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April 23rd

National Sovereignty and Children's Day

"Children are the assurance of our future and a source of joy and merriness."
Mustafa Kemal Atatürk

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AT A GLANCE

2025 Issue 2 at a Glance:

Esteemed colleagues,

In the second issue of 2025, the Turkish Journal of Ophthalmology includes five original articles, one review, two case reports and a letter to the editor.

In a study by Akagün and Altıparmak titled "Evaluation of Reasons for Discontinuation of Atropine 0.01% in Myopia Management: A Single-Center Retrospective Study from Türkiye", the need to renew the medication every month emerged as the factor that most affected treatment adherence, especially among girls. Other factors such as light sensitivity and treatment duration also played a role in treatment discontinuation but had less impact compared to difficulty acquiring the drug. The study highlights the need to develop more practical medication protocols and adopt supportive approaches tailored to the specific needs of families to increase adherence to treatment (See pages 61-66).

In their study titled "Comparison of Humphrey 24-2 SITA Standard, SITA Fast, and SITA Faster Test Strategies in Patients with Glaucoma", Köksaldı et al. found that the SITA Faster test had significantly shorter test duration, but there was no statistically significant difference between the three methods in terms of the depth and width of visual field defects. Although the findings suggest that the SITA Faster test is a reliable time-saving alternative, further studies are needed to evaluate the safety of its widespread use (See pages 67-73).

In a study titled "Microvascular and Ultrastructural Changes of the Retina and Choroid in Patients with Sickle Cell Anemia", Oruz et al. identified proliferative sickle cell retinopathy as an important risk factor for macular involvement. Significant changes such as foveal avascular zone enlargement and decreased vascular density were detected even in individuals without macular damage. Preventing such damage with early monitoring is critical for visual prognosis, and optical coherence tomography angiography imaging was shown to be an effective method for revealing these changes (See pages 74-81).

In their study titled "The Effect of Internal Limiting Membrane Peeling on Anatomical and Visual Outcomes in Patients with Macula-Off Retinal Detachment", Bağcı et al. showed that internal limiting membrane peeling performed in macula-involving retinal detachment was effective in preventing epiretinal membrane development but did not significantly contribute to visual recovery. Despite the role of surgical strategies in achieving anatomical success, these results point to the importance of long-term data in terms of preserving visual function (See pages 82-85).

In a study titled "Outcomes of Eye Examination and Vision Screening in Term Infants Presenting to a Tertiary Hospital in Türkiye", Zorlutuna Kaymak et al. observed that although family physicians and pediatricians knew the importance of the red reflex test, there were deficiencies in the application and interpretation of this test. Increasing education and awareness is recommended to enable clinicians to perform ophthalmological examinations more effectively in pediatric check-ups. In addition, the authors emphasized that the issue of whether to perform dilated fundus examination in healthy infants should be clarified according to national policies and patient profile, and further studies on this topic are needed (See pages 86-91).

In their review titled "Rational Drug Use in Extraocular Surgeries", Açar and Aslan Katırcıoğlu question the necessity and effectiveness of antibiotic prophylaxis in extraocular surgeries. Although it is known to be effective in reducing the risk of infection in some surgical interventions, the authors examined a wide range of extraocular surgeries in which antibiotic use is not necessary for every operation. While agents such as mitomycin-C and interferon alpha-2b have been shown to reduce recurrence rates and increase surgical success, it was emphasized that large, multicenter comparative studies are needed to generalize these results (See pages 92-98).

In the first case report of this issue, Özkan et al. reported the first case of bilateral chorioretinitis, unilateral foveal edema, and optic nerve damage after acute West Nile Virus (WNV) infection in Türkiye. The diagnosis was made in the absence of neurological involvement, based only on ocular symptoms. These findings highlight the importance of recognizing fundus findings specific to WNV chorioretinitis, especially for clinicians working in endemic areas (See pages 99-104).

In their case report titled "Progressive Loss of Myelinated Retinal Nerve Fibers in a Case of Open-Angle Glaucoma", Jurkiewicz et al. associated the gradual loss of previously observed myelinated retinal nerve fibers with progressive optic nerve damage resulting from open-angle glaucoma. This phenomenon may indicate retinal ganglion cell layer damage and requires investigation of underlying causes such as ischemic attacks, Behçet's disease, and pituitary adenoma. The authors emphasized that anatomic rarefication of myelinated retinal nerve fibers may be an important sign of progressive optic neuropathies and should prompt clinicians to conduct further examinations (See pages 105-108).

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AT A GLANCE

In their letter to the editor titled "Bilateral Keratoconus in Diffuse Cutaneous Systemic Sclerosis: A Rare Presentation - Is There Any Role of Autoimmunity?", Sadhu et al. discuss the role of inflammatory and autoimmune processes in keratoconus pathogenesis and note that despite not being clinically apparent, the presence of subclinical inflammation may cause changes in the structure of the cornea. They reported the need for further research and the use of corneal topography in regular follow-up in the early stages of the disease in order to better understand such relationships (See pages 109-111).

We hope that the research presented in this issue, which sheds light on issues such as myopia management, glaucoma monitoring, retinal pathologies, and ophthalmic screening programs, will guide our valued readers both scientifically and practically.

We would like to thank all the researchers who contributed to this issue. Through your contributions, we hope that each and every issue will feature even richer content.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

Original Article

Evaluation of Reasons for Discontinuation of Atropine 0.01% in Myopia Management: A Single-Center Retrospective Study from Türkiye

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Abstract

Objectives: This study aimed to identify the key factors contributing to non-adherence in patients using 0.01% atropine for progressive myopia control in a specific single-center Turkish population and to propose strategies to enhance adherence.

Materials and Methods: This retrospective study included 30 patients (mean age: 10.67±3.47 years; age range: 5-16 years; 14 males and 16 females) diagnosed with progressive myopia and prescribed 0.01% atropine treatment in our clinic between January and June 2021. All participants had discontinued 0.01% atropine treatment before completion. The reasons for discontinuation were analyzed using patient records and categorized into factors such as light sensitivity, difficulties with near vision, ocular or systemic side effects, the need for monthly eye drop renewal, and the long treatment duration. Data on patients' age, sex, treatment adherence, and reasons for discontinuation were collected. Statistical analyses were performed using IBM SPSS Statistics software.

Results: The treatment discontinuation rate in our patient population was 14.92% (95% confidence interval: 10.23-19.61). The most common reasons for discontinuation were the need for monthly drop renewal (80%), long treatment duration (70%), and light sensitivity (60%). Discontinuation rates did not significantly differ by age group ($p>0.05$). The need for monthly renewal was more frequently reported as a barrier among female patients. Informed consent procedures had highlighted the long treatment duration and the need for monthly renewal, but these still represented barriers to adherence for some families.

Conclusion: To improve adherence to 0.01% atropine treatment for progressive myopia in our patient population, patient education and enhanced support systems are essential. Implementing strategies to address challenges related to monthly renewal and providing better information about the long-term benefits of treatment could help increase adherence rates.

Keywords: Atropine 0.01%, treatment adherence, myopia management, atropine therapy in Türkiye

Introduction

The incidence of myopia is increasing worldwide.[1] Complications resulting from myopia are linked to economic and social burdens. Therefore, efficacious strategies should be implemented for myopia management.[2] These strategies may include preventing myopia onset and slowing myopia progression among school-age children. As evidence increases, many treatment strategies have been developed for clinicians to provide effective myopia management. However, this does not discredit the use of atropine eye drops, one of the earliest methods of myopia management. Atropine has been used against myopia since the mid-19th century.[3] Although its use is off-label and the mechanism of slowing axial elongation is not fully understood, topical atropine is still frequently used alone or in combination with other treatment options such as multifocal soft contact lenses, myopia control spectacles, or orthokeratology.[4,5,6] Atropine is a non-specific muscarinic antagonist that has biochemical effects on the sclera, influencing its remodeling.[7] Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.[8] A study conducted in Türkiye demonstrated that different doses of atropine (0.01%, 0.025%, and 0.05%) were effective in slowing myopia progression in a Turkish population.[9]

In the literature, patient discontinuation of atropine eye drop treatment has been reported at varying percentages due to ocular or systemic side effects. The ocular side effects of atropine eye drops include photophobia, blurred near vision,

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local allergic reactions, and ocular discomfort. Systemic side effects are uncommon with the ocular use of atropine but can include dry mouth, facial flushing, headache, increased blood pressure, constipation, and central nervous system disturbances.[10] A recent meta-analysis conducted by Gong et al.[11] reviewed the effectiveness and side effects of atropine treatment in childhood myopia and found that higher doses of atropine were associated with several adverse effects. The most common side effects of low-dose atropine were photophobia (6.3%), poor near visual acuity (2.3%), and others (4.8%), with no reported ocular or systemic allergic reactions.

In our clinical practice, we prefer using atropine 0.01% due to its reduced side effects and potentially lower rebound effect. However, treatment cessation remains an issue. This study aimed to investigate the reasons for the discontinuation of 0.01% atropine treatment in a specific single-center Turkish population and develop strategies to improve adherence based on these findings.

Materials and Methods

This retrospective cross-sectional study was conducted at the Department of Clinical Ophthalmology, Acıbadem Hospital, Ankara, from March 1 to July 31, 2024. The study was reviewed and approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board Ethics Committee (approval no: 2024-2/93, date: 15.02.2024). The study included 30 patients with progressive myopia who discontinued atropine 0.01% treatment for myopia management. The patients had a mean age of 10.67±3.47 years (age range: 5-16 years), and the cohort consisted of 14 males and 16 females. Informed consent was obtained from all parents or guardians, including detailed information about the expected treatment duration and the need to renew the eye drops monthly.

Inclusion criteria were children aged 5-16 years with progressive myopia (≥0.75 diopters annually) treated with 0.01% atropine eye drops. Exclusion criteria included the presence of other eye diseases (e.g., glaucoma, cataracts, keratoconus, or any form of strabismus), genetic syndromes, or the use of other myopia control treatments.

Atropine eye drops are not commercially available in Türkiye and were therefore prepared by pharmacies. Atropine sulfate 1 mg/1 mL ampoule (Atropin®, Türk Tıpsan, Ankara, Türkiye) was diluted with sodium hyaluronate 1.5 mg/1 mL (Eyestil®, SIFI Pharmaceuticals, Catania, Italy) to achieve a 0.01% atropine solution.[12] Due to the limited shelf life of the solution, parents must obtain a new supply from the pharmacy every month.

Treatment discontinuation was defined as the complete cessation of prescribed medical therapy without the attending doctor's recommendation. The reasons for treatment discontinuation were analyzed retrospectively based on patient and guardian reports and documented in a structured format. These reasons were categorized into factors such as light sensitivity, near-vision difficulties, ocular or systemic side effects, the need for monthly eye drop renewal, long treatment duration, and inadequate information about the treatment. Patients and their parents/guardians were interviewed to identify the most significant factor contributing to the discontinuation of atropine treatment. While participants had the option to select multiple factors influencing their decision, they were specifically asked to identify the primary reason in order to highlight the dominant barrier to treatment.

Statistical Analysis

The sample size was calculated using Python 3.10 and the statsmodels library (version 0.13.2). For the statistical analysis, IBM SPSS Statistics V29 (Released 2023; IBM Corp. Armonk, New York, USA) was utilized. The results were presented in tables, with categorical variables (light sensitivity, near-vision difficulties, ocular or systemic side effects, sex, need for monthly eye drop renewal, and long treatment duration) reported as frequencies and percentages. Numerical variables, such as age, were expressed as mean ± standard deviation. To explore potential effect modifiers, treatment discontinuation and its leading causes were stratified by age and sex. Mann-Whitney U test was used to compare continuous variables between groups, whereas categorical variables were compared using the chi-square test. Statistical significance was determined with two-sided $p<0.05$.

Results

The overall treatment discontinuation rate in our patient population was 14.92% (95% confidence interval: 10.23-19.61). The study included 30 patients with a mean age of 10.67±3.47 years. The patients were categorized into two age groups: 5-10 years (50%) and 11-16 years (50%). Moreover, 14 (46.7%) of the patients were male, and 16 (53.3%) were female (Table 1).

Monthly eye drop renewal (80%), long treatment duration (70%), and light sensitivity (60%) were the most commonly reported reasons for treatment discontinuation (Table 2). Additionally, 32% of patients mentioned near-vision difficulties, while 15% reported ocular surface side effects (e.g., redness or irritation). Notably, inadequate information about the treatment was not cited by any participant (0%), and no systemic allergic reactions were reported. Systemic side effects were also absent in our cohort (0%), as confirmed by patient records.

When stratifying medication discontinuation by sex, we did not find a statistically significant difference in the proportions of males and females ($p=0.71$). Similarly, when stratifying by age group, no statistically significant difference was observed between the two groups ($p=1$).

We also compared the individual factors leading to medication discontinuation by sex and age. Chi-square tests did not reveal significant differences between the sexes for light sensitivity ($p=0.48$). However, the parents of female children were more likely to report discontinuation due to the need for monthly eye drop renewal ($p=0.04$) and long treatment duration ($p=0.03$; Table 3). No significant differences were observed between children from different age groups regarding discontinuation because of the need for monthly renewal ($p=0.36$), long treatment duration ($p=0.23$), or light sensitivity ($p=0.46$) (Table 4).

Discussion

The primary pharmacological treatment for myopia control is atropine eye drops, which require long-term and continuous use to prevent complications and preserve vision. Therefore, we should understand the reasons for discontinuation and develop strategies to improve adherence. In our study, the most common reasons for treatment discontinuation were the need for monthly eye drop renewal (80%), long treatment duration (70%), and light sensitivity (60%). Although overall discontinuation rates did not differ statistically by sex, the parents of female children were significantly more likely to report discontinuation due to the need for monthly renewal compared to the parents of male children (p=0.04). This finding likely reflects parental responsibilities rather than differences attributable to the children themselves. One possible explanation for the higher discontinuation rate among girls is that parents may have perceived the treatment burden differently for them, possibly due to cultural expectations or daily routines affecting compliance. The reasons for discontinuation showed no significant differences between the age groups.

It is important to note that while our study focused on identifying the primary reason for discontinuation, patients and their parents were allowed to mark more than one reason if applicable. This highlights the possibility that multiple challenges may have been experienced simultaneously, contributing to treatment discontinuation. Future studies could explore the cumulative effect of these factors to provide a more comprehensive understanding of treatment adherence. Additionally, the informed consent process included detailed explanations about the long-term nature of the treatment and the need for monthly renewal, ensuring that parents were aware of these challenges before initiating therapy. This aligns with our findings, as the need for monthly renewal and long treatment duration were identified as the leading challenges contributing to discontinuation.

Generally, ocular or systemic side effects have been assumed to be the primary factors for discontinuing atropine eye drop treatment. However, the discontinuation rates and side effects of atropine 0.01% treatment vary in the literature. Diaz-Llopis and Pinazo-Durán[13] reported a discontinuation

Table 1. Demographic distribution of the study participants (n=30)

	Frequency	Percentage (%)
Age group		
5-10 years	15	50.0
11-16 years	15	50.0
Sex		
Male	14	46.7
Female	16	53.3

Table 2. Factors contributing to medication discontinuation

	Frequency	Percentage (%)
Need for monthly renewal		
Yes	24	80.0
No	6	20.0
Long treatment period		
Yes	21	70.0
No	9	30.0
Light sensitivity		
Yes	18	60.0
No	12	40.0

"Yes" indicates patients who listed the factor as a reason for discontinuation, whereas "No" indicates those who did not give the factor as a reason

Table 3. Comparison of factors leading to medication discontinuation by sex

Factor	Sex	n (%)	p value
Need for monthly renewal (n=24)	Female	14 (87.5)	**0.04**
	Male	10 (71.4)	
Long treatment duration (n=21)	Female	12 (75.0)	0.53
	Male	9 (64.3)	
Light sensitivity (n=18)	Female	10 (62.5)	0.48
	Male	8 (57.1)	

Table 4. Comparison of factors leading to medication discontinuation by age group

Factor	Age group	n (%)	p value
Need for monthly renewal (n=24)	5-10 y	12 (80.0)	0.36
	11-16 y	12 (80.0)	
Long treatment duration (n=21)	5-10 y	10 (66.7)	0.23
	11-16 y	11 (73.3)	
Light sensitivity (n=18)	5-10 y	9 (60.0)	0.46
	11-16 y	9 (60.0)	

rate of 2% due to side effects such as photophobia, reading difficulties, mydriasis, and headache. Our findings highlight light sensitivity as the most common ocular side effect leading to treatment discontinuation (60%), consistent with its frequent mention in the literature as a known side effect of atropine. Similarly, Diaz-Llopis and Pinazo-Durán[13] also reported photophobia as a notable side effect.

Sacchi et al.[14] conducted a retrospective study to evaluate the efficacy and safety of atropine 0.01% in slowing myopia progression in European pediatric patients. They reported a discontinuation rate of 0%, with only 10% of patients complaining of temporary headaches. However, while Sacchi et al.[14] reported no discontinuation due to photophobia, our study identified it as a significant reason for discontinuation. This discrepancy may reflect local cultural or environmental factors, as well as differing perceptions of tolerability among patients.

Pérez-Flores et al.[15] reported a discontinuation rate of 4% due to side effects such as tachycardia, vertigo, and ocular discomfort. In contrast, no systemic reactions were reported in our study.

Moriche-Carretero et al.[16] reported a discontinuation rate of 1% due to mydriasis and blurred vision. Kaymak et al.[17] reported side effects such as mydriasis, ocular discomfort, and photophobia, with a discontinuation rate of 0%. Similarly, our findings identified light sensitivity (60%) as a common side effect, consistent with the observations of Kaymak et al.[17] However, unlike their study, light sensitivity was a contributing factor to treatment discontinuation in our study. Myles et al.[18] conducted a retrospective analysis of Australian children prescribed low-dose atropine for myopia treatment and reported a discontinuation rate of 23% due to eye discomfort, mydriasis, photophobia, and headache.

The Myopia Outcome Study of Atropine in Children reported a discontinuation rate of 18.6% in the 0.01% atropine group.[19] Seven adverse events, including eye discomfort, temporary blurred near vision, temporary pupil dilation, and eyelid rash, were possibly or probably related to atropine 0.01%. Joachimsen et al.[20] observed 1-mm pupil dilation in children treated with atropine 0.01%, with negligible hypoaccommodation and no effect on near vision. In contrast to their findings, 32% of our patients reported near-vision difficulties.

Clark and Clark[21] conducted a study using low-concentration atropine on 60 school-aged children in California and reported that only 3 subjects in the atropine group had intermittent blurred vision or light sensitivity, which was not severe enough to discontinue treatment. Hansen et al.[22] conducted a clinical trial investigating the efficacy and safety of atropine 0.01% in the Danish pediatric population and reported that no patients discontinued the 0.01% atropine treatment during the 2-year treatment period.

Ocular surface side effects, such as redness or irritation (15%), were less frequently reported in our study compared to headache and eye discomfort in other studies. Overall, while the discontinuation rates and reasons for atropine 0.01% use vary across studies, our results are broadly consistent with the literature, though some regional differences in side effect profiles and tolerability are evident.

In the literature, the rates of atropine discontinuation vary between 2% and 23%, consistent with our results (14.92%). Although side effects were cited as the primary reason for discontinuation, our study identified additional factors unique to our population. Specifically, the unavailability of commercially prepared atropine drops in Türkiye and the long-term nature of the therapy were more significant reasons for discontinuation than side effects. These factors have not been highlighted in the previous literature.

Discontinuing medication is a key aspect of non-adherence and directly affects treatment outcomes, as the effectiveness of pharmacological treatments relies on both the drug's efficacy and the patient's adherence. Poor adherence is linked to suboptimal clinical outcomes, whereas good adherence improves treatment effectiveness.[23,24] Adherence rates for chronic disease medications range from 43% to 78%, with rates over 80% generally considered acceptable.[25,26] Patient-related factors, such as sex, age, and education, along with medication-related issues such as side effects and dosing frequency, significantly influence adherence.[27,28] Additionally, access to healthcare and cultural factors vary by country and can also affect adherence.[29,30] In our study, the key factors for reduced adherence were the need for monthly renewal of atropine drops and prolonged treatment duration. However, enhancing adherence through education, motivation, and supportive aids can address these challenges.[31]

Treatment continuity can be ensured by developing strategies to address the reasons for treatment discontinuation. For patients discontinuing treatment because of the challenges associated with monthly renewal of the medication, several strategies may be considered. A system could be established in collaboration with local pharmacies that would ensure proper preparation and allow families to pick up the ready medication from the pharmacy monthly. Alternatively, developing preprepared or more user-friendly formulations or providing patients with detailed training on medication preparation, along with written or video materials demonstrating the preparation process step by step, could be beneficial.

There are also various approaches that can be considered for patients who discontinue atropine due to its prolonged duration. Providing detailed education about the long-term benefits of atropine treatment may encourage patients to continue the treatment. Automated notification systems or applications that regularly monitor patients and remind them of the treatment process, regular follow-ups, and examinations should be considered to enhance treatment adherence. Additionally, establishing a support line or online platform where patients can ask questions and share their concerns could be useful.

Our study results also showed that another common factor for treatment discontinuation is light sensitivity. If children experience photophobia or glare associated with atropine 0.01%, using polychromatic glasses or sunglasses can encourage patients to continue the treatment.

Study Limitations

The strengths of this study include providing a thorough evaluation of adherence challenges by considering both patient- and medication-related factors. Moreover, comparing the results with international studies adds depth to the global discussion on the use of atropine in myopia control. Unlike previous studies that primarily focus on regions where commercially prepared atropine is readily available, this study sheds light on the practical barriers and adherence challenges faced in settings with limited access to such resources. As commercially prepared low-dose atropine is unavailable in Türkiye, this study provides valuable insights into the challenges and solutions for myopia management in regions with similar healthcare limitations. By addressing these issues, our study contributes a unique perspective to the international literature.

The limitations of the study include a small sample size, which may limit the generalizability of the findings, and a retrospective design that could introduce recall bias or incomplete data. Potential biases from the retrospective design were minimized by carefully reviewing patient records and excluding incomplete or conflicting data. The observational nature of the study restricts the ability to establish causality, and being a single-center study, the results may not be representative of other populations. Therefore, future research with larger, multi-center, prospective studies is needed to validate these findings.

Conclusion

The primary factor contributing to the discontinuation of atropine 0.01% treatment was the need for monthly renewal, particularly for the girls in our study sample. While treatment duration and light sensitivity also contributed to discontinuation, their impact was less significant compared to the challenge of monthly renewal. This study underscores the importance of simplifying medication protocols and developing supportive systems tailored to the specific needs of patients and their families to address adherence challenges. Particularly in healthcare settings where access to preprepared atropine solutions is limited, these findings encourage the design of globally adaptable strategies to mitigate adherence barriers. By highlighting the specific challenges in a Turkish population, this study offers actionable insights that can guide interventions in similar low-resource settings, thus broadening the applicability of myopia management strategies worldwide.

Ethics

Ethics Committee Approval: The study was reviewed and approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board Ethics Committee (approval no: 2024-2/93, date: 15.02.2024).

Informed Consent: Informed consent was obtained from the parents or guardians of the patients after explaining the study's purpose and benefits, with the understanding that it involved only data review and publication.

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Declarations

Authorship Contributions

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

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Original Article

Comparison of Humphrey 24-2 SITA Standard, SITA Fast, and SITA Faster Test Strategies in Patients with Glaucoma

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Abstract

Objectives: To compare 24-2 Swedish Interactive Thresholding Algorithm (SITA) Standard (SS), SITA Fast (SF), and SITA Faster (SFR) tests performed with Humphrey Field Analyzer (HFA3 Model 840, Zeiss) in patients with glaucomatous visual field (VF) defect.

Materials and Methods: Total of 72 eyes of 72 patients with glaucomatous VF defects were included in the study. Test duration, mean deviation (MD), pattern standard deviation (PSD), visual field index (VFI), and the width and depth of glaucomatous VF defect were compared among the three tests.

Results: The most common diagnoses were primary open-angle glaucoma in 45 eyes (62.5%) and pseudoexfoliation glaucoma in 10 eyes (13.9%). Mean test durations for the SS, SF, and SFR tests were 420.38±53.87 s, 275.94±45.52 s, and 191.89±35.48 s, respectively. Test durations were found to be statistically significantly different in all three tests ($p<0.001$). There was no statistically significant difference between the three tests in terms of MD, width, or depth of glaucomatous VF defect ($p=0.211$, $p=0.762$, and $p=0.701$, respectively). There was a statistically significant difference among the three tests in terms of VFI and PSD values ($p=0.008$ and $p<0.001$, respectively).

Conclusion: Test duration was found to be shorter in the SFR test when compared to SS and SF tests. However, all three tests were similar in terms of the width and depth of the glaucomatous VF defect.

Keywords: Glaucoma, visual field, SITA Fast, SITA Faster, SITA Standard

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Introduction

Automated perimetry was developed in the 1970s and has been used widely in glaucoma diagnosis and follow-up since then.[1] Suprathreshold tests were initially used, but full-threshold (FT) tests were introduced into clinical practice in the 1980s. In those years, the administration of threshold tests was notably time-consuming and required an average duration of 12-20 minutes (min) per eye.[2] The FT test strategy has now been replaced by the Swedish Interactive Thresholding Algorithm (SITA) tests, which are faster than FT tests.[3] Currently, SITA tests are the most popular and widely used test algorithms for computerized perimetry in clinical practice. There are currently three versions of the SITA test strategy. The first two are the SITA Standard (SS) and the less sensitive but faster alternative, SITA Fast (SF).[4,5] Although the SF can be performed in less than 5 min per eye, fatigue and loss of concentration are among the difficulties during the test.[5]

The SITA Faster (SFR) strategy was recently developed to further reduce the test duration.[2] The SFR test was created by making 7 modifications to the SF test. Firstly, in the SFR test, the test sequence begins at the age-corrected normal threshold level instead of 25 decibel (dB) stimuli at each of the 4 primary test points, leading to a reduction in the number of stimulus presentations in most eyes. Secondly, SFR requires only 1 staircase test reversal instead of 2 for primary test points. Moreover, SS and SF use normal threshold values obtained in FT tests, whereas SFR uses the distribution of SF normal values. Furthermore,

unlike older tests, perimetrically blind spots do not undergo a second confirmation and false negative catch trials are no longer performed in the SFR test. Additionally, checking fixation by projecting stimuli into the blind spot has been replaced by the use of the Humphrey gaze tracker. Lastly, the additional 300-ms delay following unseen stimuli after the response time window, before introducing a new stimulus, has been removed in SFR.[2] A recent study conducted by Heijl et al.[2] showed that SFR and SF yielded nearly identical results, with the average test duration for SFR being 30.4% shorter than for SF.

The present study aimed to compare test durations, global indices, and width and depth of glaucomatous visual field (VF) defects in the 24/2 SS, SF, and SFR tests of the Humphrey Field Analyzer (HFA, model 840, Carl Zeiss, Meditec, Dublin, CA) in patients with glaucomatous VF defects.

Materials and Methods

Adult glaucoma patients followed in the Glaucoma Unit of Dokuz Eylül University Department of Ophthalmology were included. Written informed consent was obtained from each patient following comprehensive information. Approval for the study was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2020/29-35, date: 07/12/2020).

The prospective, cross-sectional study was performed between December 2020 and January 2023 with a total of 72 eyes of 72 glaucoma patients who had VF defect (the presence of a cluster of at least 3 points depressed below 5% with at least one of them below 1% on the pattern deviation map) and had previous experience with performing standard automated perimetry. All patients underwent a comprehensive ophthalmological examination.

Patients with glaucoma were diagnosed according to the latest glaucoma guidelines.[6,7] All patients exhibited at least one glaucomatous optic disc head change (e.g., increase in cupping, increase in cup/disc ratio, an inter-eye asymmetry of the cup/disc ratio >0.2, changes in the lamina cribrosa, peripapillary atrophy, focal or diffuse loss of neuroretinal rim, notching, retinal nerve fiber layer defects attributable to glaucoma, presence of splinter hemorrhage). The inclusion criteria required a best corrected visual acuity of 20/40 or better, with a distance refractive error within ±5 diopters (D) mean sphere and ±3 D cylinder. Patients with neurological or ocular diseases that could affect VF testing, a history of systemic medication use that could affect VF, inadequate compliance with the VF test, a history of ocular trauma, or retinal pathology were not included in the study. If both eyes of a patient were eligible, one eye was randomly selected and included in the study.

VF tests were performed prospectively with the HFA using the central 24-2 program. A total of three tests (SS, SF, SFR) were performed on the same day, with the same device and in the same order (SS, SF, and SFR, respectively). A break of at least 30 min was taken between the tests to minimize the effect of fatigue. All VF tests were performed by highly skilled operators, and all patients had prior experience with perimetric testing. Test results were considered reliable if false positive and false negative rates were below 33% and fixation loss was under 20%. Only reliable tests were included in the study.

The study aimed to compare three SITA test strategies in terms of test duration, mean deviation (MD), pattern standard deviation (PSD), visual field index (VFI), and the width and depth of the glaucomatous VF defects. One half of the VF (superior or inferior) was taken into consideration when calculating the width and depth of the glaucomatous VF defect. If both halves of the VF were eligible for the study, one was randomly selected and included in the study.

The width of the glaucomatous VF defect was calculated by counting the points on the pattern deviation map in a single hemifield (superior or inferior) that made a cluster of 3 or more non-edge points depressed below 5% with at least one of them below 1%. The points at the edge of the 24-2 VF test (excluding those just below and above the extreme nasal region of the horizontal meridian) were not included in the calculation due to high variability (Figure 1). The depth of the glaucomatous VF defect was found by summing the dB threshold values of the points marked while determining the width.

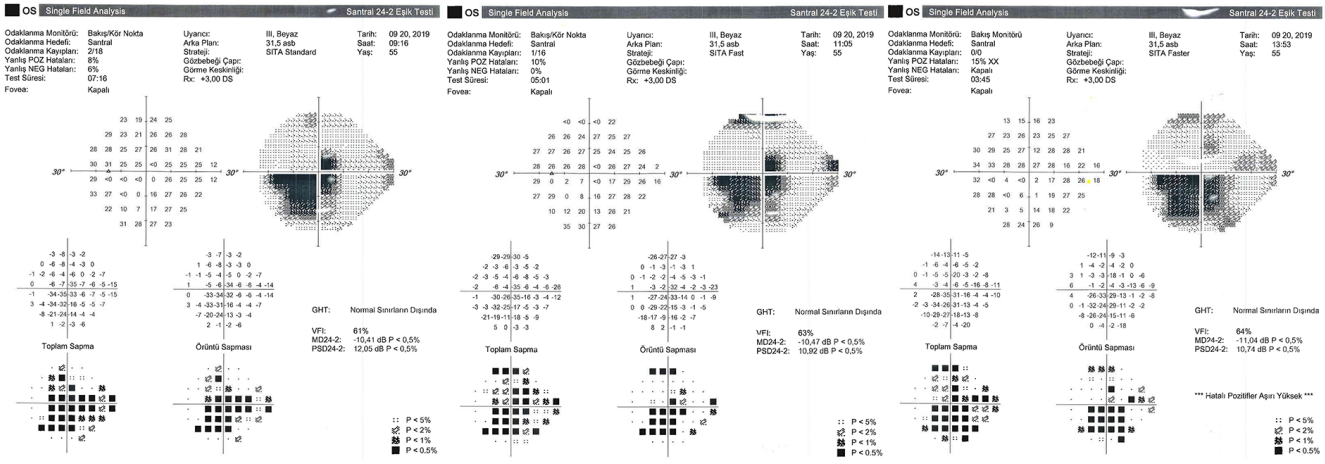

Figure 1. The SITA Standard (left), SITA Fast (middle), and SITA Faster (right) visual field analyses of the left eye of a 55-year-old male patient
SITA: Swedish Interactive Thresholding Algorithm

Statistical Analysis

Descriptive statistics of the data were given as mean, standard deviation, minimum, maximum, frequency, and percentage values. The normality assumption for quantitative data was assessed using the Shapiro-Wilk test. Differences between tests (SS, SF, and SFR) in terms of the study variables (test duration, MD, PSD, VFI, and the width and depth of the glaucomatous VF defect) were identified using repeated measures ANOVA method (Bonferroni corrected t-test for pairwise comparisons) for variables that met the assumption of normal distribution, and Friedman method (Dunn test for pairwise comparisons) for variables that were not normally distributed. Spearman's correlation analysis between the three tests was conducted for MD, PSD, VFI, and defect width and depth. The correlation strength was categorized based on the following ranges: a correlation coefficient (r) value from 0.00 to 0.25 indicated very low correlation, 0.26 to 0.49 indicated low correlation, 0.50 to 0.69 indicated moderate correlation, 0.70 to 0.89 indicated high correlation, and 0.90 to 1.00 indicated very high correlation. Bland-Altman plots were utilized to evaluate the limits of agreement among the SS, SF, and SFR strategies for the VF parameters.[8]

Statistical analysis was performed using the IBM SPSS Statistics 25.0 software package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc Statistical Software version 14.8.1 (MedCalc Software bv, Ostend, Belgium). A p value <0.05 was considered statistically significant.

Table 1. The glaucoma diagnoses of the patients (n=72)

Diagnosis	n (%)
Primary open-angle glaucoma	45 (62.5)
Pseudoexfoliation glaucoma	10 (13.9)
Normal tension glaucoma	7 (9.7)
Chronic angle-closure glaucoma	6 (8.3)
Pigmentary glaucoma	2 (2.8)
Uveitic glaucoma	1 (1.4)
Juvenile glaucoma	1 (1.4)

Results

A total of 72 eyes of 72 adult patients were enrolled in the study. The male to female ratio was 1:1 and the mean age was 66.01±10.22 years (range, 31-88 years). Most of the cases (62.5%) had primary open-angle glaucoma. The diagnoses of the patients included in the study are shown in Table 1.

The mean test durations, MD, PSD, and VFI values, and mean VF defect width and depth for the SS, SF, and SFR tests are presented in Table 2. Pairwise comparisons of the groups revealed that test duration differed statistically between all groups (Bonferroni-corrected t-test, p<0.001). The mean test duration for the SFR test was 54.3% shorter than for the SS test and 30.4% shorter than for the SF test.

There was no statistically significant difference in MD values among the three groups (Friedman test, p=0.211). In pairwise comparisons of PSD, it was noted that the mean PSD value was statistically significantly higher in the SS group compared to both the SF and SFR groups (Bonferroni corrected t-test, p<0.001 and p=0.004, respectively). When the groups were compared pairwise in terms of VFI values, only the SF group had statistically significantly higher VFI values than the SS group (Dunn's test, p=0.012). Additionally, there were no statistically significant differences among the three groups in the mean width (Friedman test, p=0.762) or mean depth (Friedman test, p=0.701) of the glaucomatous VF defects (Table 2).

In correlation analyses between the tests, there was statistically significant highly positive correlation for MD, PSD, VFI, and defect depth, and moderately positive correlation for defect width between SS and SF, SFR and SS, and SFR and SF (Table 3).

Bland-Altman plots of MD, PSD, and VFI are illustrated in Figure 2. There was a mean difference of -0.65±2.50 dB (SS-SF), -0.75±3.30 dB (SS-SFR), and -0.11±2.39 dB (SF-SFR) for

Table 2. Comparison of test durations, global indices, and width and depth of the visual field defects in different test strategies

	SS	SF	SFR	p value
	Mean ± SD (min-max)	Mean ± SD (min-max)	Mean ± SD (min-max)	
Test duration (s)	420.38±53.87 (303-568)	275.94±45.52 (190-396)	191.89±35.48 (142-273)	<0.001*
MD (dB)	-11.32±4.21 (-19.07 - -2.97)	-10.68±4.55 (-19.79 - -1.98)	-10.57±4.59 (-18.47 - -1.61)	0.211
PSD (dB)	9.82±2.91 (2.81-15.34)	8.83±3.07 (2.26-15.21)	8.89±3.30 (3.13-15.36)	<0.001*
VFI (%)	70.10±12.59 (45-95)	73.22±13.90 (42-96)	73.19±13.64 (45-94)	0.008*
Width	12.36±3.38 (6-17)	11.57±3.9 (2-18)	11.89±3.93 (3-18)	0.762
Depth (dB)	230.72±109.46 (42-457)	204.94±118.63 (16-462)	217.81±124.21 (26-486)	0.701

*Statistically significant difference (p<0.05). SS: SITA Standard, SF: SITA Fast, SFR: SITA Faster, SD: Standard deviation, Min: Minimum, Max: Maximum, MD: Mean deviation, dB: Decibel, PSD: Pattern standard deviation, VFI: Visual field index

MD; a mean difference of 1.00±1.70 dB (SS-SF), 0.92±2.36 dB (SS-SFR), and -0.07±1.76 dB (SF-SFR) for PSD; and a mean difference of -3.13±7.94% (SS-SF), -3.10±10.07% (SS-SFR), and 0.03±7.70% (SF-SFR) for VFI. For MD, the analysis suggested good agreement between SS and SFR and between SF and SFR. There was also good agreement between SF and SFR for PSD and VFI (Table 4).

Figure 3 illustrates Bland-Altman plots of the width and the depth of the VF defects. There was a mean difference of 0.80±3.11 (SS-SF), 0.47±3.32 (SS-SFR), and -0.32±3.13 (SF-SFR) for the width and a mean difference of 25.80±73.28 dB (SS-SF), 12.92±82.68 dB (SS-SFR), and -12.88±60.93 dB (SF-SFR) for the depth of the VF defects. The analysis suggested good agreement between SS and SFR and between SF and SFR for the width and depth of the VF defects (Table 4).

Table 3. Spearman's correlation analysis of MD, PSD, VFI, and visual field defect width and depth between the SS, SF, and SFR tests

		MD	PSD	VFI	Width	Depth
SF vs. SS	**r** **p**	0.843 <0.001	0.831 <0.001	0.834 <0.001	0.634 <0.001	0.791 <0.001
SFR vs. SS	**r** **p**	0.719 <0.001	0.738 <0.001	0.724 <0.001	0.603 <0.001	0.749 <0.001
SFR vs. SF	**r** **p**	0.868 <0.001	0.881 <0.001	0.870 <0.001	0.692 <0.001	0.869 <0.001

SS: SITA Standard, SF: SITA Fast, SFR: SITA Faster, SD: Standard deviation, Min: Minimum, Max: Maximum, MD: Mean deviation, PSD: Pattern standard deviation, VFI: Visual field index

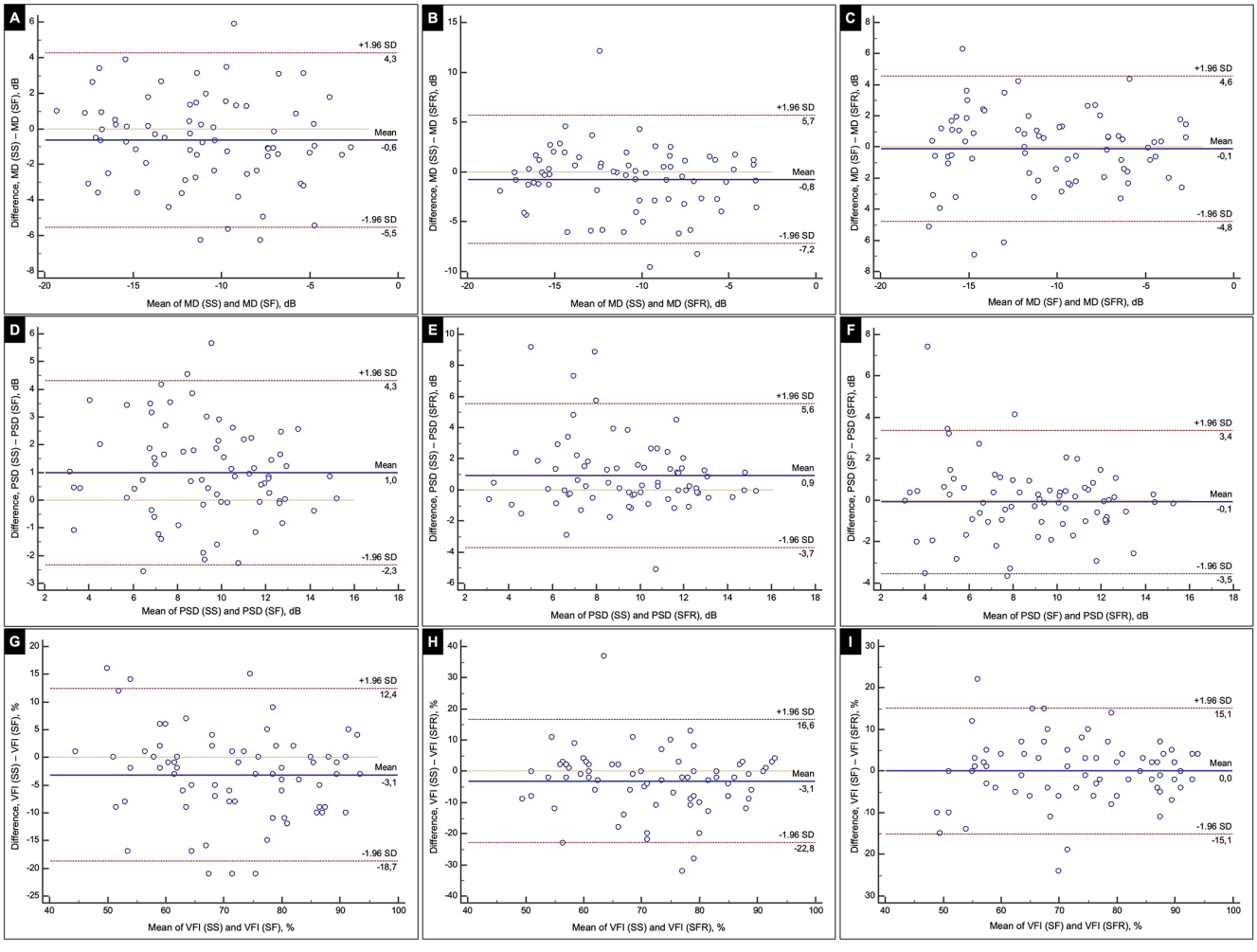

Figure 2. Bland-Altman plots for MD, PSD, and VFI. Good agreement is observed between SS and SFR (B) and between SF and SFR (C) for MD, between SF and SFR for PSD (F), and between SF and SFR for VFI (I)

MD: Mean deviation, PSD: Pattern standard deviation, VFI: Visual field index, SS: SITA Standard, SF: SITA Fast, SFR: SITA Faster

Table 4. The p values from the Bland-Altman analysis of agreement of MD, PSD, VFI, and visual field defect width and depth between the SS, SF, and SFR tests

	MD	PSD	VFI	Width	Depth
SS-SF	0.031	<0.001	0.001	0.034	0.004
SS-SFR	0.056*	0.001	0.011	0.232*	0.189*
SF-SFR	0.705*	0.741*	0.976*	0.389*	0.077*

MD: Mean deviation, PSD: Pattern standard deviation, VFI: Visual field index, SS: SITA Standard, SF: SITA Fast, SFR: SITA Faster

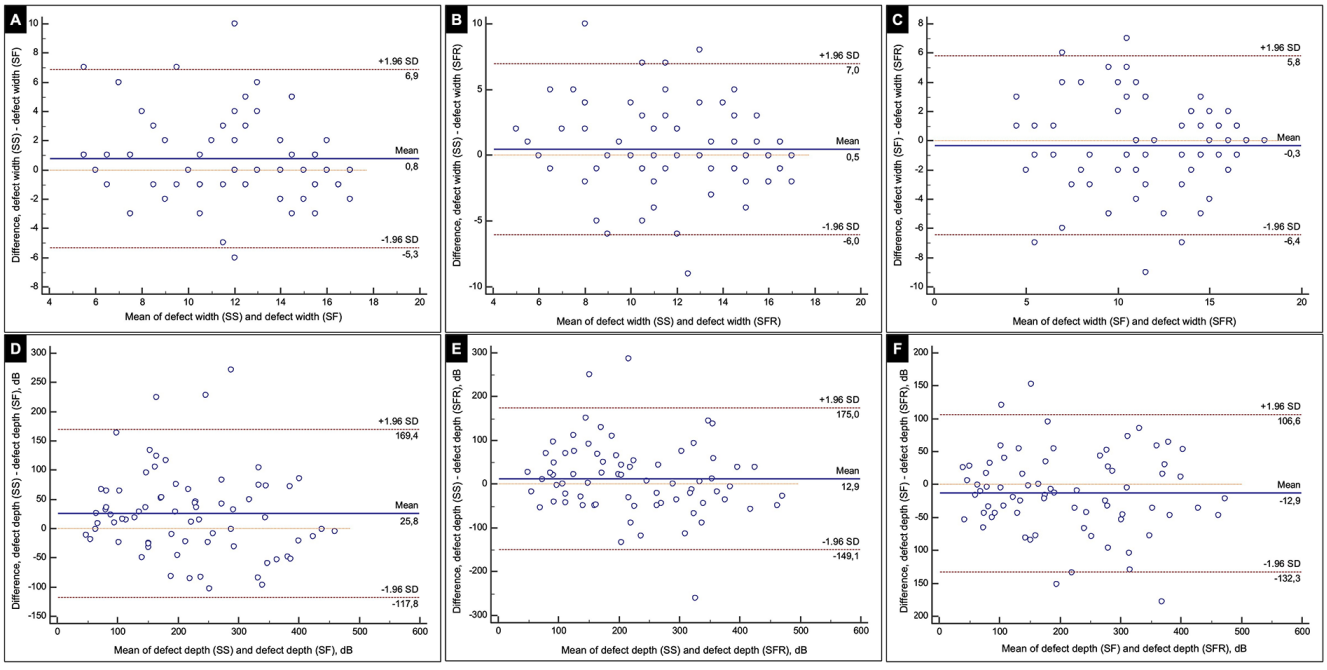

Figure 3. Bland-Altman plots for the width and depth of the VF defects. Good agreement is observed between SS and SFR (B) and between SF and SFR (C) for the width of the VF defects and between SS and SFR (E) and between SF and SFR (F) for the depth of the VF defects

VF: Visual field, SS: SITA Standard, SF: SITA Fast, SFR: SITA Faster

Discussion

In the present study, we compared a recently developed SITA program called SFR with the two conventional SITA test strategies commonly used in clinical practice, SF and SS. According to the results of this study, the mean test duration in the SFR test was significantly shorter than that in the SS and SF tests. The shortening of the test duration allows patients to perform a more reliable VF test without fatigue and also allows more patients to be tested on the same day. When global indices were analyzed, MD values were found to be similar in all three tests in our study. When the tests were compared in terms of PSD values, it was noted that the mean PSD value was statistically significantly higher (worse) in the SS test than both the SF and SFR tests, but the SF and SFR tests were similar. VFI values in the SFR test were similar to those in the SS and SF tests. When VF defects were compared in terms of width and depth, all three tests were found to be similar.

In their prospective multicenter study, Heijl et al.[2] compared SS, SF, and SFR tests in 126 eyes of 126 patients with glaucoma and glaucoma suspects. The mean test duration was 369.5±64.5 s, 247.0±56.7 s, and 171.9±45.3 s, respectively (p<0.001). It was found that the test duration in the SFR test was 30.4% shorter than the SF test and 53.5% shorter than the SS test. MD values were similar in all 3 tests. Median MD values were -6.44 dB, -6.11 dB, and -6.42 dB in the SS, SF, and SFR tests, respectively. The median VFI values were 83.3%, 84.3%, and 84.3% in the SS, SF, and SFR tests, respectively. While the VFI value in the SS test was 1.2% lower than in the other two tests, it was similar in the SF and SFR tests. Similarly, the number of significantly depressed points in the VF was slightly higher in the SS test than in the SF and SFR tests. They pointed out that the SF and SFR tests yielded very similar results and that the SFR test significantly reduced time compared to other SITA tests.[2]

Thulasidas and Patyal[9] compared the SFR, SF, and SS testing strategies in a study of 70 eyes of 70 patients with glaucoma or glaucoma suspects and observed that the test duration for SFR was 36.1% and 60.7% shorter than for SF and SS, respectively (p<0.001). They also reported that the MD value

was statistically significantly lower in the SFR test than in the SF and SS tests (p<0.001). However, they found no statistically significant differences in mean PSD and VFI values among the three test strategies. The number of points depressed at p<0.5% was lower in the SFR test than in both SF and SS tests (p=0.002). The authors noted that while the SFR test provided an advantage in terms of test duration, it might pose challenges in diagnosing early glaucoma cases. They also highlighted that the test algorithms are quite different from each other and cannot be used interchangeably in the same patient on different test sessions.[9]

In another study, Phu et al.[10] compared SFR and SS tests in 364 eyes of 364 patients (77 normal subjects, 178 glaucoma suspects, and 109 patients with glaucoma). In their study, SFR had a greater rate of unreliable test results compared to SS (29.3% and 7.7%, respectively, p<0.001). They also reported that the SFR test was shorter than the SS test (the median difference was 182 s). The authors emphasized that the sensitivity of the SFR test was higher than the SS test in eyes with glaucoma and that this is especially evident in eyes with greater VF loss. They concluded that these tests cannot be used interchangeably in eyes with severe VF loss.[10]

Previous studies comparing the SFR test with the SS and SF tests also showed that test durations were significantly shortened in SFR but the tests displayed similar characteristics.[2,5,9,11] Lavanya et al.[5] compared the global indices and test durations of the SS and SFR tests prospectively in 97 eyes of 97 subjects (63 glaucoma, 26 glaucoma suspects, and 8 normal eyes). The median test durations were 374 s for the SS test and 169 s for the SFR test (55% shorter, p<0.001). The authors reported similar median MD values (-7.3 dB vs. -7.6 dB, p=0.73) and median VFI values (88% vs. 88%, p=0.32) with both test strategies, while the median PSD value was higher (worse) in the SS test strategy (4.8 dB vs. 4.7 dB, p=0.01). They also examined and compared the overall average and the sector-wise threshold sensitivities in both tests. They found that the average general threshold sensitivity was similar in both tests, but when evaluated sectorally, the nasal threshold sensitivity was lower in the SS test than in the SFR test. They stated that the lower threshold sensitivity in the SS test may be related to the longer test duration, but they emphasized that the difference in sensitivity between these two tests is not clinically significant.[5] They also determined the test-retest variability of the VF parameters was low in the SFR strategy. The authors concluded that VF parameters measured by SFR showed good agreement with values obtained with the SS strategy, and SFR could be considered for glaucoma diagnosis and monitoring.

Qian et al.[12] compared SFR and SF tests in 93 eyes of 93 cases (60 glaucoma patients, 33 healthy subjects). The mean test duration was found to be 246.0±60.9 s and 156.3±46.3 s in SF and SFR tests, respectively. The test duration of SFR was found to be 36.5% shorter than the SF test. MD, VFI values, and numbers of depressed points at p<5%, <2%, <1%, and <0.5% in probability plots were found to be similar in both tests.[12]

Mendieta et al.[11] compared the SS and SFR tests by performing them consecutively in random order on one eye of each patient. They found that the test duration was significantly shorter (56%) in the SFR test. Additionally, the tests were found to be quite similar in terms of MD and VFI values and the number of points in the VF showing significant depression. The authors stated that the SFR test could replace the SS test in the diagnosis of glaucoma.[11] Rodríguez-Agirretxe et al.[13] compared SFR and SS tests in 118 eyes (72 glaucoma and 46 normal eyes) and found the test duration to be significantly shorter in the SFR test. While MD and VFI values were similar in mild and moderate glaucoma, they differed between the tests in eyes with severe glaucoma.[13] Pham et al.[14] retrospectively evaluated 766 eyes of 421 patients with glaucoma or suspect glaucoma who had been previously followed up with the SS test and subsequently underwent the SFR test. While MD values from SS and SFR tests were similar in patients with mild glaucoma, the SFR yielded better MD values in eyes with moderate and advanced glaucoma. The authors stated that progression may be missed when switching from the SS test to the SF test in moderate to advanced glaucoma cases.[14]

Although the results of the present study demonstrated positive correlation between SFR and both SS and SF tests in terms of MD, PSD, VFI, and the width and depth of the VF defects, Bland-Altman analysis revealed poor agreement between SS and SF or between SS and SFR in terms of PSD and VFI. This indicates that although the SFR test may be useful for evaluating glaucoma patients, it cannot precisely replace the SS and SF tests. However, irrespective of the diagnosis, the SFR test can serve as a cost-effective alternative for screening and assessing progression of glaucoma in busy clinical settings with time constraints.

Study Limitations

The present study has several limitations. Firstly, the test strategies were performed in the same order in all patients instead of in random order. However, to mitigate the potential systematic fatigue effect on the data, tests were conducted after waiting at least 30 minutes. In the literature, a 5-minute interval between tests was utilized in a study to mitigate the effects of fatigue, and it was determined that this duration was adequate.[13] Additionally, patients were not classified based on the severity of glaucoma in this study. Further studies involving a larger group of subjects with varying degrees of glaucoma are needed to conclusively determine whether SFR could completely replace SS or SF.

Conclusion

In the present study, the SFR test was found to be significantly shorter than the SS and SF tests. There was no statistically significant difference between the SS, SF, and SFR tests in terms of the depth and width of the glaucomatous VF defects. Therefore, the SFR test may be an effective and reliable alternative to the SS and SF tests in the evaluation of VF in glaucoma patients. However, further studies with a larger number of patients are needed to determine whether the SFR test can be used safely instead of other tests to take advantage of its time-saving characteristics.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2020/29-35, date: 07/12/2020).

Informed Consent: Informed consent was obtained from the patients.

This article is derived from the first author's (Seher Köksaldı) graduate thesis entitled "Comparison of Humphrey 24-2 SITA Standard, SITA Fast, and SITA Faster Test Strategies in Patients with Glaucoma", supervised by Prof. Gül Arıkan (Graduate Thesis, Dokuz Eylül University, İzmir, Türkiye, 2023).

Declarations

Authorship Contributions

Concept: G.A., Ü.G., Design: G.A., Ü.G., Data Collection or Processing: S.K., G.A., Ö.F.D., Analysis or Interpretation: Ö.F.D., G.A., Literature Search: S.K., Writing: S.K., G.A.

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Original Article

Microvascular and Ultrastructural Changes of the Retina and Choroid in Patients with Sickle Cell Anemia

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Abstract

Objectives: To determine the microvascular changes of the retina and choroid in sickle cell anemia (SCA) patients and to investigate the relationship between the severity of sickle cell retinopathy and sickle cell maculopathy (SCM).

Materials and Methods: In this cross-sectional study, 78 eyes of 39 patients with SCA were included in the patient group and 68 eyes of 34 healthy participants were included in the control group. Differences in foveal avascular zone (FAZ), retinal and subfoveal choroidal thickness (SFCT), and choroidal vascularity index (CVI) between the patient group and the control group were evaluated by swept source optical coherence tomography (OCT) and OCT angiography (OCTA) imaging. In addition, systemic and biological parameters were compared in patients with and without SCM.

Results: SCM was detected in 16 eyes of 8 patients. Proliferative sickle cell retinopathy (PSCR) was present in 10 patients. In logistic regression analysis, PSCR was found to be a risk factor for the development of SCM (p=0.015, odds ratio: 17.25, 95% confidence interval: 1.73-172.02). The temporal inner retinal layers were significantly thinner in the patient group compared to the control group. The patient group also exhibited significantly greater FAZ enlargement in both the superficial and deep capillary plexus when compared with the control group (p<0.001 for both). CVI was higher in the control group than in the patient group (p<0.001). SFCT was significantly thinner in the patient group (p=0.013). There was no significant difference between patients with and without SCM in terms of FAZ enlargement, CVI values, or systemic and biological factors.

Conclusion: In our study, PSCR was found to be a risk factor for the development of SCM. OCT and OCTA provide valuable information about microvascular changes in the retina and choroid in patients with SCM. Structural changes demonstrated by OCTA before the development of SCM are very important for follow-up and treatment in terms of visual prognosis of patients.

Keywords: Sickle cell anemia, sickle cell maculopathy, sickle cell retinopathy, optical coherence tomography angiography

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Introduction

Sickle cell anemia (SCA) affects approximately 400,000 newborns each year.[1] It is more common in Mediterranean countries, including our country, as well as in the Middle East, India, and Africa.[2] The prevalence of SCA in Türkiye is 0.3-0.6%, but it is concentrated in the Çukurova region and this rate reaches up to 44% in some communities.[2,3] The disease is characterized by the formation of hemoglobin S (Hb S), which occurs as a result of the substitution of glutamic acid by valine at the sixth position of the β-globin chain. Hb S is an abnormal form of Hb that assumes a sickle shape under conditions such as hypoxia, hyperosmolarity, and acidosis, which in turn leads to vascular stasis, thrombosis, and ischemia.[4]

In addition to systemic complications, ocular complications also occur in SCA. Ophthalmological complications observed as a result of microvascular occlusion include sickle cell retinopathy (SCR), sickle cell maculopathy (SCM), hyphema, secondary glaucoma, and orbital bone infarctions (especially affecting the sphenoid bone).[4] The main complication that threatens vision in these patients is proliferative sickle cell retinopathy (PSCR).[5] SCR is classified using a severity-based staging system defined by Goldberg.[6] In this classification, the absence of retinopathy is evaluated as stage 0, peripheral arterial occlusions as stage 1, peripheral arteriovenous anastomoses as stage 2, preretinal neovascularizations as stage 3, vitreous hemorrhage as stage 4, and retinal detachment as stage 5.[6]

In SCR, vascular pathologies typically manifest in the temporal peripheral retina and are usually associated with ischemia resulting from arteriolar occlusion.[6] However, central retinal changes such as nerve fiber layer infarcts, foveal avascular zone (FAZ) enlargement, reduced macular vessel density (VD), and microaneurysms may also occur.[7] It has even been suggested that FAZ enlargement and reduction in macular VD can occur over time despite peripheral retinopathy showing no progression.[8]

Optical coherence tomography (OCT) images of the macula in SCA patients have revealed thinning of the inner retinal layers in the temporal quadrant.[9] The patchy areas of the macula corresponding to these areas of thinning are called SCM.[5] Although its exact etiology has not been defined, pre-capillary vascular occlusions in the perimacular area were suggested as a cause of this retinal thinning.[10]

The aim of the present study was to examine the relationship between SCM and peripheral retinal vascular disease in patients followed up for SCA and to determine systemic and biological factors that may be risk factors for SCM. An additional objective was to compare the ultrastructural and microvascular structures of the retina in choroidal and macular sections with swept source (SS) OCT and OCT angiography (OCTA) in SCA patients and a healthy control group.

Materials and Methods

Ethical approval for this cross-sectional study was obtained from the Başkent University Medical and Health Units Research Board and Ethics Committee (project no: KA23/288, decision no: 23/151, date: 20/09/2023). Informed consent was obtained from all participants in the study, and the principles of the Declaration of Helsinki were adhered to during the study period.

A total of 39 patients whose diagnoses were confirmed by Hb electrophoresis and were followed up due to SCA in the Hematology clinic of the Başkent University Adana Application and Research Center were included in the study. Between January 2023 and March 2024, a full ophthalmological examination was performed, best corrected visual acuity (BCVA) was measured with the Snellen chart, intraocular pressures were evaluated, and anterior segment and dilated fundus examinations were performed. For all patients, demographic data such as age, sex, and SCA genotype were recorded, as well as systemic parameters (history of acute chest syndrome, painful crisis, cholelithiasis, cerebrovascular accident, chronic transfusion, anticoagulant use, and hydroxyurea treatment) and biological parameters (Hb, hematocrit, Hb F, platelet, neutrophil, lymphocyte, mean red cell volume, ferritin, total and indirect bilirubin, alanine transaminase, and lactate dehydrogenase values). Exclusion criteria were: age less than 18 years, presence of diabetes, uncontrolled hypertension, retinal vascular occlusions, epiretinal membrane, vitreomacular traction, history of retinal laser photocoagulation or intraocular surgery, spherical equivalent of >3 diopters (D), axial length other than 22-24 mm, and low-resolution OCT images. The control group consisted of 34 age- and sex-matched healthy participants.

All participants were imaged with SS-OCT and SS-OCTA (DRI-OCT Triton Plus; Topcon Corporation, Tokyo, Japan). As described in previous studies, SCM was evaluated as patchy areas of retinal thinning on OCT images and blue areas on color images showing retinal thickness.[5,11] All examinations were performed between 9:00 and 11:00 in the morning to avoid any effect of diurnal changes. Macular images were obtained with the Triton Plus using a linear scan (100 kHz A-scanning speed, 1050 nm wavelength) centered on the foveal center. Inner and outer retinal thicknesses were measured manually using the device software in a total of 7 regions: the fovea and 3 retinal sites at 1-mm intervals nasal and temporal to the foveal center. Inner retinal thickness was measured between the inner limiting membrane and the junction of the inner nuclear layer (INT) and outer plexiform layer (OPT), and outer retinal thickness was measured between the INT/OPT junction and the retinal pigment epithelium layer. Choroidal thickness was measured subfoveally between the outer border of the retinal pigment epithelium and the choroid-scleral junction.

The obtained choroidal images were binarized to calculate the choroidal vascularity index (CVI) (Figure 1). The binarization process was carried out using open-source image J software (version 1.53a; National Institutes of Health, Bethesda, MD, USA; https://imagej.nih.gov/ij/) as defined by Agrawal et al.[12] First, images were obtained from OCT scans using the Image J software. The images were then converted to 8-bit format and the Niblack automatic local thresholding method was applied to visualize the choroid-scleral junction. The region between the retinal pigment epithelium and choroid-scleral junction was scanned using the polygon tool, and this region was selected as the total choroidal area (TCA). The selected region was recorded as a region of interest (ROI). Next, the image was converted to red-green-blue format and saved to the ROI manager after adjusting the brightness. The two fields recorded by the ROI manager were selected and merged using the "AND" tool. Finally, luminal area (LA) and TCA were measured and CVI was calculated as a percentage by dividing the LA by TCA.

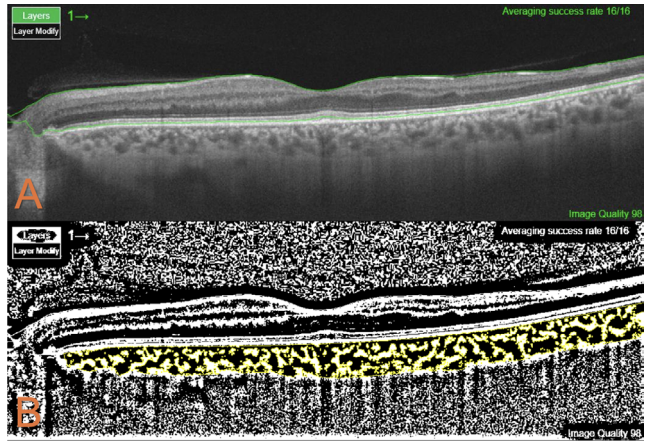

Figure 1. Optical coherence tomography images before (A) and after (B) binarization

OCTA images were measured as 6x6 mm. The superficial capillary plexus (SCP) and deep capillary plexus (DCP) were measured manually on the OCTA images as the regions extending from 2.6 µm below the inner limiting membrane to 15.6 µm below the inner plexiform layer, and from 15.6 µm to 70.2 µm below the inner plexiform layer, respectively. FAZ area (mm^2) in the SCP and DCP was measured manually with the area measurement tool in the device (Figure 2). VD in the SCP and DCP was obtained by the device software.

In patients with signs of SCR, fluorescein angiography (FA) (DRI-OCT Triton Plus; Topcon Corporation, Tokyo, Japan) was performed to determine the stage. SCR staging was done according to the Goldberg classification.[6] The patient group was then divided into 3 subgroups: non-retinopathy (Goldberg stage 0), non-PSCR (Goldberg stages 1 and 2), and PSCR (Goldberg stages 3-5). All image analyses (OCT, OCTA, and CVI) in the study were performed by two different researchers (O.O., A.İ.) and the means of their two measurements were used.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The variables were tested for normal distribution with the Shapiro-Wilk test. Mean and standard deviation values were used to present descriptive analyses. When comparing normally distributed variables between the two groups, independent samples t-test was used, and one-way analysis of variance (ANOVA) with Dunn's Bonferroni post-hoc test was used for comparisons between more than two groups. Frequency and percentage values were used when presenting categorical variables. Relationships between categorical variables were examined with chi-square or Fisher's exact test. Relationships between quantitative variables were examined with Pearson correlation analysis. According to the correlation coefficients (r), correlation strength was evaluated as very strong (0.81-1.0), strong (0.60-0.79), moderate (0.40-0.59), weak (0.20-0.39), or very weak (0-0.19).[13] Parameters that may be risk factors for SCM development were examined by binary logistic regression analysis. Comparisons with p values below 0.05 were evaluated as statistically significant.

Results

The study included a total of 146 eyes of 73 participants (39 patients with SCA and 34 healthy controls). Demographic data of the patient group are presented in Table 1. The control group included 12 females and 22 males and the mean age was 33.44±10.57 years. There was no difference between the patient and control groups in terms of age or sex distribution (p=0.706 and p=1.000, respectively). The most common systemic findings were cholelithiasis (n=21, 53.9%), avascular necrosis (n=19, 48.7%), and painful vaso-occlusive crisis (n=15, 38.5%) (Table 2). There was no significant difference in systemic findings between the sickle cell genotypes. The biological parameters of the patient group are presented in Table 3. There was no difference between patients with and without SCM in terms of systemic or biological parameters. In the patient group, 21 patients (53.9%) had the HbSS and 18 patients (46.2%) had the HbSβ genotype. BCVA was between 20/25 and 20/20 in the patient group and 20/20 for all control subjects.

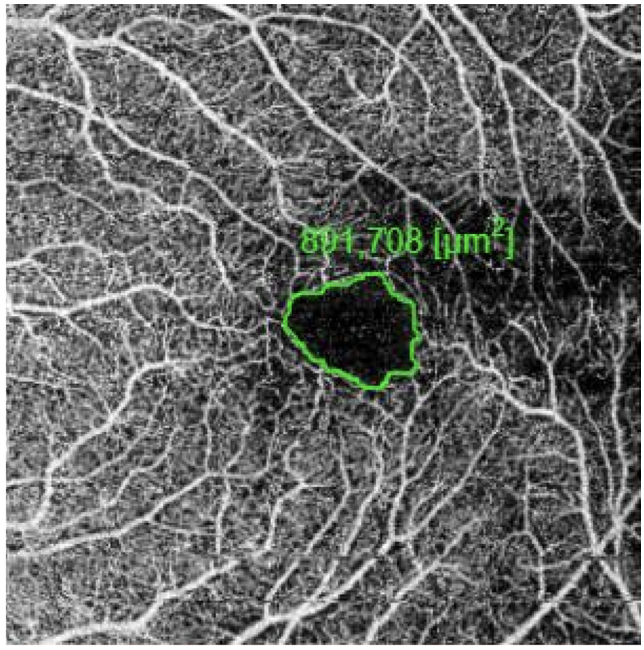

Figure 2. Manual measurement of foveal avascular zone

In the FA examination performed in patients with signs of SCR, 28 eyes (35.9%) had SCR according to the Goldberg classification. Of these, non-PSCR was present in 18 eyes (23.1%) and PSCR was present in 10 eyes (12.8%). Of the eyes with non-PSCR, 10 (12.8%) were stage 1 and 8 (10.3%) were stage 2. Fifty (64.1%) eyes had no retinopathy. There was no significant difference between these groups in terms of age and sex (p=0.463 and p=0.533, respectively). Of the 5 patients with PSCR, the SCA genotype was HbSβ in 4 patients and HbSS in 1 patient.

When OCT images were evaluated, bilateral SCM was detected in 8 (20.5%) of the 39 SCA patients. Of these, 4 patients had the HbSS and 4 had the HbSβ genotype. There was no difference between patients with and without SCM in terms of complete blood count parameters or systemic findings. When we examined the relationship between SCM and SCR, we found that the frequency of SCM increased in patients with PSCR. PSCR was observed in 37.5% (6/16) of the eyes with SCM and 6.5% (4/62) of the eyes without SCM (p<0.001). In the logistic regression analysis, the presence of retinopathy was found to be a risk factor for SCM development (p=0.042). The odds of SCM in patients with PSCR was 17.25 times higher than in patients without retinopathy (p=0.015, odds ratio: 17.25, 95% confidence interval: 1.73-172.016).

In patients with SCA, we found significant thinning of the temporal inner retinal layers in OCT images obtained 1, 2, and 3 mm from the fovea compared to the control group (p<0.001, p=0.006, and p<0.001, respectively) (Table 4). However, there was no difference in temporal inner retinal layer and foveal

thickness in patients without SCM compared to the control group. There was no significant difference between the groups in the inner nasal and outer retinal layers. Subfoveal choroidal thickness (SFCT) was significantly greater in the control group compared to the entire patient group and patients with SCM (p=0.013 and p=0.006, respectively). SFCT did not differ significantly between the control group and patients without SCM (p=0.277) or between patients with and without SCM (p=0.139).

Table 1. Comparison of the patients' demographic data

Parameters		Patient group	Sickle cell maculopathy		p value*
			Yes	No	
Patients/eyes, n		39/78	8/16	31/62	
Age (years), mean ± SD		32.59±8.26	31.13±9.37	32.71±8.12	0.861
Sex (male/female), n		13/26	3/5	10/21	1.000
Retinopathy n (%)	None	50 (64.1)	4 (25.0)	46 (74.2)	**<0.001**
	Non-proliferative	18 (23.1)	6 (37.5)	12 (19.4)	0.124
	Proliferative	10 (12.8)	6 (37.5)	4 (6.5)	**<0.001**
Genotype n (%)	HbSS	21 (53.8)	4 (50)	17 (54.9)	1.000
	HbSβ	18 (4.2)	4 (50)	14 (45.2)	1.000

*Sickle cell maculopathy group vs. non-sickle cell maculopathy group. SD: Standard deviation

Table 2. Comparison of the frequency of systemic parameters in the patient group

Systemic parameters	Patient group (n=39)	Sickle cell maculopathy		p value*
		Yes (n=8)	None (n=31)	
Acute chest syndrome (within last year)	4 (10.3)	2 (25.0)	2 (6.5)	0.180
Avascular necrosis	19 (48.7)	3 (37.5)	16 (51.6)	0.695
Painful crisis (>2 in last year)	14 (38.5)	4 (50.0)	11 (35.5)	0.686
Cholelithiasis	21 (53.9)	3 (37.5)	18 (58.6)	0.432
Cerebrovascular accident	4 (10.3)	2 (25)	2 (6.5)	0.180
Chronic transfusion	10 (25.6)	3 (37.5)	7 (22.6)	0.399
Anticoagulant use	12 (30.8)	3 (37.5)	9 (29.3)	0.682
Hydroxyurea treatment	29 (74.4)	7 (87.5)	22 (71.0)	0.653

All data are presented as number and percentage. *Sickle cell maculopathy group vs. non-sickle cell maculopathy group

Table 3. Comparison of biological parameters in the patient group

Biological parameters	Patient group (n=39)	Sickle cell maculopathy		p value*
		Yes (n=8)	No (n=31)	
Hemoglobin (g/dL)	9.10±1.36	9.74±1.62	8.93±1.26	0.138
Hematocrit (%)	27.87±4.76	27.73±4.61	27.90±4.87	0.926
Hemoglobin F >15%, n (%)	12 (30.8)	1 (12.5)	11 (35.5)	0.394
Platelets (g/L)	400.09±192.43	482.48±167.71	378.84±195.10	0.178
Neutrophils (g/L)	5.46±2.51	5.32±1.65	5.50±2.70	0.860
Lymphocytes (g/L)	3.83±2.06	4.37±1.86	3.69±2.12	0.418
MCV (fL)	92.36±15.93	93.21±17.69	92.14±15.76	0.869
Ferritin (ng/mL)	533.30±552.26	523.6±421.57	535.8±587.21	0.956
Total bilirubin (mmol/L)	2.95±1.67	3.28±1.60	2.87±1.70	0.542
Indirect bilirubin (mmol/L)	2.24±1.67	2.47±1.74	2.18±1.67	0.673
ALT (IU/L)	29.18±23.75	26.88±23.28	29.77±24.21	0.763
LDH (IU/L)	425.59±194.53	424.13±213.96	425.97±193.00	0.881

*Sickle cell maculopathy group vs. non-sickle cell maculopathy group. MCV: Mean corpuscular volume, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

When we examined OCTA parameters, we noted that the FAZ area in both the SCP and DCP was significantly greater in the patient group compared to the control group (p<0.001 for both) (Table 5). In contrast, VD in the SCP and DCP was lower in the patient group than in the control group (p=0.021 and p=0.042). There was no difference between the patients with and without SCM in terms of FAZ area or VD in the SCP and DCP. Figure 3 shows the OCTA, OCT, and retinal thickness maps of patients with and without SCM and one control subject. CVI values were also significantly lower in the patient group than in the control group (p<0.001). The presence of SCM had no effect on CVI.

Discussion

SCA is a common hemoglobinopathy as well as a sight-threatening disease due to the macular damage and retinopathy it causes. In this study, we examined choroidal and foveal microvascular and ultrastructural differences between patients with SCA and healthy volunteers. SCM is a common clinical manifestation in SCA patients that can lead to permanent visual damage; it is therefore important to identify potential risk factors.[14] We determined that PSCR was a risk factor for the development of SCM in patients being followed up for SCA. It has been suggested that this relationship stems from the fact that the macular temporal and peripheral retina are fed by small-diameter terminal arterioles, which are more susceptible to vascular occlusion.[15] Fares et al.[5] also reported that PSCR was

Table 4. Comparison of retinal and choroidal thicknesses in the patient and control groups

			Control group (n=68 eyes)	Patient group (n=78 eyes)	Sickle cell maculopathy		p^1	p^2	p^3	p^4	p^5
					Yes (n=16)	No (n=62)					
Subfoveal choroidal thickness			316.01±53.59	290.49±83.23	259±54.83	298.61±87.62	**0.013**	**0.014**	**0.006**	0.277	0.139
Retinal thickness	Foveal		183.03±15.35	181.85±20.97	181.06±25.76	182.05±19.79	0.142	0.913	1.000	1.000	1.000
	Inner nasal	1 mm	132.22±10.49	130.1±10.06	128.19±13.29	130.6±9.11	0.215	0.328	0.479	1.000	1.000
		2 mm	122.51±11.81	123.03±16.24	120.75±21.26	123.61±14.83	0.830	0.760	1.000	1.000	1.000
		3 mm	87.29±8.04	87.45±21.26	88.88±30.79	87.08±18.35	0.953	0.926	1.000	1.000	1.000
	Inner temporal	1 mm	126.88±12.35	117.21±18.27	99.63±23.41	121.74±13.59	**<0.001**	**<0.001**	**<0.001**	0.078	0.013
		2 mm	119.71±12.94	112.08±18.96	90.69±24.54	117.6±12.44	**0.006**	**<0.001**	**<0.001**	1.000	**<0.001**
		3 mm	99.4±9.24	90.41±17.81	67.81±19.84	96.24±11.63	**<0.001**	**<0.001**	**<0.001**	0.172	**<0.001**
	Outer nasal	1 mm	156.85±11.29	157.24±12.04	153.38±10.44	158.24±12.30	0.841	0.326	0.853	1.000	0.415
		2 mm	143.25±8.86	141.08±10.52	138.06±9.55	141.85±10.69	0.183	0.159	0.503	1.000	0.503
		3 mm	131.19±9.91	128.78±13.66	128.31±12.94	128.9±13.94	0.221	0.481	1.000	0.850	1.000
	Outer temporal	1 mm	157.13±10.17	154.49±11.78	153.06±11.89	154.85±11.83	0.152	0.304	0.566	0.732	1.000
		2 mm	141.96±10.98	142.14±10.60	139.31±9.60	142.87±10.80	0.918	0.498	1.000	1.000	0.721
		3 mm	132.63±8.16	130.9±9.12	131.63±9.30	130.71±9.14	0.230	0.455	1.000	0.632	1.000

p^1: Control vs. patient group (Student t-test), p^2: Control vs. sickle cell maculopathy (SCM) vs. non-SCM group (ANOVA), p^3: Control vs. SCM group (Bonferroni post-hoc), p^4: Control vs. non-SCM group (Bonferroni post-hoc), p^5: SCM vs. non-SCM group (Bonferroni post-hoc). Significance values were adjusted by Bonferroni correction for multiple comparisons

Table 5. Comparison of optical coherence tomography angiography parameters and CVI values in the patient and control groups

	Control group (n=68 eyes)	Patient group (n=78 eyes)	Sickle cell maculopathy		p^1	p^2	p^3	p^4	p^5
			Yes (n=16)	No (n=62)					
FAZ SCP (mm^2)	0.26±0.09	0.42±0.19	0.47±0.26	0.40±0.16	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.333
FAZ DCP (mm^2)	0.28±0.09	0.45±0.19	0.49±0.26	0.44±0.17	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.643
SCP-VD (%)	23.46±3.66 23.61 (13.86-29.56)	21.35±6.94 20.35 (8.63-38.17)	21.58±6.47 23.40 (8.63-31.66)	21.29±7.10 19.65 (10.46-38.17)	**0.021**	**0.009**	0.794	**0.006**	1.000
DCP-VD (%)	21.80±3.62 21.52 (15.21-31.13)	19.97±6.82 18.51 (8.01-36.77)	20.43±6.31 21.57 (8.01-30.42)	19.85±6.98 18.32 (9.23-36.77)	**0.042**	**0.023**	1.000	**0.018**	0.979
CVI (%)	71.02±2.65	68.14±2.20	67.70±2.79	68.25±2.18	**<0.001**	**<0.001**	**<0.001**	**<0.001**	1.000

p^1: Controls vs. patients (Student t-test), p^2: Control vs. sickle cell maculopathy (SCM) vs. non-SCM group (ANOVA [mean ± standard deviation] or median [range]), p^3: Control vs. SCM group (Bonferroni post-hoc), p^4: Control vs. non-SCM group (Bonferroni post-hoc), p^5: SCM vs. non-SCM group (Bonferroni post-hoc). Significance values were adjusted by Bonferroni correction for multiple comparisons. CVI: Choroidal vascularity index, FAZ: Foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, VD: Vessel density

Figure 3. Optical coherence tomography angiography, optical coherence tomography, and retinal thickness analysis images of patients with (A) and without (B) sickle cell maculopathy and a participant from the control group (C)

an independent risk factor for SCM development. In different studies, the prevalence of SCA was found to be higher in patients with PSCR compared to those without PSCR.[11] Mathew et al.[15] detected PSCR in 67% of patients observed to have SCM versus 48% of patients without SCM. In our study, PSCR was observed in 37.5% of the patients with SCM, while this rate was 6.45% in those without SCM. These findings indicate that SCM and PSCR are related.

Some studies have shown SCM to be associated with biological and systemic risk factors such as low Hb and hematocrit level, high reticulocyte, HbSS genotype, clotting disorders, and high total bilirubin level.[5,16] Grego et al.[16] found that patients who developed SCM had hemolysis markers such as low Hb and hematocrit levels and high reticulocytes and total bilirubin. However, there are other studies showing that biological risk factors have no effect on SCM development.[17] We did not find a relationship between biological factors and SCM in the present study. However, the patients' hematological parameters were evaluated on the day they were examined in our clinic, at which point they had already developed SCM. Evaluating these parameters as SCM is developing may reveal a relationship between biological parameters and SCM. Some authors have suggested that SCM is the result of hemolysis-induced endothelial damage rather than vascular occlusion.[18,19]

Thinning of the temporal inner retinal layers in SCA patients has been documented in many previous studies and case reports.[9,10,15] Thinning and atrophy of the inner retinal layers have also been shown in histopathological studies.[20] It has been suggested that atrophy occurs in the temporal region because the temporal arterioles are smaller in diameter than those on the nasal side, but the cause remains inconclusive.[15] In this study, we observed significant thinning in the temporal inner retinal layers in SCA patients compared to controls. However, this difference was not observed between the patients without SCM and the control group. We also found no significant difference in the temporal outer retinal layers or in the nasal quadrant. Dell'Arti et al.[11] reported thinning of both the inner and outer retinal layers in their study, while Hoang et al.[14] reported thinning only in the outer retinal layers. The choriocapillaris vessels that supply the outer retinal layers are larger in diameter than the vessels supplying the inner retina.[14] Since these large vessels are less susceptible to occlusion, the outer retinal layers may be more protected than the inner retinal layers in SCA patients. This may explain the thinning of the inner retinal layers and preservation of the outer retinal layers seen in our study, consistent with many previous studies in the literature.

In our study, SFCT was decreased in the patient group compared to the control group. Reduced choroidal thickness was also reported by Mathew et al.[15] in an adult patient group and by Yılmaz et al.[21] in a pediatric patient group. Decreased choroidal thickness is expected in SCA patients because of sickling and slowed blood flow in the choriocapillaris. Choroidal thickness is known to be affected by changes such as refractive error, diurnal rhythm, and age.[22] Assessing CVI can overcome these limitations of choroidal thickness measurement. As expected, we found that the CVI was lower in the patient group than in the control group. However, there was no difference in CVI between patients with and without SCM. This is consistent with the view that macular microarterial occlusions are not affected by changes in choroidal circulation.[15]

In line with the literature, we observed significant FAZ enlargement in both the SCP and DCP in the patient group. Minvielle et al.[23] and Fares et al.[5] also reported significant enlargement of the FAZ in SCA patients. These findings are also consistent with the FAZ enlargement detected in studies conducted with FA.[24] Fluorescein injection has been suggested to cause painful crises in SCA patients.[25] Therefore, the data obtained with OCTA is invaluable. Minvielle et al.[23] found that VD in both the SCP and DCP was lower in SCA patients compared to the control group. Consistent with their study, we found that VD was decreased in the patient group. We also noted that the FAZ area was significantly larger in patients with SCM compared to controls. Patients with SCM also showed enlargement of the FAZ area compared to those without, but this difference was not reflected in the statistical results. This may be because macular microvascular changes can be detected earlier on

OCTA than OCT. In support of this idea, Fares et al.[5] reported that no flow was detected on OCTA in 36 of 85 eyes without signs of SCM. The fact that macular microvascular changes that are not reflected in OCT images can be detected by OCTA shows that the latter provides useful information in the follow-up and prevention of SCM in SCA patients.

Study Limitations

Our study is the first in our country to evaluate microvascular changes in the retina and choroid in adult SCA patients. Another strength of our study is that all patients in our sample were of the same race. However, there are some limitations that should be noted. These include the cross-sectional nature of the study and the small number of patients for multivariate analyses. In the literature, the prevalence of SCM has been reported between 43% and 60%.[5,26] However, this rate was 20.5% in our study. This may be due to the absence of patients with the HbSC genotype, which is suggested to be more commonly associated with the ocular complications of SCA, although conflicting results have been reported on this subject.[27,28]

Conclusion

In this study, PSCR was identified as a risk factor for the development of SCM in patients being followed up for SCA. In addition, significant differences in both OCTA imaging and CVI values were observed in patients who had not yet developed macular damage compared to healthy individuals. It has been shown previously that there may be FAZ enlargement and reduced VD in the temporal macula even without progression of SCR.[8] OCTA imaging provides essential information in terms of disease course and visual prognosis. Monitoring from an early age is important to facilitate prevention and protect visual function before this damage occurs. More prospective studies with larger patient groups are needed to better understand the course of the disease.

Ethics

Ethics Committee Approval: Ethical approval for this cross-sectional study was obtained from the Başkent University Medical and Health Units Research Board and Ethics Committee (project no: KA23/288, decision no: 23/151, date: 20/09/2023).

Informed Consent: Informed consent was obtained from all participants in the study.

Declarations

Authorship Contributions

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

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Original Article

The Effect of Internal Limiting Membrane Peeling on Anatomical and Visual Outcomes in Patients with Macula-Off Retinal Detachment

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Abstract

Objectives: This study aimed to evaluate the anatomical and visual outcomes of internal limiting membrane (ILM) peeling in patients with macula-involving ("macula-off") retinal detachment treated with silicone oil endotamponade.

Materials and Methods: The study included 19 eyes of 19 patients (Group 1, ILM peeled) and 33 eyes of 32 patients (Group 2, ILM not peeled) who underwent surgery for macula-off retinal detachment at Ege University Department of Ophthalmology. All patients underwent detailed ophthalmological examination and macular optical coherence tomography preoperatively, at postoperative 1 month, and 1 month after silicone removal.

Results: The mean age was 60.47±9.9 years in Group 1 and 57.56±10.63 years in Group 2. The average follow-up duration was 9.13±5.29 months. Preoperative visual acuity was 1.6±1.3 logarithm of the minimum angle of resolution (logMAR) in Group 1 and 1.1±0.8 logMAR in Group 2. At postoperative 1 month, visual acuity was 0.8±0.7 logMAR in Group 1 and 0.7±0.7 logMAR in Group 2 (p=0.1). At 1 month postoperatively, epiretinal membrane (ERM) development was not observed in Group 1, while 9 eyes in Group 2 developed ERM. Visual acuity after silicone removal was similar in both groups (p=0.2). Central foveal thickness (μm) and macular volumes (mm^3) were comparable in both groups (p>0.05). Three eyes in Group 2 that developed ERM underwent surgery and their visual acuity improved.

Conclusion: ILM peeling during vitreoretinal surgery in cases of macula-off retinal detachment may be effective in preventing ERM formation, though it does not result in significant visual improvement. Further studies with longer follow-up and larger patient cohorts are needed.

Keywords: Retinal detachment, epiretinal membrane, internal limiting membrane

Introduction

Although retinal detachment was a cause of permanent blindness in the past, the success rate with surgical treatment is now up to 95%. In contrast to anatomical success, the rate of visual recovery tends to be lower.[1] Among the causes of visual impairment after vitrectomy surgery for rhegmatogenous retinal detachment (RRD), the formation of an epiretinal membrane (ERM) over the macula is one of the most common complications.[1,2] This complication occurs more frequently in chronic and macula-involving ("macula-off") retinal detachments.[1] These membranes are significant enough to require repeat ERM surgery in approximately one-third of patients.[1,3] Internal limiting membrane (ILM) peeling is a technique routinely practiced during surgery for macular pathologies.[4,5] Common indications for ILM peeling include various tractional vitreoretinal disorders such as macular hole, macular puckers, and ERM.[4,5] One study showed that the posterior vitreous cortex, cellular component, and extracellular matrix were completely removed in ILM-peeled eyes.[6] The aim of this study was to evaluate the effect of ILM peeling on anatomical and visual outcomes in patients who underwent surgical repair with silicone endotamponade for macula-off retinal detachment.

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Materials and Methods

The study included 19 eyes of 19 patients (Group 1, ILM peeled) and 33 eyes of 32 patients (Group 2, ILM not peeled) who underwent surgery for macula-off retinal detachment at Ege University Ophthalmology Department between 2021 and 2023. All patients underwent a detailed ophthalmological examination (best corrected visual acuity [BCVA], intraocular pressure measurement, and fundus examination) and postoperative macular optical coherence tomography (mOCT) preoperatively, at postoperative 1 month, and at 1 month after silicone removal. Macular volume, subfoveal thickness, foveal contour, and inner segment/outer segment (IS/OS) junction/ellipsoid zone defect were evaluated from the mOCT scans. Inclusion criteria were having macula-off RRD and no additional macular pathology (myopic maculopathy, age-related macular degeneration, macular hole), uveitis, retinal vascular diseases, or optic neuropathy. Exclusion criteria were a history of intraocular surgery (including cataract surgery) and the presence of media opacity that would interfere with OCT evaluation.

In both groups, standard phacoemulsification with intraocular lens implantation and 25-gauge pars plana vitrectomy were performed by the same vitreoretinal surgeon. In Group 2, the ILM was not peeled and the surgery was concluded by administering silicone oil (Densiron XTRA; Fluoron, Neu Ulm, Germany). In Group 1, the ILM was visualized using ILM-BLUE (DORC, Zuidland, The Netherlands) and an area of approximately 2 disc diameters was peeled. Silicone oil was administered at the end of the surgery.

The patients were examined on the first postoperative day and then around postoperative 1 week, 1 month, 3 months, and 6 months. At each follow-up visit, a complete ocular examination was performed, including visual acuity examination (using a Snellen chart), anterior segment examination, intraocular pressure measurement, posterior segment evaluation, assessment for any complications, and mOCT imaging.

Ethical approval for this study was obtained from the Ethics Committee for Medical Research of Ege University (application no: 2023-1781, decision no: 23-12.1T/18, date: 28.12.2023). As the study was retrospective, informed consent was not required.

Statistical Analysis

IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY, USA) was used to analyze the data. Snellen visual acuity measurements were converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Percent frequencies were used to present qualitative variables and the mean and standard deviation (SD) were calculated for quantitative variables. Intergroup comparisons were made with chi-square tests for demographic data and t-tests for quantitative variables, with $p \leq 0.05$ considered statistically significant.

Results

The mean age of the patients was 60.47±9.9 years (range, 31-74 years) in Group 1 and 57.56±10.63 years (range, 29-82 years) in Group 2 (p=0.394). In terms of gender distribution, there were 16 male and 3 female patients in Group 1 and 20 male and 12 female patients in Group 2 (p=0.15) (Table 1). The mean follow-up period was 9.13±5.29 months (range, 4-20 months). The mean time from retinal detachment to surgery was 15.6±25.96 days (range, 1-180 days). Preoperative BCVA was 1.6±1.3 logMAR (range, 3-1.3 logMAR) in Group 1 and 1.1±0.8 logMAR (range, 3-1 logMAR) in Group 2 (p=0.275) (Table 2). At postoperative 1 month, BCVA was 0.8±0.7 logMAR (range, 2.7-0.3 logMAR) in Group 1 and 0.7±0.7 logMAR (range, 3-0.2 logMAR) in Group 2 (p=0.1). The mean macular volume at postoperative 1 month was 9.12±2.18 mm^3 (range, 6.64-16.4 mm^3) in Group 1 and 9.14±1.16 mm^3 (range, 5.8-11.33 mm^3) in Group 2 (p=0.9), while the mean central foveal thickness was 349±136.8 µm (range, 203-823 µm) in Group 1 and 309.26±81.06 µm (range, 150-511 µm) in Group 2 (p=0.2). At postoperative 1 month, ERM was not observed in any of the eyes in Group 1 but was observed in 9 eyes (27.3%) in Group 2 (Table 3). After silicone removal, BCVA was 0.6±0.8 logMAR (range, 2.7-0 logMAR) in Group 1 and 0.6±0.6 logMAR (range, 2.7-0.1 logMAR) in Group 2 (p=0.2). The mean macular volume was 8.9±1.53 mm^3 (range, 7.11-12.87 mm^3) in Group 1 and 8.9±1.51 mm^3 (range, 4.88-13.28 mm^3) in Group 2 (p=0.9). The mean central foveal thickness was 334.2±126.7 µm (range, 173-600 µm) in Group 1 and 321.36±71.01 µm (range, 228-563 µm) in Group 2 (p=0.7). There were still no eyes in Group 1 with ERM, whereas ERM development was noted in 23 eyes (69.7%) in Group 2 (Table 4). Three of the eyes that developed ERM underwent surgery and showed an improvement in visual acuity. Intraretinal cysts were observed in 3 patients in Group 2 at postoperative

Table 1. Demographic data

	Group 1 (n=19 patients)	Group 2 (n=32 patients)	p value
Mean age (years)	60.47±9.9 (31-74)	57.56±10.63 (29-82)	0.394
Gender distribution	16 male, 3 female	20 male, 12 female	0.15

Table 2. Preoperative findings

	Group 1 (n=19 eyes)	Group 2 (n=33 eyes)	p value
Visual acuity (logMAR)	1.6±1.3 (3-1.3)	1.1±0.8 (3-1)	0.275
ERM development	0 (0%)	9 (27.3%)	0.015
Time from RD to surgery (days)	15.6±25.96 (1-180)		

logMAR: Logarithm of the minimum angle of resolution, ERM: Epiretinal membrane, RD: Retinal detachment

Table 3. Postoperative findings at 1 month			
	Group 1 (n=19 eyes)	**Group 2 (n=33 eyes)**	**p value**
Visual acuity (logMAR)	0.8±0.7 (2.7-0.3)	0.7±0.7 (3-0.2)	0.1
ERM development	0 (0%)	9 (27.3%)	0.015
Mean macular volume (mm^3)	9.12±2.18 (6.64-16.4)	9.14±1.16 (5.8-11.33)	0.9
Mean central foveal thickness (µm)	349±136.8 (203-823)	309.26±81.06 (150-511)	0.2
logMAR: Logarithm of the minimum angle of resolution, ERM: Epiretinal membrane			

Table 4. Findings after silicone oil removal			
	Group 1 (n=19 eyes)	**Group 2 (n=33 eyes)**	**p value**
Visual acuity (logMAR)	0.6±0.8 (2.7-0)	0.6±0.6 (2.7-0.1)	0.2
ERM development	0 (0%)	23 (69.7%)	0.01
Mean macular volume (mm^3)	8.9±1.53 (7.11-12.87)	8.9±1.51 (4.88-13.28)	0.9
Mean central foveal thickness (µm)	334.2±126.7 (173-600)	321.36±71.01 (228-563)	0.7
logMAR: Logarithm of the minimum angle of resolution, ERM: Epiretinal membrane			

1 month. Macular hole or lamellar hole was not observed in any patient during the follow-up. On OCT performed at postoperative 1 month, the foveal contour was intact in all patients and marked IS/OS defects were present in 7 eyes in Group 1 and 9 eyes in Group 2.

Discussion

The ILM is the basal lamina of the inner retina and plays a crucial role in retinal development. In pathological states, however, the ILM tends to thicken with age and acts as a scaffold for cellular proliferation, leading to tractional forces on the retina and making ILM peeling an indispensable step in the surgical treatment of these disorders.[2] As macular ERM remains one of the most common causes of visual impairment after RRD vitrectomy surgery, ILM peeling is performed during RRD surgery in an effort to prevent postoperative ERM formation.[1,2] In this study, none of the patients who underwent ILM peeling (Group 1) developed ERM during the 6-month follow-up. In contrast, a substantial proportion (27.2%) of the group without ILM peeling (Group 2) developed ERM as assessed by mOCT within 6 months after surgery.

Martínez-Castillo et al.[7] noted a 9% incidence of ERM within 1 year after RRD surgery and reported that the mean BCVA decreased to 20/63 with ERM development and increased to 20/40 after surgical removal of ERMs. A recent meta-analysis examining ILM peeling and non-peeling in patients undergoing primary vitrectomy for RRD showed that the rate of ERM development was 29% when ILM peeling was not performed, similar to our results. Furthermore, although ILM peeling was effective in preventing postoperative ERM formation when compared to eyes without ILM peeling, visual change did not differ between the groups despite a positive anatomical outcome.[1] In contrast, Obata et al.[8] observed no significant difference in ERM formation between the ILM peeled and non-peeled groups in their study examining the effect of ILM peeling during surgery for macula-off RRD on postoperative functional and anatomical outcomes (3.5% and 7.8%, respectively, p=0.40).

In the last 10 years, the general recommendation in studies on this subject has been that in RRD patients, visual outcomes are not favorable with ILM peeling despite its effective reduction of ERM formation, and this procedure may be more suitable for complicated RRD.[8,9,10,11,12,13]

It is interesting that there is no relationship between the reduced rate of ERM formation with ILM peeling and the visual improvement seen across studies. Authors have proposed several possible factors, one or more of which might explain this. One of them is that eyes with macula-off RRD exhibit foveal microstructural changes, and preoperative photoreceptor junction deterioration may lead to greater vision loss postoperatively.[14]

Study Limitations

In this study, a significant increase in visual acuity was observed in both groups. Despite the absence of ERM formation in the ILM peeling group, there was no significant increase in visual acuity compared to the other group. However, the short study duration, small number of patients, and retrospective nature of the study are important limitations, and long-term results have not yet been seen.

Conclusion

In macula-off retinal detachments, ILM peeling during vitreoretinal surgery is effective in preventing ERM development. However, this benefit is not reflected in visual success. Studies with longer follow-up and larger patient groups are needed to determine long-term outcomes.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee for Medical Research of Ege University (application no: 2023-1781, decision no: 23-12.1T/18, date: 28.12.2023).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

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

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Original Article

Outcomes of Eye Examination and Vision Screening in Term Infants Presenting to a Tertiary Hospital in Türkiye

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Abstract

Objectives: Ophthalmic screening is an important part of the medical care of children as some eye abnormalities can lead to irreversible vision loss if not treated in the first few months or years of life. The aim of this study is to evaluate the outcomes of the ophthalmic screening program in term infants aged ≤1 year who presented to a tertiary hospital in Türkiye.

Materials and Methods: The records of 1,035 infants ≤1 year old who underwent ophthalmic screening between November 2019 and February 2022 were reviewed retrospectively. Demographic and medical details, parental complaints about the infants' eyes, family history of ocular, adnexal, and systemic pathologies, light reactions, red reflex test results, eye movements, blink response to light, fixation and following, noticeable strabismus, conjunctivitis, epiphora, anterior segment and fundus pathologies, and treatments applied were recorded. The referring physician (family physician, pediatrician) and reason for reference were also noted.

Results: Abnormal ophthalmological findings were detected in 136 infants (13.14%). The most common finding was congenital nasolacrimal duct obstruction (72.05%), followed by strabismus (8.82%), ptosis (4,41%), absence of following (3.67%), congenital cataract (2.94%), hemangioma of the adnexa (2.94%), nystagmus (2.94%), albino fundus (1.47%), preretinal hemorrhage (1.47%), and coloboma of the iris and choroid (1.47%). We detected abnormal red reflex in 4 infants who were not referred for red reflex abnormality by the referring physician, while another 4 infants referred for red reflex abnormality had no pathology on ocular examinations including the red reflex test.

Conclusion: The importance of ophthalmic screening in infants is well appreciated but there are inadequacies in performing and interpreting the red reflex test among family physicians and pediatricians. Efforts should be directed at improving vision screening skills, especially red reflex testing.

Keywords: Congenital cataract, national vision screening program, red reflex, retinoblastoma

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Introduction

In Türkiye, pediatric ophthalmic screening has been carried out since its adoption in 2019 by the Ministry of Health. The screening aims to determine the risk factors that threaten the healthy growth and development of the eye and visual system as well as to identify infants and children with insufficient vision in the early period.[1,2] It is an important part of the medical care of children because some eye abnormalities can lead to irreversible vision loss if not treated in the first few months or years of life. The American Academy of Ophthalmology and the American Academy of Pediatrics recommend visual assessment from birth and during all routine check-ups. Moreover, children who miss screening at the recommended time should be screened as soon as they are noticed.[3] According to the circular issued by the General Directorate of Public Health, infants should be referred to an ophthalmologist immediately if they have any ocular problems detected in the screening examination, have known risk factors (prematurity; cerebral palsy; Down syndrome; family history of strabismus, amblyopia, and refractive error ≥5 diopters; metabolic disease; sensorineural hearing loss, especially Refsum disease; family history of congenital/infantile glaucoma and cataract; history of craniofacial abnormality, ptosis, hemangioma, and nasolacrimal duct pathology), or if the family suspect the child has an eye pathology.[4] In Türkiye, ophthalmic screening by family physicians is recommended at 0-3 months, 36-48 months, and in the first year of primary school.[2] Ophthalmic screening at 0-3 months includes questioning about ocular and systemic risk factors and examination of the adnexa, light responses, and red reflex test.

In this study we aimed to evaluate the reasons for referrals to ophthalmologists, examination results, and ocular problems in term infants ≤1 year of age referred to our clinic in accordance with the ophthalmic screening program.

Materials and Methods

The medical records of infants ≤1 year age who underwent ophthalmic screening between November 2019 and February 2022 were reviewed retrospectively. A total of 1,035 infants were included in the study. Infants referred for retinopathy of prematurity (ROP) were excluded.

Sex, date of birth, gestational age at birth, examination date, chronological age at examination, concomitant diseases, medications used, history of incubator care, parental complaints about the infant's eyes or vision (if any), family history of ocular, adnexal, and systemic pathologies, pupillary light responses, red reflex test results, eye movements, blink response to light flash, fixation and following, noticeable strabismus, conjunctivitis, epiphora, and anterior segment and fundus pathologies were recorded. Red reflex examinations were performed with a direct ophthalmoscope. Fundoscopic examinations were done after pupil dilation. Ophthalmologic examinations were performed by four ophthalmologists trained in pediatric retinal examination.

The referring physician (family physician, pediatrician) and reasons for referral (history of Lowe syndrome in brother, abnormal red reflex test, Horner syndrome, absence of following, albinism, and hemangioma of the adnexa) were recorded. Patients were divided into three groups according to their chronological age at the time of examination: 0-3 months, 3-6 months, and 6-12 months. The ocular pathologies, treatment applied, and follow-up examinations were noted.

The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Local Institutional Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2022/514/224/16; date: 27.04.2022). Signed informed consent was obtained from the parents of the infants.

Results

The study sample comprised 1,035 infants, including 502 girls and 533 boys. The mean gestational age at birth was 38.87±1.24 weeks (range, 35-42 weeks). The mean age at the time of examination was 83.60±58.81 days (range, 7-364 days).

Sixty infants had accompanying systemic diseases, 5 infants had coronavirus disease-2019, 195 infants had a history of incubator care, and 17 infants used medication. The demographic and clinical features of the patients are summarized in Table 1.

Referrals were made by family physicians for 319 infants (30.82%) and by a pediatrician for 569 infants (54.98%). For 109 infants (10.53%), clear information could not be obtained from the family about which physician referred the infant for examination. The parents of 38 infants (3.67%) self-referred for ophthalmologic examination because they noticed an eye problem in their infants. These problems included facial asymmetry, conjunctivitis, tearing, strabismus, ptosis, nystagmus, leukocoria, family history of cataract, strabismus, and heterochromia.

Of the 1,035 infants, 136 (13.14%) had abnormal ophthalmological findings. Congenital nasolacrimal duct obstruction (CNLDO) was the most common finding and was detected in at least one eye of 98 infants. This accounted for 72.05% of all abnormalities and 9.46% of all screened infants. Strabismus was the second most common finding, detected in 12 infants (11 with esotropia, 1 with exotropia), accounting for 8.82% of all abnormalities and 1.15% of all screened infants. Other abnormalities were ptosis (6; 4.41%), absence of following (5; 3.67%), congenital cataract (4; 2.94%), hemangioma of the adnexa (4; 2.94%), nystagmus (4; 2.94%), albino fundus (2; 1.47%), preretinal hemorrhage (2; 1.47%), coloboma of iris and choroid (2; 1.47%), heterochromia (1; 0.73%), corneal opacity (1; 0.73%), chalazion (1; 0.73%), retinal white changes (1; 0.73%), corneal dystrophy (1; 0.73%), intraocular tumor

Table 1. Demographic and clinical features of the infants screened in our clinic

Sex, n (%)	
Male	533 (51.50%)
Female	502 (48.50%)
Gestational age at birth, mean (SD) [range], weeks	38.87 (1.24) [35-42]
Age at screening, mean (SD) [range], days	83.60 (58.81) [7-364]
Comorbidity, n (%)	60 (5.79%)
Congenital hypothyroidism	10 (0.96%)
Hearing loss	2 (0.19%)
Anal atresia	1 (0.09%)
Diabetes mellitus	1 (0.09%)
Epilepsy	3 (0.28%)
Renal pathologies	9 (0.86%)
Cardiac disease	8 (0.77%)
Hip dislocation	1 (0.09%)
Hydrocephaly	2 (0.19%)
Scaphocephaly	1 (0.09%)
Trigonocephaly	1 (0.09%)
Microcephaly	1 (0.09%)
Systemic toxoplasmosis	1 (0.09%)
Systemic cytomegalovirus infection (West syndrome)	1 (0.09%)
COVID-19 infection	5 (0.48%)
Lowe syndrome	1 (0.09%)
Rett syndrome	1 (0.09%)
Sandhoff disease	1 (0.09%)
Joubert syndrome	1 (0.09%)
Down syndrome	2 (0.19%)
Horner syndrome	2 (0.19%)
Brachial plexus damage	1 (0.09%)
Biotinidase deficiency	1 (0.09%)
Corpus callosum agenesis	1 (0.09%)
Cleft lip and palate	1 (0.09%)
Cleft lip	
History of incubator care, n (%)	195 (18.84%)
Medication use, n (%)	17 (1.64%)

n: Number of patients, SD: Standard deviation, COVID-19: Coronavirus disease-2019

(1; 0.73%), facial asymmetry (1; 0.73%), conjunctivitis (1; 0.73%), cherry red spot (1; 0.73%), megalocornea (1; 0.73%), optic disc hypoplasia (1; 0.73%), and suspected congenital glaucoma (1; 0.73%). Eleven infants had more than one ocular pathology.

Intervention was required in 7 infants, which accounted for 5.14% of all abnormalities and 0.67% of all infants screened. Two infants had cataract surgery, 1 infant with corneal opacity had corneal debridement, 1 infant with intraocular tumor diagnosed as retinoblastoma received intravitreal chemotherapy, and 1 infant with CNLDO in the left eye underwent probing while another infant with CNLDO underwent bilateral probing and right balloon dilatation. In addition, 1 infant with corneal dystrophy underwent ocular examination under general anesthesia. Five infants were given spectacles and occlusion therapy was prescribed for at least one eye as needed. Once the ophthalmologic diagnosis was made, 4 infants were referred to a pediatric neurologist for testing for possible systemic disease. Demographic data of the patients with ocular abnormality and the interventions done are summarized in Table 2.

Discussion

Although infant ophthalmic examinations are routinely performed in Türkiye as part of the national screening program, there are no studies evaluating the results of this program in term infants. To the best of our knowledge, our study is the first to present the ophthalmologic examination results obtained within the scope of the National Ophthalmic Screening program in our country.

We divided our patients into three groups according to their chronological age at the time of examination: 0-3, 3-6, and 6-12 months. The vast majority of the infants screened were 0-3 months of age. This could be attributable to parents understanding the importance of the screening program and showing good compliance, as well as to effective implementation of the screening program in our country.

In the literature there are various publications regarding the results of neonatal eye screening, with abnormality rates ranging from 4.7% to 41.2%.[5,6,7,8] Our data revealed that a significant proportion (13.14%) of infants younger than 1 year of age exhibited ocular abnormalities. Similar rates were reported by Jac-

Table 2. Demographic and clinical data of the patients with ocular abnormality and interventions done

Ocular diagnosis	Frequency in screened infants, n (%)	Mean age ± SD (range), days	Previous ophthalmological examination, n	Intervention (surgical/medical/follow-up) n
Cataract	4 (0.38%)	57.25±46.97 (7-111)	1	2/0/4
Dacryocystitis	98 (72.05%)	80.61±51.61 (27-346)	22	2/22/98
Esotropia	11 (1.06%)	159.63±71.71 (43-278)	7	0/6/11
Exotropia	1 (0.09%)	140	1	0/1/1
Retinal white changes	1 (0.09%)	82	0	0/0/1
Ptosis	6 (0.57%)	108.50±109.31 (52-279)	3	0/0/6
Hemangioma on the lids	4 (0.38%)	63.50±28.89 (33-102)	2	0/0/4
Conjunctivitis	1 (0.09%)	115	0	0/1/1
Optic disc hypoplasia	1 (0.09%)	177	0	0/0/1
Corneal dystrophy	1 (0.09%)	99	1	0/1/1
No following	5 (0.48%)	110.60±63.46 (70-209)	3	0/0/5
Facial asymmetry	1 (0.09%)	118	0	0/0/1
Suspect congenital glaucoma	1 (0.09%)	113	0	0/0/1
Iris and choroid coloboma	2 (0.19%)	144.00±26.87 (125-163)	0	0/0/2
Megalocornea	1 (0.09%)	288	0	0/0/1
Corneal opacity	1 (0.09%)	244	1	1/1/1
Nystagmus	4 (0.38%)	156.25±72.18 (70-242)	3	0/1/4
Chalazion	1 (0.09%)	85	1	0/1/1
Albino fundus	2 (0.19%)	189.00±74.95 (136-242)	2	0/1/2
Heterochromia	1 (0.09%)	98	1	0/0/1
Preretinal hemorrhage	2 (0.19%)	39.50±9.19 (33-46)	0	0/0/2
Cherry red spot	1 (0.09%)	60	1	0/0/1
No red reflex/exophytic mass in fundus	1 (0.09%)	87	1	0/1/1

n: Number of patients, SD: Standard deviation

Okereke et al.[9] (15.5%) and Goyal et al.[6] (14.93%). In contrast, Li et al.[5] and Ma et al.[8] found higher rates of ocular abnormality (24.4% and 41.2%, respectively), while Vinekar et al.[7] reported a lower rate of 4.7%. These studies included heterogeneous groups in terms of chronological age at examination, which may explain the variable results. All the authors performed dilated fundus examination with digital widefield retinal imaging, whereas Jac-Okereke et al.[9] did not perform fundus examination during vision screening. We included only term infants in our study, excluded preterm infants referred for ROP examination, and performed dilated fundus examination on all infants.

CNLDO, the most common ocular abnormality in our study, was detected in 98 infants and was bilateral in 36 infants. The disease accounted for 9.46% of 1,035 infants screened and 72.05% of 136 infants with ocular abnormality. In 8 infants, CNLDO was accompanied by preretinal hemorrhage, eyelid hemangioma, strabismus, coloboma of the iris and choroid, suspected congenital glaucoma, absence of following, optic disc hypoplasia, nystagmus, or sutural cataract. The prevalence of CNLDO in our study seems higher than reported in previous vision screening studies. Ma et al.[8] detected CNLDO in 4 (0.8%) of 481 infants. Jac-Okereke et al.[9] examined 142 infants up to 12 months old and detected CNLDO in 14%. CNLDO occurs in 5-20% of newborns and often resolves spontaneously or with conservative treatment, although persistent cases require surgical treatment.[10,11,12] Medical treatment consists of massaging the nasolacrimal sac and applying topical antibiotics when discharge is present. We explained lacrimal sac massage to the parents of all infants with CNLDO, assuming they either did not know it or had not performed it effectively. We prescribed topical antibiotics to the infants as needed. Two infants (2.04%) underwent surgical treatment, but we cannot say whether the massage actually improved the recovery rate because we are not certain how parents performed the massage.

Strabismus, the second most common finding in our study, was detected in 12 infants, accounting for 8.82% of all abnormalities and 1.15% of all screened infants. None of our patients required strabismus surgery. They were prescribed spectacles and occlusion therapy as needed.

Ptosis is another ocular abnormality which we encountered frequently. Treatment of congenital ptosis is indicated when the upper eyelid obscures the visual axis, causing stimulus deprivation, or induces astigmatism that is amblyogenic.[13] In our study, none of the 6 patients with congenital ptosis required surgical intervention.

Tang et al.[14] examined 199,851 neonates by RetCam imaging and found that approximately 9% (18,198) of the infants had abnormal findings, with retinal hemorrhage being the most common (12,810, 70.39%). Callaway et al.[15] reported the prevalence of fundus hemorrhages as 20.3%. In the study by Ma et al.[8], retinal white areas were the most common abnormality (42.9% of abnormalities and 17.7% of all screened infants), followed by retinal hemorrhage (16.2% of abnormalities and 6.7% of all screened infants). In our study, only 2 infants had preretinal hemorrhages, accounting for 1.47% of all abnormalities and 0.19% of all screened infants. Retinal hemorrhages in infancy are often self-limited and resolve quickly with no effect on visual development, although some can persist and have a long-term impact on vision.[16] Some authors hypothesize that any obstruction of the visual axis that persists for a sufficient period can induce amblyopia that appears later in life without ophthalmoscopic findings, referred to as idiopathic.[5] Therefore, detection of retinal hemorrhages may be a warning sign that should prompt vigilance for visual problems that may appear later in life. This is only possible with dilated fundus examination. However, to advocate for detailed fundus examinations in every newborn would have staffing, economic, and logistic implications. Each country must evaluate and implement the details of the ophthalmological examinations to be carried out within the scope of national eye screening programs.

Red reflex testing is a simple screening test that can be performed by anyone and enables early diagnosis of vision-threatening and sometimes life-threatening ocular pathologies such as cataract and retinoblastoma.[3,17,18,19] Although the definitive diagnosis of these diseases is made by dilated fundus examination, the red reflex test helps identify patients who need a detailed fundus examination. In our study, 4 infants (0.38%) had abnormal red reflex test, accounting for 2.94% of all abnormalities. However, none of these infants were referred for red reflex abnormality. In one of these infants, the reason for referral by their pediatrician was a history of Lowe syndrome in his brother. Three of four infants had cataract in at least one eye and two of them underwent cataract surgery. According to our study and studies concerning ophthalmic screening in infants, the red reflex test is sufficient for screening congenital cataract, especially those that require surgery.[17] In Sweden, where routine eye screening in the maternity ward is recommended, congenital cataract is detected earlier than in Denmark, where screening is done at 5 weeks of age with a penlight.[20,21] However, dilated ophthalmologic examination is needed to diagnose some cataracts. In our study, one infant with sutural cataract exhibited a normal red reflex and was diagnosed by dilated fundus examination.

Another disease that can be detected by red reflex examination is retinoblastoma.[22] In our study, retinoblastoma was detected in the left eye of one infant who had an abnormal red reflex. She was 87 days old, giving the advantage of early intervention, and she was treated with intravitreal chemotherapy. It has been estimated that about 40% of infants with neonatal retinoblastoma have a positive family history, which itself should prompt referral for a pediatric ophthalmologic examination.[23] However, this infant did not have family history.

In Türkiye, there are no data regarding the ratio of congenital cataract and retinoblastoma that are detected by red reflex examination. Gürsel Özkurt et al.[24] questioned family physicians about their knowledge and practice of red reflex screening. They reported that 12% of the respondents had never heard of the red reflex test, 12% did not know how to use a direct ophthalmoscope, 33% knew this test should be performed in

every infant, 36% knew about but had never performed the test, and 16% performed it regularly.

In our study, of 997 infants (96.33%) referred by either a family physician or pediatrician, 4 were referred due to abnormal red reflex test. However, these infants exhibited normal red reflexes in our ophthalmologic examination, and two of them were diagnosed with conjunctivitis and CNLDO.

Our study demonstrates that the importance of the screening program is well understood among physicians and parents, but almost all of the screening tests are performed by ophthalmologists instead of primary care physicians. We examined the patients with an indirect ophthalmoscope, which is time-consuming compared to digital imaging systems. These differences influenced the results of our study. Our study also showed some differences in the diagnoses when compared with similar studies. The most common ocular abnormality in our study was CNLDO, while retinal pathologies were rare (8.08%). Although we excluded infants referred for ROP screening, we included all term infants, even those with infectious disease and signs of systemic disease.

Study Limitations

Our study has some limitations. It was a single-center study with a relatively small sample size. Although our sample size was adequate to detect common ocular pathologies, a larger sample is needed to detect rare ocular abnormalities. Further studies involving multiple centers with large samples and long follow-up times are needed to discuss the prevalence, etiology, clinical course, and prognosis of ocular abnormalities and document patterns of regression. Though our study did not aim to document follow-up results, the impact of the pathologies on quality of life and visual development could have provided additional information and allowed us to see the impact of ocular abnormalities on the visual system.

Conclusion

Our study showed that although the importance of red reflex test is well appreciated, there are inadequacies in performing and interpreting this test among family physicians and pediatricians. Thus, it is important to encourage these clinicians to perform all steps of the ophthalmic screening, and efforts should be directed at improving ophthalmic screening skills (particularly red reflex testing) among physicians who see children for infant and well-child visits. Another issue is whether dilated fundus examination should be performed even in healthy infants to detect certain pathologies. Although the exact answer of who should be examined in detail may vary according to each country's politics and patients, further studies will be more instructive. The outcomes would help in formatting guidelines for the scalability of the nationwide expansion of this program planned by the government.

Ethics

Ethics Committee Approval: Local Institutional Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2022/514/224/16; date: 27.04.2022).

Informed Consent: Signed informed consent was obtained from the parents of the infants.

Declarations

Authorship Contributions

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

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Rational Drug Use in Extraocular Surgeries

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Abstract

Extraocular surgeries include a broad spectrum of procedures such as pterygium excision, removal of conjunctival tumors, and orbital exenteration. The objective of these surgeries is to address various ocular conditions, enhance visual function, and rectify cosmetic concerns. Nonetheless, as with any invasive procedure, these surgeries carry a risk of infection. To curtail this risk, prophylactic antibiotics are commonly used after extraocular surgeries. Administered via topical, oral, or intravenous routes, these antibiotics aim to prevent potential postoperative bacterial infections. The selection of these antibiotics is guided by their efficacy against prevalent pathogens associated with ocular infections, including *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. The choice of antibiotic, its route of administration, and duration of therapy can vary depending on the specifics of the surgery and individual patient risk factors. Moreover, in the context of extraocular surgeries, specific agents such as mitomycin C (MMC), interferon (IFN) alpha-2b, and 5-fluorouracil serve unique roles extending beyond infection prevention. MMC, an antitumor agent, aids in averting scarring and fibrosis in procedures like pterygium and glaucoma surgeries. IFN alpha-2b, with its antiviral and antiproliferative properties, is utilized to decrease the recurrence of conjunctival and corneal neoplasias postoperatively. This review examines the current understanding of prophylactic antibiotic use in certain extraocular surgeries and the role of antibiotics and some specific agents in enhancing surgical outcomes.

Keywords: Extraocular surgeries, prophylactic antibiotics, mitomycin C, interferon alpha-2b, 5-fluorouracil, amphotericin B

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Introduction

Prophylactic antibiotics, also termed preventive antibiotics, represent a class of pharmaceutical agents primarily employed not for the treatment of established infections, but rather for their prevention. They are frequently utilized in the context of surgical procedures, administered before, during, or after the operation to minimize the risk of postoperative infections. Additionally, they may be employed in other circumstances characterized by elevated infection risk.

The selection of prophylactic antibiotic is multifactorial, determined by the nature of the infection being forestalled, the bacterial species most likely implicated, and patient-related factors such as allergic history and concurrent medical conditions. A few representative examples of these antibiotics include cefazolin, vancomycin, and gentamicin.[1]

Antibiotic prophylaxis, employed in numerous scenarios and through diverse routes of administration, is a wide-ranging domain encompassing fluoroquinolones and aminoglycosides, among others. The selection of prophylactic agents and administration routes, such as topical, subconjunctival, oral, and parenteral, depend closely on the timing of administration, which could be preoperative, intraoperative, perioperative, or postoperative. In support of this, a survey conducted by the American Society of Cataract and Refractive Surgery in 2014 reported that 90% of surgeons employed topical antibiotics perioperatively and 97% opted for their use postoperatively.[1]

These prophylactic measures aim to prevent infections predominantly caused by Gram-positive organisms, including coagulase-negative *Staphylococcus*, *Streptococcus viridans*, and *Staphylococcus aureus*. Gram-negative organisms such as *Pseudomonas* or *Haemophilus*, though less common, also warrant prophylaxis, while fungi and *Nocardia*, being rare, require it less frequently.[1]

However, it is crucial to deliberate the potential risk associated with prophylactic antibiotic usage-the theoretical threat of engendering bacterial antibiotic resistance following prolonged and repeated administration, a concern of significant clinical relevance in contemporary medicine.[1]

Additionally, it is important to shed light on the importance of the incorporation of specific agents like mitomycin C (MMC), interferon (IFN) alpha-2b, 5-fluorouracil (5-FU), and amphotericin B into extraocular surgical protocols, which has significantly enhanced the treatment and management of various ocular conditions. MMC for instance, an antineoplastic agent, has found utility in ocular surgeries for its inhibitory effects on fibroblast proliferation, thus preventing postoperative scarring and fibrosis.[2] IFN alpha-2b, though not an antibiotic in the classical sense, has potent antiviral and antiproliferative properties, and has been successfully employed in the management of ocular surface squamous neoplasia.[3] Amphotericin B, a potent antifungal agent, is indispensable in the treatment of sino-orbital fungal infections and is often used in conjunction with surgical debridement for effective disease control.[4] These agents signify the diverse roles antibiotics can play in improving the outcomes of extraocular surgeries, beyond their traditional role in infection control.

In extraocular surgeries, the use of prophylactic antibiotics and certain special agents is very important to prevent infections and improve surgical results. When planning treatment, patient factors, surgical procedure, and the auxiliary agents to be used should be evaluated together. In this review, we evaluated the accepted use in the literature of antibiotics used for prophylaxis in extraocular surgeries and some specific agents used to improve surgical outcomes.

Prophylactic Antibiotic Use in Extraocular Surgeries

The field of extraocular surgery encompasses a broad range of interventions, including strabismus correction, pterygium excision, and retinoblastoma treatment. Other operations involve enucleation for malignancies and repair of ocular trauma. In this complex field, the application of antibiotic prophylaxis to prevent surgical site infection (SSI) presents a considerable challenge that varies for each case and disease.

In a multicenter retrospective study evaluating the development of SSI after various oculoplastic surgical procedures performed on 947 eyes of 795 patients, the patients were divided into two groups. The first group included patients who received postoperative local antibiotic ointment (LATB group) (505 patients, 617 procedures) and the second group included patients who received no postoperative local antibiotics (LATB-free group) and only topical vitamin A ointment (229 patients, 330 procedures). No patient received postoperative eye drops. Eight hundred and fifty-three procedures were classified as Altemeier class 1 (clean) and 80 procedures as class 2 (clean-contaminated). Postoperative SSI was seen in 4 of 617 eyes (0.65%) in the LATB group and 5 of 330 eyes (1.52%) in the LATB-free group, and there was no statistically significant difference between the groups. This study suggests that it is appropriate to perform oculoplastic surgery without the use of systemic and topical antibiotics in Altemeier class 1 and 2 procedures.[5]

Strabismus Surgery

Strabismus surgery, a common extraocular procedure with a low incidence of major complications, necessitates postoperative management to curtail infections and alleviate inflammation. The postoperative antibiotic regimen varies based on surgeon preference, with most opting for antibiotic/steroid combinations and a minority using topical antibiotics. Recently, a single postoperative dose of povidone-iodine has been explored as an alternative.[6]

In a non-comprehensive study including 1,603 patients, pediatric ophthalmologists either employed a single dose of 5% povidone-iodine (n=953) or continued the traditional week-long topical antibiotic/steroid course at a frequency contingent on surgeon preference (n=650).[6] Fornix incisions were performed in 1,074 patients, limbal incisions in 467, and a combination of both in 62. Signs and symptoms suggestive of postoperative infection were observed in 46 patients (2.87%). Of these, 20 (3.08%) were from the antibiotic/steroid group, and 26 (2.83%) from the povidone-iodine group. The study's outcomes suggest no significant difference in infection rates between the povidone-iodine group and the antibiotic/steroid group. However, povidone-iodine was shown to decrease bacterial colonies by 91% when used preoperatively, reducing the risk of endophthalmitis after intraocular surgery by 75%, which has led to its acceptance as standard preoperative care.[7]

Evisceration and Enucleation Surgery

Unlike general, orthopedic, and plastic surgery, there is limited available data on the necessity of prophylactic antibiotics in eyelid and orbital surgeries, specifically periocular plastic surgeries. To address this gap, Fay et al.[8] examined the effectiveness of prophylactic antibiotics in preventing postoperative infections after enucleation and evisceration surgeries. These procedures were selected as representative models for periocular plastic surgeries in general due to their standardized nature and frequent utilization of alloplastic implants, which potentially increase the risk of postoperative infections. The authors reviewed the records of 644 patients who underwent enucleation or evisceration with alloplastic implants and divided them into two groups: those who received postoperative prophylactic antibiotics (n=381, 59%) and those who did not (n=263, 41%). The antibiotic group included 404 enucleations with implant cases, 31 enucleations without implant cases, 174 eviscerations with implant cases, and 35 eviscerations without implant cases. The patients in the study were prescribed different antibiotics, with the most common ones being cephalexin, clindamycin, or fluoroquinolone. However, there were instances where amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or amoxicillin were also used. Two patients showed signs of infection, one in the group that received antibiotics and one in the group that did not. While patients with indications for infectious surgery were more likely to receive antibiotics, there was no statistically significant difference in infection rates based on antibiotic administration. Importantly, none of the patients with infectious indications who did not receive antibiotics developed a postoperative infection. These findings suggest that withholding postoperative prophylactic antibiotics in orbital surgery, even with alloplastic material, is clinically safe. However, it is important to note that

these results may not be applicable to non-sterile surgeries such as sinonasal or nasolacrimal procedures.[8]

Orbital Fracture

Orbital fractures, ranking among the most frequent facial injuries, often necessitate surgical interventions and subsequent treatment due to their potential complications. Postoperative infections are a known risk following orbital fracture surgeries, but prophylactic antibiotics can significantly mitigate this likelihood. Despite the noted benefits, consensus remains elusive regarding the optimal duration of postoperative antibiotic administration. The documented range for antibiotic prophylaxis following facial fractures extends from a single dose to 7 or even 10 days postoperatively. It is important to consider that the use of antibiotics may invite certain risks, including allergic reactions, toxicity, adverse effects, drug interactions, and the escalation of bacterial resistance.[9]

A study by Chole and Yee[10] demonstrated a decrease in infectious complications in facial fractures from 42.2% to 8.9% through the administration of an antibiotic dose 1 hour preoperatively and 8 hours postoperatively.

Zix et al.[9] conducted a prospective, single-center, randomized, double-blind, placebo-controlled clinical trial to assess the efficacy of postoperative prophylaxis in preventing infections after orbital fracture surgeries. In their study, 62 patients suffering from orbital blow-out fractures were randomly divided into two groups. All patients were administered 1.2 g of intravenous amoxicillin/clavulanic acid every 8 hours, starting from the admission time until 24 hours postoperatively. Afterward, the first group received an oral dose of 625 mg amoxicillin/clavulanic acid every 8 hours for an additional 4 days, forming the 5-day group. The second group, known as the 1-day group, were given an oral placebo thrice daily. Follow-up was scheduled at 1, 2, 4, 6, and 12 weeks and 6 months postoperatively, with orbital region infection as the primary end point. The findings revealed no significant difference in the rate of wound infection between the two groups. This suggests that antibiotic prophylaxis extending beyond 24 hours postoperatively does not significantly contribute to the prevention of postoperative infection and infectious complications in patients with displaced orbital fractures.[9]

Habib et al.[11] performed a meta-analysis and systematic review to evaluate the effect of postoperative antibiotic prophylaxis on the incidence of SSI in patients undergoing surgery for maxillofacial fractures. This review included 7 randomized controlled trials and 6 cohort studies, representing a robust sample of 1,268 patients in the intervention group and 968 patients in the control group. The addition of postoperative antibiotic prophylaxis to a standard preoperative and/or perioperative antibiotic regimen showed no significant impact on the risk of SSI. This study does not support the routine use of postoperative antibiotic prophylaxis in patients with maxillofacial fractures.[11]

Blepharoplasty

Infectious complications following blepharoplasty can include both preseptal and orbital cellulitis. Similar to other SSIs, *Streptococcus* and *Staphylococcus* species, particularly *S. aureus*, have been identified as potential causative agents.[12]

In the outpatient setting, the overall incidence of postoperative infections associated with eyelid surgery remains low. In a retrospective study conducted by Carter et al.[13] including 1,861 patients who underwent blepharoplasty with or without laser resurfacing, only 5 individuals were found to have postoperative infections. Topical antibiotics were administered to most patients in the study, and cases of infection were successfully managed with postoperative topical antibiotic treatment.

Despite the low incidence of postoperative infections, it is noteworthy that there has been a rise in the utilization of prophylactic antibiotics. However, there is not enough evidence supporting the effectiveness of antibiotic prophylaxis in blepharoplasty procedures.

Cefazolin has been established as the preferred preoperative antibiotic for facial cosmetic surgery, with selection based on expected pathogens. Nevertheless, the use of antibiotic prophylaxis in blepharoplasty remains a subject of debate, and there remains no universally accepted standard of care, resulting in varying practices worldwide. Gonzalez-Castro and Lighthall[14] acknowledged the absence of compelling evidence to support routine antibiotic prophylaxis in blepharoplasty and advocated for further research in this area, while Carter et al.[13] concluded from their study that topical antibiotic prophylaxis alone was sufficient for blepharoplasty procedures.

At present, specific guidelines regarding antibiotic prophylaxis for blepharoplasty are lacking, necessitating individual judgment on the part of the surgeon. In cases where a measurable risk of SSI is present, the administration of a single dose of intravenous cefazolin or cefuroxime 1 hour before the procedure has shown effectiveness. However, for procedures with extremely low infection rates, the routine use of antibiotic prophylaxis may not provide significant benefits, and potential risks should be taken into account.[12]

In a study of 232 patients investigating whether systemic prophylactic antibiotics reduce SSI in elective lid surgery, 99 patients were given combined systemic and topical antibiotics, while 133 patients were given only topical antibiotics.[15] Three patients in the combined group and two patients in the topical antibiotic group needed additional treatment. This study suggests that routine systemic antibiotic prophylaxis is not necessary in these patients.[15]

Dacryocystorhinostomy

Data on SSI rates in external dacryocystorhinostomy (DCR) surgery are scarce. Therefore, the question of whether routine postoperative antibiotic prophylaxis is necessary in external DCR remains somewhat controversial, as there is limited literature available to provide clear recommendations on preferred practice.[16]

Sheth et al.[16] conducted a study to compare the efficacy of postoperative oral antibiotics versus a single intravenous perioperative bolus dose of antibiotic prophylaxis in preventing SSIs after external DCR. The study included 338 adult patients

(aged 18 years or older) with primary acquired nasolacrimal duct obstruction who underwent external DCR. It is important to note that a minimum of 4 weeks of postoperative follow-up was required for inclusion. The patients were randomly divided into two groups. Group A received a single intravenous perioperative bolus dose of 1 g cefazolin (a first-generation cephalosporin) administered within 15 minutes before the surgical incision. On the other hand, Group B received postoperative oral antibiotic prophylaxis consisting of 500 mg cefalexin taken twice daily for 5 days. The final analysis included 155 patients in Group A and 156 patients in Group B because of some loss to follow-up. The main outcome assessment took place 4 weeks after the postoperative follow-up. None of the patients in Group A, who received the single perioperative intravenous bolus dose of antibiotic, showed any evidence of SSI. Only one patient in Group B, who received the 5-day postoperative oral antibiotic regimen, developed an SSI, which was successfully managed with medical treatment. The study findings suggest that, in the current clinical setting, the use of a single intravenous bolus dose of antibiotic is as effective as the more commonly used 5-day oral antibiotic regimen in preventing postoperative SSI in external DCR.[16]

In another retrospective study including 1020 eyes of 899 patients, external DCR was performed on 747 eyes and endonasal DCR was performed on 273 eyes. None of the patients received preoperative prophylactic systemic antibiotic therapy. Postoperative SSI was observed in 8 patients who underwent external DCR (0.8% of all patients, 1.1% of external DCR patients), whereas no SSI was observed in any endoscopic DCR patient. The 8 patients diagnosed with postoperative SSI were successfully treated with oral systemic antibiotic therapy. No statistically significant difference was observed between the external and endonasal DCR groups in terms of postoperative SSI development. The authors concluded that lacrimal surgery is safe without the routine administration of prophylactic systemic antibiotics.[17]

In a retrospective study conducted to investigate the effect of preoperative, perioperative, and postoperative antibiotic use on the risk of infection after endoscopic DCR, postoperative infection was observed in 22 (6.6%) of 331 patients.[18] There was no significant difference in postoperative infection rates among patients who did not have acute dacryocystitis preoperatively and received peri- and postoperative antibiotics. However, patients who received antibiotics within 2 weeks before surgery for acute dacryocystitis but did not receive peri- or postoperative antibiotics had a higher postoperative infection rate. This study suggests that antibiotics may be beneficial when there is recent or active dacryocystitis before surgery, but otherwise, routine antibiotic prophylaxis is not necessary in endoscopic DCR.[18]

Special Agents

Mitomycin C

Pterygium

The primary treatment for pterygium removal involves surgical excision paired with conjunctival autograft (CAG).[19] Various adjunctive treatments have been designed to minimize the risk of pterygium recurrence. Among these, the antineoplastic agent MMC (0.02%) is the most commonly utilized due to its safety profile. By interfering with cell proliferation, MMC effectively controls endothelial cell proliferation during pathophysiological angiogenesis. However, the precise effectiveness and safety of MMC remain uncertain.[20,21]

To elucidate the efficacy and safety of MMC, Taher et al.[20] conducted a systematic review and meta-analysis. Their study aimed to thoroughly evaluate the combinations of CAG with MMC and amniotic membrane transplantation (AMT) with or without MMC in comparison to surgical excision with CAG alone for the treatment of primary pterygium. Outcome measures included recurrence rates and adverse events. The study included a total of 557 participants who received CAG alone, 520 who received AMT, and 67 who received CAG + MMC. The patients' mean ages ranged from 37 to 63 years across all treatment arms. Statistically significant reductions in recurrence rates were observed in the subgroup analysis of patients treated with CAG + MMC. Furthermore, 0.02% MMC was associated with lower recurrence rates compared to 0.01% MMC. The study findings underscored the effectiveness of CAG + MMC over other tissue grafting techniques in pterygium treatment. A one-time topical application of 0.02% MMC during pterygium excision followed by CAG transplantation was found to reduce the pterygium recurrence rate to 1.4% without causing serious complications.[20]

In a retrospective study, Katircioğlu et al.[22] compared the techniques of AMT, CAG, and MMC combined with excision in the treatment of primary and recurrent pterygium. A total of 49 cases, including 30 primary and 19 recurrent pterygium, were included in the evaluation. The patients were divided into three groups: Group 1 underwent excision with CAG (n=25; 18 primary, 7 recurrent pterygium), Group 2 underwent AMT (n=16; 12 primary, 4 recurrent pterygium), and Group 3 received low-dose MMC (0.02%) with CAG (n=8; all recurrent pterygium). AMT and CAG were equally effective in preventing recurrence in primary pterygium, and the combination of MMC and CAG was found to be at least as effective as CAG and AMT in the treatment of recurrent pterygium. The authors emphasized that a combined technique with MMC would be better reserved for recurrent or resistant cases, while one of the other two procedures should be used for the treatment of primary cases.[22]

Interferon Alpha-2b

Conjunctival Melanoma

The primary treatment for conjunctival melanoma (CM) is surgical excision with wide margins and double freeze-thaw cryotherapy.[23,24] However, there remains a lack of consensus regarding a standard topical adjuvant therapy. Primary acquired melanosis (PAM) with atypia can evolve into CM, leading to local recurrence after removal and possible regional or systemic spread.[23] IFN alpha-2b is an immunomodulatory glycoprotein with a direct impact on tumor cells, potentially activating the

host immune system to target the tumor. Given the rarity of the condition (0.24-0.8 cases/million people), it is challenging to assess the effectiveness of topical IFN alpha-2b after CM resection. Topical IFN alpha-2b may be an alternative for recurrence. This treatment has seen success as either a primary or adjunctive treatment for ocular surface squamous neoplasia, and has been used in isolated cases of conjunctival PAM with positive outcomes and good tolerance.[25]

In a retrospective study by Huerva et al.[25], two patients with CM (a 66-year-old man and a 68-year-old woman) were treated with surgical excision using the "no-touch technique" followed by topical IFN alpha-2b (1,000,000 UI/mL) applied 4 times daily for 12 weeks as the primary treatment. The results demonstrated that supplementary IFN alpha-2b may extend survival up to 6 years post-resection in stage T1 patients, regardless of margin involvement, which aligns with previous studies. The authors concluded that IFN alpha-2b can continue to be used as an adjunctive therapy after CM resection due to its overall tolerability and proven efficacy in preventing recurrence.[25]

Squamous Cell Carcinoma

Ocular surface giant squamous cell carcinoma (SCC) is an invasive malignant lesion that can occur on the conjunctiva and cornea. It exhibits diverse presentations from inter-epithelial neoplasia to full-fledged squamous carcinoma with metastatic potential.

Recent studies have demonstrated the efficacy of early surgical excision followed by IFN alpha-2b as a coadjuvant topical treatment for invasive giant SCC. In one case report, biopsies from various parts of the conjunctiva, cornea, and limbus after treatment showed no signs of cellular dysplasia, and the patient remained tumor-free for 24 months. Mild hyperemia was the sole adverse event and resolved post-treatment.[26]

Traditionally, the primary modality for treating ocular surface SCC has been surgical resection. However, it carries a recurrence rate of 25-53%.[26] The usage of topical or intralesional antineoplastic agents like MMC or IFN alpha-2b has gained traction in recent years.[26,27,28] Despite its widespread use, MMC has been associated with multiple side effects, including scleral thinning, corneal perforation, and squamous metaplasia.[26,28] In contrast, IFN alpha-2b offers a safer topical treatment with superior patient tolerability.[26] Intralesional IFN alpha-2b has shown promising results in managing primary lesions and recurrences, typically as standalone treatment. In certain instances, it is applied preoperatively to decrease tumor size.[26] Research has indicated that complete remission is achieved in 72% of giant tumors treated solely with IFN alpha-2b either topically or via intralesional administration, while the remaining 28% display a substantial reduction in size.[26,29]

5-fluorouracil

Squamous Cell Carcinoma

SCC is the most common malignant conjunctival tumor and is characterized by invasion of the conjunctival stroma. The standard treatment strategy involves extensive local excision, supplemental cryotherapy, and thorough histological evaluation of the surgical margins. Despite these measures, there is a high rate of recurrence, even when the primary excision margins are devoid of malignant cells.[30,31] Topical chemotherapeutics such as MMC and 5-FU, either as monotherapy or as an adjunct to surgical excision, have been found effective against conjunctival and corneal intraepithelial neoplasia.[30,31,32]

A recent study evaluated the efficacy of topical 5-FU applied after conjunctival and corneal mass biopsies. Ten patients diagnosed with SCC of the conjunctiva, cornea, or both were treated with 1% topical 5-FU (administered as pulse doses four times daily for 4 days at monthly intervals for six cycles) and followed up for an average of 14.53 months (range, 6-30 months). All tumors responded to the topical 1% 5-FU treatment, with most patients achieving tumor resolution after the initial treatment series and requiring no further 5-FU treatment after six cycles. One patient who previously underwent three excisions and two cycles of 0.02% MMC eye drops in a different ophthalmic department had early disease recurrence. However, the tumor resolved after administering six cycles of topical 5-FU at monthly intervals, and the patient remained recurrence-free for 12 months after the final treatment cycle. This study supports the effectiveness of topical 1% 5-FU in managing SCC with no observable side effects. However, retreatment becomes necessary if the lesion recurs, and excisional biopsy is recommended if treatment fails.[31]

Anophthalmic Contracted Socket

A contracted socket can be described as the consequence of orbital tissue shrinkage and shortening, leading to a reduction in orbital volume and fornix depth. This results in the incapacity to hold a prosthesis in place. The impact of this condition can be both functional and psychological, significantly affecting the patient's well-being. Irrespective of the specific method or graft employed for reconstruction, the primary goal is to establish a socket that can accommodate a prosthesis, thereby achieving a satisfactory cosmetic outcome. The key to successful postoperative outcomes in socket procedures is the prevention of scarring. Recurrent socket contraction is often seen due to surgical bed contracture, necessitating multiple surgical interventions.[33]

Kamal et al.[33] conducted a retrospective comparative case series study to assess the efficacy of 5-FU following anophthalmic contracted socket surgery. The study included 15 adult patients exhibiting signs of recurrent socket contraction following reconstructive surgery using a buccal mucosa graft. The patients were split into two groups, with 8 patients (Group A) receiving serial subconjunctival 5-FU, and 7 patients (Group B) serving as a control group. Notably, none of the patients had previously had an implant in the socket. All patients underwent socket reconstruction with a full-thickness buccal mucosal graft from the lower lip used to augment the surface area in a standard manner. Patients in Group A were administered subconjunctival injections of 10 mg 5-FU in the superior and inferior fornices on a weekly basis for a total of four injections. In contrast, patients in Group B were managed conservatively. After 5-FU treatment,

substantial improvement in fornix depth and socket volume was observed in 7 out of 8 patients in Group A, allowing for the fitting of larger conformers and subsequently prostheses with pleasing cosmetic results. Thus, weekly 5-FU injections were proven to be highly effective in mitigating recurrent fibrosis and contraction when applied early after reconstructive surgery. However, the authors noted that further evaluation is necessary to assess the optimal dose for serial subconjunctival 5-FU injections and the long-term effects of this treatment.[33]

Amphotericin-B in Sino-orbital Fungal Infections

While infrequent, sino-orbital fungal infections can lead to considerable adverse health effects, even resulting in death. Fungal colonization or non-invasive infections in the paranasal sinuses are more common, arising from inhaling fungal spores. In those with robust immune systems, these conditions can be managed effectively, often leading to favorable outcomes. However, for individuals with compromised immune systems, these infections can become invasive, causing substantial tissue damage and potentially fatal outcomes. These infections often spread from the paranasal sinuses to the orbit, which can exacerbate the condition due to the direct connections to the intracranial space.[4,34,35]

Conventional treatment modalities encompass systemic antifungal treatment, extensive surgical removal of affected tissues through sinus surgery and potential orbital exenteration, and enhancing the patient's immune capabilities and metabolic condition when possible. However, several older studies reported promising outcomes with limited orbital debridement paired with localized irrigation with amphotericin B alongside systemic antifungal treatment.[36]

To assess the effectiveness of amphotericin B, a study was conducted on 7 consecutive patients diagnosed with sino-orbital fungal infections. As soon as the diagnosis was suspected or confirmed by biopsy, each patient was administered intravenous amphotericin B (25-50 mg/day). Certain surgical procedures were also performed. Firstly, necrotic tissue was cautiously removed until healthy tissue with sufficient blood supply was visible. Crucial orbital structures, such as the medial and lateral rectus muscles and the globe, were identified and preserved whenever feasible. Prior to wound closure, intraoperative irrigation of the orbit and sinuses with an amphotericin B solution was performed. Care was taken to observe the outflow of the amphotericin B solution within the orbit and sinuses to ensure accurate placement and prevent significant proptosis during irrigation. The wound was subsequently closed in layers. Postoperatively, patients were subjected to three to four daily irrigations with 3-4 mL of amphotericin B. The study outcomes showed that a treatment regimen consisting of surgical debridement, local amphotericin B irrigation, and systemic amphotericin B therapy was successful in managing sino-orbital fungal infection in these seven cases. Most patients who had excellent preoperative vision were able to maintain their visual acuity postoperatively. Thus, the authors concluded that conservative orbital debridement combined with local amphotericin B irrigation is an effective supplementary treatment strategy for managing sino-orbital fungal infections.[36]

Conclusion

The use of prophylactic antibiotics is crucial in reducing the risk of infection in certain extraocular surgical procedures, but their effectiveness may not be significant in other surgeries. Antibiotic prophylaxis may not be required for every extraocular surgery. Multicenter, comparative, controlled studies are needed regarding the effectiveness and efficiency of prophylactic antibiotic use. Agents such as MMC and IFN alpha-2b have demonstrated efficacy in reducing the recurrence of extraocular conditions and enhancing surgical results. However, studies involving larger patient populations are required to solidify these findings and aid in the development of standardized treatment protocols.

Declarations

Authorship Contributions

Concept: D.D.A., Y.A.K., Design: D.D.A., Y.A.K., Data Collection or Processing: D.D.A., Analysis or Interpretation: D.D.A., Literature Search: D.D.A., Writing: D.D.A.

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Case Report

West Nile Virus Chorioretinitis: First Case with Ocular Involvement in Türkiye

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Abstract

A 59-year-old man who experienced severe visual loss in the right eye for two days following a febrile illness (high fever lasting for 15 days) presented to our center for a second opinion. On examination, his Snellen best corrected visual acuity (BCVA) was 1/10 in the right eye and 9/10 in the left eye. On fundoscopy, we observed a few track-like, cream-colored linear lesions in the superior fundus of the left eye and a small whitish foveal discoloration together with a temporally pallid disc in the right eye. On autofluorescence imaging, there were some scattered hyperautofluorescent patchy areas bilaterally and, most notably, several hyperautofluorescent track-like lines in the left eye. A complete systemic evaluation was carried out and a blood sample was sent via the Provincial Health Directorate for West Nile virus (WNV) polymerase chain reaction and immunoglobulin (Ig) M and G testing. IgM and IgG antibodies were detected by immunofluorescence assay. The diagnosis was bilateral WNV chorioretinopathy. Magnetic resonance imaging of the brain ruled out any central nervous system involvement. A right intravitreal ranibizumab injection was administered for the intraretinal edema. A month later, Snellen BCVA was 2/10 in the right eye 10/10 in the left. Hyperautofluorescent lesions were no longer detectable in either eye but the right optic disc still appeared pallid. Clinicians should suspect WNV horioretinitis in cases presenting with characteristic fundus lesions and a history of febrile illness.

Keywords: Chorioretinitis, fundus autofluorescence, optical coherence tomography, ranibizumab, West Nile virus infection

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Introduction

West Nile virus (WNV) is a single-stranded ribonucleic acid (RNA) flavivirus conveyed mainly by the bite of infected mosquito species of the genera *Culex* and *Aedes*.[1] Though WNV was reported in a Ugandan patient in 1937,[2] the first reports from the western hemisphere about the virus did not appear until the 1999 meningoencephalitis outbreak in the New York City metropolitan area.[3] In 2002, a case of optic neuritis with meningoencephalitis involvement was documented.[4]

WNV infection is asymptomatic in approximately 80% of cases, presents as influenza-like illness in around 20% of cases, and causes meningoencephalitis in less than 1% of cases.[5] Its incubation period is between 3 and 14 days, after which fever, headache, generalized myalgia, asthenia, gastrointestinal symptoms, and maculopapular rash may occur. Neurologic involvement can manifest as meningitis, encephalitis, and meningoencephalitis.[6] The mortality rate is approximately 10% when the central nervous system is involved.[7]

The first case of WNV with chorioretinitis was confirmed by positive immunoglobulin M (IgM) serological test in 2003.[8] WNV-related ocular manifestations described to date include anterior uveitis, vitritis, bilateral multifocal chorioretinitis, non-occlusive or occlusive retinal vasculitis, retinitis, focal lesions without uveitis, macular edema, optic neuritis, neuroretinitis, papilledema, optic atrophy retrogeniculate damage, ocular nerve palsy, and nystagmus.[9,10,11,12,13,14] However, the most common manifestation of ocular WNV infection is chorioretinitis, which is observed in more than 85% of cases presenting with ocular involvement.[12]

We hereby present a case of WNV chorioretinitis diagnosed in Türkiye and share its multimodal imaging features and outcome.

Case Report

A 59-year-old man who experienced severe visual loss in the right eye for two days following a febrile illness (high fever lasting for 15 days) presented to our center for a second opinion. On examination, his Snellen best corrected visual acuity (BCVA) was 1/10 and 9/10 in the right and left eye, respectively. No relative afferent pupillary defect (RAPD) was noted, and his Ishihara color vision test results were 18/21 in the right and 21/21 in the left eye. Slit-lamp examination was unremarkable and intraocular pressure was within normal range bilaterally. On fundoscopy, we observed a few track-like, cream-colored linear lesions in the superior fundus of the left eye and a small whitish foveal discoloration and temporally pallid-looking disc in the right eye (Figure 1a, b). On autofluorescence imaging, there were some scattered hyperautofluorescent patchy areas bilaterally, and most notably, a few track-like linear hyperautofluorescent lesions in the left eye (Figure 1c, d). Optical coherence tomography (OCT) demonstrated some hyperreflective dots in the posterior vitreous, foveal intraretinal cysts, and focal alterations in the retinal pigment epithelium (RPE) and ellipsoid zone (EZ) in the right eye, as well as focal alterations in the RPE and EZ corresponding to the hyperautofluorescent linear changes in the left eye (Figure 1e, f). Fluorescein angiography (FA) showed a few hyperfluorescent lesions at the posterior pole in both eyes, and hyperfluorescent linear lesions extending towards the retinal periphery corresponding to the hyperautofluorescent lines were noted in the left eye (Figures 2a, b and 3a, b). A macular 6x6 mm optical coherence tomography angiography (OCTA) scan exhibited areas of flow void in the right fovea (Figure 2c), whereas OCTA features of the left macula were unremarkable (Figure 3c).

The patient's history of febrile disease and the bilateral multifocal chorioretinitis suggestive of WNV chorioretinopathy prompted us to look for a possible West Nile fever infection in addition to other infectious causes. A complete physical examination, pertinent laboratory tests, and chest X-ray were carried out at the infectious disease department, and a blood sample was sent via the Provincial Health Directorate for WNV serological evaluation. Antibody serology by immunofluorescence assay showed the presence of IgM and IgG antibodies, but RNA polymerase chain reaction was negative for WNV. Magnetic resonance imaging (MRI) of the brain ruled out central nervous system involvement. After reviewing the current literature and discussing the options with the patient, we administered a single intravitreal 0.5-mg ranibizumab injection to the right eye.

One month after the injection, Snellen BCVA was 2/10 in the right and 10/10 in the left eye. No RAPD was noted and Ishihara color vision was 1/21 in the right and 21/21 in the left eye. Autofluorescence, FA, OCTA, and OCT of the right eye showed that the posterior pole looked almost normal with only temporal optic disc pallor (Figure 4a, b, d, e). The central fixation point was slightly shifted in the right eye (Figure 4c). There was retinal nerve fiber loss in the temporal quadrant (Figure 4f). The left fundus appeared normal on multimodal imaging, and the previously observed hyperautofluorescent lines were no longer visible (Figure 5).

Discussion

WNV infection has been detected previously in Türkiye. Serter[15] reported 29.1% seropositivity in a study conducted in the Aegean part of Türkiye in 1980. Several studies between 2007 and 2010 showed seropositivity rates of 9.4% and 0.56% respectively among blood donors in the South-East and Central Anatolia regions, while 9.2% IgM and 3.4% IgG seropositivity was reported in patients with aseptic/viral meningitis/encephalitis.[16,17,18] In 2010, 47 cases of WNV in humans (median age 58 years, mainly from western provinces) were identified in Türkiye.[19] However, only 12 could be confirmed by the laboratory. Forty of the patients had central

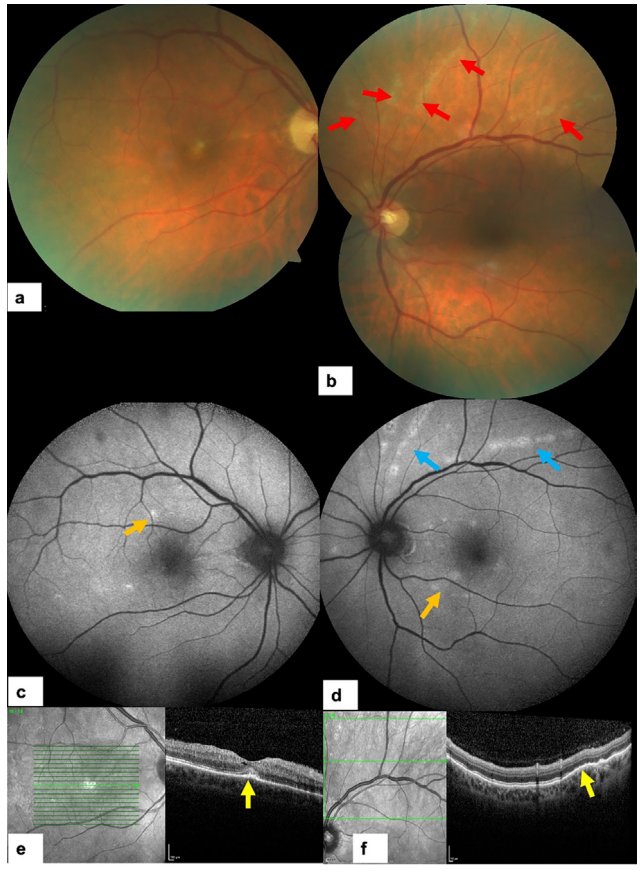

Figure 1. Imaging obtained at first presentation (August 2024): color fundus photographs depicting the small whitish area at the foveal center in the right eye (a) and normal looking macula with path-like cream-colored linear lesions in the superior retina (red arrows) in the left eye (b). Fundus autofluorescence images showing a few hyperfluorescent lesions at the macula (orange arrow) in the right eye (c) and linear hyperautofluorescent lesions extending from posterior pole to periphery (blue arrows) and a few hyperfluorescent lesions at the macula (orange arrow) in the left eye (d). Optical coherence tomography (OCT) of the right eye (e) demonstrating intraretinal cysts, subfoveal hyperreflective material deposition (yellow arrow), a few hyperreflective dots in the posterior vitreous, and foveal retinal pigmented epithelium (RPE) and ellipsoid zone (EZ) alterations. An OCT section taken over the linear lesions in the left eye (f) delineating focally altered RPE and EZ with focal choroidal thickening (yellow arrow)

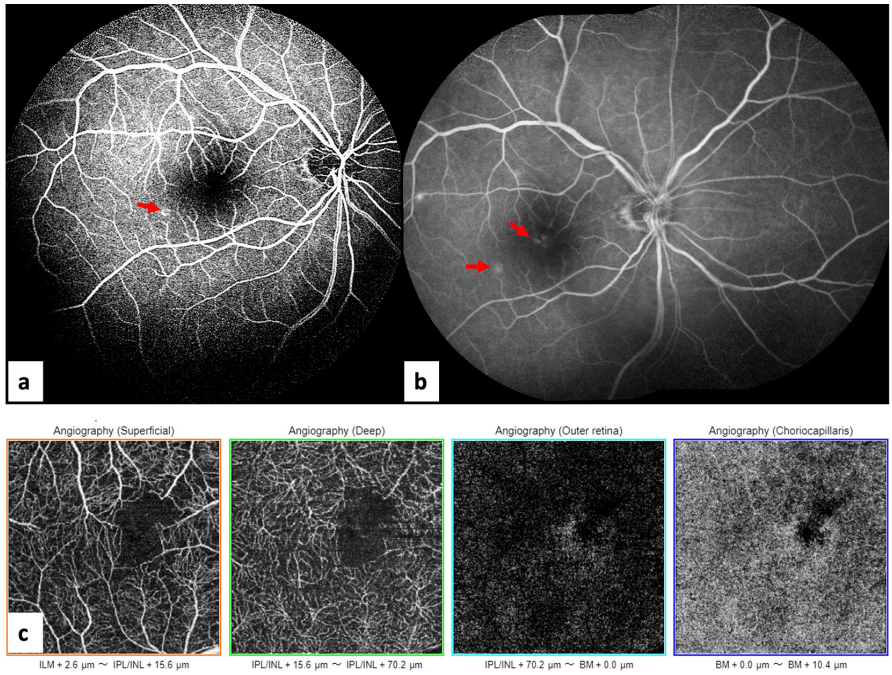

Figure 2. Right eye at first presentation (August 2024): early (a) and late (b) phase fluorescein angiographic images showing central hyperfluorescence together with some hyperfluorescent punctate areas around the macula (red arrows). c) 6x6 mm optical coherence tomography angiographic scans exhibiting a central flow void

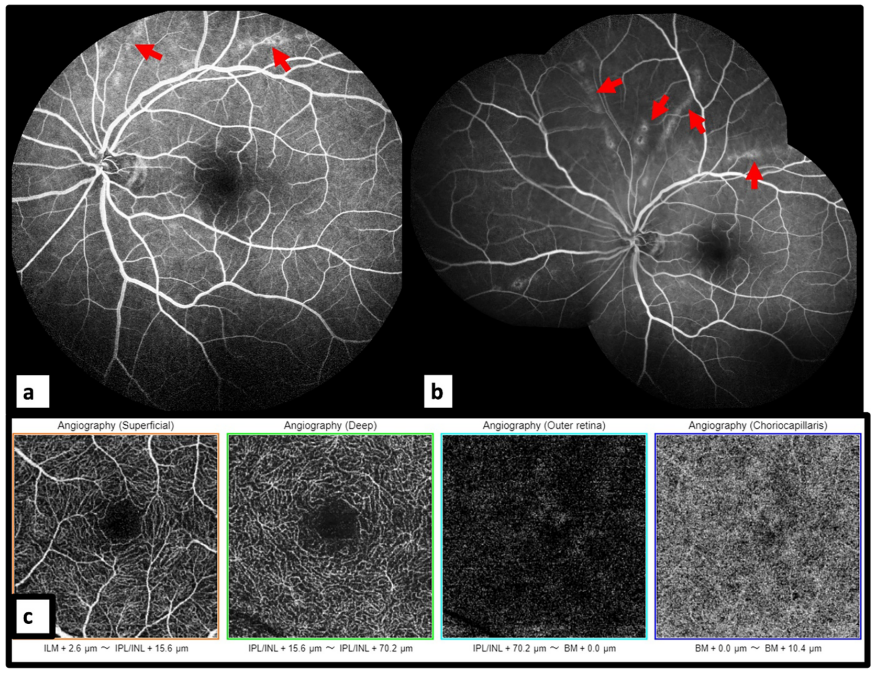

Figure 3. Left eye at first presentation (August 2024): a, b) fluorescein angiographic images showing hyperfluorescent linear lesions (red arrows) extending from the posterior pole to the fundus periphery. c) Normal-looking optical coherence tomography angiography (6x6 mm scans)

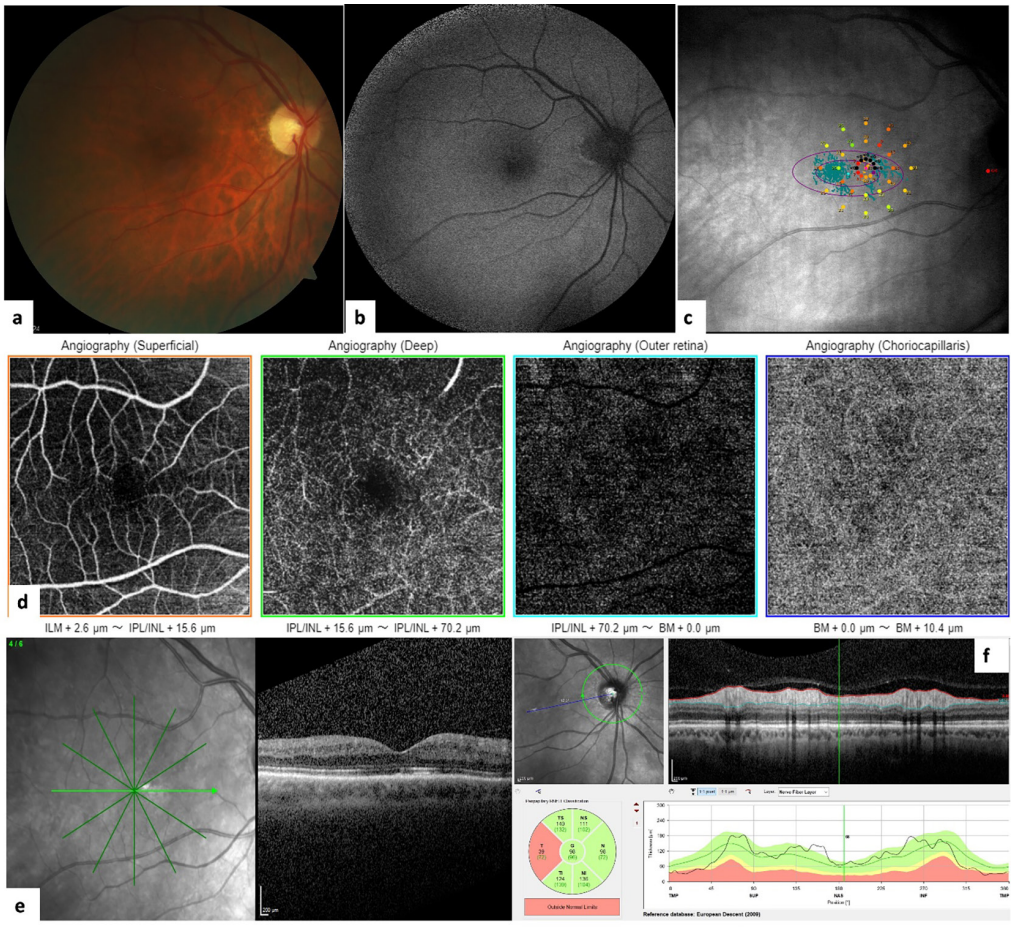

Figure 4. Right eye at last visit (one month after injection): a) almost normal-looking fovea with some temporal optic disc pallor. b) Fundus autofluorescence image exhibiting the disappearance of previously noted hyperautofluorescent lesions. c) Microperimetry depicting the shift of the foveal fixation point. d) Normal optical coherence tomography angiography (6x6 mm scans). e) Optical coherence tomography showing resolution of the intraretinal foveal edema. f) Retinal nerve fiber loss at the temporal quadrant on retinal nerve fiber layer analysis

nervous system manifestations and a total of 10 patients died. However, no case with ocular involvement was noted.[19]

A group of WNV-positive patients in Houston, Texas were followed prospectively for a median of 6.8 years (range, 0.1-11 years) from the time of acute infection, and WNV chorioretinitis occurred in nearly a quarter of them (27/111).[20] Seventeen (49%) of the 35 patients who presented with encephalitis had evidence of WNV chorioretinitis, compared to none (0%) of the 14 meningitis cases, 9 (25%) of 36 uncomplicated fever cases, and 1 (4%) of 26 asymptomatic cases. WNV chorioretinitis was seen more frequently in patients over 60 years of age and patients with diabetes mellitus and signs of encephalitis. Thus, WNV chorioretinitis seemed to be more commonly detected in patients with severe neurological sequelae. Very recently, Ruiz-Lozano et al.[21] reported a case of ocular WNV infection and performed a review of the relevant literature through October 2023. They included only cases with ocular involvement and serologic and/or cerebrospinal fluid confirmation. Overall, 111 eyes of 60 patients were taken into consideration. The median time from the viral prodrome to onset of ocular symptoms was 7 days, and neurologic involvement was noted in 47 patients (78%). Posterior segment findings were observed in 107 eyes (96%), including characteristic multifocal chorioretinal lesions in 86% of eyes. Topical and systemic treatment was administered for 35% and 28% of the eyes, respectively.[21] Our patient had no neurologic manifestations, as evidenced by normal MRI, but had apparent bilateral chorioretinitis.

Multimodal imaging has a crucial role in establishing the diagnosis of WNV chorioretinitis.[14,21,22,23,24] Chorioretinal lesions in acute cases are classically described as deep, round, cream-colored lesions.[9,22,23] Typical fundus autofluorescence imaging shows characteristic lesions such as multiple well-delineated, mixed hypo- or hyper-autofluorescent punctate chorioretinal lesions or a linear pattern that helps the clinicians to distinguish WNV from other forms of chorioretinitis.[22] These curvilinear

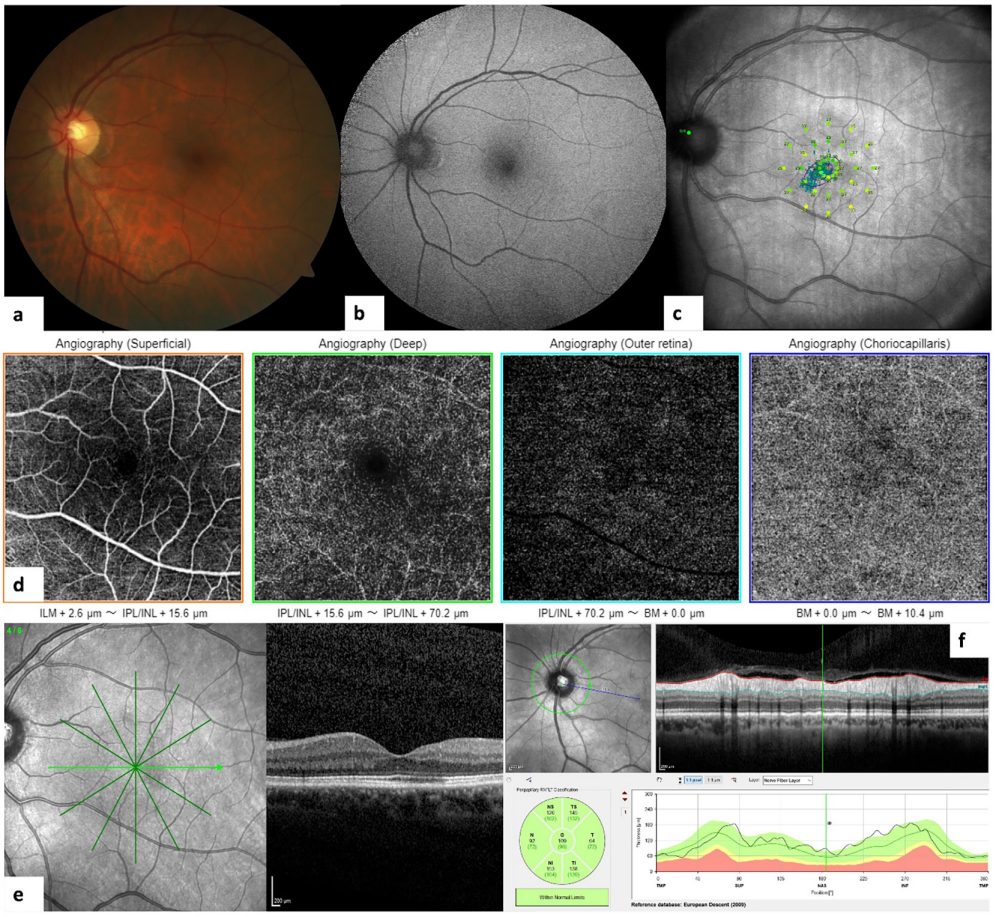

Figure 5. Left eye at last visit: a) normal fundus appearance. b) Disappearance of hyperfluorescent linear lesions previously noticed on fundus autofluorescent images at presentation. c) Normal fixation pattern on microperimetry. d) Unremarkable optical coherence tomography angiography appearance (6x6 mm scans). e) Normal foveal contour on optical coherence tomography. f) Normal nerve fiber layer thickness analysis

retinal lesions are thought to be related to spread of virus from the central nervous system to the retina via the optic nerve.[25] Hematogenous spread may also occur via the choroidal circulation.[26,27] FA usually shows pathognomonic target-like lesions (central hypofluorescence with a hyperfluorescent rim) extending curvilinearly from the optic nerve head.[25] OCT reveals deeper lesions that do not involve the inner retinal layers and nerve fiber layer and may show signs of macular edema.[23,26,27,28,29] The autofluorescence images obtained in the present case encouraged us to investigate the possibility of WNV infection.

Optic neuritis or chorioretinitis in a patient with possible meningoencephalitis during mosquito season should raise suspicion of WNV infection.[30] Diagnosis of WNV-associated ocular lesions is based on ophthalmological examination, detection of specific IgM antibodies, and exclusion of other more common forms of uveitis.[13,14] While treatment is mainly supportive, topical and systemic steroids may be employed for the ophthalmic findings, but there is no clear data regarding their efficacy.[31] Except for the most severe cases requiring hospitalization, WNV chorioretinitis is considered a self-limiting pathology with partial visual recovery unless secondary inflammatory choroidal neovascularization (CNV) occurs.[26]

Macular edema may also occur due to increased vascular permeability resulting from WNV chorioretinitis and retinal vasculitis.[32] The utilization of intravitreal anti-vascular endothelial growth factor agents was reported in patients with WNV infection developing macular edema[32] and CNV.[5,26] In our case, a single intravitreal ranibizumab injection was administered to alleviate the right macular edema. A month later, partial resolution of macular edema was noted on OCT. However, associated probable optic nerve damage limited visual improvement. No additional injection was given.

To the best of our knowledge, the present case is the first documented case in Türkiye of WNV-associated ocular involvement consisting of bilateral chorioretinitis with unilateral foveal edema and optic nerve damage following an acute WNV infection. Clinicians in endemic regions should be alert to the classic fundus features of WNV chorioretinopathy to establish the correct diagnosis even in the absence of neurological involvement.

Ethics

Informed Consent: The patient's consent has been obtained.

Declarations

Authorship Contributions

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

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Case Report

Progressive Loss of Myelinated Retinal Nerve Fibers in a Case of Open-Angle Glaucoma

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Abstract

Myelinated retinal nerve fibers (MRNFs) result from a developmental anomaly in which ectopic oligodendrocytes myelinate retinal ganglion cell fibers. These fibers typically remain stable over time in the absence of pathology. We identified unilateral MRNFs in a patient during an ophthalmological examination associated with ocular hypertension. Over an 8-year follow-up period, we observed a progressive decrease in the retinal nerve fiber layer and a rarefaction of MRNFs, which we attributed to the lack of regular follow-up and treatment compliance. The absence of neuropathy control in this patient makes this description close to the natural evolution of the disease. Similar progressive disappearance of MRNFs has been observed in cases of Behçet's disease, pituitary adenoma, and open-angle glaucoma. In patients with known MRNFs, their disappearance should alert clinicians to potential optic nerve damage and prompt further examinations to determine the underlying cause.

Keywords: Open-angle glaucoma, myelinated retinal nerve fibers, glaucomatous optic neuropathy

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Introduction

Myelinated retinal nerve fibers (MRNFs) appear as white striated patches with poorly defined borders. This rare and predominantly benign congenital anomaly results from ectopic oligodendrocytes myelinating retinal ganglion cell fibers. Their prevalence is low, ranging from 0.34% to 1.03%,[1,2] and they tend to remain stable over time in the absence of associated pathology.[3] In the scientific literature, MRNFs are most frequently associated with strabismus, anisometropia, and/or amblyopia.[4,5,6]

MRNFs do not impact vision but can interfere with optical coherence tomography (OCT) acquisition due to the masking effect of myelin. When extensive, the software can misinterpret them as a large papilla, resulting in incorrect automatic centering.[7] Their presence can delay the diagnosis of open-angle glaucoma, as reported in a clinical case where the entire optic nerve was covered.[7] Although MRNFs are not associated with an increased risk of glaucomatous neuropathy, a syndrome has been reported in children of consanguineous parents.[8] This report presents a unique case of progressive glaucomatous neuropathy associated with MRNF rarefaction and explores its clinical implications.

Case Report

A 47-year-old woman presented for a renewal of optical correction. Her ophthalmological history included strabismus surgery on the left eye during childhood. Examination revealed a best corrected visual acuity of 20/20 in both eyes. Intraocular pressure (IOP) measured by air puff tonometry was normal in the right eye (13 mmHg; pachymetry of 516 µm) but showed moderate ocular hypertension in the left eye, confirmed by Goldmann applanation tonometry (23 mmHg; pachymetry of 518 µm). Fundus examination revealed MRNFs in the inferior optic nerve region of the left eye. Anterior segment examination was normal in both eyes, and the iridocorneal angle was open.

OCT (Cirrus HD-OCT 4000; Carl Zeiss Meditec, Dublin, CA, USA) showed a normal retinal nerve fiber layer (RNFL) but a slight decrease in ganglion cell layer thickness in the left eye (Figure 1). Three months later, unilateral ocular hypertension was reconfirmed by Goldmann applanation tonometry (10 mmHg in the right eye and 21 mmHg in the left eye). Visual field testing (Octopus Interzeag 1-2-3, Interzeag, Schlieren, Switzerland) was inconclusive, even after repeated attempts. Consequently, a latanoprost eye drop (Monoprost 50 µg/mL; Théa Pharma, Clermont-Ferrand, France) was prescribed at the end of the consultation. A month later, another visual field test revealed a minor nasal defect in the left eye, but the patient did not return for follow-up interpretation with the ophthalmologist.

Eight months later, the patient presented with conjunctivitis at another ophthalmology center, without mention of her recent examinations. IOP without medication, measured by air puff tonometry, was normal in the right eye (14 mmHg) but elevated in the left eye (26 mmHg). OCT (Topcon 3D OCT-1 Maestro, Oakland, NJ, USA) showed normal RNFL thickness in the right eye but a small inferior temporal defect in the left eye. Eleven months later, IOP in the left eye remained elevated (27 mmHg), with thinning of the RNFL in the inferior temporal region. Local treatment was prescribed for the left eye (latanoprost 50 µg/mL; Monoprost). At the check-up appointment, her IOP had decreased to 21 mmHg and the patient was informed of the risks associated with noncompliance with treatment. Investigations were conducted to explore secondary causes of intraocular hypertension in the context of this unilateral affection.

After 1 year, the target IOP (>18 mmHg) was not achieved (22 mmHg in the left eye). Progressive RNFL thinning was observed in both the superior and inferior quadrants. Glaucomatous optic neuropathy was confirmed, with fundus photographs showing rarefaction of MRNFs (Figure 2). Despite a reminder of the importance of regular control and compliance with treatment, the patient's visits remained irregular. Ten months later, the IOP in the left eye was 21 mmHg, due to the self-reported non-compliance with treatment.

The patient was referred to the initial ophthalmology center for consultation with a glaucoma specialist. IOP was measured as 26 mmHg in the left eye (Goldmann applanation tonometry). OCT (Cirrus HD-OCT 5000; Carl Zeiss Meditec, Dublin, CA, USA) was not interpretable due to miosis, and the patient declined an examination with mydriatic eye drops. Due to the failure of previous treatments, combination therapy with

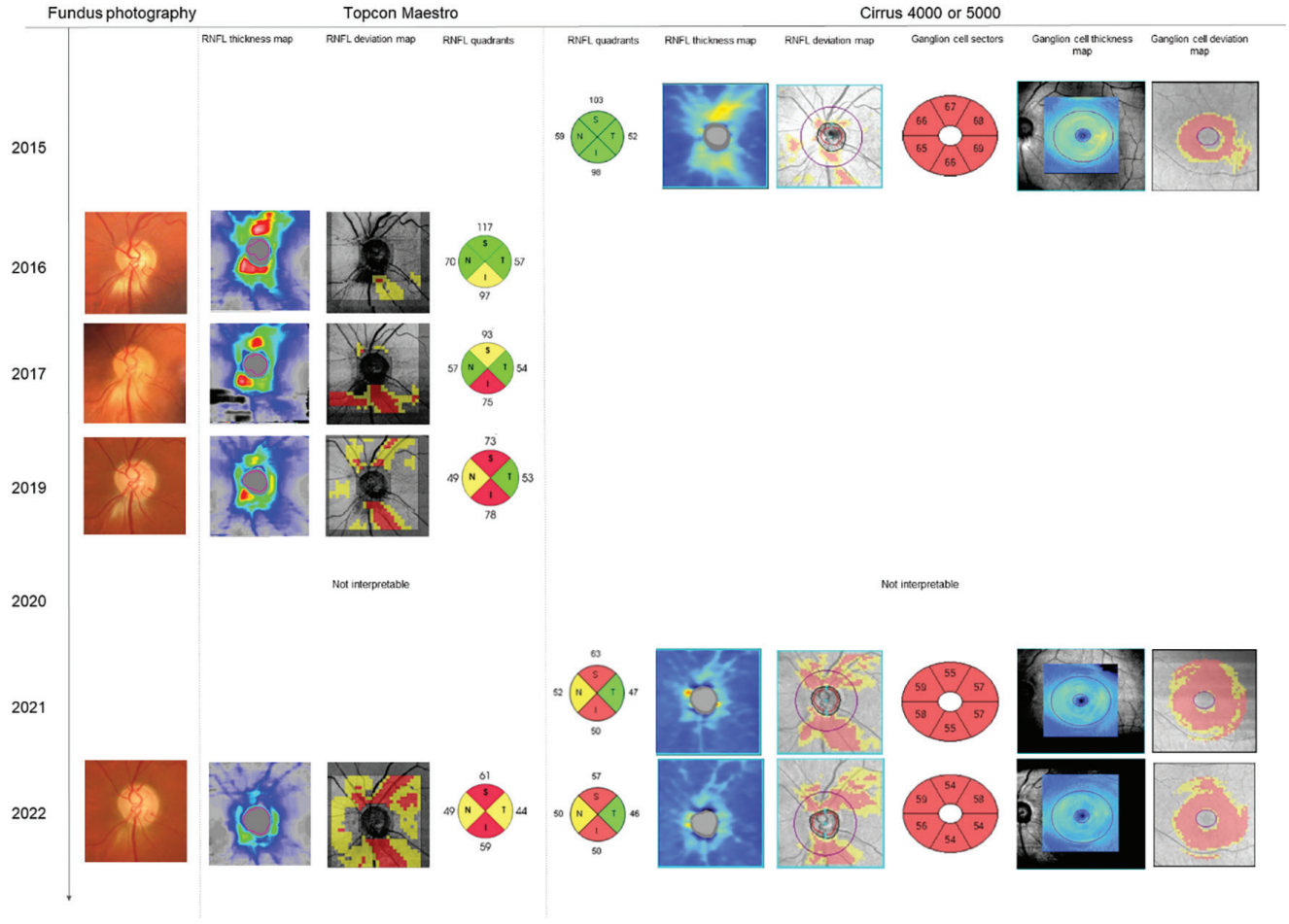

Figure 1. Evolution of the retinal nerve fiber layer and ganglion cells of the patient during follow-up

latanoprost 50 µg/mL (Monoprost) and dorzolamide 20 mg/mL + timolol 5 mg/mL (Dualkopt; Théa Pharma, Clermont-Ferrand, France) was initiated.

Ten months later, target IOP was still not achieved (19 mmHg in the left eye). RNFL thinning progressed in the superior and inferior quadrants. The patient declined selective laser trabeculoplasty and modifications to treatment due to compliance issues. Eight months later, IOP decreased to 17 mmHg in the left eye. Topcon Maestro OCT and fundus photography were performed to compare results with those from the previous clinic.

Discussion

This case highlights the progressive rarefaction of MRNFs in association with uncontrolled glaucomatous optic neuropathy, documented through fundus photography and OCT. The poor treatment compliance of the patient allowed for an observation close to the natural progression of the disease, providing unique insights into MRNFs and glaucoma. The unilateral manifestation of glaucomatous damage enables a comparison with the stability of the RNFL in the fellow eye.

To our knowledge, the regression of MRNFs has been reported in only two other articles.[9,10] In the first case, the patient

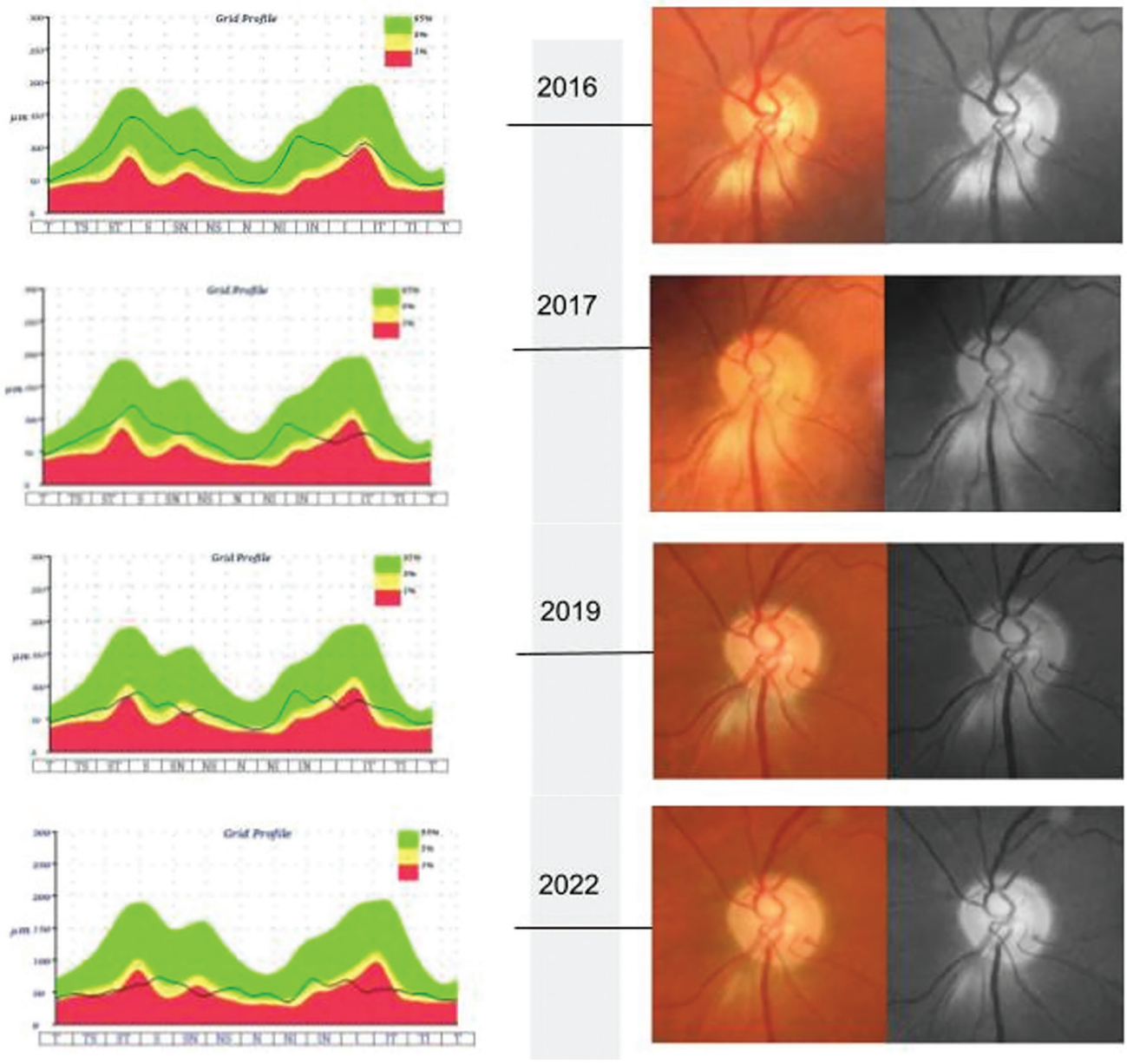

Figure 2. Evolution of the retinal nerve fiber layer and comparison with fundus photography on the Topcon Maestro (3D OCT-1 Maestro, Oakland, NJ, USA)

had a history of diabetes, high myopia, amblyopia, and bilateral glaucoma with high IOP (>37 mmHg).[10] Sellem and Poli[9] also described a patient with unilateral ocular hypertension and MRNFs, similar to this case. However, the current case provides a more detailed description of the progressive RNFL and MRNF rarefaction.

The disappearance of known MRNFs should alert clinicians to possible optic nerve damage. Various potential etiologies exist, including ischemic attacks, Behçet's disease, pituitary adenoma, retinal astrocytoma, Gorlin syndrome, and open-angle glaucoma.[9,10,11,12,13,14,15] These conditions share a common pathway of ganglion cell layer damage. Additional investigations are essential to rule out secondary causes in cases of unilateral ocular hypertension with MRNFs. The association between RNFL thinning and anatomic rarefaction of MRNFs should alert clinicians to potential progressive optic neuropathy.

Ethics

Informed Consent: The patient's consent has been obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: T.L., P.G., Concept: T.J., C.Z., Design: C.Z., Data Collection or Processing: T.J., Analysis or Interpretation: T.L., P.G., Literature Search: T.J., Writing: T.J., T.L., C.Z.

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Bilateral Keratoconus in Diffuse Cutaneous Systemic Sclerosis: A Rare Presentation - Is There Any Role of Autoimmunity?

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Keywords

Case report, systemic sclerosis, collagen vascular disease, autoimmune diseases, keratoconus, collagen-cross linking, secondary Sjögren syndrome dry eye

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Dear Editor,

Keratoconus (KC) has long been defined as a non-inflammatory disease of the cornea. However, recent evidence increasingly suggests the possibility of an underlying subclinical inflammation that may contribute to KC pathogenesis.[1,2] Studies have linked KC to various systemic illnesses such as allergy, atopy, collagen vascular diseases, and autoimmune diseases like ulcerative colitis, rheumatoid arthritis, and Hashimoto's thyroiditis.[1,2] Systemic sclerosis (SSc) or scleroderma is a chronic multi-system autoimmune connective tissue disorder that primarily affects the skin.[3] Ocular involvement is mostly in the form of eyelid abnormalities, dry eye, and retinal and choroidal vasculopathy.[4] In the literature, there are a few solitary reports of KC in SSc.[5,6,7] Here we present two cases of bilateral KC associated with the diffuse cutaneous type of SSc.

Case 1: A 24-year-old Asian female with a history of SSc (anti-SCL70+) diagnosed 2 years earlier presented with complaints of worsening vision in both eyes for 6 months. She was on oral corticosteroids and immunosuppressives that included oral hydroxychloroquine sulfate 200 mg once daily (IPCA Laboratories Ltd., Mumbai, India), mycophenolate mofetil 500 mg twice daily (Panacea Biotec Ltd., New Delhi, India), and nifedipine 20 mg once daily (Cipla Ltd., Mumbai, India) for the last 2 years. There was no history of parental consanguinity, family history of KC, or personal history of chronic eye rubbing, allergic eye disease, atopic disease, or any other systemic diseases. Physical examination revealed generalized skin tightening, taut eyelid skin, and puffy pale fingers suggestive of Raynaud's phenomenon (Figure 1A). The best corrected Snellen's visual acuity (BCVA) was 6/6 in both eyes. Slit-lamp examination showed an incomplete Fleischer's ring (Figures 1B and C) and corneal tomography revealed an inferior cone in both eyes (Figures 1D and E). Dry eye investigations and ocular surface staining were normal. Fundus examination was also normal. Based on the tomographic findings, a diagnosis of stage 1

and stage 2 KC of the right and the left eye respectively was made (as per the Amsler-Krumeich classification system). The patient underwent collagen cross-linking (CXL) in the left eye as per the Dresden protocol. A combination of moxifloxacin eye drops (Cipla Ltd., Mumbai, India) 4 times a day for 1 week and loteprednol etabonate (Sun Pharmaceutical Industries Ltd., Mumbai, India) starting at 4 times a day and tapering weekly over 4 weeks was administered in the immediate postoperative period. The cornea was fully epithelized within 4 days of the procedure. At 1-year follow-up, there was no progression of KC in either eye, and the patient continued to maintain a BCVA of 6/6 binocularly.

Case 2: A 32-year-old Asian female with a 14-year history of diffuse cutaneous SSc (anti-SCL70+) presented with complaints of increased discomfort of dryness for 6 months. The patient was on oral mycophenolate mofetil 500 mg twice daily (Panacea Biotec Ltd., New Delhi, India), methotrexate 5 mg once a week (IPCA Laboratories Ltd., Mumbai, India), deflazacort 6 mg once daily (Sun Pharmaceutical Industries Ltd., Mumbai, India), and pilocarpine hydrochloride 5 mg once daily (FDC Ltd., Mumbai, India) for 6 years. Ocular medications included cyclosporine 0.05% twice daily (Allergan India Pvt. Ltd., Bangalore, India) and a combination of polyethylene glycol and hydroxymethyl cellulose eye drops (Allergan India Pvt. Ltd., Bangalore, India) several times a day. She underwent CXL in both eyes for progressive KC and had secondary Sjögren syndrome dry eye (SSDE). Topical treatment continued with cyclosporine 0.05% twice daily and hydroxymethyl cellulose eye drops several times a day. No familial history of KC or personal history of chronic eye rubbing, allergic eye disease, atopic disease or any autoimmune diseases was reported. Physical examination revealed significant skin stiffness, atrophic patches, digital ulcerations, and dental abnormalities (Figure 2A and B). Her BCVA was 6/12 in the right eye and 6/18 in the left eye. Slit-lamp examination revealed incomplete Fleischer's ring, Vogt's striae, and CXL haze in both eyes (Figure 2C and D) along with moderate papillary changes in the upper tarsal conjunctiva. Dry eye evaluation revealed Schirmer values of 3 mm/5 min, a tear breakup time of 3 seconds, and diffuse corneal and conjunctival punctate staining in both eyes suggestive of SSDE. Corneal tomography revealed an inferior-temporal cone in both eyes (Figure 2E and F). Fundus examination was normal. The topographical parameters seemed stable when compared with previous images. The diagnosis of stage 4 KC and secondary SSDE associated with SSc was made. She was recommended punctal cautery for severe dryness and advised to continue her same ocular medications.

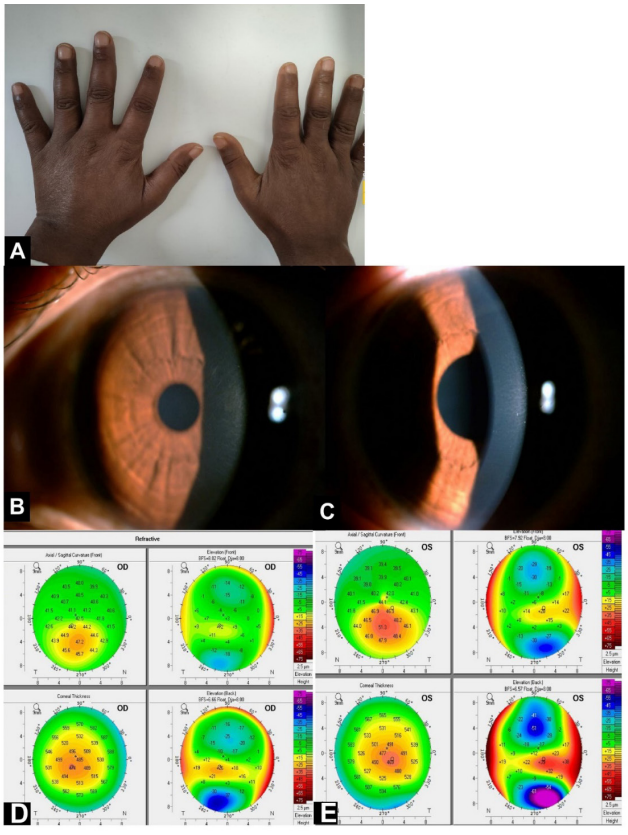

Figure 1. Dorsal view of both hands (A) showing pale fingertips suggestive of Raynaud's phenomenon, sclerodactyly, and skin atrophy. Slit-lamp photographs of the right (B) and left (C) eyes after collagen cross-linking (CXL) therapy. Note the mild post-CXL haze in the left eye. Corneal topography maps of the right (D) and left (E) eyes show an inferior cone corresponding to the thinnest pachymetry suggestive of keratoconus. Both eyes had moderate (stage 2) keratoconus (Amsler-Krumeich classification)

To date, only three cases of KC associated with SSc have been reported in the literature, all with bilateral involvement.[5,6,7] Of these, one case was successfully treated with bilateral CXL,[7] one patient had advanced KC in both eyes and was therefore recommended corneal transplantation,[5] and one was offered hard contact lenses.[6] The outcome of CXL in all five eyes (including the three eyes in this paper) with KC was satisfactory, with no complications or further progression. Case two in this paper reports the longer follow-up post CXL in KC associated with SSc.

SSc is a complex disease involving primary microangiopathy, immune dysregulation, and abnormal T lymphocyte differentiation. It involves the overexpression of extracellular matrix, uncontrolled fibroblast activation, and collagen synthesis, resulting in tissue fibrosis.[3] The sclera, uvea, and cornea are primarily composed of collagen fibers, are susceptible to connective tissue and collagen vascular diseases. The rich vascular supply may provoke immune-complex depositions that can manifest in the form of limbitis, peripheral ulcerative keratitis, and peripheral corneal thinning. There is growing consensus on the role of ocular surface and systemic inflammation in the pathogenesis of KC.[1,2,4] Higher levels of tear cytokines, including interleukin (IL)-4, IL-6, IL-8, tumor necrosis factor (TNF)-alpha, TNF-beta, and tear proteases such as matrix metalloproteinase (MMP)-1, MMP-3, and MMP-9 have been reported in KC eyes.[8,9] In a nationwide study of 2051 cases, KC was associated with various systemic immune-mediated diseases, such as Hashimoto's thyroiditis, inflammatory skin conditions, rheumatoid arthritis, ulcerative colitis, autoimmune chronic active hepatitis, and arthropathy.[2] Another study reported a

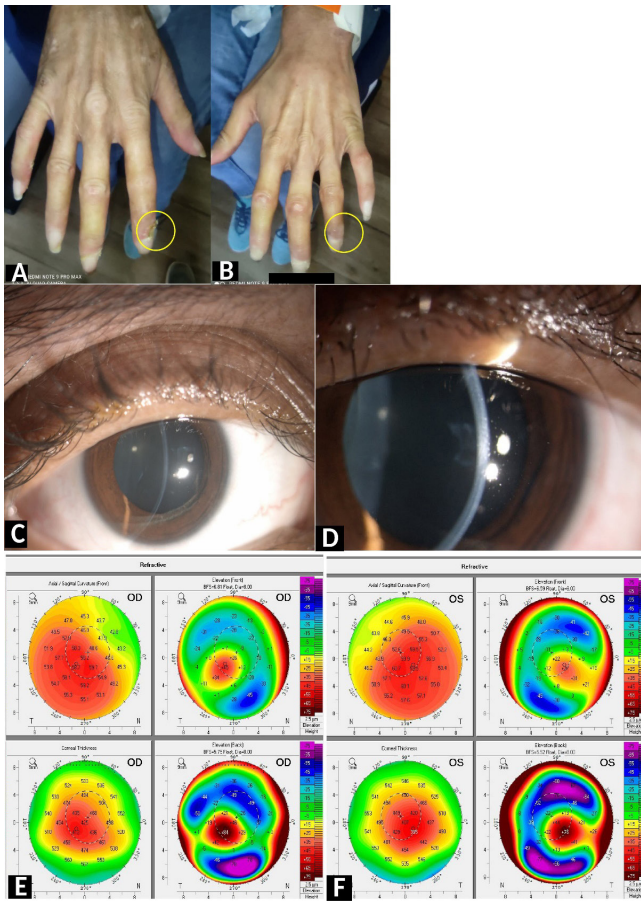

Figure 2. Dorsal views of the right (A) and left (B) hands show sclerodactyly, Raynaud's phenomenon, areas of ulcerations (yellow circles), flexion contracture, and atrophic changes affecting hand function. Slit-lamp photographs show the corneal slit section of the right (C) and left (D) eyes. Corneal topography shows an inferior-temporal cone in both eyes (E and F). Both eyes had stage 4 keratoconus (Amsler-Krumeich classification

significantly higher density of mature corneal Langerhans cells in KC eyes, indicating an immune-related inflammatory response and an active state of inflammation.[10] These findings collectively suggest that the immune system and inflammatory pathways may play a potential role in the pathogenesis of KC.

SSc is associated with upregulation of transforming growth factor-beta and ILs that induce chronic fibroblast activation, as well as increased collagen synthesis and deposition of ultrastructurally altered extracellular matrix.[3] KC, on the other hand, is associated with loss of keratocytes, breakdown of stromal crosslinks with collagen lamellae, and corresponding corneal thinning. The association of these seemingly dissimilar diseases is thus both interesting and intriguing. Chronic systemic inflammation may add synergistically to other forms of KC-related inflammation.[4] CXL effectively stabilizes KC, but its safety and efficacy in patients on immunosuppressants and with autoimmune diseases remain unclear because of potential healing complications and infection risks. Therefore, the authors recommend that systemic disease activity must be controlled before performing CXL to avoid corneal complications.

In conclusion, this report presents rare cases of bilateral KC in diffuse cutaneous SSc, challenging the non-inflammatory classification of KC and suggesting possible autoimmune contributions. Though ocular surface inflammation may not be clinically visible, subclinical inflammatory processes could be present. Further research into KC-autoimmune disease connections may reveal underlying mechanisms and guide anti-inflammatory treatments. Clinicians should monitor corneal topography in SSc patients, particularly early in the disease.

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms both for the use of the patient's images and the reporting of other clinical information in the journal.

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Declarations

Authorship Contributions

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

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