bulbar conjunctiva adjacent to the lesion was cut with Westcott scissors and carefully undermined. A brown colored, soft to touch, splinter-like FB (most likely organic in nature) was embedded in the episcleral tissue. An excisional biopsy of the conjunctiva and episclera involving the whole lesion was performed. The defect was covered with a conjunctival autograft. The patient was given ofloxacin (Exocin®, Allergan, Dublin, Ireland) and loteprednol (Lotemax®, Bausch & Lomb, Laval, Canada) 3 times a day postoperatively. Systemic corticosteroid treatment was tapered rapidly.

Histopathological examination confirmed the presence of a brownish organic FB and revealed some degree of surrounding lymphohistiocytic infiltrate with giant cells (Figure 2).

The patient was seen at 1 week, 1 month, 3 months, and 6 months postoperatively. Topical loteprednol was tapered gradually and switched to topical cyclosporine 0.05% (Restasis®, AbbVie, North Chicago, United States). Best corrected visual acuity was 20/20 and slit-lamp exam revealed no recurrent inflammation at the excision site during 6 months of follow-up. Full ophthalmological examination revealed no abnormal findings except for mild scar tissue at the nasal bulbar conjunctiva and mild scleral thinning in the left eye (Figure 3).

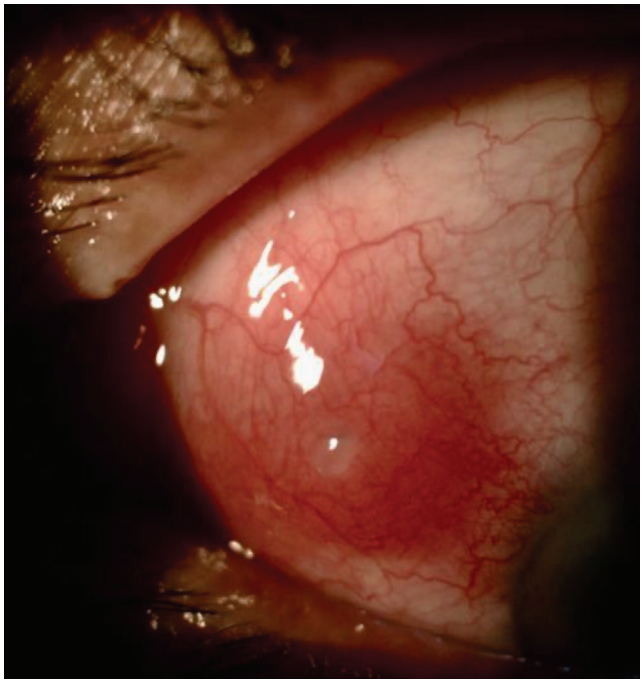

Figure 1. A focal nodular anterior scleritis-like appearance was observed on slit-lamp examination of the left eye at the first visit

Discussion

Intraocular FBs may present with various clinical manifestations and affect both the anterior and posterior segments of the eye.[1,8] Young male workers are the most frequently affected patient group due to work accidents.[8]

Detection of intrascleral/episcleral FBs may not be easy on slit-lamp examination due to the presence of a small penetrating wound covered by a large subconjunctival hemorrhage accompanied by minimal or no signs of inflammation.[1] However, underlying inflammation may ensue and the patients may present with a clinical picture resembling scleritis, as in our case.

FB granuloma formation on the episcleral/scleral surface is rare. A scleritis-like clinical presentation of FBs has been previously reported in the literature. Khoo et al.[7] reported a 45-year-old female who developed a suture-related granulomatous reaction related to a previous strabismus surgery and presented with a clinical manifestation of scleritis. Kapoor et al.[9] also published a 36-year-old male who presented with a scleritis-like clinical presentation after a motorcycle accident. Topical and systemic corticosteroid and antibiotic treatments were not able to control inflammation; therefore, surgical intervention and FB removal were necessary in both of these cases. An intraorbital wooden FB was detected in the second case. Coelho et al.[10] also reported a 76-year-old male who underwent nasal pterygium surgery and subsequently developed focal necrotizing scleritis secondary to FB entrapment under the conjunctival autograft. They treated the patient with FB removal and a conjunctival graft. Focal scleral melting continued to progress, and the patient was placed under

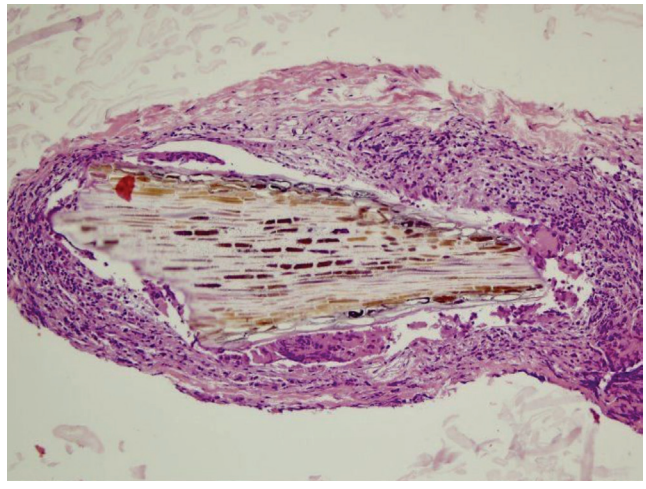

Figure 2. Histopathological examination of the episcleral biopsy revealed organic material (wood) surrounded by lymphohistiocytic infiltration and foreign body giant cells (original magnification x20, hematoxylin & eosin staining)

systemic corticosteroid therapy together with an amniotic membrane graft surgery. Sen et al.[11] reported a 5-year-old girl who was misdiagnosed as relapsing conjunctivitis for 1 year. During examination performed under general anesthesia, a 1.5 cm-long grass inflorescence located beneath the conjunctiva was discovered and successfully extracted.

FBs may be classified as metallic and non-metallic.[12] They both possess various risks if left untreated. Iron-containing metallic FBs have been associated with ocular siderosis, while the organic subgroup of non-metallic FBs can incite acute inflammation that is likely to become chronic with serious consequences.[13,14] Moreover, these organic materials encourage the growth of various microbes and can lead to severe infectious complications such as orbital cellulitis, periorbital abscess, central nervous system extension, endophthalmitis/panophthalmitis, orbitocutaneous fistula, granuloma formation, and injury to the optic nerve and extraocular muscles if left untreated.[15]

Episcleritis, which refers to inflammation of the superficial episcleral tissues and blood vessels, is the primary condition that needs to be differentiated from scleritis. When 2.5% topical phenylephrine is administered to the affected eye, superficial blood vessels will constrict and exhibit blanching in episcleritis, but deep hyperemia remains unaffected in scleritis.[16] Upon diagnosing scleritis, a comprehensive evaluation for potential infectious and immunological factors should precede the commencement of treatment. Furthermore, as exemplified by the present case, it is important to consider the potential presence of an FB.

Whenever the diagnosis of anterior scleritis is presumed, the presence of an FB should always be ruled out for an accurate differential diagnosis and appropriate management. Surgical exploration might be necessary in addition to careful history-taking and clinical examination to detect scleral/episcleral FBs in particular.

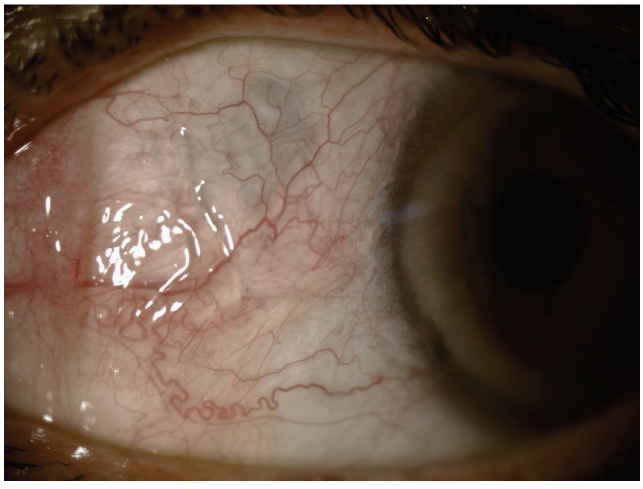

Figure 3. Slit-lamp examination of the left eye at the last visit showed mild conjunctival scar tissue with underlying scleral thinning

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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

A Rare Association: Neovascular Glaucoma Accompanying Anterior Chamber Synchysis Scintillans

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Abstract

Synchysis scintillans, also known as cholesterolosis bulbi, is a degenerative eye pathology characterized by the accumulation of cholesterol crystals in the vitreous. It is typically observed bilaterally but can rarely be unilateral. It can be triggered by severe trauma, chronic inflammation, chronic retinal detachment, hyphema, vitreous hemorrhage, Coats' disease, and retinoblastoma. In this report, we present a case with an uncommon association of anterior chamber synchysis scintillans and neovascular glaucoma.

Keywords: Anterior chamber, cholesterolosis bulbi, neovascular glaucoma, retinal detachment, synchysis scintillans

Introduction

Synchysis scintillans is an uncommon degenerative ocular condition.[1,2,3,4] This entity is also known as cholesterolosis bulbi due to the presence of cholesterol crystal accumulations in the vitreous humor, resulting in the appearance of small, reflective opacities in the posterior segment of the eye.[2,3,4] The crystals observed in synchysis scintillans have been confirmed via chromatography to be pure cholesterol,[5] and they move freely in a gravity-dependent manner, creating a snow globe-like effect.[6] The condition can be caused by severe trauma, chronic inflammation, chronic retinal detachment, hyphema, vitreous hemorrhage, Coats' disease, and retinoblastoma.[2,3,4,6,7,8] Although synchysis scintillans is typically observed in eyes with severe disease, it is often discovered incidentally as an asymptomatic finding.

Limited epidemiological studies have been conducted on synchysis scintillans, but the available literature suggests that it is a relatively rare condition.[4] It usually presents in the third decade of life, although cases have been reported in individuals of all ages.[4] Bilateral presentation is typical, while unilateral occurrence is extremely rare.[2,4]

Although synchysis scintillans is typically observed in the vitreous cavity, there have been rare reports of anterior chamber cholesterolosis.[3,4,7,8,9] The underlying causes of synchysis scintillans in the anterior chamber are not well-established, but some theories suggest that cholesterol crystals may either form in the anterior chamber following hyphema or more commonly pass from the posterior segment to the anterior segment.[4,8,9] Additionally, synchysis scintillans can arise in the anterior chamber due to long-term synchysis.[4]

Herein, we report an extremely unusual presentation in the form of anterior chamber synchysis scintillans in a patient with neovascular glaucoma secondary to chronic diabetic tractional retinal detachment.

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Case Report

A 45-year-old man presented with a 5-year history of vision loss and a 1-week history of pain in his left eye. His medical history revealed type 1 diabetes mellitus, and his ophthalmological history revealed panretinal photocoagulation in the right eye for proliferative diabetic retinopathy and phacoemulsification surgery combined with pars plana vitrectomy in the left eye for tractional retinal detachment 5 years ago. His best corrected visual acuity was 20/25 on the right and no light perception in the left eye. Anterior segment examination was unremarkable in the right eye. Slit-lamp examination of the left eye revealed posterior chamber intraocular lens, rubeosis iridis, and anterior chamber synchysis scintillans presenting as multiple free, mobile, polychromatic, shiny cholesterol crystals (Figure 1, 2). Intraocular pressure was 13 mmHg in the right and 43 mmHg in the left eye. Dilated fundus examination revealed panretinal photocoagulation scars along with regressed neovascularization in the right (Figure 3) and tractional retinal detachment in the left eye. Anterior chamber injection of 1.25 mg bevacizumab (Altuzan, Roche, Germany) was performed and topical dorzolamide-timolol fixed combination (Oftomix, Bilim İlaç, İstanbul, Türkiye) and brimonidine (Alphagan P, AbbVie, İstanbul, Türkiye) were initiated twice daily. His clinical follow-up was stable for both eyes with no pain in the left eye for 3 years, and no additional bevacizumab injection was needed.

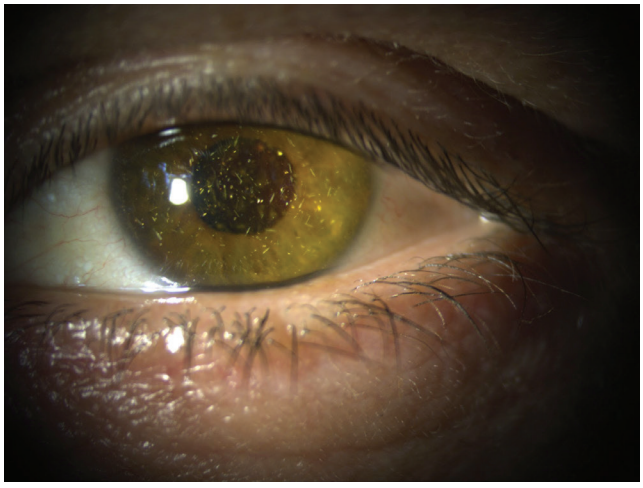

Figure 1. Anterior segment photograph of the left eye

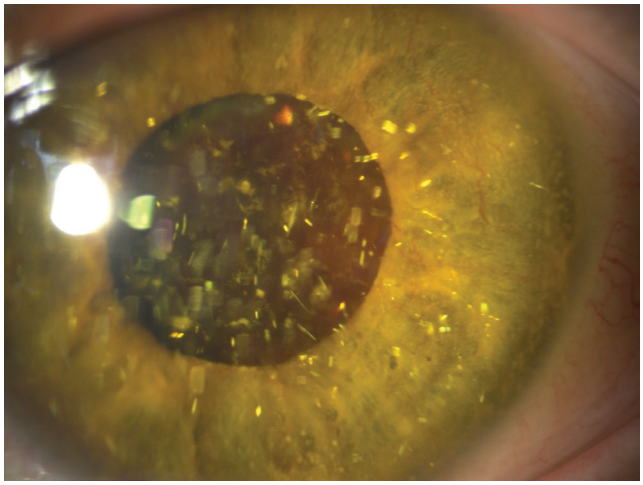

Figure 2. Anterior segment photograph of the left eye revealed anterior chamber synchysis scintillans, rubeosis iridis, and posterior chamber intraocular lens

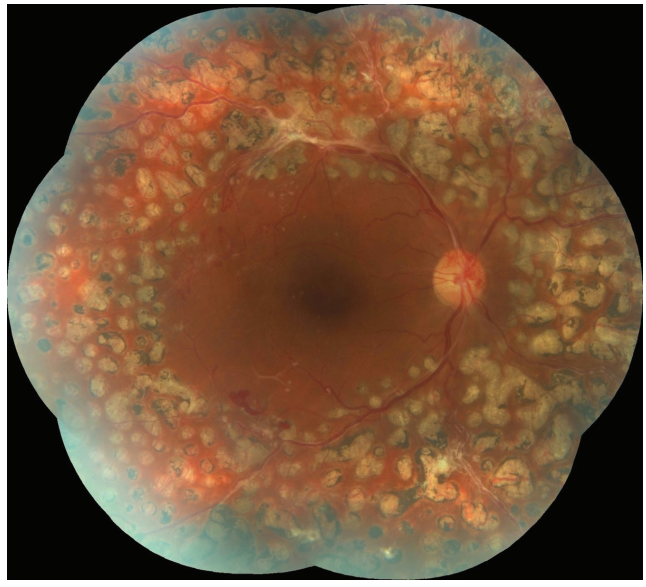

Figure 3. Fundus photograph of the right eye showing panretinal photocoagulation scars along with regressed neovascularization

Discussion

Synchysis scintillans, also known as cholesterolosis bulbi, is an uncommon condition.[1,2,3,4] Parfait-Landrau first reported the presence of sparkling crystals in the human ocular vitreous body in 1828, and three years later Schmidt determined these crystals were made of cholesterol.[8] Synchysis scintillans is thought to be caused by a variety of factors, including hemorrhage, trauma, and chronic inflammation.[2,3,4,7,8] Although the pathogenesis of anterior chamber synchysis scintillans is not well understood, it is believed to occur either due to the formation of cholesterol crystals following hyphema, or the migration of cholesterol crystals from the posterior segment to the anterior chamber.[4,7] The anterior passage of posterior crystals is facilitated by factors such as pre-existing trauma, aphakia, pseudophakia, and subluxation of the lens.[4] The major source of intraocular cholesterol crystals is probably degrading extravascular blood.[4] Postprandial or familial hyperlipemia may play a role in the formation of cholesterol crystals following vitreous hemorrhage or hyphema.[4,8] However, some authors argue that there is no correlation between cholesterolosis bulbi and blood cholesterol levels.[9,10] Additionally, neovascularization and repeated hemorrhages in a diabetic eye prone to bleeding may create a hyperlipemic environment that facilitates synchysis

scintillans, which is probably the underlying cause in our presented patient.

In the vitreous cavity, synchysis scintillans should be differentially diagnosed from asteroid hyalosis, a degenerative condition of the vitreous.[10,11] Unlike synchysis scintillans, which is composed of cholesterol crystals, asteroid hyalosis is composed of hydroxyapatite and phospholipids. In the anterior chamber, both phenomena may appear similarly as pseudohypopyon.[10,11] A definite diagnosis of cholesterol crystals can be confirmed through histopathological examination, which reveals the characteristic birefringence of cholesterol crystals under polarized light and positive staining with lipid stains such as oil red O.[10,11] Nevertheless, clinical diagnosis of cholesterol crystals is also relatively easy due to their typical characteristics and limited differential diagnosis, which includes calcium oxalate crystals, proteinaceous crystals, and aqueous cells. Cholesterol crystals are easily distinguishable due to their polychromatic appearance and larger size compared to these other substances.[10,11]

Although we could not confirm the differential diagnosis from asteroid hyalosis by histopathological examination, the clinical findings were suggestive of synchysis in this case. While synchysis scintillans is seen in a younger age group, asteroid hyalosis is commonly observed in older adults. Asteroid hyalosis is rarely associated with other pathologies, whereas synchysis is usually secondary to other ocular diseases or tumors. Moreover, synchysis freely moves and falls to the vitreous floor due to gravity, whereas asteroid hyalosis moves with the vitreous and returns to its original position. The patient in this case was young and had proliferative diabetic retinopathy, and the clinical presentation was consistent with synchysis. These clinical findings strongly supported the diagnosis of synchysis. Only the unilateral presentation observed in this case is atypical of synchysis, which is usually bilateral.

In conclusion, anterior chamber synchysis scintillans is an extremely rare ocular pathology that may occasionally be encountered in a patient with neovascular glaucoma.

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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Letter to the Editor Re: Predictive Factors of Complications and Visual Outcomes after Pediatric Cataract Surgery: A Single Referral Center Study from Türkiye

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Keywords

Congenital cataract, aphakia, visual outcomes, complications, posterior optic capture

Dear Editor,

We have read Dericioğlu et al.'s[1] study entitled "Predictive Factors of Complications and Visual Outcomes after Pediatric Cataract Surgery: A Single Referral Center Study from Türkiye" with great interest. However, we would like to share with our colleagues some issues that we believe will be useful for the entire readership and are important to clarify.

Pediatric cataract surgery involves serious intraoperative and postoperative complications, and the management of surgery remains a challenging issue for surgeons.[2] The first of these problems is whether the patient will be left aphakic or an intraocular lens (IOL) will be implanted. The authors left some of the patients older than 12 months (group IIA, n=21 eyes) as aphakic. Among these patients, were there cases in which the integrity of the capsular bag was completely disrupted and was scleral IOL fixation considered in these cases? On the other hand, according to their results, pseudophakic eyes (0.49±0.40 logarithm of the minimal angle of resolution [logMAR]) had significantly better final best-corrected visual acuity than aphakic eyes (0.65±0.59 logMAR). This reflects that IOL implantation is important for better visual outcomes in patients older than 12 months.

The authors reported pupillary membrane development in 5 cases (4 [10.5%] in group 1 and 1 [4.8%] in group 2), and the postoperative treatment protocol included the use of 1% prednisolone acetate four times a day for one month. To avoid this complication, we would like to underline that, in addition to a more intense topical anti-inflammatory treatment protocol, intraoperative intracameral triamcinolone acetonide, which we frequently use in pediatric cataract surgery in our clinical practice, can be extremely beneficial.[3,4]

On the other hand, the authors performed posterior continuous curvilinear capsulorhexis (CCC) in all cases and stated that they did not perform anterior vitrectomy except

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for unintentional anterior hyaloid rupture. They also reported visual axis opacification in 8 cases (4 [10.5%] in group 1 and 4 [19.0%] in group 2) in the postoperative period. In order to overcome this problem, prevent visual axis opacification, and avoid serious vitreous-related complications after anterior vitrectomy, it has been reported that posterior optic capture (optic capture buttonholing) combined with posterior CCC can be an effective and safe alternative, without routinely performing anterior vitrectomy.[5]

Once again, we congratulate the authors for this new and different study, and we think that prospective, randomized advanced clinical studies with more pediatric cataract patients from multiple centers in the future will further shed light on this issue.

Ethics

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Reply

We would like to thank Dr. Uçar for his insightful comments and interest in our study titled "Predictive Factors of Complications and Visual Outcomes after Pediatric Cataract Surgery: A Single Referral Center Study from Türkiye."[1] His observations and suggestions are valuable contributions that merit further discussion and consideration within the context of pediatric cataract surgery.

Regarding the management of patients older than 12 months left aphakic in our study, we appreciate your query concerning cases where the integrity of the capsular bag was disrupted, possibly necessitating scleral intraocular lens (IOL) fixation. We excluded patients who underwent secondary IOL implantation, and among the cases where patients were left aphakic, there were no instances of complete capsular bag disruption that warranted scleral IOL fixation in the primary surgery. However, we acknowledge the significance of this consideration and its potential impact on surgical outcomes, particularly in cases involving compromised capsular integrity, which could benefit from scleral IOL fixation method.[2]

This retrospective study covers a period of 10 years, and although IOL implantation was performed in some patients during this period, our clinic's protocol for pediatric cataract cases primarily involves utilizing aphakic contact lenses for patient follow-up. In addition, as stated in the methodology section, select patients received IOLs primarily based on socioeconomic considerations and the potential impracticability of employing contact lenses. The debate about the optimal approach -aphakic versus IOL implantation- for pediatric cataracts continues. Notably, a large-scale prospective study discouraged routine IOL implantation in children under the age of 2 years.[3] Conversely, a recent meta-analysis suggests that IOL implantation results in better visual acuity but with an increased risk of visual axis opacification.[4] Consequently, we advocate for larger-scale studies to comprehensively elucidate this intricate issue.

The use of intracameral triamcinolone in pediatric cataract cases is routinely performed in our clinic following the completion of posterior curvilinear capsulorhexis (PCC). However, your suggestion of a more intense topical anti-inflammatory treatment, along with intraoperative intracameral triamcinolone acetonide subsequent to both PCC and viscoelastic removal holds promise in potentially reducing such complications. Moreover, studies investigating posterior optic capture alongside PCC have reported fewer fibrinous complications, while randomized prospective studies have demonstrated comparable long-term outcomes between IOL implantation in the capsular bag and the mentioned technique.[5,6] In addition to the methodology employed in this single-center retrospective study, investigating the posterior optic capture technique may hold significance in the management of fibrin reactions in pediatric cataracts.

We appreciate your commendation of our study and concur that prospective, randomized advanced clinical studies encompassing a larger cohort from multiple centers will significantly enhance our understanding of pediatric cataract surgeries. The collaboration among various centers in future studies will undoubtedly provide more comprehensive insights and further elucidate the complexities associated with this intricate surgical domain.

Ethics

Authorship Contributions

Surgical and Medical Practices: E.Ç., Concept: V.D., M.O.S., E.B.V., E.Ç., Design: V.D., M.O.S., E.B.V., E.Ç., Data Collection or Processing: V.D., E.B.V., Analysis or Interpretation: V.D., M.O.S., E.Ç., Literature Search: V.D., E.B.V., Writing: V.D.

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Erratum

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The mistake was made inadvertently by the author.

The ORCID-ID number of the corresponding author mentioned in the "Address for Correspondence" section on page 115 of the relevant article is corrected as follows:

Incorrect ORCID-ID number:

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