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AT A GLANCE

2026 Issue 4 at a Glance:

Esteemed colleagues,

The 4th issue of the Turkish Journal of Ophthalmology for the year 2026 brings together current studies that can directly contribute to our clinical practice. The featured articles span a wide spectrum of topics, ranging from myopia control to anterior segment imaging, from oculoplastic oncology to strabismus and uveitis, and from vitreoretinal surgery to rare hereditary retinal diseases.

In the editorial article of this issue, titled "The Evolution of Myopia Control Spectacle Lenses in Türkiye," Altıparmak addresses the development of myopia control spectacle lenses in Türkiye from a historical perspective. This journey, from progressive and bifocal designs to peripheral progressive lenses and later to next-generation technologies like DIMS, CARE, and HAL, actually reflects a broader paradigm shift: The objective in childhood myopia is no longer solely to correct existing refractive error, but to also strive to prevent future high myopia (See pages 220-221).

In the original research section, Bibi et al. compare Pentacam and MS-39 measurements of white-to-white distance, an important biometric parameter in refractive and anterior segment surgeries. Their findings of no significant difference and a good level of agreement between the two devices in this measurement are reassuring for daily clinical practice (See pages 222-228).

The study by Osagie et al. examines 100 cases of periocular basal cell carcinoma and once again demonstrates the importance of histopathological subtype and anatomical location in surgical success. The association of infiltrative tumors with the risk of perineural invasion and incomplete excision highlights the importance of a risk-based approach and Mohs surgery (when applicable), particularly in surgically challenging areas such as the medial canthus (See pages 229-235).

Dizdar Yiğit et al. present the validity and reliability study of the Turkish Adult Strabismus Quality of Life Questionnaire (AS-20). This study is important because it allows clinicians in Türkiye to measure not only the motor and sensory but also the psychosocial consequences of adult strabismus. The Turkish-adapted scale exhibited good psychometric properties, thus providing our clinical practice with a valuable tool for assessing treatment success from the patient's perspective (See pages 236-241).

In a study by Kılıçarslan et al. investigating the clinical features and long-term outcomes of Fuchs uveitis syndrome in Türkiye, heterochromia was observed in less than half of the patients, while diffuse stellate keratic precipitates were much more frequent, serving as a reminder that the classic finding of heterochromia should not be given undue weight during diagnosis. Other clinically noteworthy findings from the study are that cataracts are the most frequent complication and that vision can generally be preserved in the long term (See pages 242-247).

The study by Kalita et al. on the acute effects of caffeine on ocular parameters in young adults hits somewhat closer to daily life. Following a single 240 mg dose of caffeine, improvements were observed in accommodation, vergence, and contrast sensitivity, while small but significant increases were detected in pupil diameter and intraocular pressure. This interesting study shows that morning coffee temporarily affects not only our alertness but also our visual system (See pages 248-255).

In the review section, Avcı et al. discuss current surgical options for large, high myopia-associated, refractory, or traumatic macular holes in their comprehensive article titled "Current Approaches in the Management of Complicated Macular Holes." Methods ranging from the inverted internal limiting membrane flap to autologous retinal transplantation, as well as various tissue grafts such as amniotic membrane and lens capsule, are discussed along with their indications, advantages, and limitations. In particular, the treatment algorithm presented by the authors serves as a highly guiding framework for individualizing surgical choices in complex cases (See pages 256-268).

In the case report section, İşbilir et al. describe four members of the same family with Malattia Leventinese/Doyne honeycomb retinal dystrophy confirmed by detection of an *EFEMP1* gene mutation. In this rare autosomal dominant disease, which can mimic age-related macular degeneration, the presence of diffuse, radially distributed drusen-like deposits, especially in young patients, should raise suspicion of inherited macular dystrophies. The fact that this study represents the first genetically confirmed familial series from Türkiye also carries special significance (See pages 269-278).

In the Letters to the Editor section, Yabanoğlu et al. use a case study to remind us that inherited retinal dystrophies can sometimes present with inflammatory findings, mimicking uveitis. It is an instructive piece that beautifully demonstrates the diagnostic value of multimodal imaging, electrophysiology, and, when necessary, genetic testing in patients who are followed for uveitis but do not respond as expected to treatment (See pages 279-282).

An article by Gönül et al. presents the coexistence of retinitis pigmentosa and Coats-like vitreoretinopathy, drawing attention to a rare but challenging clinical picture. The combined evaluation of genetic testing, wide-field imaging, and the treatment of peripheral vascular changes demonstrates the importance of a personalized approach in these patients (See pages 283-286).

A case of bilateral ocular hypotony secondary to severe dehydration and uremia, presented by Aksoy et al., serves as a reminder that a marked decrease in intraocular pressure may not always stem from a primary ocular disease. It is a highly instructive case in terms of illustrating the clinical implications of the relationship between systemic hemodynamic status and ciliary body perfusion (See pages 287-289).

Finally, Kaderli et al. present a case of serous retinal detachment secondary to hypotony following trabeculectomy in a highly myopic patient, along with its successful treatment using intravitreal SF6 gas. Reminding us of the unique risks of glaucoma surgery in highly myopic eyes, the article also demonstrates a practical treatment option that can be applied when facing a rare but serious complication (See pages 290-293).

This issue offers current answers to frequently encountered clinical problems while simultaneously expanding our differential diagnosis perspectives with rare diseases and unusual clinical presentations. We thank all our authors, reviewers, and colleagues for their contributions and wish you pleasant and productive reading.

On behalf of the Editorial Board,

Sait Eğrilmez, MD

Editorial

The Evolution of Myopia Control Spectacle Lenses in Türkiye

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Treatments for myopia control are becoming increasingly available in Türkiye. This development is encouraging for both clinicians and families, because myopia is currently recognized not only as a refractive error but also as a significant public health problem. High myopia, in particular, is closely associated with vision-threatening diseases such as myopic maculopathy, retinal tears and detachment, glaucoma, and cataract. The risk of developing these complications increases significantly as the degree of myopia increases.

Therefore, any treatment approach capable of slowing myopia progression during childhood is of great importance. Currently, methods used to control myopia are broadly classified into four main categories: atropine therapy, orthokeratology, myopia control soft contact lenses, and specially designed spectacle lenses.

Among these methods, spectacle lenses are becoming increasingly preferred in our country, as they are worldwide, due to their non-invasive nature, high patient compliance, and ease of use in daily life.

One of the first spectacle lenses used for myopia control in Türkiye was the Myopilux design developed by Essilor. For many years, these lenses have been utilized in various designs, including progressive addition and executive bifocal. Notably, a 2014 study by Cheng et al.[1] demonstrated that executive bifocal spectacles with a near addition of +1.50 diopters significantly slowed myopia progression. The results achieved with prismatic bifocal designs were even more remarkable. However, the efficacy reported for progressive addition spectacles was more limited, with the majority of the effect being observed within the first year.[2] Although the efficacy of these lenses lags behind that of new-generation myopia control technologies when evaluated by today's standards, it is clear that they played a significant role in popularizing the concept of myopia control in our country.

Later, spectacle lenses with a peripheral progressive design (Myopi-X, NOVAX) introduced a novel approach to myopia control in Türkiye. It is believed that the optical changes created in the peripheral zones of these lenses may alter the retinal image profile and influence eye growth. Clinical studies conducted in Türkiye have reported that these lenses can slow myopia progression, demonstrating an efficacy comparable to that of low-dose atropine therapy.[3] However, they provided no additional benefit when used in combination with atropine.[4] These findings are noteworthy, as they demonstrate that not every combination therapy necessarily produces a more potent effect in myopia control.

Recent years have seen the introduction of much more advanced optical technologies in myopia control spectacle lenses, including DIMS (defocus incorporated multiple segments), CARE (cylindrical annular refractive elements), and HAL (highly aspherical lenslets) technologies.

DIMS technology consists of a central optical zone, which provides clear vision, surrounded by hundreds of microlens segments. These microlenses aim to slow axial eye growth by creating myopic defocus in front of the retina. International studies of spectacle lenses utilizing DIMS technology have demonstrated significant decelerations in both myopia progression and axial elongation. Initial real-

Keywords: Myopia control, myopia management, myopia control spectacle lenses, childhood myopia, axial length

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world data collected in Türkiye also support these results, with retrospective studies in Turkish children showing that DIMS technology provides clear superiority over single-vision spectacle lenses.[5,6] Furthermore, recent comparative studies have reported that the DIMS design is more effective than peripheral progressive lenses.[7]

CARE technology employs a different optical approach. A central optical zone, which provides distance correction, is surrounded by cylindrical annular refractive elements that simultaneously generate varying focus signals across different regions of the retina. This optical structure aims to suppress axial eye elongation. Initial results obtained in Türkiye indicate that CARE technology is effective in reducing both axial elongation and refractive progression.[8]

In HAL technology, a large volume of myopic defocus is created in the mid-peripheral retina using numerous highly positive aspherical microlenses located in the lens periphery. This approach aims to exert a stronger influence on the retinal signals that regulate eye growth. Recent studies suggest that HAL technology is one of the most effective spectacle lens designs available today.[9] We eagerly await the outcomes related to this lens from our country as well.

From the perspective of Türkiye, a remarkable transformation has occurred over the last few years. While myopia control was previously practiced only in specific centers and by a limited number of physicians, an increasing number of ophthalmologists are now integrating myopia control approaches into their routine daily practice. This shift is believed to be driven not only by the growing body of scientific evidence but also by the increased accessibility of myopia control lenses in Türkiye.

Perhaps the most significant change is not technological, but conceptual. In the past, correcting a child's existing refractive error was seen as the primary goal, whereas today, the goal is to prevent or reduce the risk of high myopia in the future. In other words, there has been a transition from the era of myopia correction to the era of myopia management.

It is evident that in the coming years, real-world data with longer follow-up periods and new clinical studies from Türkiye will expand the knowledge base in this field. However, in light of the current data, we can conclude that the success of myopia control spectacle lenses will be measured not only by the diopters gained today, but also by the cases of severe myopia prevented in the future.

Declarations

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

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Original Article

Comparison of White-to-White Measurements Between Pentacam and MS-39 and Their Relationship with Visual and Refractive Status

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Abstract

Objectives: To compare white-to-white (WTW) measurements obtained by Pentacam and MS-39 and to assess their relationship with visual and refractive status.

Materials and Methods: This prospective cross-sectional study included 126 participants (one eye per participant). Visual acuity was measured with and without correction using a Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR). Refractive status was determined by manifest refraction, and the spherical equivalent was calculated. WTW measurements were determined using Pentacam and MS-39. For paired comparisons, Wilcoxon signed-rank test was used. Intraclass correlation coefficients (ICC) and Bland-Altman plots were used to assess agreement between the two devices. Spearman test was used to evaluate the correlation with visual and refractive variables.

Results: The mean age of the participants was 27.21±5.64 years. Mean uncorrected distance and corrected visual acuities were 1.11±0.45 logMAR and 0.05±0.20 logMAR, respectively. The mean spherical equivalent was -4.02±2.03 diopters. The mean WTW distance was 11.82±0.41 mm with Pentacam and 11.83±0.43 mm with MS-39. No statistically significant paired difference was found between the devices (W=3839.5, p=0.584). A Bland-Altman mean bias of -0.009 mm suggested a small systematic difference between the two devices. Intraclass correlation showed good agreement (ICC=0.847, 95% confidence interval: 0.789-0.890; p<0.001). While there was no significant correlation with corrected distance visual acuity, both WTW measures had weak but significant correlations with uncorrected distance visual acuity and spherical equivalent.

Conclusion: Pentacam and MS-39 produce comparable results overall and show strong agreement for WTW measurements. While the inter-device difference was unaffected by visual and refractive state, WTW showed minor correlations with unaided visual acuity and refractive error.

Keywords: Pentacam, MS-39, white-to-white, visual acuity

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Introduction

White-to-white (WTW) distance is a crucial parameter in modern cataract and refractive surgical procedures, including anterior chamber, phakic, and collamer intraocular lens (IOL) implantation.[1,2] It is necessary to precisely measure the WTW horizontal limbal diameter before surgery because an improperly sized IOL can result in complications such as cataracts or angle-closure glaucoma.[3] The size of the IOL to be inserted is determined by inferring the ciliary sulcus distance from the WTW horizontal limbal diameter, adding or subtracting approximately 0.5 mm depending on the degree of myopia or hyperopia.[4]

The corneal WTW diameter can be measured using both invasive and non-invasive techniques. Traditionally, the Castroviejo caliper was used to measure the WTW distance under local anesthesia.[1] Currently, the WTW distance can be measured using a variety of methods. These can be grouped into automated methods, such as ultrasonic biomicroscopy and anterior segment optical

coherence tomography (OCT); direct imaging methods or magnetic resonance imaging; and manual methods, including surgical calipers, corneal gauges, and scales in slit-lamp ocular rings. It has previously been demonstrated that automated measurements yield more accurate findings than operator-dependent methods.[5]

The Pentacam AXL (Oculus Optikgeräte GmbH, software version 1.25r15), introduced in 2015, is a Scheimpflug camera with an optical biometer for partial-coherence interferometry. It provides anterior segment tomography, anterior chamber depth, WTW corneal diameter measurements, corneal thickness, anterior and posterior corneal surfaces and aberrations, axial length, and corneal topography.[6,7] In contrast, the MS-39 combines spectral-domain OCT technology with Placido-disk topography, allowing a thorough assessment of corneal shape and associated biometric data. The MS-39 has also been used to measure corneal diameter, reported as the WTW distance.[8,9]

Several previous studies have compared WTW measurements obtained from various ophthalmic imaging devices, reporting varying levels of agreement depending on the instruments evaluated. However, evidence of agreement between Pentacam and the recently introduced MS-39 is limited. Furthermore, little research has examined whether variations in WTW values across devices are related to visual acuity or refractive status. Thus, this study contributes additional evidence by comparing WTW measurements obtained with the Pentacam and MS-39, assessing the degree of agreement between the two instruments, and examining how these measurements relate to visual and refractive status in healthy adults with myopia.

Materials and Methods

This prospective cross-sectional comparative study was conducted at Amanat Eye Hospital to compare WTW measurements obtained with Pentacam and MS-39 and to assess their correlation with visual and refractive status. Participants aged 18 years or older undergoing routine anterior segment or refractive evaluations were included in this study. Patients with corneal scarring, active ocular disease, significant media opacity, prior ocular surgery, or low-quality scans on either instrument were excluded. To prevent inter-eye correlation, one eye from each participant was included in the analysis. Based on the sample size formula for Bland-Altman limits of agreement ($n=3(1.96s/d)^2$) assuming a precision (d) of 0.5s, the required sample size was determined to be 47 eyes. However, to increase the accuracy and reliability of the results, 126 eyes were included.

A standardized ocular examination was performed on each subject. Visual acuity was measured using a Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR) units for analysis. Uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) were obtained, and the spherical equivalent (SE) was computed by adding half of the cylinder to the sphere. To reduce the possibility of diurnal variation, all measurements were taken between 9:00 AM and 2:00 PM during regular clinic hours. The Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany) and MS-39 (CSO S.r.l., Scandicci, Florence, Italy) were used to obtain WTW measurements. For each participant, a single measurement was obtained with each device, and the recorded value from each scan was used for analysis. Measurements were first taken with the Pentacam and then with the MS-39 in a predetermined order, and the examiner was not blinded to the first device's results. The analysis included only scans that met the manufacturer's recommended quality standards, including appropriate fixation, proper centration, and the absence of motion artifacts and blinking. Only scans of acceptable quality were included in the analysis.

Instruments

The Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany) is a rotating Scheimpflug camera that captures three-dimensional, non-contact images of the anterior segment using a blue light source at 475 nm. It collects 25,000 data points in about 1-2 seconds by acquiring 25 cross-sectional images at angles between 0° and 180° during a single scan.[10] The Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany) was selected for our investigation due to its exceptional accuracy in imaging the anterior segment and its ability to quantify WTW corneal diameter with minimal operator dependence.

MS-39 (CSO S.r.l., Scandicci, Florence, Italy) is a non-contact anterior segment imaging tool that integrates Placido-based topography with spectral-domain OCT. It provides a comprehensive evaluation of the cornea and anterior segment using a variety of biometric parameters and high-resolution images. Its sophisticated imaging capabilities support its potential use in anterior segment biometric assessments and WTW measurements.[11]

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki's tenets. Before data collection, the appropriate Amanat Eye Hospital Ethics Review Committee granted ethical approval (decision no: IRB#26/03-001, date: 01.01.2026). Before enrollment, all subjects provided written informed consent, and patient confidentiality was rigorously upheld throughout the study.

Statistical Analysis

Statistical software R (version R 4.5.0) was used to enter and analyze the data. The Shapiro-Wilk test was used to assess the normality of the data. For normally distributed data, continuous variables were expressed as the mean and standard deviation; for non-normally distributed data, they were expressed as the mean. Frequencies and percentages were used to summarize categorical variables. The Wilcoxon signed-rank test was used to compare WTW values from Pentacam and MS-39 because the data were non-normally distributed. Bland-Altman analysis and the intraclass correlation coefficient (ICC) were used to evaluate the degree of agreement between the two devices. The mean difference and accompanying 95% limits of agreement between Pentacam and MS-39 WTW readings were assessed using the Bland-Altman plot. Spearman's rank correlation was used to assess the association between WTW measurement and visual and refractive status. Statistical significance was defined as a p value less than 0.05.

Results

This study included 126 participants with a mean age of 27.21±5.64 years. The mean UDVA and CDVA values were 1.11±0.45 logMAR and 0.05±0.20 logMAR, respectively. The study population was primarily myopic, with a mean SE of -4.02±2.03 diopters. The mean WTW measurement was 11.82±0.41 mm with Pentacam and 11.83±0.43 mm with MS-39 (Table 1). The distribution of continuous variables is illustrated in Figure 1.

Normality of the continuous variables was evaluated using the Shapiro-Wilk test (Table 2). The only WTW readings that were normally distributed were those generated by the MS-39 (W=0.9886, p=0.381). All other variables showed significant deviation from normality (p<0.05), including Pentacam-derived WTW, the paired differences in WTW measurements (ΔWTW), UDVA, CDVA, and SE. The paired-comparison and correlation analyses employed nonparametric techniques because most variables were not normally distributed.

Table 1. Descriptive analysis for continuous variables

Variable	Mean and SD
Age (years)	27.21±5.64
UDVA	1.11±0.45
CDVA	0.05±0.2
Spherical equivalent (D)	-4.02±2.03
WTW Pentacam (mm)	11.82±0.41
WTW MS-39 (mm)	11.83±0.43

WTW: White-to-white distance, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, D: Diopters, SD: Standard deviation

Pentacam and MS-39 data were compared using the Wilcoxon signed-rank test because ΔWTW values were not normally distributed. The Wilcoxon signed-rank test indicated that the difference between Pentacam and MS-39 WTW readings was not statistically significant (W=3839.5, p=0.584) (Table 3). Paired comparison of WTW measurements between Pentacam and MS-39 is illustrated in Figure 2.

Agreement analysis of Pentacam and MS-39 WTW yielded a single-measure two-way agreement ICC of 0.847 (95% confidence interval: 0.789-0.890; p<0.001) (Table 3). Furthermore, Bland-Altman analysis found a mean bias of -0.009 mm with 95% limits of agreement ranging from -0.462 mm to 0.444 mm. A Bland-Altman plot showing agreement between Pentacam and MS-39 WTW measurements is shown in Figure 3, and a scatter plot of WTW measurements from Pentacam and MS-39 relative to the line of identity is shown in Figure 4.

Spearman correlation analysis showed that WTW measures obtained from both Pentacam and MS-39 were weakly negatively associated with UDVA and weakly positively associated with SE (Table 4). No significant correlation was found between the absolute WTW values and CDVA, nor was there any significant correlation between ΔWTW and either CDVA or SE. A Spearman correlation heatmap showing the association of WTW measurements with visual and refractive status is shown in Figure 5.

Discussion

According to this study, Pentacam and MS-39 yield similar WTW measurements, with good agreement and no significant paired differences. Although the Bland-Altman limits of agreement suggest some variability at the individual level, the small mean bias indicates little systematic variation between the devices. As a result, even though the two instruments appear comparable overall, caution may be warranted when interpreting specific WTW values.

WTW readings from Pentacam and MS-39 showed weak but significant correlations with SE and UDVA. Specifically, both WTW measures were negatively correlated with UDVA, indicating that larger WTW values were associated with slightly better unaided visual acuity in logMAR terms. Both measures also showed a weak positive correlation with SE, suggesting that larger WTW values were associated with less myopic refractive status. No significant correlation was found between ΔWTW and CDVA or SE, indicating that inter-device differences in WTW measurements were not affected by visual or refractive status.

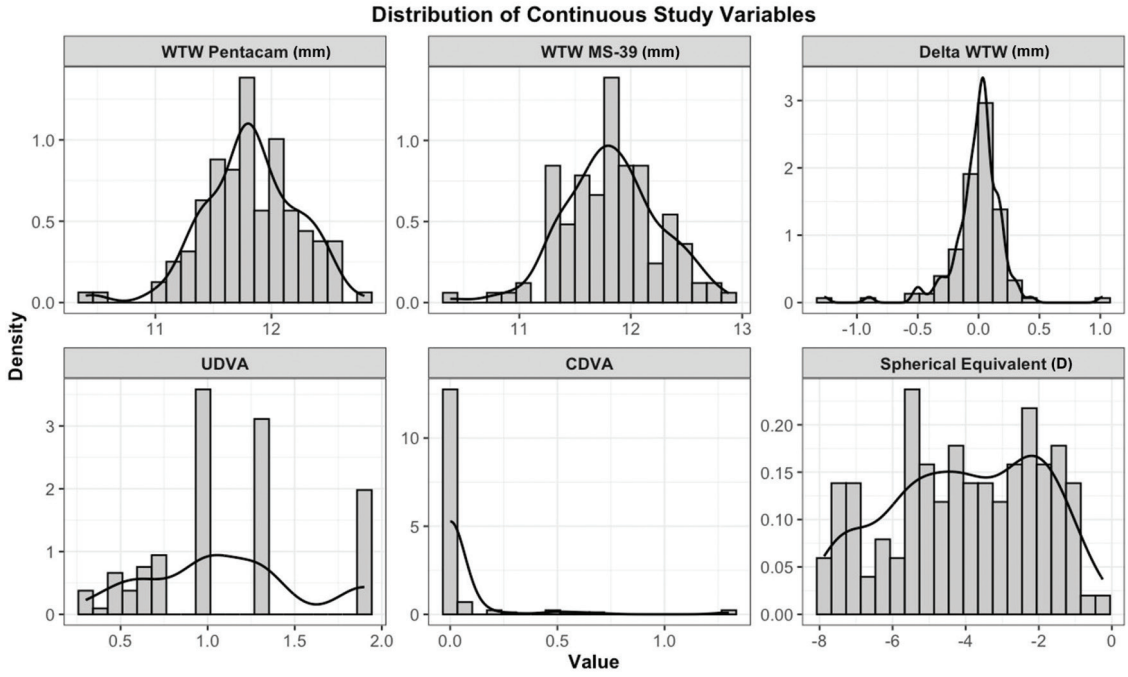

Figure 1. Distribution of continuous variables
WTW: White-to-white distance, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, D: Diopters

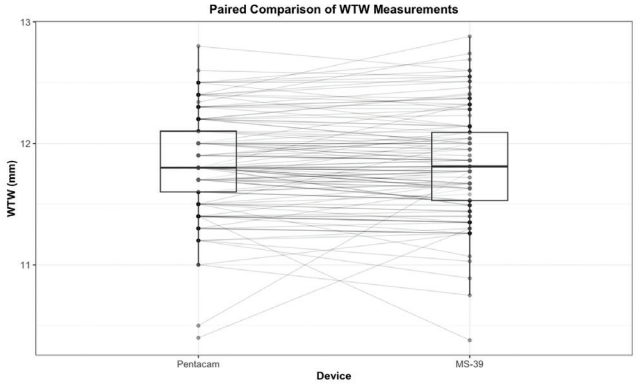

Figure 2. Paired comparison of white-to-white (WTW) measurements between Pentacam and MS-39

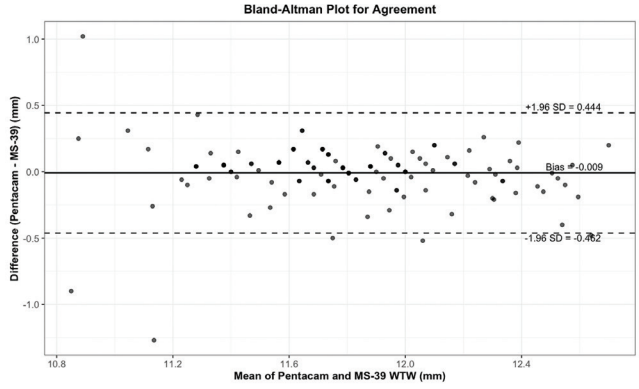

Figure 3. Bland-Altman plot for agreement between Pentacam and MS-39 white-to-white (WTW) measurements
SD: Standard deviation

Table 2. Shapiro-Wilk normality test for continuous variables			
Variable	**W statistic**	**p value**	**Interpretation**
WTW Pentacam	0.9739	0.0152	Not normal
WTW MS-39	0.9886	0.3814	Normal
ΔWTW	0.8228	<0.001	Not normal
UDVA	0.9081	<0.001	Not normal
CDVA	0.2980	<0.001	Not normal
WTW: White-to-white distance, ΔWTW: Paired difference between Pentacam and MS-39 WTW measurements, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity			

Our findings align with a previous study comparing Pentacam HR, Keratograph 5M, and manual slit-lamp measurements. The study demonstrated very good reproducibility across all devices and found no significant differences among them. Additionally, the authors found no discernible diurnal fluctuation in corneal diameter, indicating that the WTW distance is a reasonably reliable and consistent anterior segment metric.[12]

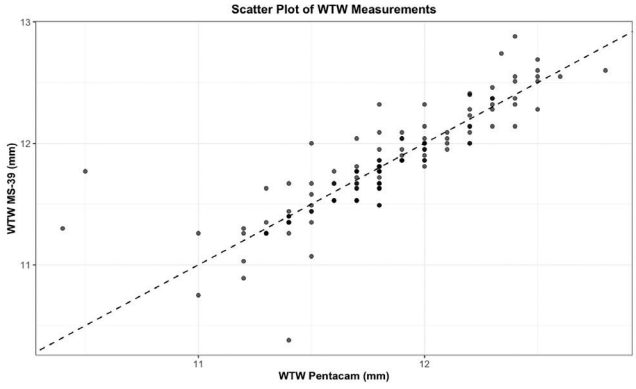

Figure 4. Scatter plot of white-to-white (WTW) measurements of Pentacam and MS-39 relative to line of identity

Evidence from other Pentacam-related investigations indicates that WTW measurements are device-dependent, with notable inter-device variations documented for several instrument combinations.[13] For instance, one study concluded that IOLMaster 500 and Pentacam should not be used simultaneously for phakic IOL calculations

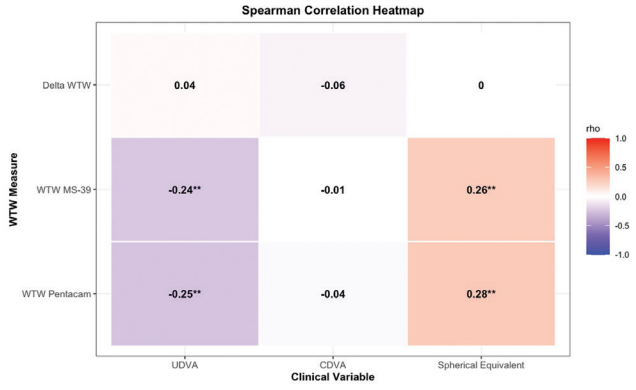

Figure 5. Heatmap of Spearman correlation of white-to-white (WTW) measures with visual and refractive status
UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity

Table 3. Paired comparison and agreement analyses for white-to-white measurements between Pentacam and MS-39

Analysis	Statistical parameter	Value
Paired comparison	Wilcoxon W statistic	3839.5
	p	0.584
Agreement (Bland-Altman)	Mean bias (mm)	-0.009
	Standard deviation, mm	0.231
	95% limits of agreement (mm)	-0.462 to 0.444
Reliability	Intraclass correlation coefficient	0.847
	95% confidence interval	0.789 to 0.890
	p	<0.001

Table 4. Spearman correlation of WTW measurements with visual and refractive status

WTW measure	Clinical variable	Rho	p value
WTW Pentacam	UDVA	-0.254	0.0042
	CDVA	-0.036	0.6919
	SE	0.278	0.0016
WTW MS-39	UDVA	-0.240	0.0068
	CDVA	-0.014	0.8729
	SE	0.260	0.0033
ΔWTW	UDVA	0.035	0.6954
	CDVA	-0.063	0.4851
	SE	-0.003	0.9759

WTW: White-to-white distance, ΔWTW: Paired difference between Pentacam and MS-39 WTW measurements, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, SE: Spherical equivalent

because IOLMaster 500 recorded substantially higher WTW values.[14] In the same vein, a preoperative myopia study found that WTW values varied among measurement tools, which included caliper, Pentacam HR, IOLMaster 700, and ultrasonic biomicroscope.[15] Inter-device bias was evident in another investigation, which found that WTW measurements made with BioGraph were substantially wider than those made with Pentacam.[16] Collectively, these previous studies emphasize that even small variations in WTW may be clinically significant, especially in contexts such as implantable collamer lens sizing and anterior segment parameters.[16] This underscores the clinical relevance of comparing Pentacam with more recent devices like MS-39.

Interestingly, there was no statistically significant difference between Pentacam and MS-39 in this investigation, indicating that the level of disagreement in WTW measurement is not consistent across all devices. However, in our study, individual WTW readings still differed by almost ±0.45 mm between the devices, indicating that considerable measurement variability persisted at the individual level despite good overall agreement. Therefore, even though Pentacam and MS-39 appear similar overall, it is important to exercise caution before assuming perfect interchangeability in any individual eye.

The relationship between WTW and visual and refractive status was also investigated in this study, which provides a new clinical dimension. WTW readings from Pentacam and MS-39 both showed a slight but statistically significant negative correlation with UDVA. As visual acuity values were analyzed in logMAR units, this indicates that larger WTW values were associated with marginally better unaided visual acuity. Furthermore, there was a slight positive association between WTW measurements and SE, indicating that higher WTW values were associated with less myopic refractive status.

However, the weakness of these relationships suggests that WTW is unlikely to be a reliable indicator of refractive and visual conditions. Instead, it appears to remain predominantly an anatomical anterior segment feature with a weak refractive correlation. This conclusion is supported by the lack of a substantial correlation between WTW and CDVA, which is more strongly influenced by refractive correction and overall visual system integrity than by corneal diameter alone.

Another noteworthy finding was that UDVA, CDVA, and SE showed no significant correlation with ΔWTW, the difference between Pentacam and MS-39 readings. This implies that the slight difference between the two devices was not attributable to refractive or visual characteristics and most likely reflects technical measurement variability rather than clinically significant patient-related issues.

Study Limitations

This study has certain limitations. The single-center design of this study, the relatively young and predominantly myopic study group, and the inclusion of only one eye per participant are specific drawbacks that could restrict the generalizability of the results. Additionally, only one measurement was taken from each device, measurements were carried out in a predetermined order (MS-39 after Pentacam), and the examiner was not blinded to the first device's results, all of which could have introduced procedural bias or measurement variability. To confirm these results, more multicenter research with larger and more varied populations, repeated assessments, randomized device order, and masked examiners is necessary.

Conclusion

Pentacam and MS-39 showed comparable WTW measures and strong agreement at the group level. However, when precise individual measurements are needed, the two devices should not be considered fully interchangeable due to observed individual-level variability, with 95% limits of agreement of up to ±0.45 mm. Additionally, inter-device measurement variances were unaffected by visual or refractive status, despite WTW measures showing minimal correlations with UDVA and SE. These results support the use of Pentacam and MS-39 in clinical assessment by providing additional evidence of device agreement. They also emphasize the importance of interpreting measurements from the two devices cautiously in circumstances requiring high measurement precision.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki's tenets. Before data collection, the appropriate Amanat Eye Hospital Ethics Review Committee granted ethical approval (decision no: IRB#26/03-001, date: 01.01.2026).

Informed Consent: Before enrollment, all subjects provided written informed consent, and patient confidentiality was rigorously upheld throughout the study.

Declarations

Authorship Contributions

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

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Original Article

Surgical Outcomes and Histopathological Risk Factors in Periocular Basal Cell Carcinoma: A Single-Centre Study of 100 Patients

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Abstract

Objectives: To evaluate the histological subtypes, surgical margin status, and high-risk features of periocular basal cell carcinomas (BCC) excised over a one-year period at a secondary referral centre in England.

Materials and Methods: This retrospective audit included 100 consecutive periocular BCC excisions performed at James Paget University Hospital between August 2024 and August 2025. Demographic, clinical, and histopathological data were extracted from operative records and histopathology reports. Surgical margins were classified as complete (≥0.4 mm), close (0.1-0.3 mm), or incomplete (tumour present at the inked margin or <0.1 mm). Fisher's exact test was used to evaluate the association between infiltrative histological subtype and the presence of perineural invasion.

Results: Of the 100 patients included (58% male, 42% female; mean age 75.7 years), nodular BCC was the most common histological subtype (83%), followed by infiltrative (14%), superficial (2%), and basosquamous (1%) variants. Complete excision was achieved in 83% of cases, while close and incomplete margins were observed in 8% and 9% of excisions, respectively. Perineural invasion was identified in 2% of tumours, both of which demonstrated infiltrative histology. The infiltrative subtype showed a statistically significant association with perineural invasion (p=0.007). The majority of BCCs were located in the medial canthus (56%), an anatomically complex region associated with increased surgical difficulty and a higher risk of incomplete excision.

Conclusion: High rates of complete excision were achieved in this cohort of periocular BCCs. Infiltrative histological subtype was associated with an increased risk of perineural invasion and incomplete excision, particularly when located in the medial canthus. These findings support a risk-adapted surgical strategy as well as consideration of Mohs micrographic surgery for aggressive tumour subtypes and anatomically complex periocular locations.

Keywords: Basal cell carcinoma, periocular tumours, Mohs micrographic surgery

Introduction

Basal cell carcinoma (BCC) is the most common cutaneous malignancy, accounting for approximately 75% of all non-melanoma skin cancers.[1] It predominantly arises in sun-exposed areas, with the periocular region representing one of the most cosmetically and functionally sensitive anatomical sites. Although nodular BCC is the most frequent histological subtype, infiltrative and basosquamous variants demonstrate more aggressive biological behaviour, with higher rates of incomplete excision, perineural invasion (PNI), and tumour recurrence. Periocular BCCs may result in significant morbidity due to eyelid distortion, involvement of the lacrimal drainage system, and, in advanced cases, orbital invasion, stressing

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the importance of optimal surgical management and accurate histopathological risk stratification.

This study was conducted in the far eastern part of England, centred on Great Yarmouth and the surrounding area, which has a predominantly Caucasian population of approximately 200,000 residents, an older age demographic, and relatively high cumulative ultraviolet (UV) exposure, particularly related to outdoor and agricultural activity common in East Anglia. Over a one-year audit period (August 2024 to August 2025), 100 periocular BCCs were excised at James Paget University Hospital, serving this population, signifying a considerable local disease burden. For comparison, Lin et al.[2] reported an incidence of approximately 22 periocular BCC cases per 100,000 population in an English region. The higher case volume observed in our cohort may reflect regional demographic factors, referral patterns to the oculoplastic service, and possible limitations of national incidence estimates, which may underrepresent private referrals or untreated lesions.

Our research provides updated regional data and aims to evaluate surgical clearance outcomes, histological subtypes, and high-risk pathological features in a contemporary cohort of periocular BCCs managed at a secondary centre in England.

Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the James Paget University Hospital's Audit Service (26/03/2025; approval no: 1705/2025). According to the NHS governance guidelines, approval from the Research Ethics Committee is not required for clinical audit studies evaluating current clinical practices. Written informed consent was obtained from all of the participants.

A retrospective audit was conducted of 100 consecutive periocular BCC excisions performed between August 2024 and August 2025. All patients who underwent surgical excision of a histologically confirmed periocular BCC in the Ophthalmology Department of James Paget University Hospital within this one-year period were included in the study.

Data were collected from operative records and histopathology reports, including patient age and sex, tumour laterality (right or left), precise periocular location, histological subtype, excision margin status, and the presence of PNI or vascular invasion. In routine oculoplastic practice at our unit, a 3-mm clinical excision margin from the visible or clinically perceived tumour edge was generally aimed for where anatomically feasible. The clinical margin was marked preoperatively using a surgical caliper. However, the final planned margin was individualised according to tumour size, clinical definition, anatomical location, suspected histological risk, and the need to preserve eyelid position, lacrimal drainage function, and periocular cosmesis. In anatomically constrained sites, particularly the medial canthus, or in lesions with poorly defined borders or suspected aggressive histology, the margin was adjusted according to surgical judgement.

Histopathological margin clearance was recorded separately for peripheral and deep margins where available. These histological measurements were extracted from the final pathology report and are distinct from the intended clinical excision margin marked at surgery. Histological margins were classified according to the Royal College of Pathologists and local histopathology reporting recommendations. Margins were defined as complete if both peripheral and deep margins measured ≥0.4 mm, close if any margin measured 0.1-0.3 mm without tumour at the inked edge, and incomplete if tumour was present at the inked margin or within <0.1 mm of it.[3,4]

Statistical Analysis

Data were presented as frequencies and percentages for demographic and clinical variables. Group comparisons were performed using parametric or non-parametric tests as appropriate. Fisher's exact test was applied to assess the association between histology subtype and the presence of PNI, given the small number of PNI-positive cases. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Demographics

A total of 100 consecutive periocular BCC excisions (n=100) in 100 patients were analysed. The cohort comprised 58% males (n=58) and 42% females (n=42). The mean age at surgery was 75.7 years (range: 45-93 years). Female patients presented at a slightly younger mean age than male patients (73.3 vs. 77.6 years, respectively). Left-sided lesions were marginally more common (53%, n=53) than right-sided lesions (47%, n=47).

Histological Subtypes

Nodular BCC was the most common histological subtype, accounting for 83% of cases (n=83). Infiltrative BCC comprised 14% (n=14), superficial BCC 2% (n=2), and basosquamous BCC 1% (n=1). A small number of tumours demonstrated mixed histological features and were classified as infiltrative if any infiltrative component was present. While nodular BCC represented the majority of

cases, infiltrative subtype accounted for a disproportionate number of high-risk features.

Surgical Outcomes

Overall, 83% of tumours (n=83) were excised with histologically clear margins meeting the pre-set criteria for complete excision (≥0.4 mm clearance). Margins were classified as close (0.1-0.3 mm) in 8% of cases (n=8), and incomplete excision (tumour at ink or within <0.1 mm) occurred in 9% of cases (n=9). In the majority of incompletely excised cases, re-excision was subsequently undertaken where feasible, or patients were referred for further management. The high complete-excision rate reflects an emphasis on achieving adequate margins at the initial surgical procedure (Table 1). Mean histological clearance of all 100 cases was 1.52 mm peripherally and 2.27 mm in depth. Nodular BCCs demonstrated mean peripheral and deep clearances of 1.52 mm and 1.93 mm, respectively. In contrast, infiltrative tumours showed lower mean clearances (1.34 mm peripherally and 1.33 mm in depth) and a substantially higher rate of incomplete excision (28.6%) (Table 2).

High-Risk Features

The medial canthus was the most common site for BCC, accounting for 56% of all cases. Notably, infiltrative tumours showed a strong predilection for this location, with 8 of 14 infiltrative BCCs (57.1%) arising in the medial canthal region (Table 3). Incomplete excision was more common and statistically significant in medial canthal tumours (p=0.021) (Table 4). Achieved histological mean margin clearance was lower in the medial canthal area (Table 5). PNI was identified in 2% of cases (n=2). Both tumours demonstrating PNI exhibited infiltrative histology. No definite vascular invasion was identified in any case. However, 14% of histopathology reports did not explicitly comment on PNI (5%) or vascular invasion (9%).

Table 1. Histological subtypes and excision margin of periocular BCC (n=100)

Histopathological subtype	n (%)	Complete excision, n (%)	Close margin, n (%)	Incomplete excision, n (%)
Nodular	83 (83.0)	73 (88)	5 (6.0)	5 (6.0)
Infiltrative	14 (14.0)	7 (50)	3 (21.4)	4 (28.6)
Superficial	2 (2.0)	2 (100)	0 (0)	0 (0)
Basosquamous	1 (1.0)	1 (100)	0 (0)	0 (0)
Total	100 (100)	83 (83.0)	8 (8.0)	9 (9.0)

Data are presented as number (n) and percentage (%); Incomplete excision was more common in infiltrative BCC: p=0.045 (Fisher's test)
BCC: Basal cell carcinoma

Table 2. Histological margin distances according to histopathological subtype

Histopathological subtype	n (%)	Peripheral margin (mm), mean (range)	Deep margin (mm), mean (range)
Nodular	83 (83.0)	1.52 (0.0-5.6)	1.93 (0.1-6.1)
Infiltrative	14 (14.0)	1.34 (0.0-3.8)	1.33 (0.2-4.2)
Superficial	2 (2.0)	2.00 (1.8-2.2)	3.45 (3.1-3.8)
Basosquamous	1 (1.0)	1.20 (1.2-1.2)	2.40 (2.4-2.4)
Total	100 (100)	1.52 (0.0-5.6)	2.27 (0.1-6.1)

Data are presented as number (n) and percentage (%)

Table 3. Distribution of periocular BCC type by site

Location	Nodular, n (%)	Infiltrative, n (%)	Superficial, n (%)	Basosquamous, n (%)	Total, n (%)
Medial canthus	48	8	0	0	56 (56.0)
Lower lid	27	1	2	1	31 (31.0)
Lateral canthus	3	2	0	0	5 (5.0)
Eyebrow	5	3	0	0	8 (8.0)
Total	83 (83.0)	14 (14.0)	2 (2.0)	1 (1.0)	100 (100)

Data are presented as number (n) and percentage (%)
BCC: Basal cell carcinoma

Table 4. Histological margin clearance by anatomical location				
Location	**n (%)**	**Complete excision, n (%)**	**Close margin, n (%)**	**Incomplete excision, n (%)**
Medial canthus	56 (56.0)	42 (75.0)	6 (10.7)	8 (14.3)
Lower lid	31 (31.0)	28 (90.3)	2 (6.5)	1 (3.2)
Lateral canthus	5 (5.0)	5 (100.0)	0 (0.0)	0 (0.0)
Eyebrow	8 (8.0)	8 (100.0)	0 (0.0)	0 (0.0)
Total	100 (100.0)	83 (83.0)	8 (8.0)	9 (9.0)
Data are presented as number (n) and percentage (%); Incomplete excision was more common in medial canthal tumours: p=0.021 (Fisher's test)				

Table 5. Histological margin distances by anatomical location			
Location	**n (%)**	**Peripheral margin (mm), mean (range)**	**Deep margin (mm), mean (range)**
Medial canthus	56 (56.0)	1.21 (0.0-5.3)	1.00 (0.1-5.8)
Lower lid	31 (31.0)	1.69 (0.0-3.4)	2.4 (0.2-6.1)
Lateral canthus	5 (5.0)	2.60 (0.3-5.6)	3.8 (1.8-4.2)
Eyebrow	8 (8.0)	2.12 (1.2-3.8)	2.0 (0.8-3.0)
Total	100 (100)	1.52 (0.0-5.6)	2.27 (0.1-6.1)
Data are presented as number (n) and percentage (%)			

The association between infiltrative histology and the presence of PNI was statistically significant (Fisher's exact test, p=0.007), underscoring that infiltrative tumours were significantly more likely to demonstrate perineural spread than non-infiltrative subtypes.

Discussion

This one-year audit of 100 periocular BCC excisions demonstrates high rates of complete surgical excision and provides insight into the histological risk profile of different BCC subtypes. Overall, 83% of tumours were completely excised with clear histological margins, which compares with the 83.7% complete excision rate reported by Lin et al.[1] in a multicentre and multispecialty cohort of 1012 periocular BCCs. In their series, infiltrative BCCs were also disproportionately associated with incomplete excision (12.6%) despite achieving wider mean peripheral margins (2.06 mm) and a mean deep clearance of 1.90 mm. Notably, although our cohort achieved a smaller mean peripheral clearance (1.52 mm vs 2.06 mm) but a greater mean deep clearance (2.27 mm vs 1.90 mm), the overall complete excision rate was higher. This variation may reflect differences in case mix, referral patterns to a tertiary oculoplastic service, tumour location distribution, surgical decision making, or histopathological reporting practices. Collectively, these findings reinforce the concept that histological subtype, particularly infiltrative growth patterns, is a more critical determinant of margin positivity than absolute measured clearance, supporting a risk-adapted surgical approach for periocular BCC.[1,5]

A modest predominance of left-sided periocular tumours was observed in our cohort, with 53% of BCCs occurring on the left side and 47% on the right side. Although driving-related UV exposure has been implicated as a factor in the left-sided predominance of head and neck cancers,[6] this is unlikely in the UK, where drivers sit on the right side of the vehicle. In temperate climates such as the UK, cumulative lifetime UV exposure is more strongly influenced by outdoor activities, including walking, gardening, and recreational pursuits, than by time spent driving. Gorman et al.[7] also reported a statistically notable excess of left-sided facial lentigo maligna in a UK cohort. Similarly, Brewster et al.[8] demonstrated a consistent left-sided predominance of invasive melanoma across numerous countries, with left-to-right tumour ratios of approximately 1.1 or greater, and an estimated 18% excess of left-sided melanomas in Scotland.

Women in this audit presented with periocular BCC at a mean age approximately 4.3 years younger than men. This observation mirrors findings reported in other Western populations and may be explained by several interacting factors. Epidemiological studies have demonstrated age-dependent sex differences in BCC incidence, with a relative increase in cases among younger women and later presentation among men.[9] Women's periocular skin is often thinner and subject to closer cosmetic scrutiny, which may facilitate earlier detection of subtle lesions. Behavioural factors may also contribute, as women are generally reported to be more proactive in seeking medical evaluation for changes in appearance or health concerns.[10] Historical differences in UV exposure patterns may further

influence age at presentation; men have traditionally experienced greater cumulative occupational sun exposure, possibly leading to later-onset disease, whereas women may experience more intermittent but intense UV exposure earlier in life. Finally, healthcare-seeking behaviours influenced by social and cultural factors may result in delayed presentation among men, particularly for lesions perceived as minor.[11] These findings imply that targeted evaluation of periocular lesions may be beneficial in older men or individuals with significant sun exposure histories.

Nodular BCC constituted the majority of BCCs in our series (83%). This rate is higher than that reported by Ho et al.[12] in their large excision study (around two-thirds). The smaller subset of lesions with an infiltrative histology pattern (14%) demonstrates a distinctly higher-risk profile. All cases of PNI occurred in infiltrative-type tumours, and these lesions were more frequently associated with close or involved surgical margins. This observation is consistent with the established behaviour of infiltrative BCC, characterised by irregular microscopic tumour strands extending beyond the clinically apparent margins, thereby increasing the likelihood of incomplete excision with standard surgical techniques.[13]

In our cohort, the distribution of tumours across anatomical sites was significantly non-uniform, with the medial canthus representing the largest anatomical subgroup (56%). Notably, this area had the lowest achieved peripheral (1.21 mm) and deep (1.0 mm) mean margin clearance. This is an anatomically complex region containing the medial canthal tendon, angular vessels, and the nasolacrimal drainage system. Incomplete excision was more common in infiltrative BCCs (p=0.045), which were predominantly found in this anatomical area (57.1%). Malhotra et al.[14] reported in a periocular Mohs micrographic surgery (MMS) cohort that recurrences were most commonly at the medial canthus, with the infiltrating subtype as a significant predictor. These structures may act both as barriers and conduits for tumour spread, facilitating extension along tissue planes and perineural pathways, particularly via branches of the infratrochlear and supratrochlear nerves. Surgical excision in this region is challenging, as achieving wider margins risks functional impairment of eyelid position or lacrimal drainage. Furthermore, medial canthal BCCs may masquerade as benign inflammatory conditions such as chronic dacryocystitis, chalazion, or dermatitis, potentially postponing diagnosis and definitive treatment. Collectively, these factors help explain the increased rates of margin involvement and recurrence reported for infiltrative BCCs in the medial canthus.[3,4,7]

Given these considerations, an elevated level of suspicion and proactive management strategy is warranted for infiltrative or other high-risk periocular BCCs involving the medial canthus.[8] In our oculoplastic practice, a 3-mm clinical margin was generally aimed for where anatomically feasible and marked with a surgical caliper. This approach reflects the need to balance tumour clearance against preservation of eyelid position, lacrimal drainage function, and periocular cosmesis. However, in high-risk tumours, including infiltrative, morphoeic, basosquamous, recurrent, poorly defined, or medial canthal lesions, a fixed 3-mm margin may be insufficient or anatomically difficult to achieve. In such cases, particularly those that are infiltrative, recurrent, large, or adjacent to critical periocular structures, MMS offers superior margin control and high cure rates while maximising tissue preservation.[15] Finally, multidisciplinary team discussion is recommended for extensive or complex tumours, especially when PNI, nasolacrimal involvement, or orbital extension is suspected, to guide decisions regarding imaging, adjuvant radiotherapy, or alternative surgical approaches.

The high complete excision rate of 83% achieved in this audit is encouraging and compares favourably with previously published periocular BCC series, where reported clearance rates typically range between 80% and 85% for standard excision techniques.[1,2] Low-risk tumours demonstrated an excellent clearance rate of 93%, while even high-risk lesions achieved complete excision in 78.6% of cases, reflecting careful surgical planning and margin control in anatomically sensitive periocular sites.

In a tertiary centre series, Nemet et al.[16] reported that approximately one-quarter of periocular tumours had incomplete initial excision, with higher rates in medial canthal lesions. Weesie et al.[17] demonstrated a high complete excision rate of 99% for periocular BCCs treated with MMS. They also reported a low overall recurrence rate of 3% in the combined BCC and squamous cell carcinoma (SCC) cohort after a median follow-up of 46 months (total 20 BCC and 2 SCC recurrences). Their results support MMS as a preferred strategy for high-risk histology and anatomically constrained sites.

Study Limitations

In our study, variability was identified in the reporting of certain pathological features. In 5% and 9% of cases respectively, histopathology reports did not explicitly state the presence or absence of PNI or vascular invasion. Comprehensive pathology reporting is essential to guide postoperative management and surveillance. Current recommendations emphasise that pathology reports should

consistently include explicit statements regarding PNI, vascular invasion, histological subtype, and precise margin clearance in millimetres, even when these features are absent.[3]

Conclusion

Periocular BCC excision in this audit achieved a high rate of complete tumour clearance, with only a small proportion of cases demonstrating close or positive margins. This finding reflects effective surgical management of these common periocular malignancies. Nevertheless, a subset of BCCs, particularly those with infiltrative histology and those arising in the medial canthus, remain challenging in terms of tumour spread and PNI. These high-risk tumours accounted for all instances of PNI in this series and a high proportion of incomplete excisions.

The findings support an individualised, risk-adapted approach to periocular BCC management. Infiltrative or recurrent tumours, especially those located in anatomically high-risk regions, should encourage consideration of wider initial excision or MMS to optimise margin clearance. In addition, meticulous histopathological evaluation is essential, including standardised reporting of margin distances and perineural or vascular involvement, as this information is critical for guiding subsequent management and follow-up. Ongoing surveillance of surgical outcomes and future studies will help determine whether these strategies translate into reduced recurrence rates and improved patient care.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the James Paget University Hospital's Audit Service (26/03/2025; approval no: 1705/2025). According to the NHS governance guidelines, approval from the Research Ethics Committee is not required for clinical audit studies evaluating current clinical practices.

Informed Consent: Written informed consent was obtained from all participants.

Declarations

Authorship Contributions

Surgical and Medical Practices: R.B., S.A., Concept: H.J.O., R.B., Design: H.J.O., R.B., Data Collection or Processing: H.J.O., R.B., S.A., Analysis or Interpretation: H.J.O., R.B., S.A., D.K.B., Literature Search: H.J.O., R.B., S.A., D.K.B., Writing: H.J.O., R.B., S.A., D.K.B.

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Original Article

The Turkish Adult Strabismus Quality of Life Questionnaire (AS-20): A Psychometric Validation Study

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Abstract

Objectives: To translate the Adult Strabismus Quality of Life Questionnaire (AS-20) into Turkish and evaluate its reliability and validity in Turkish adult patients with strabismus.

Materials and Methods: Adult patients diagnosed as having strabismus and followed at the pediatric ophthalmology and strabismus unit of a tertiary university hospital were consecutively recruited. Patients with previous strabismus surgery, cognitive impairment, or insufficient Turkish language proficiency were excluded. A group of 15 participants completed the questionnaire a second time after a 2-week interval to evaluate test-retest reliability.

Results: A total of 111 adult patients (63.1% female) were included in the analysis. The mean age was 32.0±14.5 years, and exotropia was the most common deviation pattern (85.1%). Diplopia was present in 7.2% of participants. The Turkish AS-20 demonstrated good internal consistency, with a total Cronbach's alpha of 0.874. The psychosocial subscale showed a Cronbach's alpha of 0.862, and the functional subscale demonstrated a Cronbach's alpha of 0.822, indicating good reliability. Test-retest reliability analysis demonstrated excellent temporal stability for the psychosocial subscale, the functional subscale, and the total score ($p<0.001$).

Conclusion: The Turkish version of the AS-20 is a reliable and valid instrument for assessing strabismus-specific quality of life, demonstrating good internal consistency, high temporal stability, and applicability in both clinical practice and research settings.

Keywords: Adult strabismus, AS-20, health-related quality of life, patient-reported outcomes, quality of life

Introduction

Strabismus in adulthood is associated with functional impairments such as diplopia and asthenopia, but also with a profound psychosocial burden.[1] Adult patients with strabismus frequently report social anxiety, reduced self-esteem, difficulty maintaining eye contact, impaired interpersonal interactions, and limitations in daily activities.[2,3,4,5] In addition to its effects on self-esteem, this condition may lead to social prejudice that negatively affects job and relationship opportunities.[5,6] Standard ophthalmologic examinations, such as ocular alignment, motility, and visual acuity, may not fully capture the multidimensional impact of the disease. Therefore, patient-reported outcomes (PROs) have gained increasing importance.[7,8] Condition-specific questionnaires are essential for revealing concerns within a particular patient population and may enable more sensitive detection of change than a generic instrument.[9]

Several validated health-related quality of life (HRQoL) instruments may be appropriate for use in adult patients with strabismus, such as the Adult Strabismus-20 Questionnaire (AS-20).[10] The AS-20 was originally developed by Hatt et

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al.[10] in 2008 to quantify the psychosocial and functional consequences of strabismus in adults. It is a validated, disease-specific quality of life (QoL) instrument for adults with strabismus, and has been translated into multiple languages worldwide.[11,12,13,14] During the item generation process, 181 items were developed through interviews with groups of adult patients with strabismus. Among them, 20 items were selected as highly disease-specific. Items that discriminated against patients based on economic or educational status (e.g., driving) were excluded. The original validation demonstrated high internal consistency (Cronbach's alpha [α] >0.90), strong test-retest reliability, and high discriminative ability between patients with strabismus, patients with other ophthalmologic pathologies, and visually normal controls.[10] Moreover, the AS-20 was designed to be responsive to changes in the degree of strabismus, thereby establishing its value as both a research and a clinical tool.[10] Systematic reviews and PRO-focused analyses emphasize that the AS-20 remains a reliable, reproducible, and disease-specific QoL tool for adults with strabismus.[15,16,17]

Despite the widespread international use of the AS-20, a fully validated Turkish version does not currently exist. Considering the cultural and linguistic differences that may influence the interpretation of psychosocial items and the growing emphasis on patient-centered care, the availability of a validated Turkish AS-20 is essential. A culturally adapted Turkish version will enable physicians and researchers to reliably assess strabismus-related QoL, compare outcomes across studies, and incorporate PROs into routine clinical practice. The primary aim of this study was to evaluate the validity and reliability of the Turkish version of the AS-20.

Materials and Methods

Study Design and Participants

This prospective methodologic study was conducted to evaluate the validity and reliability of the Turkish version of the AS-20 questionnaire. Adult patients (aged over 18 years) who were diagnosed as having strabismus and followed at the Pediatric Ophthalmology and Strabismus Unit of Marmara University Hospital were consecutively recruited. Patients with previous strabismus surgery, best-corrected visual acuity (BCVA) worse than 0.3 (decimal), cognitive impairment, or insufficient Turkish language proficiency were excluded.

The study was approved by the Institutional Ethical Review Board of Marmara University on June 2, 2023 (protocol no: 09.2023.818) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Clinical Evaluation

All participants underwent a comprehensive ophthalmologic examination performed by an experienced ophthalmologist (D.D.Y.). Deviation angles were measured using the prism cover test or the Krimsky method, depending on fixation status. BCVA was recorded in decimal notation. Refractive errors were assessed using autorefractometry (Nidek ARK-530, Gamagori, Japan).

Adult Strabismus-20 Questionnaire

The AS-20 is a disease-specific QoL instrument comprising 20 items, divided into two subscales: a Psychosocial subscale (10 items) and a Functional subscale (10 items) (Supplemental Table 1). Each item is rated on a 5-point Likert scale ("never," "rarely," "sometimes," "often," "always") and scored on a 0-100 scale, with higher scores indicating better HRQoL. Subscale and total scores are calculated as the mean of completed items.

Translation and Cultural Adaptation

The original English version of the AS-20 was independently translated into Turkish by two psychiatrists (H.S.B. and S.I.A.) fluent in English. A consensus Turkish version was generated following reconciliation. Five participants were asked to evaluate the clarity, comprehensibility, and conceptual relevance of each item in the Turkish AS-20. No major comprehension difficulties, ambiguities, or culturally inappropriate expressions were identified, and no changes to the Turkish wording were considered necessary. Back-translation into English was performed by two independent translators who were blinded to the original questionnaire. Discrepancies were resolved by expert consensus to ensure conceptual equivalence rather than a literal translation.

All participants completed the Turkish AS-20 (Supplemental Table 2), and a subset of 15 patients completed the questionnaire again after 2 weeks to assess test-retest reliability.

Statistical Analysis

Statistical analyses were performed using Jamovi version 2.6 (The Jamovi Project) and R version 4.4 (R Core Team) software. Descriptive statistics were calculated for demographic and clinical variables. Internal consistency was assessed using Cronbach's α coefficients for the total scale and subscales. Item-rest correlations were examined to evaluate individual item performance.

Temporal stability was assessed using test-retest reliability with two-way mixed single measure intraclass correlation coefficients (ICC). Construct validity was examined through principal component analysis (PCA)

with varimax rotation. Sampling adequacy was evaluated using the Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity. The number of components retained was determined using eigenvalues, a scree plot, and parallel analysis. P values <0.05 were considered statistically significant.

Results

Participant Characteristics

A total of 111 adult patients were included in the analysis. The mean age was 32.0±14.5 (range, 18-69) years. The majority of participants were female (63.1%). Exotropia was the most common deviation pattern (85.1%), followed by esotropia (12.9%). Diplopia was present in 7.2% of participants. Baseline demographic and clinical characteristics are summarized in Table 1.

Reliability Analysis

The Turkish AS-20 demonstrated good internal consistency, with a total Cronbach's α of 0.874. The Psychosocial subscale showed a Cronbach's α of 0.862, while the Functional subscale demonstrated a Cronbach's α of 0.822, indicating good reliability.

Item-rest correlation analysis revealed that all items were positively correlated with the total score of the remaining items. Item 8 exhibited the lowest item-rest correlation; however, removal of this item resulted in only a minimal and statistically non-significant increase in the overall alpha coefficient (from 0.874 to 0.876). Therefore, item 8 was retained in the final version of the scale (Table 2).

Table 1. Demographic and clinical characteristics of the study population (n=111)

Variable	Value
Age (years), mean ± SD (range)	32.0±14.5 (18-69)
Sex, n (%)	
Female	70 (63.1)
Male	41 (36.9)
Type of deviation, n (%)	
Exotropia	96 (86.4)
Esotropia	13 (11.7)
Other (e.g., hypertropia)	2 (2.0)
Diplopia, n (%)	
Present	8 (7.2)
Absent	103 (92.8)
Angle of deviation at distance, mean ± SD (range)	34.8±13.6 (10-80)

SD: Standard deviation

Test-retest reliability analysis conducted in 15 participants demonstrated temporal stability. ICC values for the psychosocial subscale, functional subscale, and total score between the two administrations were 0.996, 0.997, and 1.000, respectively (Table 3).

Construct Validity: Principal Component Analysis

Prior to PCA, the suitability of the data for factor analysis was confirmed. The KMO measure of sampling adequacy was 0.69, and Bartlett's test of sphericity was statistically significant (χ^2=1400, df=190, p<0.001), indicating that the correlation matrix was appropriate for factor extraction. The KMO value of 0.69 falls within the mediocre range according to Kaiser's classification, and

Table 2. Reliability analysis of the Turkish AS-20

Item reliability statistics

Item	Item-rest correlation	If item dropped Cronbach's α
1	0.562	0.865
2	0.426	0.869
3	0.388	0.871
4	0.543	0.865
5	0.578	0.864
6	0.632	0.862
7	0.585	0.864
8	0.196	0.876
9	0.541	0.866
10	0.559	0.865
11	0.385	0.871
12	0.313	0.873
13	0.462	0.868
14	0.509	0.867
15	0.443	0.869
16	0.456	0.868
17	0.548	0.865
18	0.447	0.869
19	0.341	0.873
20	0.507	0.867

AS-20: Adult Strabismus-20 Questionnaire

Table 3. Test-retest reliability of the Turkish AS-20

Scale	ICC	95% CI	p value
Psychosocial subscale (factor 1)	0.996	0.99-1.00	<0.001
Functional subscale (factor 2)	0.997	0.99-1.00	<0.001
Total AS-20 score	1.000	1.00-1.00	<0.001

AS-20: Adult Strabismus-20 Questionnaire, ICC: Intraclass correlation coefficient, CI: Confidence interval

the two components explained 45.1% of the total variance. Therefore, these findings provide moderate support for the proposed two-component structure.

PCA with varimax rotation revealed a two-component structure, consistent with the original AS-20 design. These two components explained 24.1% and 21.0% of the total variance, respectively, with a cumulative explained variance of 45.1%. Inspection of the scree plot demonstrated a clear inflection point after the second component, supporting retention of a two-component solution (Figure 1). This structure was further confirmed by parallel analysis, in which only two components exhibited eigenvalues exceeding those derived from randomly generated datasets of equal size (Table 4). Component loadings indicated that items clustered meaningfully within the Psychosocial and Functional domains, with acceptable uniqueness values, supporting the construct validity of the Turkish AS-20. Items 5, 13, 14, and 17 exhibited cross-loadings. Items 5 (0.570 vs. 0.349) and 13 (0.452 vs. 0.314) were assigned to the factor with the higher loading. For items 14 (0.435 vs. 0.401) and 17 (0.466 vs. 0.399), where the difference between loadings was relatively small, theoretical integrity and consistency with the original scale structure were considered in addition to the statistical results. These items were therefore retained within their original domains.

Table 4. Principal component analysis component loadings of the Turkish AS-20

Item	Component 1* (psychosocial)	Component 2* (functional)	Uniqueness
1	0.721		0.469
2	0.386		0.764
3	0.580		0.663
4	0.780		0.392
5	0.570	0.349	0.554
6	0.756		0.394
7	0.710		0.464
8	0.543		0.627
9	0.729		0.463
10	0.680		0.511
11		0.682	0.532
12		0.645	0.580
13	0.314	0.452	0.698
14	0.435	0.401	0.650
15		0.611	0.604
16		0.789	0.377
17	0.466	0.399	0.624
18		0.659	0.552
19		0.424	0.792
20		0.810	0.338

*Component loadings ≥0.30 were reported
AS-20: Adult Strabismus-20 Questionnaire

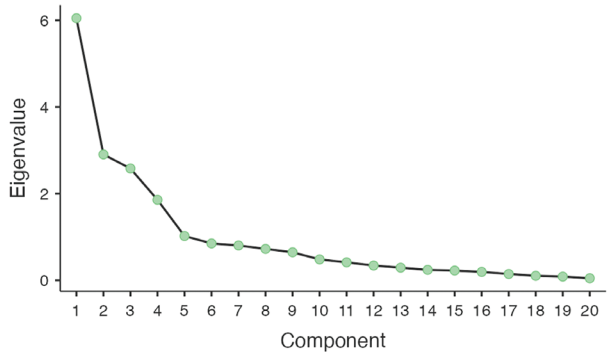

Figure 1. The scree plot with a clear inflection point after the second component

Discussion

In this study, the Turkish version of the AS-20 demonstrated good reliability and validity, with strong internal consistency and excellent test-retest reliability, indicating stable and reproducible measurements over time. Item-level analyses supported the coherence of the scale without the need for item removal. In addition, construct validity was confirmed by a two-component structure consistent with the original instrument, further supported by parallel analysis.

Clinical practices are evolving in a way that increases the importance of PROs.[7,8,18] The United States Food and Drug Administration defines PRO as "any report coming from patients about a health condition and its treatment."[18] Condition-specific instruments are considered more sensitive, reliable, and practical than generic instruments because they enable the detection of even subtle changes within a specific patient population using a limited number of items.[9,19]

Identifying the aspects of strabismus most relevant to patients is essential for clinical decision-making, and the AS-20 was designed to assess both functional impairments and psychosocial concerns associated with the condition. The AS-20 items were developed based on patient interviews, ensuring that they directly reflect the PROs of adults with strabismus. The AS-20 has been shown to address the majority of adult patients with strabismus, regardless of strabismus type, and is also sensitive in measuring treatment outcomes following strabismus surgery.[20,21] It is one of the most widely used instruments

for evaluating HRQoL in adult strabismus and has been translated into many languages.[11,14,15]

Comparing previous studies on the translation of AS-20 is highly challenging due to differences in age, sex, deviation angle, and symptoms across populations. The mean ages of the Indian (28 years) and Chinese (30 years) samples may be considered comparable to our study's mean age (32 years), but they were lower than the Dutch population means (52 years).[13,14,15] Furthermore, diplopia was observed in 36% of the Chinese and 74% of the Dutch samples, while this rate was only 7.2% in our sample.[13,14] This discrepancy may be due to differences in the etiology of strabismus across samples, such as neurogenic or amblyogenic causes, or to differences in chronicity.

The results of this study indicate that the Turkish version of the AS-20 is a reliable and valid instrument for assessing strabismus-related QoL. The scale demonstrated good internal consistency, with a Cronbach's α of 0.874, comparable to that of the original AS-20 (0.94). The psychosocial and functional subscales also showed good reliability, with Cronbach's α values of 0.862 and 0.822, respectively.

These findings are consistent with previous validation studies, including the Dutch and Chinese versions of the AS-20.[10,13,14,22] In the Dutch version, Cronbach's α values were reported as 0.93 for the psychosocial subscale and 0.87 for the functional subscale, with test-retest reliability coefficients of 0.91 and 0.88, respectively.[14] Similarly, the Turkish version demonstrated excellent test-retest reliability, with ICCs of 0.996 for the psychosocial subscale and 0.997 for the functional subscale, confirming its high temporal stability.

PCA was preferred in the present study as an exploratory, data-driven approach to evaluate whether the underlying factor structure of the Turkish AS-20 was consistent with that of the original instrument. Given that this study represents the first validation of the scale in a Turkish population, PCA was considered appropriate to assess dimensionality without imposing a predefined model. The emergence of a stable two-component structure, supported by eigenvalues, scree plot inspection, and parallel analysis, confirms the conceptual integrity of the AS-20's psychosocial and functional domains. Although item 8 showed the lowest item-rest correlation, it was retained because its removal did not significantly improve internal consistency and it represents a key psychosocial construct relevant to strabismus-related QoL, thereby preserving content validity and comparability with the original instrument. While several items (5, 13, 14, and 17) exhibited cross-loadings between the two components, they were ultimately retained in their respective domains. This decision was guided by their primary factor loadings, alongside considerations of theoretical integrity and alignment with the original scale's structure, as these items conceptually represent constructs that frequently bridge psychosocial and functional dimensions. Future studies may further evaluate these items in larger and more diverse samples.

Study Limitations

Several limitations of this study should be acknowledged. First, the sample was recruited from a single tertiary referral center, which may limit the generalizability of the findings to broader or community-based populations. Second, although the overall sample size was adequate for psychometric analyses, the test–retest reliability assessment was conducted in a relatively small subsample, which may limit the robustness of temporal stability estimates. Third, the cross-sectional design precluded evaluation of responsiveness to clinical change or sensitivity to treatment effects over time. Fourth, the predominance of exotropia and the low prevalence of diplopia limit the generalizability of the functional subscale findings to patients with paralytic, restrictive, traumatic, or other symptomatic forms of strabismus. Future studies should include more diverse samples and evaluate floor/ceiling effects and differential item functioning. Finally, confirmatory factor analysis was not performed. Although PCA provided preliminary evidence of the internal structure of the Turkish AS-20, Rasch analysis, confirmatory factor analysis, other item response theory methods, and convergent, known-groups, or criterion validity were not performed. Future studies should apply these methods in larger, more diverse samples.

Conclusion

The findings of this study demonstrate that the Turkish version of the AS-20 exhibits sound psychometric properties for assessing strabismus-specific QoL in Turkish adults. Both the psychosocial and functional subscales showed good internal consistency and excellent test-retest reliability. In addition, the scale demonstrated a stable structure consistent with the original questionnaire, supporting its construct validity.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethical Review Board of Marmara University on June 2, 2023 (protocol no: 09.2023.818) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Declarations

Authorship Contributions

Surgical and Medical Practices: D.D.Y., Concept: D.D.Y., E.K., H.Ş.B., S.İ.A., Ö.Ş., Design: D.D.Y., E.K., H.Ş.B., S.İ.A., Ö.Ş., Data Collection or Processing: D.D.Y., E.K., H.Ş.B., S.İ.A., Analysis or Interpretation: D.D.Y., H.Ş.B., S.İ.A., Literature Search: D.D.Y., E.K., Writing: D.D.Y., E.K., H.Ş.B., S.İ.A., Ö.Ş.

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Original Article

Clinical Patterns, Complications, and Long-Term Visual Outcomes of Fuchs' Uveitis Syndrome in Turkish Population: Retrospective Study in a Tertiary Uveitis Referral Center

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Abstract

Objectives: In this study, we aimed to characterize the clinical presentation patterns, complications, and visual prognosis of Fuchs' uveitis syndrome (FUS) patients at a tertiary center in Türkiye.

Materials and Methods: Sixty-one FUS patients (64 eyes) were enrolled in this retrospective study. Detailed ophthalmic and systemic history was obtained from patients at the initial examination. Visual acuity measurement (decimal values, converted to logarithm of the minimum angle of resolution [logMAR]), slit lamp examination, dilated fundus examination, intraocular pressure measurement with Goldmann applanation tonometry were performed at each visit.

Results: Keratic precipitates (KP) were present in 57 eyes (89.06%) at initial examination. Diffuse small stellate greyish KPs were observed in 50 eyes (78.13%). Thirty eyes (46.88%) presented with heterochromia. Twenty-seven eyes (42.19%) had vitreous debris/fibrillary appearance or condensation. The most common complication was cataract (79.69%), of which the most common type was posterior subcapsular cataract. At presentation, anterior chamber cells were seen in 32 eyes (50%). The mean visual acuity was 0.28±0.56 logMAR at the first examination and 0.25±0.48 logMAR at the final examination (p=0.542).

Conclusion: According to our findings, unilateral uveitis accompanied by low-grade anterior chamber inflammation, diffuse small stellate KPs, and diffuse stromal iris atrophy, with or without vitreous debris, remains the most characteristic clinical presentation among patients with FUS. Iris findings such as heterochromia and iris nodules are less frequently observed in Turkish patients, likely due to ethnic variations.

Keywords: Fuchs' uveitis syndrome, keratic precipitates, cataract, glaucoma, uveitis

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Introduction

Fuchs' uveitis syndrome (FUS) is a specific type of uveitis characterized by low-grade inflammation and generally unilateral involvement.[1] The hallmark signs of FUS include chronic mild intraocular inflammation, stellate and mostly diffuse keratic precipitates (KPs), and iris stromal atrophy, which frequently leads to heterochromia.[2] The absence of posterior synechiae (PS) is another diagnostic clue. The clinical presentation may also involve posterior segment findings such as inflammatory vitreous debris and chorioretinal scars. In the long term, FUS can lead to vision-threatening complications, including cataracts, glaucoma, and severe vitreous haze.

The diagnosis of FUS is primarily based on clinical examination, although no definitive diagnostic criteria have been established. The variable presentations and frequency of clinical signs make diagnosis challenging. The SUN Working Group proposed unilateral anterior uveitis, stellate KPs, and unilateral diffuse iris atrophy as key diagnostic criteria for FUS.[3] However, some researchers have criticized the SUN criteria, arguing that they have low sensitivity

and place undue emphasis on unilateral involvement.[4] Atypical bilateral cases further complicate the diagnostic process.[5] Additionally, the absence of diagnostic tests (ocular or systemic) increases the risk of misdiagnosis. The exact pathogenesis of FUS remains unknown, but several theories have been proposed. The detection of antibodies against the rubella virus and cytomegalovirus in aqueous humor samples,[6] as well as the presence of chorioretinal scars resembling toxoplasmosis[7] in some patients with FUS suggest a potential infectious etiology.

FUS is an important cause of anterior uveitis worldwide.[8] Yang et al.[9] reported that FUS was the most common cause of anterior uveitis in China. It is also a frequent cause of uveitis in Türkiye. A multicenter study identified FUS as the second most common diagnosis among Turkish patients with uveitis.[10] Another study reported that FUS accounts for 6.3% of all uveitis cases in Türkiye, ranking as the third most common noninfectious uveitis etiology nationwide.[11]

In this study, we aimed to characterize the presentation, frequency of clinical signs, complications, and visual prognosis of patients with FUS at a tertiary center in Türkiye. Our objective is to enhance the current understanding of the clinical patterns of this disease and the reasons for its misdiagnosis.

Materials and Methods

Sixty-one patients (64 eyes) diagnosed with FUS in the Uvea Division of the Department of Ophthalmology at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine were enrolled in the present study. The medical records of patients with FUS who were examined between 2012 and 2022 were retrospectively reviewed. The study was conducted in accordance with the tenets of Declaration of Helsinki. Ethics approval was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (number: E-83045809-604.01.02-134482, date: 09.07.2021).

A detailed ophthalmic and systemic history was obtained from all patients during the initial examination. Presenting symptoms, systemic diseases, systemic and ocular medications (e.g., corticosteroids, antiglaucoma agents), previous surgeries, and other noninvasive procedures were recorded. At each visit, patients underwent visual acuity measurement (decimal values were converted to logarithm of the minimum angle of resolution [logMAR]), slit-lamp examination, dilated fundus examination, and intraocular pressure (IOP) measurement by Goldmann applanation tonometry. The presence of anterior chamber and vitreous cells, the types and locations of KPs, and the presence of heterochromia, vitreous haze, and other fundus findings were documented. Optical coherence tomography (OCT) and fundus fluorescein angiography (FA) were performed as needed for differential diagnosis in patients with confounding vitreous findings or suspected retinal vasculitis.

The diagnosis of FUS was based on the presence of clinical findings such as chronic uveitis with mild or low-grade intraocular inflammation, diffuse iris atrophy with or without heterochromia, predominantly small and stellate KPs, and the absence of PS (except in cases with history of previous intraocular surgery). The diagnosis was confirmed by a single clinician (D.U.). However, follow-up examinations were performed by different clinicians. To ensure diagnostic accuracy, patients with other types of uveitis (anterior, posterior, or intermediate) or systemic comorbidities that could mimic FUS were excluded. Cases presenting with heterochromia and sectorial/partial iris atrophy or corneal opacification were excluded due to their resemblance to viral uveitis. Patients with active chorioretinitis or a history of ocular toxoplasmosis were also excluded. In uncertain cases, a diagnostic workup was performed, including complete blood count, erythrocyte sedimentation rate, C-reactive protein and angiotensin-converting enzyme levels, chest X-ray, syphilis serology, pathergy test, QuantiFERON, high-resolution computed tomography of the lung, and magnetic resonance imaging of the brain.

Prior to receiving a definitive diagnosis, some patients were treated with topical corticosteroids, which are not typically indicated for the management of FUS. This treatment was discontinued in all patients following the confirmed diagnosis of FUS. The use of other systemic or peribulbar treatments administered at other centers was also documented. For patients presenting with elevated IOP or glaucoma, topical antiglaucoma agents were the first-line therapy, particularly combined beta-blockers and carbonic anhydrase inhibitors, or alpha agonists. Oral acetazolamide or intravenous mannitol was administered for effective IOP control in cases with IOP ≥40 mmHg. Patients with glaucoma refractory to medical treatment were evaluated for glaucoma surgery.

Statistical Analysis

All analyses were performed using SPSS version 22.0 software. The Shapiro-Wilk test was used to evaluate the distribution of continuous variables. Accordingly, descriptive statistics were expressed as mean and standard deviation for normally distributed quantitative data, and as median and interquartile range for non-normally distributed data. Categorical variables were presented as frequencies and percentages, with comparisons performed using the chi-square test. A paired t-test was used to

compare visual acuity values between the first and last examinations.

Results

Sixty-four eyes of sixty-one patients with FUS were included in the present study. Thirty-one patients (50.82%) were male and 30 (49.18%) were female. The mean age of the study group was 33.93±10.03 years (33.00±11.46 years for male patients and 34.90±8.40 years for female patients). The patients' presenting symptoms are summarized in Table 1. Fifty-eight patients (95.08%) presented with unilateral involvement and 3 patients (4.92%) had bilateral disease.

At initial examination, KPs were present in 57 eyes (89.06%). Diffuse small grayish stellate KPs were observed in 50 eyes (78.13%), whereas medium-sized nonpigmented globular KPs were observed in 6 eyes and a granulomatous mutton-fat-like KP appearance was seen in one eye. At presentation, anterior chamber cells were seen in 32 eyes (50.00%): 4 (6.25%) with +0.5, 16 (25.00%) with +1, 11 (17.19%) with +2, and 1 eye (1.56%) with +3 cells. All eyes exhibited some degree of iris atrophy. Thirty eyes (46.88%) presented with heterochromia. Iris nodules at the pupillary margin were observed in 3 eyes (4.69%).

Thirty-one eyes (48.44%) had cataract at presentation, of which 30 (96.77%) exhibited posterior subcapsular cataract (PSC) and 1 (3.23%) had nuclear cataract. Fourteen eyes (21.88%) were pseudophakic at initial presentation, while 19 eyes (29.69%) were phakic with no cataract. During follow-up, 11 eyes (17.19%) underwent cataract surgery with intraocular lens (IOL) implantation. Posterior capsular opacity (PCO) developed in 3 eyes (12.00% of all pseudophakic eyes) during follow-up, one of which underwent neodymium-doped yttrium aluminum garnet laser capsulotomy.

Twenty-seven eyes (42.19%) had vitreous debris, fibrillary appearance, or condensation. Epiretinal membrane was present in 2 eyes (3.13%). Chorioretinal scars were observed in 3 eyes (4.69%). Snowball-like vitreous opacities were seen in one patient with multiple sclerosis. This patient exhibited the classic FUS phenotype, characterized by unilateral uveitis, stellate KPs, iris stromal atrophy, and debris in anterior vitreous.

The mean IOP at presentation was 14.09±4.68 mmHg. Six eyes (9.38%) had elevated IOP requiring the use of topical antiglaucoma therapy (a single agent in 4 eyes [6.25%] and a combination of two agents in 2 eyes [3.13%]). Glaucoma was diagnosed in 2 eyes (3.13%). In two eyes, IOP was uncontrolled despite topical therapy. One of these patients was treated with oral acetazolamide alone (once daily), while the other received oral acetazolamide (three times daily) along with intravenous mannitol during follow-up, and subsequently underwent trabeculectomy with mitomycin-C (MMC).

Twenty-seven eyes (42.19%) received topical medication either before presentation or during the follow-up period. Topical steroids, cycloplegics, peribulbar steroids, oral corticosteroids, or other immunosuppressive agents had been administered in other centers before a definitive diagnosis was made in our department.

Complications observed during follow-up are presented in Table 2. The most common complication was cataract (79.69%), with PSC being the most predominant type. Nuclear cataract was observed in only one eye during follow-up. FA was performed in 14 eyes, revealing optic disc staining in 4 eyes (6.25%) and cystoid macular edema (CME) in 3 eyes (4.69%). CME was also observed on OCT in these three eyes, all of which developed the condition after phacoemulsification surgery. FA findings were normal in the other 7 eyes (10.94%).

The mean visual acuity was 0.28±0.56 logMAR at the initial examination and 0.25±0.48 logMAR at the final examination (p=0.542). Visual acuity remained stable in

Table 1. Presenting symptoms in patients with Fuchs' uveitis syndrome

Presenting symptom	Number of patients (%)
Blurred vision	36 (59.02)
Floaters	16 (26.23)
Ocular pain with decreased vision	2 (3.28)
Ocular pain	1 (1.64)
Incidental finding During general examination During glaucoma screening During workup for Behçet disease	6 (9.84) 3 2 1

Table 2. Complications of Fuchs' uveitis syndrome

Complication	Number of eyes (%)
Cataract Cumulative rate at the end of follow-up At presentation	51 (79.69) 31 (48.44)
Vitreous debris or condensation	27 (42.19)
Elevated IOP	6 (9.38)
Posterior capsular opacity	3 (4.69)
Cystoid macular edema	3 (4.69)
Glaucoma	2 (3.13)
Epiretinal membrane	2 (3.13)
Optic disc membrane	2 (3.13)

IOP: Intraocular pressure

31 eyes (48.44%), improved in 17 eyes (26.56%), and worsened in 16 eyes (25.00%). The decrease in visual acuity during follow-up was associated with cataract formation or progression in all 16 eyes. Improved visual acuity was attributed to cataract surgery in 11 eyes (17.19%) and resolution of vitreous opacities in 4 eyes (6.25%).

Discussion

FUS is among the main etiologies of uveitis worldwide. Its prevalence varies according to ethnicity and geographic region. Yang et al.[9] reported that FUS is the second most common type of anterior uveitis in China, following idiopathic anterior uveitis. Another study similarly showed that FUS is the second most common etiology of anterior uveitis in China, noting a higher prevalence among women.[8] According to a multicenter study, FUS accounts for 6.3% of all uveitis cases in Türkiye, ranking as the third most common noninfectious uveitis etiology, with a male-to-female ratio of 0.79.[11] However, no sex-based difference was observed in the present study.

The diagnosis of FUS can sometimes be quite challenging, and patients may receive inappropriate treatment for years until the correct diagnosis is established. The SUN Working Group proposed specific diagnostic criteria for FUS.[3] However, even with these criteria, the wide spectrum of atypical presentations can make it difficult to distinguish FUS from other entities. In particular, atypical and bilateral cases may require additional diagnostic procedures.[5] Alternative essential findings have also been proposed in contrast to the SUN criteria. Yang et al.[4] argued that the SUN criteria had lower sensitivity than their own proposed criteria and overemphasized the unilaterality of the disease. They suggested diffuse iris depigmentation, the absence of PS, and mild inflammation as the essential diagnostic findings.

In the present study, the most common presenting symptom was blurred vision (59.02%). Most previous studies have also reported decreased vision as the primary presenting symptom,[12,13,14,15] although others identified floaters as the most frequent symptom of FUS.[16] Nevertheless, these studies noted that visual impairment was the main reason patients sought ophthalmic care. Unilaterality rates in the literature range from 84.4% to 96.0%.[12,15,17,18,19] Similarly, 95.1% of our patients had unilateral involvement.

The KPs in FUS are usually described as diffuse, white, stellate endothelial precipitates with characteristic fibrillary extensions. Most previous reports have documented this KP morphology in the majority of patients.[13,15,16,18] In contrast, Tugal-Tutkun et al.[17] reported that medium-sized, nonpigmented, globular KPs are the most common type observed in FUS. In our study, KPs were predominantly small and stellate, consistent with the general literature.

Iris stromal atrophy was present in all patients across the majority of previous studies.[12,16,18] Reported rates of heterochromia range from 13.9% to 90.3% in the literature. In the present study, heterochromia was observed in 46.9% of eyes. Despite the disease's historical name, "Fuchs heterochromic iridocyclitis," heterochromia is not a principal sign. This feature may be absent or difficult to detect, particularly in darkly pigmented eyes, which are highly prevalent among the population in our region. Other studies from Türkiye noted similar rates of heterochromia.[15,17]

Iris nodules have also been recognized as an important finding in some cases, with reported prevalence rates ranging from 13% to 37.7%.[12,14,15,17,19] However, iris nodules were observed in only 4.69% of the eyes in our study. Ethnic variations or difficulties in clinical detection during examination may account for this relatively low rate.

Chronic low-grade anterior chamber inflammation is also characteristic of FUS. Fifty percent of the eyes in our study had some degree of anterior chamber cells, mostly mild (+1 cells). Jones[13] reported +1 cells in 44.1% and no cellular activity in 53.1%, whereas Tugal-Tutkun et al.[17] observed anterior chamber cells in 74% of cases, mostly graded as less than +2. Other studies have reported mild to moderate anterior chamber inflammation in all cases.[12]

Cataract was the most frequent complication of FUS in our study, consistent with the literature.[15] PSC has been reported previously as the most frequent type.[15,17] However, the prevalence of PSC among cataract types in our study was exceptionally high at 97%. Our results suggest that PSC is highly characteristic of FUS in this population.

Thirty-nine percent of the eyes in the current study were pseudophakic at the end of follow-up. Higher rates have been noted in other reports.[12,13] In our cohort, the PCO rate was 12% among eyes with cataract surgery and 4.7% overall. PCO has been identified as the most common postoperative complication across various types of IOL.[20] Nalçacıoğlu et al.[15] reported a higher PCO rate (19.8%) in patients with FUS who underwent cataract surgery. The varying rates among studies may be related to differences in follow-up duration or IOL materials.

Chorioretinal scars, inflammatory vitreous debris, and epiretinal membrane are among the posterior segment findings reported in FUS. The frequency of chorioretinal scars in patients with FUS ranges between 2.3% and 20% in the literature.[12,13,15,17,18,19] Vitreous opacification or debris is another important finding, with a reported prevalence spanning a wide spectrum of 15.7% to 84%.[12,13,15,17,18,19]

In the present study, inflammatory vitreous debris was observed in 42.2% of eyes, a rate consistent with other studies from Türkiye.[17] Epiretinal membrane has been reported in a minority of patients in previous reports, similar to our results.[15] The definitive cause of epiretinal membrane and vitreal changes remains unknown.

Glaucoma is the leading cause of severe visual loss in FUS.[14] In our study group, 6 eyes (9.38%) developed elevated IOP during the course of the disease, and 2 eyes (3.13%) were diagnosed with glaucoma during follow-up. The prevalence of elevated IOP or glaucoma has been reported to range from 11.1% to 27.6% in various studies.[12,15,16,18] Tugal-Tutkun et al.[17] reported rates of elevated IOP and glaucoma similar to our results (12.7% and 1.1%, respectively). One patient in our series required trabeculectomy with MMC. Nalçacıoğlu et al.[15] noted an 18% glaucoma prevalence, with trabeculectomy performed in 25.8% of those cases. Furthermore, Tugal-Tutkun et al.[17] reported that in the majority of patients, elevated IOP could be managed successfully with medical therapy alone. The findings of the present study are consistent with these reports.

Study Limitations

The present study has several limitations. The sample size was relatively small because of the single-center study design. In addition, although the diagnosis of FUS was confirmed by a single clinician (D.U.), follow-up examinations and documentation were performed by different clinicians, potentially introducing bias in the evaluation of clinical findings. Furthermore, laser flare photometry and intraocular fluid sampling were not performed. Finally, some patients were treated with topical corticosteroids prior to a definitive diagnosis, which may have impacted the incidence and progression of cataract and glaucoma in these individuals.

Conclusion

The findings of the present study are largely consistent with those previously reported for Turkish patients with FUS, with some minor differences. Iris findings such as heterochromia and iris nodules seem to be less frequent among Turkish patients, which is likely attributable to ethnic variations. Furthermore, PSC was a highly characteristic finding in our study, whereas the PCO rate after cataract surgery was lower than that reported in other studies from Türkiye. According to our results, the presentation of unilateral uveitis with low-grade anterior chamber inflammation, diffuse small stellate KPs, and diffuse stromal iris atrophy with or without vitreous debris remains the most accurate clinical description of FUS.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the tenets of Declaration of Helsinki. Ethics approval was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (number: E-83045809-604.01.02-134482, date: 09.07.2021).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

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

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Original Article

Acute Effects of Caffeine on Ocular Functions in Young Adults

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Abstract

Objectives: To assess the short-term effects of a standardized dose of caffeine on selected ocular parameters in young adults and to examine its possible influence on visual performance during screen-based activities.

Materials and Methods: This prospective experimental study included 52 healthy university students aged 18-30 years. Participants consumed a standardized dose of 240 mg of caffeine in the form of black coffee. Ocular parameters including intraocular pressure (IOP), pupil diameter, contrast sensitivity, near point of accommodation, accommodative facility, vergence facility, visual reaction time, stereopsis, and ocular motility were assessed before and 30 minutes after caffeine intake. Pre- and post-intervention measurements were compared using paired t-tests, with $p<0.05$ considered statistically significant.

Results: Significant improvements were observed in accommodative facility (right eye [OD]: $p=0.04$; left eye [OS]: $p<0.001$; both eyes [OU]: $p=0.0003$), vergence facility ($p=0.01$), and contrast sensitivity in OU (OD and OS: $p<0.001$). The near point of accommodation decreased significantly, indicating improved accommodative ability (OD: $p=0.02$; OS: $p=0.009$; OU: $p<0.001$). Visual reaction time improved in most participants, although the change was not statistically significant ($p=0.08$). Pupil diameter increased significantly ($p<0.001$). IOP showed a small but statistically significant increase ($p<0.001$), remaining within normal physiological limits. Changes in stereopsis were not statistically significant ($p=0.06$). Minor changes were also observed in saccadic and pursuit eye movements.

Conclusion: A single dose of caffeine led to measurable short-term improvements in visual performance, particularly in accommodation and contrast sensitivity, along with a modest improvement in reaction time. Small increases in pupil diameter and IOP were also observed. These findings suggest that moderate caffeine intake may offer some benefit during visually demanding tasks. However, caution may be needed for individuals at risk of ocular hypertension. Larger, placebo-controlled, and multicenter studies are recommended to confirm these findings and to evaluate long-term effects.

Keywords: Caffeine, pupil diameter, accommodation, intraocular pressure, visual reaction time, contrast sensitivity, ocular performance

Introduction

Caffeine is one of the most widely consumed psychoactive substances worldwide and is commonly used to improve alertness and reduce fatigue. It primarily acts as an adenosine receptor antagonist, thereby increasing neural activity and enhancing cognitive performance.[1] While its systemic effects are well established, its influence on ocular physiology and visual performance remains incompletely understood.[2]

Several visual functions, including accommodation, pupil dynamics, contrast sensitivity, intraocular pressure (IOP), and eye movements, are regulated by neural and autonomic mechanisms susceptible to the effects of caffeine intake.[3] Previous studies have reported that caffeine may improve accommodative function, increase pupil diameter, and enhance reaction time.[4,5,6] However, findings remain inconsistent, and most studies have evaluated only a limited number of parameters.

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Young adults, particularly university students, frequently consume caffeine during prolonged near-work and screen use. Understanding its short-term effects on visual performance may have both clinical and practical relevance in this population.

Therefore, the present study aimed to evaluate the acute effects of a standardized dose of caffeine on selected ocular parameters in healthy young adults.

Materials and Methods

Study Design and Participants

This prospective experimental study was conducted at Parul Sevashram Hospital and Pragya Advanced Skills and Simulation Centre, Parul University, Vadodara, Gujarat, over a period of six months (January to June 2025). The study was approved by the Institutional Ethics Committee of Parul University (approval no: PUIECHR/PIMSR/00/081734/8214; date: 31 December 2024) and written informed consent was obtained from all participants.

A total of 52 university students aged between 18 and 30 years were enrolled through purposive sampling. Participants were generally healthy and regular caffeine consumers, with no history of ocular or systemic disease. Inclusion criteria required participants to have no significant refractive error (refractive error within ±1.00 diopter [D] sphere and ±0.50 D cylinder), no ocular or systemic pathology, and no use of any medication affecting vision or caffeine metabolism. Exclusion criteria included pregnancy or breastfeeding, a history of systemic conditions such as diabetes or hypertension, caffeine allergy, ocular trauma or surgery, and substance abuse or excessive caffeine dependency.

Intervention and Ocular Assessments

Each participant consumed a standardized dose of 240 mg caffeine in the form of black coffee. Ocular parameters were assessed before and 30 minutes after caffeine intake (Table 1). All measurements were taken under controlled lighting conditions between 9:00 AM and 12:00 PM. Post-intervention measurements occurred 30 minutes after caffeine intake, using the same instruments and procedures. The following variables were analyzed:

a. Visual Acuity

Distance visual acuity was assessed monocularly using a standard Snellen chart at a testing distance of 6 m under standardized room illumination. Participants wore their habitual refractive correction, if required. Visual acuity was recorded as Snellen fractions, converted to decimal notation, and subsequently converted to logarithm of the minimum angle of resolution for analysis.[7]

b. Contrast Sensitivity

Contrast sensitivity was measured monocularly using the Pelli-Robson Contrast Sensitivity Chart (Precision Vision, Woodstock, IL, USA) at a testing distance of 1 m under standardized photopic illumination.[8] Participants identified letters of progressively decreasing contrast until the threshold level was reached, and the score was recorded in log contrast sensitivity units.

Table 1. Instruments and techniques used for assessing visual and ocular parameters

Parameters	Tools/methods used	Units
Visual acuity	Snellen chart	logMAR (converted from decimal)
Pupil diameter	Millimeter scale in constant lighting	Millimeter (mm)
Stereopsis	Random Dot 2S test	Seconds of arc (arc sec)
Contrast sensitivity	Pelli-Robson Chart (Precision Vision, Woodstock, IL, USA)	logCS
Near point of accommodation	RAF ruler (Good-Lite Co., Elgin, IL, USA)	Centimeters (cm)
Accommodative facility	±2.00 D flipper lenses	Cycles/min
Vergence facility	Base-in/base-out prism flippers	Cycles/min
Visual reaction time	Computerized reaction time test	Milliseconds (ms)
Saccades and pursuits	Adult Developmental Eye Movement test	Seconds (s)
Intraocular pressure	Goldmann applanation tonometer (Haag-Streit, Köniz, Switzerland)	Millimeters of mercury (mmHg)

logMAR: Logarithm of the minimum angle of resolution, logCS: Log contrast sensitivity

c. Pupil Diameter

Pupil diameter was measured under constant ambient illumination using a millimeter scale before and 30 minutes after caffeine consumption. Measurements were obtained with participants fixating on a distant target to minimize accommodative influence and were recorded in millimeters.

d. Stereopsis

Stereoacuity was assessed using the Random Dot 2S stereopsis test under habitual near correction at a working distance recommended by the manufacturer.[9] Participants identified stereoscopic targets, and the smallest disparity correctly identified was recorded in seconds of arc.

e. Intraocular Pressure

IOP was measured using a Goldmann applanation tonometer (Haag-Streit, Köniz, Switzerland).[10] Following instillation of topical anesthetic and fluorescein dye, measurements were obtained according to standard Goldmann applanation tonometry procedures. The average of two consecutive readings was recorded for each eye.

f. Near Point of Accommodation (NPA)

NPA was measured using a RAF (Royal Air Force) rule.[11] A near accommodative target was moved slowly towards the participant along the midline until the first sustained blur was reported. Measurements were obtained monocularly for each eye and binocularly, and the distance was recorded in centimeters.

g. Accommodative Facility

Accommodative facility was assessed using ±2.00 D flipper lenses with a near target positioned at 40 cm. Participants alternately viewed through plus and minus lenses while maintaining a clear image. The number of complete cycles achieved within one minute was recorded as cycles per minute. Monocular and binocular measurements were obtained.[12]

h. Vergence Facility

Vergence facility was evaluated using 12Δ base-out and 3Δ base-in prism flippers while participants fixated on a near accommodative target at 40 cm. The number of complete prism cycles achieved in one minute was recorded in cycles per minute.[13]

i. Visual Reaction Time

Visual reaction time refers to the time interval between the presentation of a visual stimulus and the initiation of an appropriate motor response. It reflects the efficiency of visual information processing, cognitive decision-making, and motor execution. In the present study, visual reaction time was assessed using the Human Benchmark Reaction Time Test.[14] Participants were instructed to click the mouse as quickly as possible when the screen changed from red to green, indicating the appearance of the visual stimulus. Before data collection, participants completed practice trials to familiarize themselves with the testing procedure. Five consecutive trials were recorded for each participant, and the average reaction time was calculated and expressed in milliseconds. Testing was performed under standardized lighting conditions using the same computer system for all participants.

j. Saccades and Pursuits

Ocular motor performance was assessed using the Adult Developmental Eye Movement test. Participants were instructed to read the numerical targets as quickly and accurately as possible, following the standardized test procedure. The time required to complete the assessment was recorded in seconds, with lower completion times indicating faster performance.[15,16]

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Paired t-tests were used to compare pre- and post-intervention values. A p value <0.05 was considered statistically significant.

Results

A total of 52 participants completed the study. Comparison of pre- and post-caffeine measurements revealed significant changes in several ocular parameters. Visual acuity showed no change following caffeine intake and therefore was not included among the reported outcome measures. However, following caffeine intake, accommodative facility demonstrated a statistically significant improvement in both monocular and binocular conditions, with the greatest improvement observed in binocular measurements (Figure 1; Table 2). Vergence facility also showed a significant increase after the intervention (Table 2).

NPA values decreased significantly in both monocular and binocular measurements, indicating enhanced accommodative ability after caffeine intake (Figure 2; Table 2).

Contrast sensitivity exhibited a small but statistically significant improvement bilaterally (Figure 3; Table 2).

IOP showed a modest but statistically significant increase in both eyes, though values remained within normal physiological limits (Figure 4; Table 2). Pupil diameter also showed a small but consistent increase following caffeine intake (Table 2).

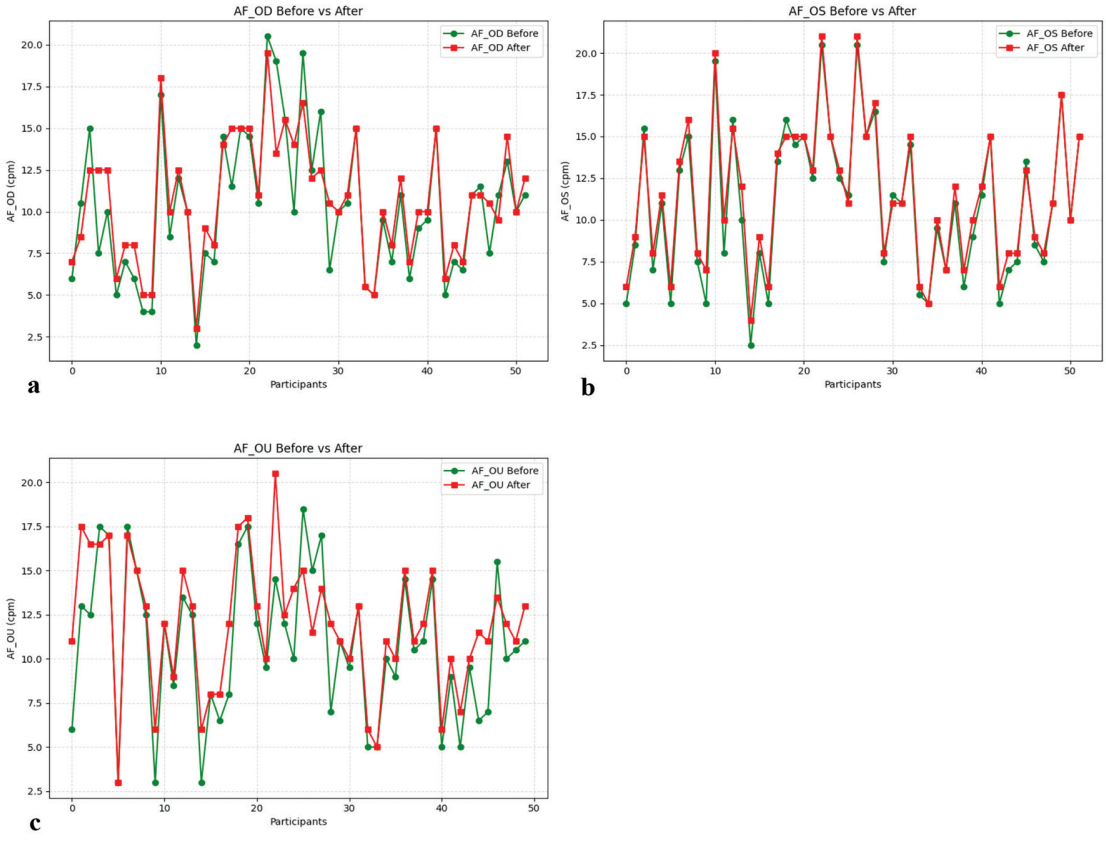

Figure 1. Changes in accommodative facility (AF, in cycles/min) before and after caffeine intake in the right eye (OD; a), left eye (OS; b), and both eyes (OU; c)

Table 2. Summary of ocular measurements before and after caffeine consumption

Parameter		Pre-caffeine		Post-caffeine		p value	t statistic
		Mean	SD	Mean	SD		
AF (cycles/min)	OD	10.21	4.26	10.72	3.61	0.04	-2.048
	OS	10.98	4.47	11.46	4.19	<0.001	-5.471
	OU	10.81	4.22	11.95	3.74	0.0003	-3.853
CS (logCS)	OD	2.04	0.08	2.07	0.08	<0.001	-6.171
	OS	2.03	0.08	2.07	0.08	<0.001	-6.171
IOP (mmHg)	OD	12.96	2.31	13.94	2.33	<0.001	-10.536
	OS	13.42	2.45	14.37	2.54	<0.001	-6.945
NPA (cm)	OD	10.96	3.74	10.19	2.72	0.02	2.362
	OS	10.71	3.21	10.04	2.45	0.009	2.695
	OU	9.52	2.42	9.00	2.00	<0.001	4.397
PD (mm)	OD	2.02	0.42	2.19	0.52	<0.001	-3.656
	OS	2.02	0.42	2.19	0.52	<0.001	-3.656
A-DEM completion time (s)		59.67	10.27	57.48	11.74	<0.001	1.865
Stereopsis (arc sec)		44.38	23.26	39.83	23.3	0.06	1.856
VF (cycles/min)		13.85	3.61	14.89	3.74	0.01	-2.61
VRT (ms)		483.73	131.52	455.07	90.53	0.08	1.743

SD: Standard deviation, AF: Accommodative facility, CS: Contrast sensitivity, logCS: Log contrast sensitivity, IOP: Intraocular pressure, NPA: Near point of accommodation, PD: Pupillary diameter, A-DEM: Adult Developmental Eye Movement test, VF: Vergence facility, VRT: Visual reaction time, OD: Right eye, OS: Left eye, OU: Both eyes

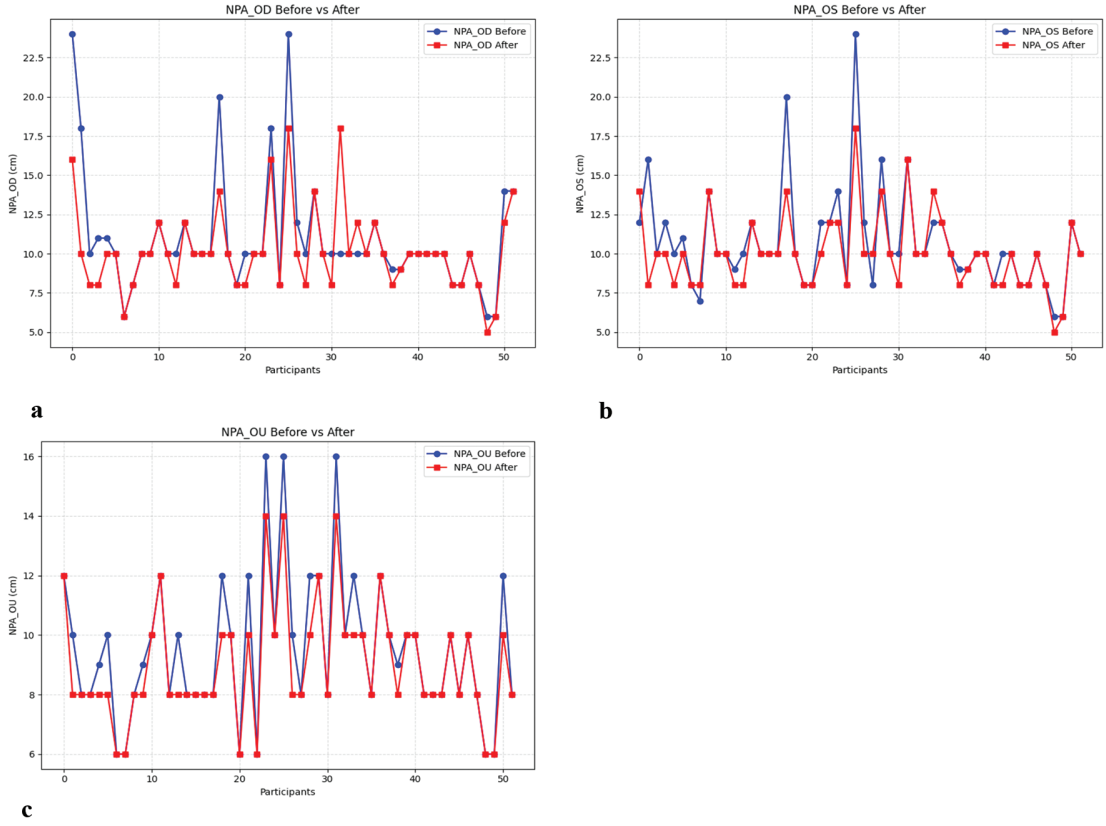

Figure 2. Changes in near point of accommodation (NPA, in cm) before and after caffeine intake in the right eye (OD; a), left eye (OS; b), and both eyes (OU; c)

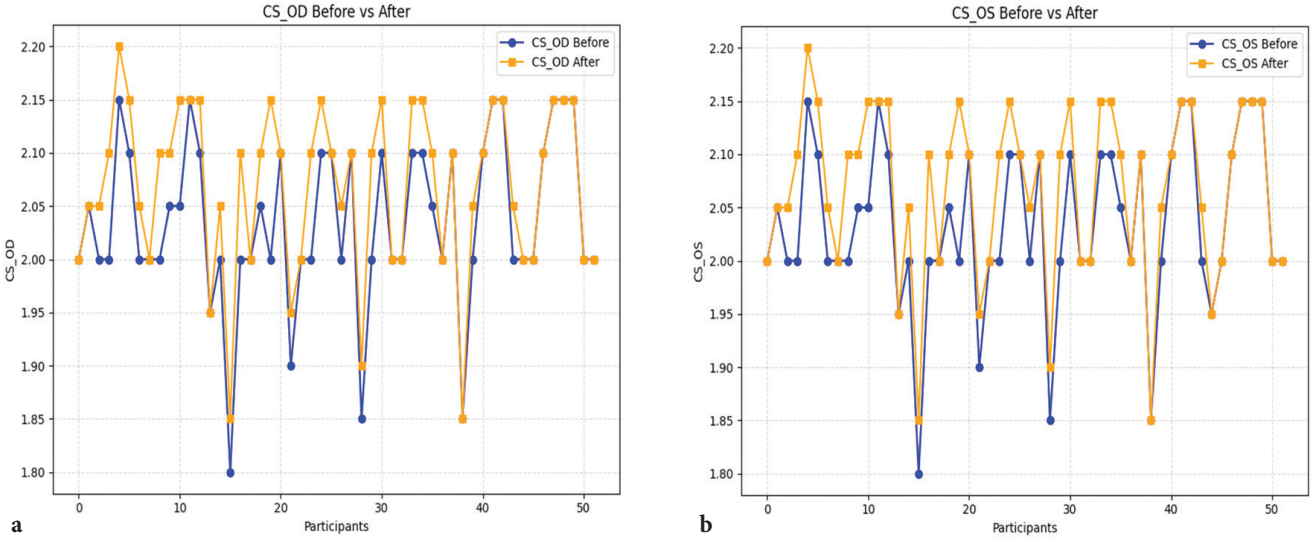

Figure 3. Changes in contrast sensitivity (CS, in logCS) before and after caffeine intake in the right eye (OD; a) and left eye (OS; b)
logCS: Log contrast sensitivity

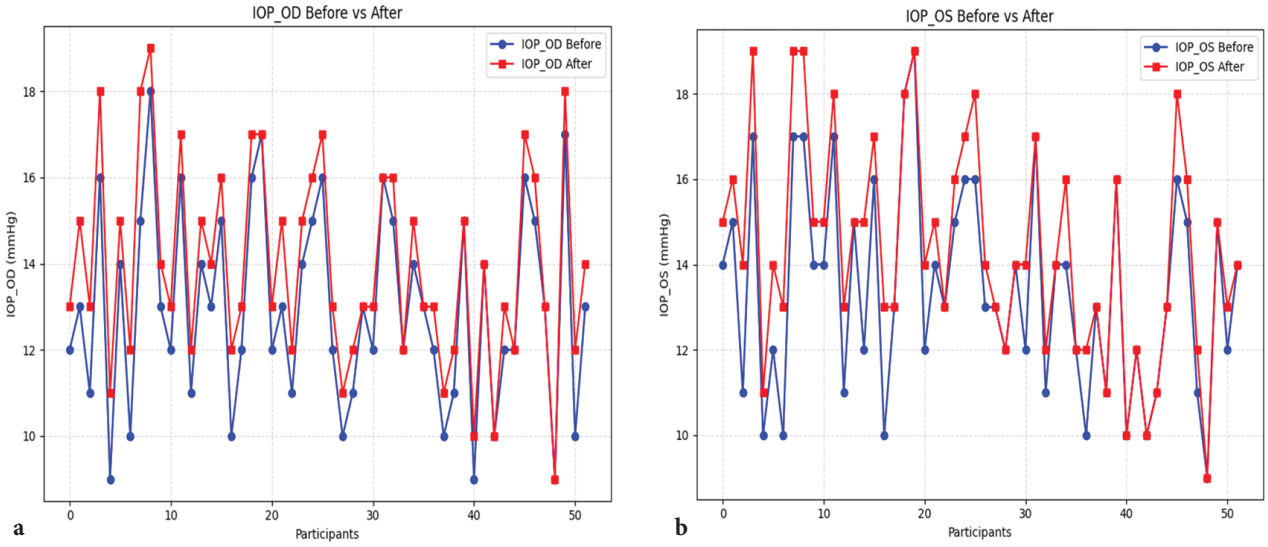

Figure 4. Changes in intraocular pressure (IOP, in mmHg) before and after caffeine intake in the right eye (OD; a) and left eye (OS; b)

While stereopsis and visual reaction time demonstrated trends toward improvement, these differences did not reach statistical significance (Table 2).

Minor changes were observed in pursuits and saccades, indicating slight alterations in oculomotor performance after caffeine intake (Table 2).

Discussion

This study investigated the acute effects of a single 240 mg dose of caffeine on various visual and ocular parameters in healthy young adults. Following caffeine intake, significant improvements were observed in accommodative facility, vergence facility, NPA, and contrast sensitivity. Furthermore, pupil diameter and IOP increased significantly, although the IOP values remained within the normal physiological range (approximately 10-21 mmHg). While slight improvements in visual reaction time and stereopsis were also observed, these did not achieve statistical significance. Overall, the findings indicate that acute caffeine consumption induces measurable short-term changes in several aspects of visual performance.

One of the most notable findings was the improvement in accommodative facility and NPA following caffeine intake. Similar improvements have been reported by Abokyi et al.[17], who observed enhanced accommodative performance after caffeine consumption. Likewise, Redondo et al.[1,18] demonstrated significant improvements in dynamic accommodative response and binocular accommodative facility after acute caffeine intake. Earlier work by Kirshner and Schmid[19]also suggested that caffeine positively influences accommodative performance by improving near point plus acceptance. Together, these findings support the hypothesis that caffeine enhances accommodative efficiency during near visual tasks. A possible mechanistic explanation is the antagonistic effect of caffeine on adenosine receptors, which increases central nervous system stimulation and improves the neuromuscular responsiveness of the accommodative system.[20] Consequently, moderate caffeine intake may temporarily reduce visual fatigue and enhance performance during prolonged near work such as reading and computer use.

Vergence facility also improved significantly after caffeine consumption. Although relatively few studies have evaluated the direct effect of caffeine on vergence function, the improvement observed in the present study may be related to increased cortical alertness and better neuromuscular coordination. As accommodation and vergence are closely linked through the accommodative convergence/accommodation (AC/A) relationship, enhancement of accommodative performance may also contribute to improved vergence facility.[21] Further research is needed to better understand the mechanisms underlying these changes.

A small but statistically significant improvement in contrast sensitivity was also observed. This finding aligns with a study by Obinna et al.[5] that demonstrated increased contrast sensitivity following caffeine intake among healthy young adults. These findings may be attributable to improved neural processing within the visual pathways together with increased cortical arousal.[4,20] Although the observed improvement was modest, even small changes in contrast sensitivity can enhance visual performance during demanding visual tasks and under low-contrast conditions.

Pupil diameter increased significantly following caffeine intake. This finding is consistent with the observations of Abokyi et al.[17] and with a systematic review and meta-analysis by Hartmann et al.[6], both of which reported mild pupillary dilation after caffeine consumption. Caffeine-induced sympathetic stimulation may reduce parasympathetic activity at the iris sphincter muscle, resulting in mild mydriasis.[20,22] In addition, Lazar et al.[23] demonstrated that pupil size is influenced by autonomic balance, environmental illumination, and cognitive state, supporting the possibility that the increased alertness associated with caffeine contributes to the observed pupillary changes.

A modest but significant increase in IOP was also found after caffeine consumption. Similar findings have been reported by Higginbotham et al.[24], who demonstrated transient increases in IOP following caffeine intake in patients with glaucoma. Kim et al.[3] identified an association between caffeine consumption and IOP in genetically susceptible individuals. Although the increase observed in this study remained within the normal physiological range, it may be clinically relevant in individuals with glaucoma or ocular hypertension. The transient rise in IOP may result from changes in aqueous humor dynamics induced by caffeine.

Although visual reaction time decreased after caffeine intake, indicating faster responses, the difference was not statistically significant. Visual reaction time reflects the efficiency of visual information processing, cognitive function, and motor response. Caffeine is known to enhance alertness and psychomotor performance through blockade of adenosine receptors and increased neuronal activity.[20,25,26,27] The lack of statistical significance in the present study may be due to individual variability in caffeine sensitivity, habitual caffeine consumption, or the relatively small sample size. Larger studies are required to determine whether caffeine consistently improves visual reaction time.

Minor improvements were observed in saccadic and pursuit eye movements after caffeine intake. These findings may reflect enhanced oculomotor control associated with increased cortical activation. Connell et al.[28] similarly reported that caffeine increased the velocity of rapid eye movements in healthy individuals, supporting the possibility that caffeine positively influences ocular motor performance. Future studies using objective eye-tracking systems would provide a more detailed evaluation of these changes.

Although stereopsis showed a trend toward improvement, the difference was not statistically significant. Stereoacuity relies on accurate binocular sensory integration and cortical processing, and the short interval between caffeine intake and testing may have been insufficient to produce measurable changes.[29] Studies involving larger populations and different caffeine doses are required to further investigate the effect of caffeine on stereoscopic vision.

A major strength of the present study is the simultaneous evaluation of multiple visual and ocular parameters following acute caffeine consumption. While most previous studies have focused on individual outcomes such as accommodation, pupil diameter, or IOP, the present study provides a broader assessment of the short-term effects of caffeine on visual function. This comprehensive approach offers a more complete understanding of how caffeine influences different components of the visual system.

From a clinical perspective, the findings suggest that moderate caffeine intake may temporarily improve accommodative function, vergence facility, and contrast sensitivity, which could enhance visual performance during prolonged near work and other visually demanding activities. However, the observed increase in IOP suggests that individuals with glaucoma or ocular hypertension should consume caffeine cautiously.

Study Limitations

The study has several limitations. The sample size was relatively small and consisted only of healthy young adults from a single institution, which may limit the generalizability of the findings. The absence of a placebo-controlled, double-blind design may also have introduced expectation bias. Furthermore, only the short-term effects of a single caffeine dose were investigated, and habitual caffeine intake was not quantified. As plasma caffeine concentrations were not measured, inter-individual differences in caffeine metabolism could not be evaluated. Future studies should include larger and more diverse populations, randomized placebo-controlled designs, different caffeine dosages, and longer follow-up periods to better understand the effects of caffeine on ocular physiology and visual performance.

Conclusion

In this study, a single dose of caffeine produced measurable short-term changes in several visual and ocular parameters, particularly in accommodative function, vergence facility, and contrast sensitivity. A modest improvement in visual reaction time was also observed. These findings suggest that moderate caffeine intake may have a beneficial effect on visual performance during visually demanding tasks. However, while IOP values remained within normal physiological limits, the slight increase highlights the need for caution in individuals at risk of ocular hypertension or glaucoma. Further large-

scale, placebo-controlled clinical studies are required to confirm these findings and evaluate their long-term clinical significance.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Parul University (approval no: PUIECHR/PIMSR/00/081734/8214; date: 31 December 2024).

Informed Consent: Written informed consent was obtained from all participants.

Declarations

Authorship Contributions

Concept: R.K., Design: R.K., Data Collection or Processing: R.K., B.G., S.D., K.M., Analysis or Interpretation: R.K., S.D., M.R., Literature Search: R.K., S.D., M.R., Writing: R.K., M.R., S.P.

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Review

Current Approaches in the Management of Complicated Macular Holes

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Abstract

Kelly and Wendel reported the first successful intervention for idiopathic full-thickness macular holes in 1991. Since then, pars plana vitrectomy and internal limiting membrane peeling have become the standard treatment approach, with >90% hole closure rates. However, the results were not satisfactory in cases of complicated macular holes, including large, recurrent, refractory, and myopic macular holes. To date, several surgical approaches, including the inverted internal limiting membrane flap technique, autologous retinal transplantation, the human amniotic membrane plug, and the autologous Tenon's capsule plug, have been described by various authors to improve the anatomical and functional outcomes of challenging cases. Although these techniques have significantly increased hole closure rates, each technique has its own strengths and weaknesses. Currently, there is no consensus among vitreoretinal surgeons on a single ideal technique for treating challenging macular holes. In this review, the inventors of each innovative surgical technique will discuss the indications, pros and cons, complications, and anticipated future applications.

Keywords: Amniotic membrane, autologous retinal graft, inverted internal limiting membrane flap, macular hole, Tenon's capsule

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Introduction

Following Kelly and Wendel's first successful macular hole (MH) surgery in 1991, advancements in technology and the development of new techniques over the past 30 years have enabled closure rates of over 90% to be achieved in standard cases. However, in complex MHs, such as large, myopic, refractory, or traumatic cases, anatomical closure rates achieved with traditional approaches remain lower, and these cases continue to present a challenge. This review will address six surgical techniques currently used in the treatment of complicated MHs, all of which have high reported success rates. The advantages and disadvantages of each technique, key surgical points, and complications will be discussed.

1. Inverted Internal Limiting Membrane Flap

Small idiopathic MHs often respond favorably to pars plana vitrectomy (PPV), regardless of positioning or internal limiting membrane (ILM) peeling. Larger, myopic, chronic MHs, or MHs secondary to other diseases—particularly those associated with proliferative diabetic retinopathy,

age-related macular degeneration (AMD), trauma, or uveitis—have historically exhibited lower closure rates and poorer functional outcomes.[1,2] The advent of the inverted ILM flap technique, introduced by Michalewska et al.[3], has dramatically changed this landscape, virtually eliminating type 2 closure patterns (flat margins of the hole and bare retinal pigment epithelium [RPE]) and achieving closure in the vast majority of complicated cases regardless of hole size or chronicity.

The standard surgical procedure for the inverted ILM flap technique typically begins with a core vitrectomy (without indentation of the periphery), followed by staining of the ILM with MembraneBlue-Dual (DORC, Zuidland, the Netherlands) to enhance visualization of the vitreous, epiretinal membranes (ERM), and ILM. In the classical approach, circumferential ILM peeling was performed to create multiple flaps, which were then trimmed and carefully placed over the MH, taking care to avoid inserting the flap into the MH itself (flower technique).[3] This distinction is important because placement of the ILM inside the hole has been associated with less favorable restoration of retinal microarchitecture, particularly the external limiting membrane (ELM) and ellipsoid zone (EZ), both critical to photoreceptor function and therefore to vision.[3,4] However, the classical approach has been abandoned, and Michalewska et al.[5] currently perform the temporal inverted ILM flap technique. The ILM is only peeled on the temporal side of the fovea and positioned on top of the MH. In some cases, viscoelastics are used for better stabilization. The procedure is completed with air tamponade, and patients are instructed to maintain prone positioning for three days to facilitate proper anatomical closure. Long-acting gases are not usually required for MH repair.[5]

The mechanism underlying the success of the inverted ILM flap technique appears to involve both mechanical and biological factors. The ILM acts as a basement membrane for Müller cells, which proliferate and migrate along the scaffold provided by the inverted flap. This cellular activity facilitates centripetal contraction, leading to gradual closure of the MH and subsequent restoration of the ELM and EZ layers.[3,4] Animal models have confirmed Müller cell activation and migration along the ILM scaffold,[6] while *in vitro* experiments have shown that the adult retina retains some degree of regenerative potential when supported by this substrate.[7] Thus, the inverted ILM flap technique not only provides a physical barrier but also promotes cellular processes essential for both anatomical and functional recovery.

Clinical outcomes with the inverted ILM flap technique have consistently demonstrated its superiority over traditional ILM peeling across diverse and challenging scenarios (Table 1).[3,8,9] In large and chronic MHs, randomized studies have reported closure rates of 98% with the inverted ILM flap technique compared to 88% with standard peeling, with type 2 closures effectively eliminated in the inverted ILM flap technique group.[3] Primary closure was observed in 95-96% of large idiopathic MHs using both classical and superior flap techniques, with comparable improvements in best-corrected visual acuity (BCVA) at six months postoperatively.[10]

In highly myopic MHs with or without retinal detachment (RD), the inverted ILM flap technique has yielded particularly striking results. Comparative studies by different authors confirm that the clinical advantage of the inverted ILM flap technique is even more pronounced in these cases than in large MHs. Mete et al.[11] demonstrated a 22-fold higher likelihood of anatomical closure with the inverted ILM flap technique compared to conventional peeling, while Rizzo et al.[9] reported closure rates of 88.4% versus only 38.9% with peeling alone in high myopia. Importantly, functional outcomes are superior when the ILM flap is positioned over the MH rather than tucked into it, further emphasizing the role of the flap as a scaffold for retinal repair rather than a mere physical plug (Table 2).[9,11,12,13,14]

Proliferative diabetic retinopathy-associated MHs present a unique surgical challenge due to their often markedly high base-to-minimum diameter ratio (approximately 10:1), which resembles that of MHs in high myopia. Furthermore, these cases may involve the coexistence of tractional RD. Michalewska and Nawrocki[15] observed that the inverted ILM flap technique achieves closure beginning at the inner retina, followed by gradual reattachment of the outer retinal layers over several weeks to months, offering a level of success not previously attainable with standard techniques (Figure 1).

Table 1. Summary of clinical outcomes with the inverted ILM flap technique compared to ILM peeling in MH repair

Author, year[ref]	ILM peeling % closed	Visual acuity	Inverted flap % closed	Visual acuity
Michalewska et al., 2010[3]	88% (19% type 2)	0.17 Snellen	98%	0.28 Snellen
Kannan et al., 2018[8]	75%	0.69 logMAR	89.3%	0.48 logMAR
Rizzo et al., 2018[9]	78.75%	0.77 logMAR	91.93%	0.74 logMAR

MH: Full-thickness macular hole, ILM: Internal limiting membrane, logMAR: Logarithm of the minimum angle of resolution

Table 2. Summary of clinical outcomes with the inverted ILM flap technique compared to ILM peeling for the repair of highly myopic MHs

Author, year[ref]	ILM peeling % closed	Visual acuity (logMAR)	Inverted flap % closed	Visual acuity (logMAR)
Mete et al., 2017[11]	61%	0.58	94%	0.39
Chen and Yang, 2016[12]	35%	1.17	100%	1.32
Baba et al., 2017[13]	36%	0.75	80%	1.0
Matsumura et al., 2016[14]	33%	1.56	90%	1.1
Rizzo et al., 2018[9]	38.9%	N/A	88.4%	N/A

MH: Full-thickness macular hole, ILM: Internal limiting membrane, logMAR: Logarithm of the minimum angle of resolution, N/A: Not reported

Similarly, the inverted ILM flap technique is also indicated for AMD-related MHs, whether occurring in the context of dry or neovascular AMD (Figure 2). This approach has been shown to achieve both anatomical closure and clinically meaningful improvements in vision, including in cases where MHs developed during ongoing anti-VEGF therapy.[16,17] Interestingly, in dry AMD, disappearance of drusen was observed in some cases. This might be due to phagocytosis of the drusenoid material. In neovascular AMD, it is of high importance to continue anti-VEGF treatment if vitrectomy is delayed for any reason. Shortly after vitrectomy and MH closure, the anti-VEGF treatment should be resumed. The authors did not observe a change in injection intervals in the operated cases.

Secondary MHs resulting from uveitis, trauma, Coats disease, or retinitis pigmentosa have likewise been successfully managed with the inverted ILM flap technique, with high closure rates and substantial visual gains documented across multiple case series.[18,19] In those cases, a longer regeneration time might be expected when compared to idiopathic MHs. However, the technique cannot be applied in refractory cases where the ILM has been completely removed in prior surgeries. In such cases, other surgical techniques are advised.

Reoperations following failure of the inverted ILM flap technique occur in only about 4-5% of cases. These interventions can be performed using either flap repositioning techniques or by creating a new flap, often employing the temporal inverted approach for its technical simplicity and tissue-sparing advantages.[20] Michalewska and Nawrocki[20] proved that the choice of tamponade during the second intervention does not play a statistically significant role in the results. However, silicone oil should be advised in patients with failure associated with positioning problems. Final vision after repeated surgery is usually worse when compared with the primary success.

From a practical standpoint, several key principles have emerged to optimize surgical success with the inverted ILM flap technique. It is recommended to place the ILM flap over the MH rather than inside it to promote physiological retinal healing and reduce the risk of delayed microstructural recovery.[21] Intraoperative stabilization with viscoelastic agents can be employed. Although originally conceived for large and chronic defects, the inverted ILM flap technique can also be applied to smaller MHs to minimize the risk of surgical failure. In particular, repeated surgery with the available ILM is considerably simpler when compared to other techniques and is associated with superior functional outcomes.

In conclusion, the inverted ILM flap technique and its various modifications have fundamentally transformed the surgical management of complicated MHs. By combining mechanical support with biological stimulation of retinal repair, this technique achieves high closure rates, facilitates restoration of retinal microarchitecture, and delivers meaningful visual improvement across a wide spectrum of challenging clinical scenarios. Technique selection should be individualized based on MH characteristics, comorbidities, and the patient's ability to comply with postoperative positioning. However, both classical and modified approaches have proven to be safe, effective, and widely adaptable in modern vitreoretinal surgery.

2. Autologous Retinal Transplant

The conventional surgical approach to MH repair, consisting of PPV, elevation of the posterior hyaloid, ILM peeling, and gas tamponade, yields primary closure rates of over 90% for simple MH.[1,22,23] Conversely, complex MHs, such as myopic MH[24] and primary, refractory, and/or chronic MH with a minimum linear diameter (MLD) ≥535 μm (i.e., CLOSE study group classification of X-large, XX-large, or giant), have poorer closure rates with an isolated conventional approach and may benefit from adjunctive techniques to facilitate MH closure.[1,24] One such technique is autologous retinal transplantation (ART), which was first described for refractory myopic MH closure in 2016.[24] As originally described, the method consists of a bimanual approach with chandelier illumination to harvest a full-thickness neurosensory retinal graft approximately two disc-diameters in size from the midperipheral retina, reposition the graft over the macula in its correct orientation, instill perfluorocarbon liquid (PFCL) over the graft to flatten its edges and ensure it lies flat over the MH, and perform a PFCL-to-silicone oil exchange.

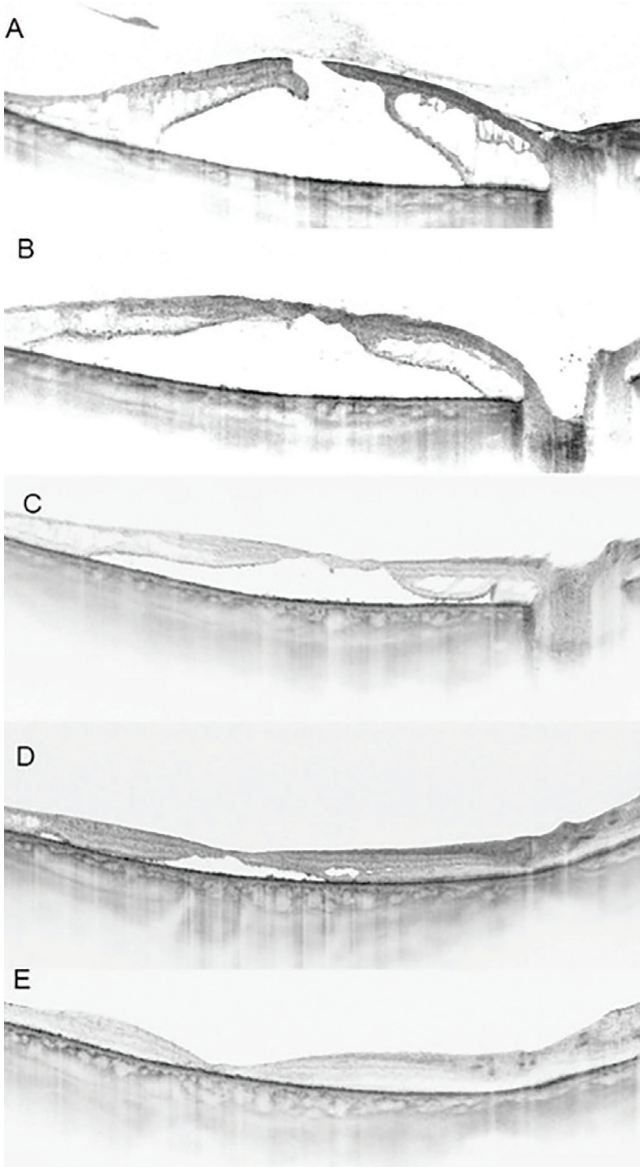

Figure 1. A 68-year-old male patient with proliferative diabetic retinopathy presented with a full-thickness macular hole (MH) associated with foveal detachment. The posterior vitreous remained attached. The minimum diameter was 589 µm and the base diameter was 5485 µm (A; visual acuity 20/1000 [1.7 logMAR]). One week after surgery, the MH was closed but subretinal fluid was still visible (B; visual acuity 20/320 [1.2 logMAR]). One month after surgery, the MH remained closed while the subretinal fluid persisted (C; visual acuity 20/320 [1.2 logMAR]). Six months after surgery, the amount of subretinal fluid had decreased (D; visual acuity 20/320 [1.2 logMAR]). Nine months after surgery, retinal thinning was visible at the fovea (E; visual acuity 20/500 [1.4 logMAR]) (*Source: Archive of Michalewska et al.*)

logMAR: Logarithm of the minimum angle of resolution

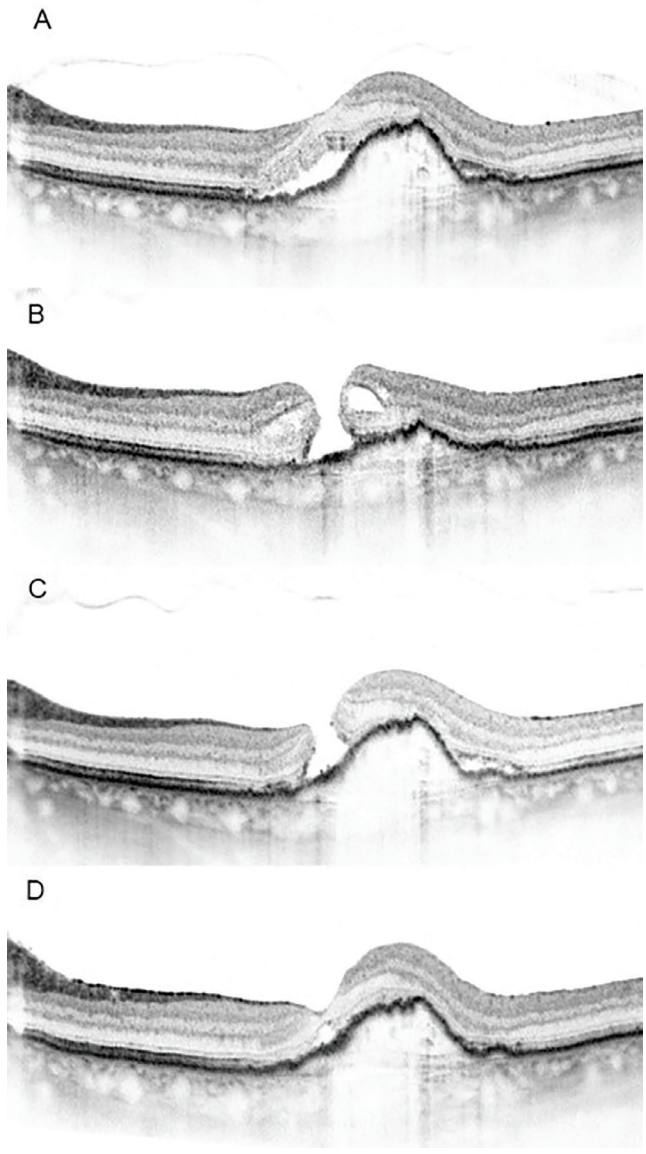

Figure 2. Spectral-domain optical coherence tomography (SD-OCT) confirmed the presence of a neovascular membrane with subretinal fluid (A). SD-OCT revealed a full-thickness macular hole (MH) and visible type 1 neovascular age-related macular degeneration with persistent subretinal fluid (B). SD-OCT image of the closed MH one week after vitrectomy with the temporal inverted ILM flap technique (C). SD-OCT one year after surgery (D). Aflibercept injections were administered using a treat-and-extend regimen during the entire postoperative follow-up period (*Source: Archive of Michalewska et al.*)

ILM: Internal limiting membrane

Since its introduction, many variations of the technique have been described, including ILM peeling over the donor site, differing endotamponade types and graft harvest sites, and combination with other adjunctive techniques such as macular hydrodissection or human amniotic membrane (hAM) graft.[1,25,26] There is no consensus in the literature on optimal modifications of the technique. The preferred approach includes harvesting a graft from the superior midperipheral retina that is approximately 25% larger than the MH to account for shrinkage of the graft after integration, followed by endotamponade with perfluoro-n-octane (PFO; Perfluoron; Alcon, Dallas, TX, USA) for approximately two weeks. The benefits of PFO tamponade may include theoretically superior retinal oxygenation and an anecdotally reduced risk of graft dislocation.[27] We generally default to a unimanual approach and consider bimanual surgery on a case-by-case basis, such as for the repair of MH with concomitant RD. We recommend supine positioning for one day, followed by the avoidance of face-down positioning. Two weeks after MH repair with ART, the graft is inspected intraoperatively, and the decision for air versus gas endotamponade is made based on how secure the graft's position appears.

Indications for ART as an adjunct in MH repair surgery are evolving and include, but are not limited to: primary, refractory, and/or chronic MH that is XX-large (XXL; 800 μm < MLD ≤1000 μm) or giant (MLD > 1000 μm) according to CLOSE study group classification; primary and refractory myopic MH; refractory macular telangiectasia MH; and MH with concomitant RD.[1,24,28,29,30]

Importantly, transverse measurements such as MLD should be adjusted for axial length (e.g., via linear scaling).[31] The use of ART as an adjunctive procedure is less favorable when ischemic, neovascular, or inflammatory retinal diseases are present and when there is insufficient tissue for a viable retinal transplant, such as in the setting of diffuse chorioretinal scarring.[32] There is no consensus regarding the most appropriate adjunctive technique (ART, hAM, or macular hydrodissection) for XXL and giant MH repair. The CLOSE study group performed a pooled analysis and found significant improvement in BCVA after giant MH repair with ART but not with hAM or macular hydrodissection. However, these findings should be interpreted with caution due to the asymmetric and small sample sizes of cohorts after stratifying by both treatment and MH size.[1]

Anatomical success rates with ART are generally high.[32,33,34] The Multicenter International Collaborative Study Group investigated the outcomes of ART for refractory MH and found an approximately 90% closure rate.[32] The Global Consortium included 130 eyes from 33 surgeons and found anatomical closure with ART in 85.7% of primary MH cases, 88% of refractory MH cases, and 95% of MHs with concomitant RD. Visual acuity significantly improved after ART in each of these subgroups, with 43% gaining 3 lines, 29% gaining more than 5 lines, and 12% reaching 20/50 or better, simulating macular function from a peripheral retinal graft.[33] Similarly, a recent meta-analysis of large MHs treated with ART found a closure rate of 91% for primary MH, 93% for refractory MH, and 88% for MH with concomitant RD. Postoperative visual acuity improved after ART in each of these groups as well.[34] A subanalysis of hyperopic patients in the refractory MH group found successful closure in 98% of patients. The first case of ART for a high myopic MH showed visual acuity improvement to 20/80. Ten years later, it improved even further to 20/50, indicating the importance of long-term follow-up.[24]

ART is generally well tolerated with a low risk of complications.[33] In addition to the general complications of vitrectomy (e.g., endophthalmitis and RD) and anesthesia, complications specific to adjunct ART procedures include dislocation of the ART graft and subretinal PFCL. These occurred in 3.8% and 1.5% of cases, respectively, in the Global Consortium Study[33] and can easily be prevented and treated.[35]

Although the exact mechanism of how ART improves the outcomes of complex MH repair surgery is not entirely understood, it is theorized that benefits are derived from its plugging the MH, providing a scaffold for glial tissue proliferation or migration, and integrating into the donor site with some reconstitution of more physiological retinal morphology.[24,32] Indeed, imaging studies evaluating postoperative morphological changes have shown that some patients demonstrate alignment and integration of the host and donor retinal layers, as well as EZ reconstitution (Figure 3).[33] EZ reconstitution after ART was found to be a positive prognostic factor for final surgical outcomes.[33,34,35,36] Progressive increased vascularization of the graft has also been observed in some MH cases during the postoperative period.[33,34,35,36,37]

The introduction of adjunctive techniques for MH repair, such as ART, has enabled the successful treatment of many cases that were previously deemed inoperable. Indeed, these advancements have shifted the paradigm of MH treatment. Further study, refinement, and development of these adjunctive approaches would be prudent.

3. Human Amniotic Membrane

The hAM is derived from the innermost layer of the placenta and exhibits distinctive biological properties that render it a suitable scaffold for retinal repair. The membrane demonstrates antifibrotic properties by downregulating transforming growth factor-β signaling and exerts anti-inflammatory effects via the expression of interleukin-1

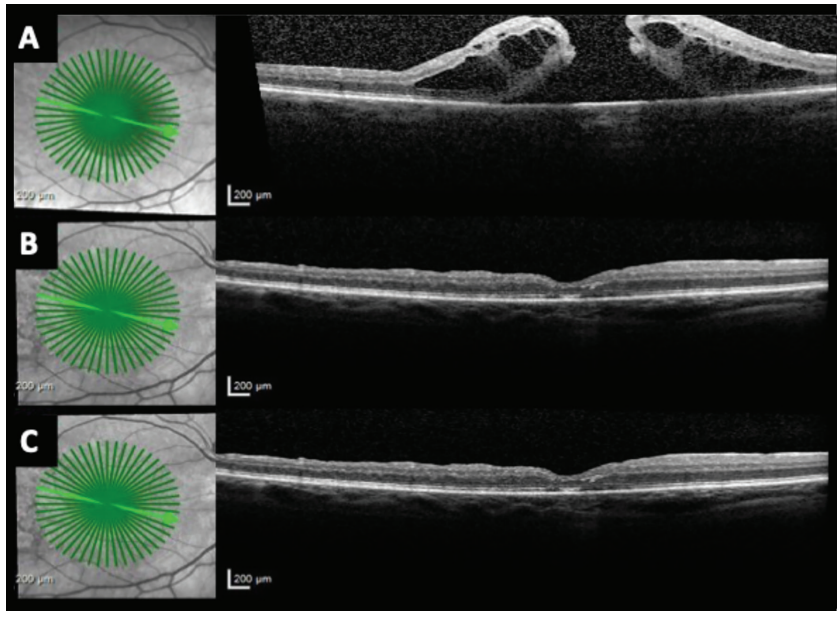

Figure 3. Refractory macular hole (A; visual acuity 20/400) after a failed wide internal limiting membrane peeling, treated with an autologous retinal transplant. Gradual improvement in visual acuity at postoperative month 12 (B; visual acuity 20/60) and month 30 (C; visual acuity 20/25) with alignment of the neurosensory layers, recovery of the ellipsoid zone, and foveal depression (*Source: Archive of Mahmoud et al.*)

receptor antagonist. It also contains growth factors such as epidermal growth factor and basic fibroblast growth factor, which promote tissue repair.[38,39,40,41] It is crucial to emphasize that hAM has low immunogenicity, as it does not express HLA antigens.

Rizzo et al.[42] first reported the use of hAM for recurrent MHs in vitreoretinal surgery. Since then, its applications have broadened considerably, with the ReMaHo study group identifying hAM as an optimal treatment for large MHs.[43]

Preparation Method

Cryopreservation and lyophilization (freeze-drying) are the two primary methods of preparation. Cryopreserving hAM in -80 °C glycerol preserves its structural integrity and most biological factors. Cryopreserved grafts are attached to carrier paper, which allows trimming of the grafts to the optimal size without the need for rehydration. Lyophilized hAM is freeze-dried, which results in a dehydrated membrane that is stored at room temperature and rehydrated prior to subsequent use. While this preparation offers storage and transportation benefits and increases mechanical strength, biological activity may be reduced.[42,43] According to a recent meta-analysis, cryopreserved hAM may provide superior results in the enhancement of visual acuity and anatomical closure, as the cryopreservation procedure more effectively preserves bioactive factors.[42,43,44]

Surgical Technique

Current approaches to MH treatment include four main surgical techniques that employ hAM grafts. Subretinal MH plugging has become the technique of choice among retinal specialists for refractory MHs.[45] This intricate procedure requires advanced surgical expertise to accurately place the hAM graft beneath the neurosensory retina. The subretinal placement of the hAM may be achieved through localized RD, manipulation of the MH borders, or utilization of a pre-existing detachment to position the graft beneath the neurosensory retina, ensuring contact with the RPE.[46]

The application of epiretinal patches has achieved growing popularity due to its technical simplicity and consistent clinical results.[44,47] This approach represents a significant change in surgical theory, as surgeons recognize that simplified approaches can yield excellent therapeutic outcomes.

Moreover, the hAM plug without subretinal placement is a technique that successfully positions the graft within the macular defect while minimizing extensive manipulation of the retina.[48,49,50] Despite its potential advantages, this intermediate approach seems to be decreasing in clinical practice.

The dual-layer technique represents a significant advancement in the field of MH surgery.[51,52] This innovative method integrates principles from established approaches

by employing two distinct hAM grafts in a stratified configuration (Figure 4). Preliminary findings from early-adopting surgeons indicate significant therapeutic potential.

Primary and Recurrent Macular Holes

Rizzo et al.[42] conducted a pioneering study that achieved 100% anatomical success with subretinal implantation in 8 eyes with recurrent MH. The results showed that mean visual acuity improved from 1.48 logarithm of the minimum angle of resolution (logMAR) preoperatively to 0.48 logMAR at six months. Caporossi et al.[53] conducted a prospective trial in 36 eyes with recurrent MHs, achieving a 100% closure rate and improved visual acuity in 91.6% of the participants. Similarly, Bamberger et al.[54] achieved a 91% closure rate using hAM plugs for chronic or persistent MHs in two Canadian tertiary care centers. Ferreira et al.[55] conducted a retrospective, multicentric, interventional study on large and refractory MHs in 19 eyes. Following a single intervention, 100% closure was achieved over a mean follow-up period of 9±3.87 months, with a postoperative BCVA of approximately 20/200 and with a median visual improvement of three lines.

Furthermore, the ReMaHo study group examined 116 eyes, including 19 (16%) undergoing primary repair and 97 (84%) refractory cases, and found that MHs over 680 µm in diameter demonstrated higher closure rates with hAM compared to autologous ILM free flap transplantation, establishing its superiority for closing large MHs.[45] Other recent studies have explored innovative approaches, including split-thickness thin amniotic membrane grafts and autologous blood clot-assisted lyophilized hAM, with encouraging long-term outcomes.[56,57]

Finally, a recent extensive meta-analysis of 8 studies encompassing 103 eyes with recurrent MH demonstrated visual acuity improvement in 66% of cases, a 94% MH closure rate, and a 6% hAM graft dislocation rate.[44,45] Cryopreserved hAM grafts have shown exceptional outcomes, achieving 99% closure rates and a mere 3% dislocation rate.[42] Regarding tamponade selection, sulfur hexafluoride (SF_6) gas was predominantly preferred, followed by air, silicone oil, and perfluoropropane (C_3F_8) gas.[46,60]

Myopic Macular Holes

MHs related to high myopia and posterior staphyloma present distinct challenges due to altered architecture and increased tractional forces. Caporossi et al.[53] achieved a 100% closure rate with hAM in severely myopic eyes with an axial length of 30 mm or greater. The same group demonstrated success in recurrent high myopic MHs associated with RD treated with hAM. Qiao et al.[59] evaluated 17 eyes with high myopic MHs associated with RD after unsuccessful initial surgery, successfully achieving closure and reattachment in all cases. Visual acuity increased in 88.24% of eyes, with only 1 eye (5.89%) requiring an adjustment of the hAM graft.

Innovative surgical techniques have been developed for myopic MHs. Iannetta et al.[47] reported epiretinal positioning of hAM for primary MH accompanied by RD in a patient with high myopia, in contrast to the more common subretinal placement. Fan et al.[60] introduced an innovative method utilizing biological ultrathin amniotic membrane flaps (<10 µm thick) for refractory MHs, providing adequate support while reducing visual impairment.

However, challenges specific to myopic eyes have been recognized. Tsai et al.[61] reported parafoveal atrophy in 40% of eyes with extremely myopic MHs after hAM graft transplantation. However, this finding did not significantly impact visual outcomes in the majority of cases.

Pediatric and Syndromic Cases

The hAM is also applicable in pediatric populations and syndromic conditions. Abdullah et al.[51] described a sandwich-type double-layer amniotic membrane graft approach for the treatment of myopic MH-associated RD in a pediatric patient with Knobloch syndrome.

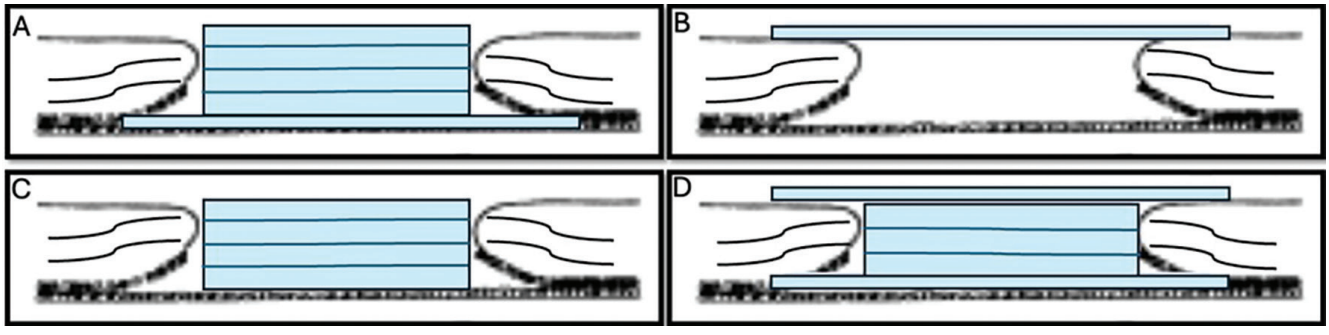

Figure 4. Schematic illustration of the human amniotic membrane (hAM) placement techniques with cross-sectional representation. A) hAM plug with subretinal placement; B) Epiretinal patch technique; C) hAM plug without subretinal placement; D) Double-layer technique (*Source: Archive of Rizzo et al.*)

Complications and Safety

Despite promising outcomes, potential complications include intraoperative difficulties in membrane handling and positioning, especially with cryopreserved hAM due to its flexibility and tendency to fold. Dislocation and contracture are other significant surgical complications. However, cryopreserved grafts exhibit these complications at a favorable 3% rate, in contrast to a troubling 26% rate associated with dehydrated preparations.[42] The difference indicates that cryopreservation more effectively preserves the structural integrity of hAM, thereby significantly decreasing the risk of postoperative graft instability and contracture, which can contribute to surgical failure.[42]

Postoperative displacement of the hAM has been reported in 3-7% of cases with epiretinal placement, appearing less common with subretinal placement, where the membrane is more securely positioned between the retina and RPE.[43,62,63,64] Other reported complications include peripheral retinal tears occurring postoperatively, suprachoroidal hemorrhage, and localized RPE atrophy.[54,65,66] As mentioned above, complications specific to myopia include parafoveal atrophy and graft contraction leading to secondary detachment.[61]

Clinical and *in vitro* safety assessments of epiretinal amniotic membrane conducted by Hillenmayer et al.[46] yielded positive findings concerning the biocompatibility of intravitreal hAM, with no evidence of cellular immunological rejection. Similarly, overall safety data for subretinally implanted hAM reveals no reported immunological or inflammatory rejection, nor any major complications such as RD or endophthalmitis.

Future Directions and Outcomes

Current evidence demonstrates that hAM grafts offer consistent anatomical benefits, with closure rates typically exceeding 90%. Advanced multimodal diagnostic imaging including spectral-domain optical coherence tomography (OCT), OCT-angiography, microperimetry, and adaptive optics reveals tissue growth, layer formation, and signs of remodeling at both the retinal capillary plexus and cellular levels. These findings suggest an ongoing biological integration that may continue to improve functional outcomes over time.

The development of scaffold-based approaches offers tailored solutions to achieve better anatomic and functional outcomes in eyes with large or complicated MHs. While anatomical success is consistently achievable, functional improvement remains variable and depends on multiple factors, including the chronicity of the hole, baseline macular architecture, and surgical technique. The development of innovative techniques such as ultrathin grafts, combined approaches, and temporary placement methods, as described by various authors, continues to expand the therapeutic potential of hAM in MH surgery.[57,67,68]

Future research should focus on standardizing techniques, conducting randomized controlled trials, and establishing definitive guidelines for optimal patient selection and surgical approaches.

4. Autologous Tenon's Capsule Plug

Tenon's capsule is a thin, elastic fibrovascular tissue that envelops the eyeball from the optic nerve to the corneal limbus, creating a nest in which the globe can move freely. This connective tissue membrane is firmly attached to the episcleral tissue approximately 1.5 mm behind the limbus, attaches to the fascial sheaths of the extraocular muscles, and finally joins the meningeal sheath of the optic nerve.[69,70]

Tenon's capsule is divided into anterior and posterior portions at the point of insertion of the recti muscles.[69] The anterior part of the capsule consists of collagen, smooth muscle, and elastic fibers and is firmly attached to the underlying episclera.[71,72] As the rectus muscle sheath is an extension of Tenon's capsule, it is assumed that the anterior capsule develops during the early stages of embryonic development, before the rectus muscles reach their insertion points.[73] The posterior part of Tenon's capsule, in contrast, forms during later stages of development and is simply composed of a condensation of collagen fibers.[74] Therefore, the anterior and posterior portions of Tenon's capsule appear to have different origins. The anterior part of the capsule contains corneal epithelial stem cells located within the limbus to maintain healthy epithelial turnover and preserve epithelial integrity.[75,76]

As a connective tissue matrix containing stem cells, Tenon's capsule is suggested to improve wound healing. Successful results have been reported for the management of several ocular pathologies, including penetrating eye injuries, phaco burns, exposure of glaucoma drainage device tubes, and limbal or scleral ischemia due to chemical injuries.[77,78,79,80] Based on these studies, Yilmaz et al.[81] introduced the autologous Tenon's capsule plug technique for the treatment of giant (>1000 μm) and refractory MHs in 2024. The authors suggested that this novel technique can provide a simple, cost-effective, repeatable, and readily available surgical solution for the treatment of complicated MHs.

Surgical Technique

Illumination with a disposable Eckardt Twinlight Chandelier (DORC, Zuidland, the Netherlands) is used to enable bimanual surgery. For giant MHs, following core vitrectomy and removal of the posterior hyaloid, the ILM

is stained and peeled for approximately 3 disc diameters around the fovea using ILM forceps. In previously vitrectomized, recurrent MH cases, the procedure begins directly with obtaining the Tenon's capsule plug. The graft is harvested from the lower temporal quadrant of the operated eye due to its easily accessible location and safe distance from the rectus muscles.

To facilitate the separation of Tenon's capsule from the conjunctiva, approximately 0.3-0.4 mL of balanced salt solution is injected into the subconjunctival space. The conjunctiva is then incised using conjunctival scissors (McPherson-Westcott conjunctival scissors), and a small piece (measuring approximately 2 × 2 mm) of the underlying Tenon's capsule is carefully harvested. The tissue is delivered into the vitreous cavity using serrated microforceps. The plug size is reduced to approximately 1 disc diameter using microscissors and microforceps in the anterior vitreous cavity. Subsequently, a drop of PFCL is instilled onto the MH to facilitate manipulation, and the Tenon's capsule plug is gently placed over the hole under the PFCL. Owing to the adhesive nature of Tenon's capsule, it readily adheres to the defect.

A 360-degree peripheral retinal examination is performed with scleral indentation. Prophylactic endolaser photocoagulation is applied if needed. A fluid-air exchange is then performed, the PFCL drop is aspirated, and an 8% C_3F_8 gas tamponade is administered. To ensure graft stabilization in the early postoperative period, a small drop (0.05-0.1 mL) of viscoelastic (Viscoat; Alcon Laboratories, Fort Worth, TX, USA) can be injected over the autologous Tenon's plug. Patients are instructed to remain in a prone position for one week after surgery.

Results

In their initial description of the autologous Tenon's capsule plug technique for giant and refractory MHs, Yilmaz et al.[81] reported the outcomes of 3 cases (2 refractory, 1 giant). Successful closure and visual acuity improvement was achieved in all cases (Figure 5). In addition, a significant improvement in microperimetric fixation stability was achieved in all three patients. Only one of the patients who could not maintain prone positioning in the early postoperative period required a second surgery due to dislocation of the Tenon's plug into the vitreous cavity. This patient underwent a repeat autologous Tenon's capsule plug, including placing a freshly harvested Tenon's plug in the hole, fluid–air exchange, and an 8% C_3F_8 gas tamponade injection. One month after the second surgery, the hole was completely closed.

In all cases, the Tenon's capsule plug gradually reduced in size during the postoperative period, becoming nearly invisible on OCT within 6 to 12 months. Simultaneously, microstructural regeneration of the retina at the edges of the plug was observed. This behavior pattern of Tenon's capsule resembles that of the hAM plug. No serious complications, including endophthalmitis, RD,

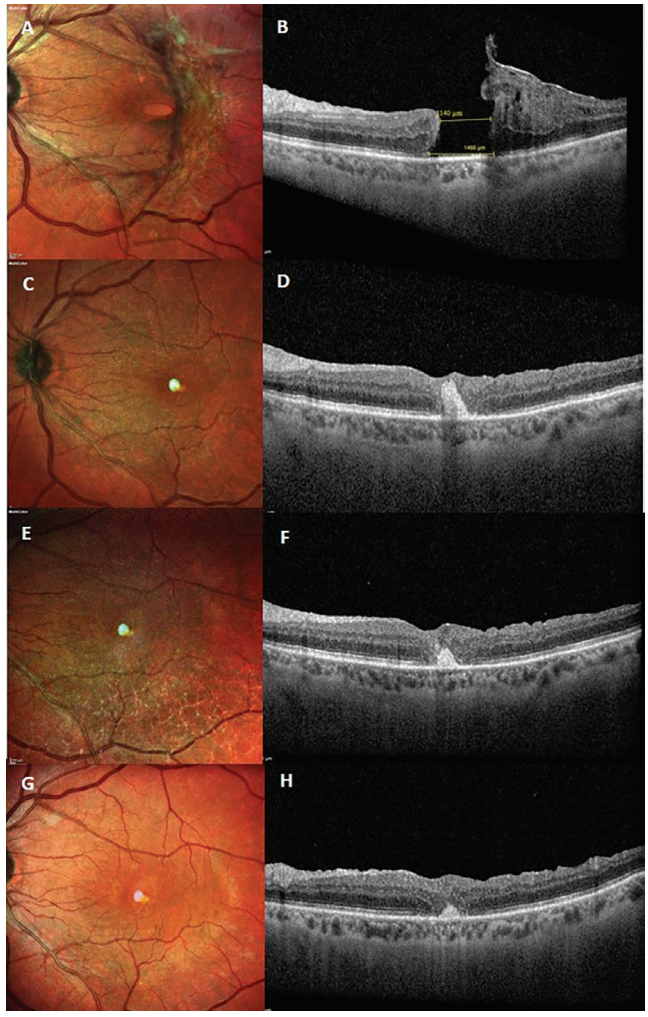

Figure 5. A 69-year-old female presented with an irregular, giant macular hole and a dense, tractional epiretinal membrane (ERM) temporal to the fovea (A). The minimum and base hole diameters were 1154 µm and 1403 µm, respectively (B). The patient underwent 23-gauge pars plana vitrectomy and membranectomy. As a considerable amount of ILM was simultaneously removed during the ERM peeling, it was not possible to create an ILM flap. Therefore, the autologous Tenon's capsule plug technique was performed. Five weeks after the surgery, the hole was closed and the Tenon plug was stable under the retina (C, D). Gradual shrinkage of the Tenon plug and simultaneous regeneration of the retinal layers was observed at 3 months (E, F) and 6 months (G, H) after the surgery (*Source: Archive of Yılmaz et al.*)
ILM: Internal limiting membrane

proliferative vitreoretinopathy, or secondary choroidal neovascularization, occurred in any of the patients during follow-up.

The authors concluded that the autologous Tenon's capsule plug may be a good alternative for treating complex MHs in clinical settings where access to amniotic membrane is not possible. The advantages of this novel technique can be summarized as follows:

1. Autologous nature and lack of immunogenicity.
2. High accessibility and repeatability: The tissue is easily accessible, and a new graft can readily be obtained if the initial attempt is unsuccessful.
3. Technical simplicity: The surgical technique has a flat learning curve and is relatively easy to apply.
4. Tissue-sparing approach: As no tissue is harvested from any layer of the retina (e.g., ILM or autologous retinal graft), it causes no additional damage or complications.
5. Cost-effective: There is no additional cost beyond that of standard vitrectomy.

However, despite these encouraging results, it is important to acknowledge that the data represent preliminary results characterized by limited clinical evidence.

5. Retracting Door Internal Limiting Membrane Flap

The ILM retracting door was first described by Finn and Mahmoud[82] in 2017 for the treatment of myopic MHs. This technique involves creating a nasal ILM flap, extending it temporally over the fovea and the MH, leaving the temporal edge of the flap as a hinge, then draping the flap back over the hole. The retracting door flap offers the advantages of the temporal inverted ILM flap and provides a scaffold for Müller cell proliferation. The ILM remains partially intact, which is beneficial if reoperation is required. Moreover, as the original position of the ILM is preserved, there is no risk of flap reversal, which is one of the most significant postoperative complications associated with the temporal inverted ILM flap. It is also technically less complicated and less dependent on early postoperative head positioning.

Later, in 2022, Marlow et al.[83] reported the use of the retracting door ILM flap for larger MHs with concurrent ERM. As the tangential traction exerted by the ERM contributes to MH development, its removal is a primary objective during surgery. However, due to the tight adhesions between the ERM and the ILM, the ILM is usually partially or completely removed when the ERM is peeled away. This eliminates the ILM flap option, which is known to improve surgical success in challenging MHs. In such scenarios, a combined ERM and ILM retracting door flap technique may offer a relatively simple and successful method for hole closure. Despite these advantages, there are still only a limited number of reports in the literature regarding this method, and they are largely restricted to case series.

6. Lens Capsule Transplant

Lens capsule transplantation to manage refractory or persistent MHs was first described by Chen and Yang[84] in 2016. The technique demonstrated high success rates in closing large, complex MHs.

Lens capsule transplantation is a promising option for refractory MHs where extensive ILM removal has been performed during the initial surgery, making the use of an ILM flap impossible. This technique involves harvesting a piece of the anterior or posterior lens capsule and placing it into the hole to help facilitate closure. It has been hypothesized that the lens capsule might behave like a basement membrane and provide a vitreous-free environment, similar to an ILM flap, for optimal glial proliferation and MH closure.

In 2022, Peng et al.[85] reported the use of lens capsule transplantation as the primary treatment for the management of large MHs. An autologous capsule flap was used in more than half of the patients, while an allogeneic capsule flap was used in the others. In addition, whole blood was used in some cases to enhance flap stability. The authors stated that all of the MHs were closed successfully. Studies in the literature show that this technique offers promising results and increases the MH closure rate, particularly in refractory cases.[86,87]

Conclusion

The aims of MH surgery are to eliminate or reduce the forces causing the defect, provide scaffolding to join the edges of the hole together, and thereby achieve anatomical closure and improve vision. As not all MHs arise from the same pathophysiology, there is no single ideal technique for managing all complex cases. Substantial evidence supports the inverted ILM flap as the primary treatment for large and myopic MHs. However, in cases of refractory MH where the ILM flap technique cannot be performed, as well as for XXL MHs (exceeding 800-1000 μm), various autologous or allogeneic tissue grafts may be considered, such as autologous retinal transplants, hAM, lens capsule transplants, and Tenon's capsule plugs (Figure 6). The choice of graft tissue depends on numerous factors, including the surgeon's experience, the technical and logistical capabilities of the operating room, and the specific clinical characteristics of the patient.

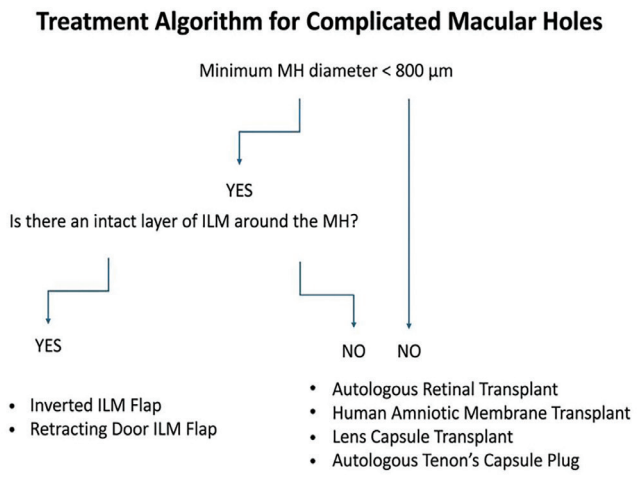

Figure 6. Treatment algorithm for complicated macular hole cases
MH: Macular hole, ILM: Internal limiting membrane

Declarations

Authorship Contributions

Surgical and Medical Practices: R.A., Z.A.N., S.R., S.Y., T.H.M., Concept: R.A., A.M.Y., Design: R.A., A.M.Y., Data Collection or Processing: Z.A.N., S.R., S.Y., E.A., F.G., A.L., T.H.M., Analysis or Interpretation: R.A., A.M.Y., Z.A.N., S.R., S.Y., E.A., T.H.M., Literature Search: A.M.Y., Z.A.N., S.R., E.A., F.G., A.L., T.H.M., Writing: A.M.Y., Z.A.N., S.R., F.G., A.L., T.H.M.

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Case Report

The First Case Series of Malattia Leventinese/Doyne Honeycomb Retinal Dystrophy in Türkiye Identified with *EFEMP1* Gene Mutation

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Abstract

This report aims to describe the clinical characteristics of the first Turkish family diagnosed with Malattia Leventinese/Doyne honeycomb retinal dystrophy (ML/DHRD) associated with an *EFEMP1* mutation. Four affected individuals from the same family (one male and three females; aged 25, 51, 53, and 73 years) underwent comprehensive ophthalmological evaluation. The assessment included best-corrected visual acuity, spectral-domain optical coherence tomography (OCT), color fundus photography, and OCT angiography. In addition, genetic analysis for *EFEMP1* mutations was performed. The *EFEMP1* variant was identified in all four patients. Clinical examination revealed numerous drusen-like deposits with a radial distribution in the posterior pole, consistent with the ML/DHRD phenotype. OCT imaging demonstrated subretinal and retinal pigment epithelium alterations, which were more advanced in the 73-year-old female patient. Visual acuity was largely preserved in the youngest patient but markedly reduced in older individuals. This case series describes the first Turkish family with genetically confirmed ML/DHRD. Structural imaging demonstrated progressive macular changes associated with aging, highlighting the value of multimodal imaging in assessing disease course.

Keywords: Doyne honeycomb retinal dystrophy, Malattia Leventinese, *EFEMP1*

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Introduction

Malattia Leventinese/Doyne honeycomb retinal dystrophy (ML/DHRD) is a rare autosomal dominant retinal dystrophy. It was first identified in patients living in the Leventina Valley in southern Switzerland, from which it derives its name.[1]

This disease is caused by a defect in the *EFEMP1* (epidermal growth factor-containing fibulin-like extracellular matrix protein 1) gene, which encodes the fibulin-3 protein. It presents in the early stages with radially arranged drusen, while macular atrophy may develop in the advanced stages.[2,3,4,5]

Drusen is the most common finding in age-related macular degeneration (AMD), and ML/DHRD is the inherited macular disease that most closely resembles AMD in terms of clinical features. Aside from the later age of onset, the clinical findings of AMD largely overlap with those of ML/DHRD.[6,7,8]

Here we describe a Turkish family that underwent comprehensive clinical evaluation, revealing four patients with fundus and optical coherence tomography (OCT) findings consistent with ML/DHRD. Subsequent genetic analysis identified an *EFEMP1* gene mutation in these individuals, definitively establishing the diagnosis. This study is the first published case series related to this disease in Türkiye.

Informed consent was obtained from all participants in the study. The included cases comprised four related individuals aged 25, 51, 53, and 73 years determined to be carriers of *EFEMP1* mutations. The general clinical characteristics of these cases are summarized in Table 1.

Case Reports

Case Presentations and Genetic Evaluation

Case 1 (Index Case-Proband)

A 51-year-old male patient was evaluated in our clinic for a routine examination. His best-corrected visual acuity (BCVA) measured with a Snellen chart was 0.7 in the right eye and 0.5 in the left eye. Anterior segment examination was unremarkable, whereas fundus examination revealed dense drusen formations in the macula and peripapillary region (Figure 1A, B).

Fundus autofluorescence (FAF) imaging demonstrated distinct hyperautofluorescent areas corresponding to drusen with a tendency to coalesce around the fovea (Figure 1C-F). On spectral-domain OCT examination, diffuse, dome-shaped hyperreflective materials consistent with the presence of drusen were observed at the sub-retinal pigment epithelium (RPE) level, along with structural changes in the RPE (Figure 1G, H). Optical coherence tomography angiography (OCTA) images showed no macular neovascularization (MNV) in either eye. The foveal avascular zone (FAZ) was preserved in the superficial and deep capillary plexuses, while areas consistent with microvascular irregularities and decreased capillary density were observed in the perifoveal region. At the choriocapillaris level, diffuse, heterogeneous flow deficits and a mottled appearance were detected (Figure 1I, J).

Due to the patient's young age and clinical findings suggestive of ML/DHRD, his other family members also underwent ophthalmological evaluation. Upon observing a similar fundus appearance in three individuals (Cases 2, 3, and 4), they and the proband were referred to the medical genetics department for genetic analysis. Four other examined individuals from the same family did not exhibit any clinical findings, and two of these individuals underwent genetic analysis. The family pedigree is shown in Figure 2. The patient's father, who had died prior to the study, had a history of Behçet syndrome with associated visual loss (I.1). The genetic analysis performed on the four patients with fundus findings revealed a mutation in the *EFEMP1* gene. No mutations were detected in the two individuals (II.4 and III.7) in the family pedigree who exhibited no clinical findings.

Case 2

A 73-year-old female patient, the mother of the index case, presented with a complaint of significant visual impairment. Visual acuity was measured as 0.05 in both eyes using a Snellen chart. Fundus examination revealed widespread drusen accumulation and pigmentary changes, which were particularly dense in the peripapillary region (Figure 3A, B). FAF imaging demonstrated hypoautofluorescent areas consistent with RPE atrophy (Figure 3C-F). OCT revealed hyperreflective materials consistent with sub-RPE drusen and RPE atrophy (Figure 3G, H).

Case 3

The 53-year-old older sister of the index case presented with decreased vision in both eyes, which was more pronounced in the right eye. BCVA using a Snellen chart was 0.15 in the right eye and 0.8 in the left eye. Fundus examination of both eyes revealed numerous drusen that showed a radial distribution and tendency toward confluence in the macula and peripapillary region (Figure 4A, B). Broad hyperautofluorescent areas were present on FAF imaging (Figure 4C-F). OCT examination demonstrated diffuse sub-RPE deposits and disrupted ellipsoid zone integrity in both eyes (Figure 4G, H).

Case 4

The 25-year-old daughter of the index case had no visual complaints. Visual acuity was measured as 1.0 in both eyes with a Snellen chart. Fundus examination revealed a small number of small, radially arranged drusen in the macular region bilaterally, as well as a few small drusen nasal to the optic disc (Figure 5A, B). FAF imaging showed a few small hyperautofluorescent areas in the parafoveal region (Figure 5C-F). A few drusen were also identified in the parafoveal region on macular OCT (Figure 5G, H). OCTA imaging confirmed that the FAZ was preserved in the superficial and deep capillary plexuses of both eyes, with mild microvascular irregularities noted in the perifoveal region. The deep capillary plexus generally maintained a normal appearance. Focal flow deficits and mild heterogeneity were present in places at the choriocapillaris level, though these findings were more limited and less pronounced compared to the index case. No abnormal vascular network indicative of MNV was observed (Figure 5I, J).

Mutation Analysis

Total genomic DNA was isolated from the peripheral blood of six individuals, including the proband (Case 1) and his family members, using the HiPurA® Pre-filled Clinical Multipurpose Nucleic Acid Purification Kit (HiMedia, USA) in accordance with the manufacturer's

Table 1. General clinical characteristics of the cases

Case	Age (years)	Sex	BCVA	Lens status	Intraocular pressure	Fundus view	FAF	OCT	OCTA	Mutation
1	51	Male	OD: 0.7, OS: 0.5	OU: Phakic	OD: 12 mmHg OS: 14 mmHg	Dense drusen in the macula and peripapillary region	Hyperautofluorescent areas corresponding to the drusen showing a tendency to coalesce around the fovea	Diffuse, dome-shaped hyperreflective materials originating from drusen in the sub-RPE region and RPE changes	No macular neovascularization	*EFEMP1* (heterozygous)
2	73	Female	OU: 0.05	OU: Phakic	OD: 10 mmHg OS: 11 mmHg	Diffuse drusen deposition and pigmentary changes, more concentrated in the peripapillary region	Hypoautofluorescent areas consistent with RPE atrophy	Sub-RPE hyperreflective materials and widespread RPE loss	No macular neovascularization	*EFEMP1* (heterozygous)
3	53	Female	OD: 0.15, OS: 0.8	OU: Phakic	OD: 16 mmHg OS: 18 mmHg	Diffuse drusen showing radial arrangement and a tendency to coalesce in the macula and peripapillary region	Broad areas of hyperautofluorescence	Widespread deposits in the sub-RPE area in both eyes	No macular neovascularization	*EFEMP1* (heterozygous)
4	25	Female	OU: 1.0	OU: Phakic	OD: 17 mmHg OS: 18 mmHg	A small number of small, radially arranged drusen in the macula and a few small drusen nasal to the optic disc	A few small areas of hyperautofluorescence in the parafoveal region	A few drusen in the parafoveal region	No macular neovascularization	*EFEMP1* (heterozygous)

BCVA: Best-corrected visual acuity (Snellen), FAF: Fundus autofluorescence imaging, OCT: Optical coherence tomography, OCTA: OCT angiography, OD: Right eye, OS: Left eye, OU: Both eyes, RPE: Retinal pigment epithelium

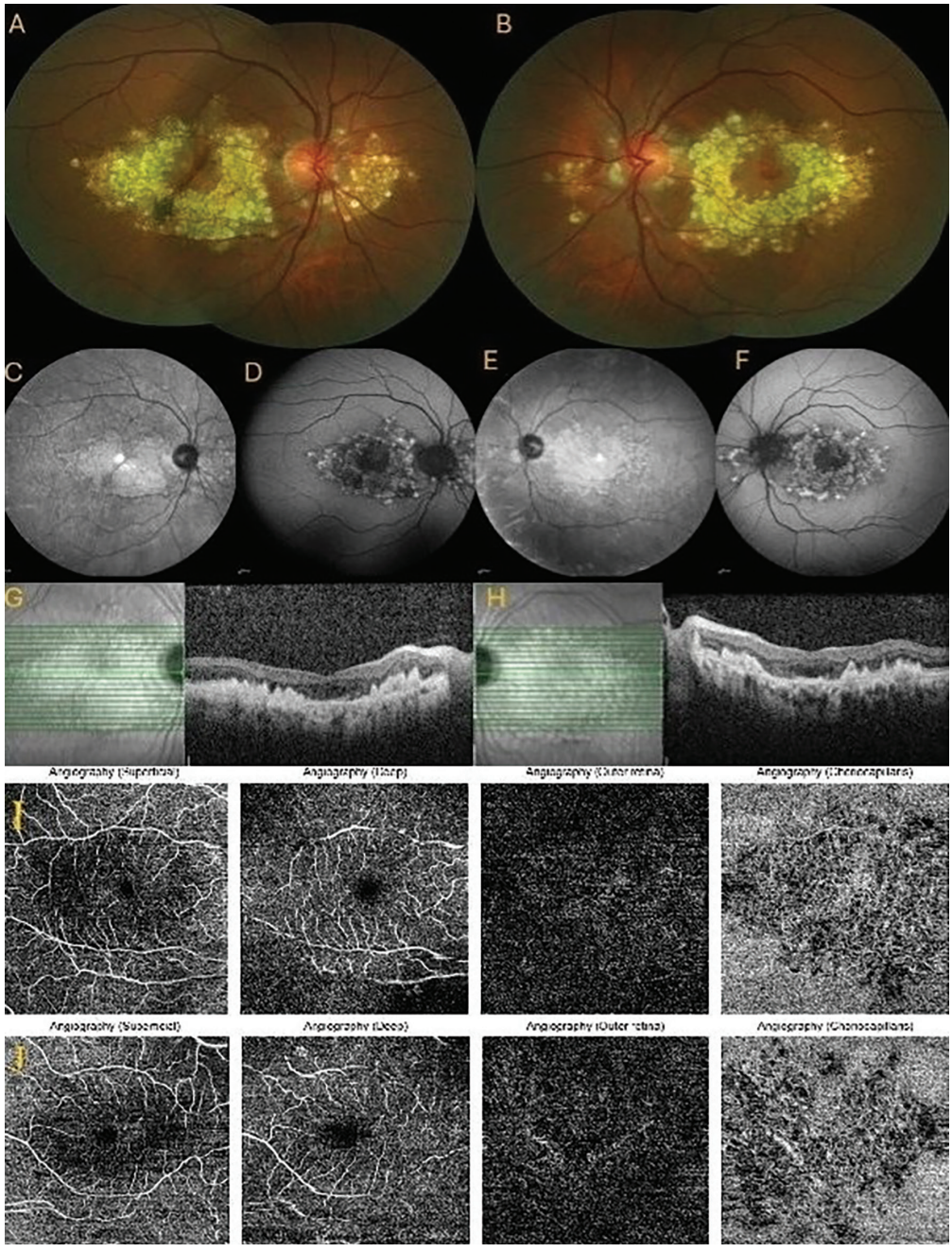

Figure 1. Color fundus photographs of the index case show clustered drusen involving the macular and peripapillary regions in the right (A) and left (B) eyes. Fundus autofluorescence images of the right (C, D) and left (E, F) eyes demonstrate multiple hyperautofluorescent foci corresponding to drusen, particularly in the perifoveal region, with a tendency toward confluence. Optical coherence tomography images (G, H) reveal diffuse, dome-shaped hyperreflective deposits located between the Bruch's membrane and the retinal pigment epithelium (sub-RPE deposits). Optical coherence tomography angiography images show no evidence of macular neovascularization in the right (I) and left (J) eyes. The superficial and deep capillary plexuses demonstrate a preserved foveal avascular zone, with perifoveal microvascular irregularities and areas suggestive of reduced capillary density. At the level of the choriocapillaris, widespread heterogeneous flow deficits with a mottled appearance are observed

RPE: Retinal pigment epithelium

protocols. The NanoDrop ND1000® Spectrophotometer (Thermo Fisher Scientific, USA) was used for DNA concentration and purity measurements. After obtaining DNA of sufficient quality (50-100 ng/µL concentration and A260/A280: 1.8-2.0 purity), polymerase chain reaction (PCR) amplification was performed using primers targeting all exons and exon-intron boundaries of the *EFEMP1* gene (NM_001039348.3). AmpliTaq Gold™ 360 DNA Polymerase (Applied Biosystems/Thermo Fisher Scientific, USA) and an Eppendorf 5332 Mastercycler (Eppendorf AG, Germany) device were used in the standard PCR procedure. PCR products were prepared for next-generation sequencing using the Nextera XT DNA Library Preparation Kit (Illumina, USA). The Miniseq® (Illumina, USA) platform was used for the runs. The obtained raw data were uploaded to and analyzed on the SEQ analysis platform (Genomize, Türkiye). Manufacturer protocols were followed at all stages. Data with 100% coverage at a minimum reading depth of 1000x were obtained for all cases.

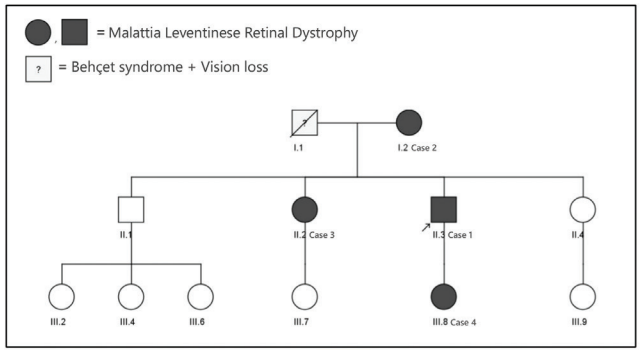

Figure 2. Pedigree chart. A heterozygous pathogenic *EFEMP1* mutation was identified in individuals I.2, II.2, II.3, and III.8. Genetic testing yielded normal results in individuals II.4 and III.7

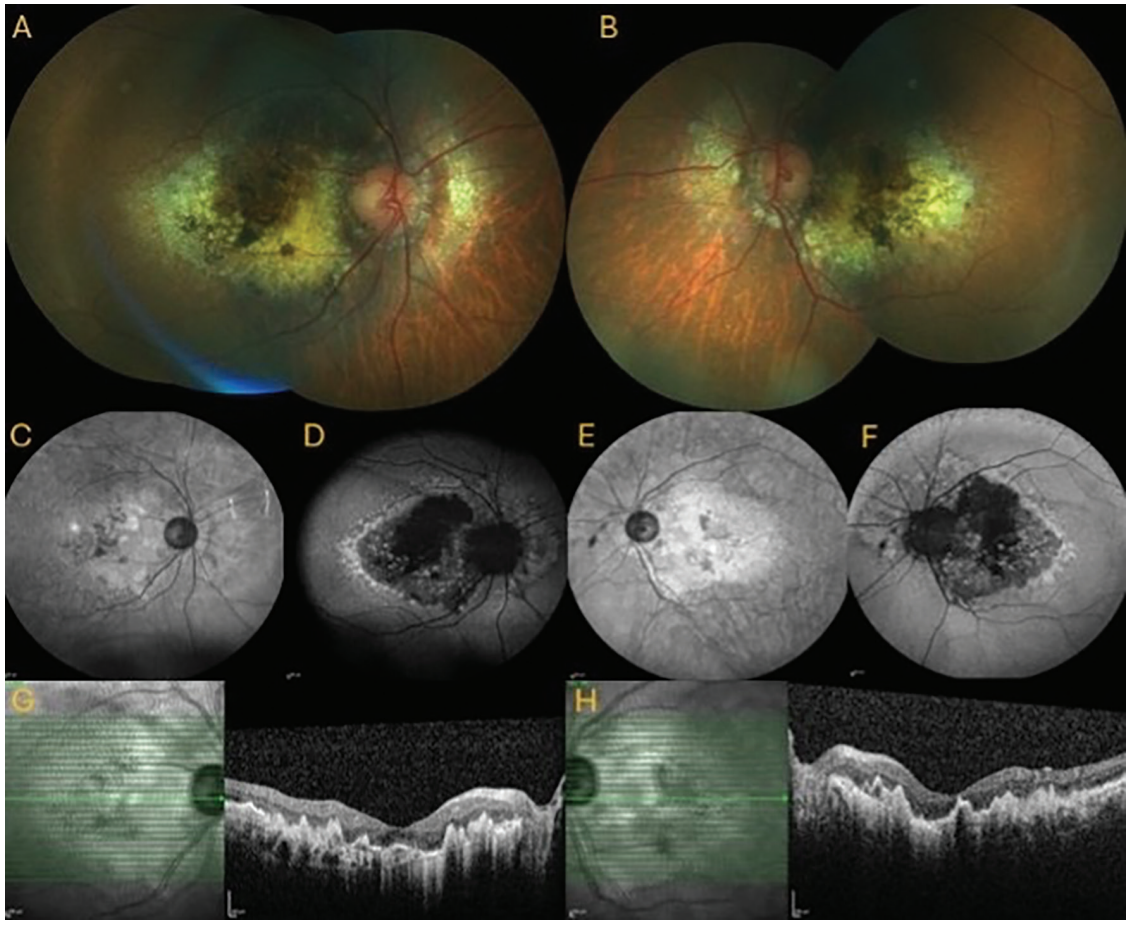

Figure 3. Color fundus photographs of Case 2 demonstrate widespread drusen accumulation and pigmentary changes in the right (A) and left (B) eyes, more prominently in the peripapillary region. Fundus autofluorescence imaging shows hypoautofluorescent areas consistent with retinal pigment epithelium (RPE) atrophy in the right (C, D) and left (E, F) eyes. Optical coherence tomography reveals RPE atrophy together with hyperreflective sub-RPE deposits consistent with drusen in both the right (G) and left (H) eyes

The c.1033C>T (p.Arg345Trp) alteration in exon 10 of the *EFEMP1* gene was detected as heterozygous in all 4 patients presenting with fundus findings. The p.Arg345Trp variant identified in the *EFEMP1* gene is the variant most strongly associated with ML/DHRD in the literature and is considered characteristic of the disease. This alteration leads to the misfolding of the fibulin-3 protein, causing abnormal accumulation in the extracellular matrix, which constitutes the fundamental pathophysiological mechanism of drusen formation.[5,8,9,10] The fact that this specific variant has been detected in the vast majority of cases reported in the literature supports the notion that it exhibits high penetrance and strong genotype-phenotype correlation. The two patients with normal fundus examination findings also had normal genetic analysis results. The detected alteration was evaluated as pathogenic in accordance with current guidelines using the criteria "PM1" (located in a functionally critical region), "PM2" (absent in the general population), "PP3" (*in silico* pathogenicity predictions), and "PP5" (reported as pathogenic in reliable databases).[11] Furthermore, the long-established and repeatedly demonstrated strong association of the p.Arg345Trp variant with ML/DHRD in the literature supports the acceptance of this variant as the disease-causing mutation.[5,8,9,10]

Discussion

ML/DHRD is a disease most commonly seen in young individuals and is characterized by radial drusen. Clinically, patients typically present with complaints of decreased vision, metamorphopsia, and scotoma. The drusen show a radial distribution along the arcades, in the peripapillary region, and in the central macula and gradually enlarge and approximate each other to create a honeycomb-like appearance.[3,5,7]

FAF examinations reveal hyperautofluorescent drusen and areas of hypoautofluorescence associated with RPE atrophy. Patients generally have good visual acuity in the

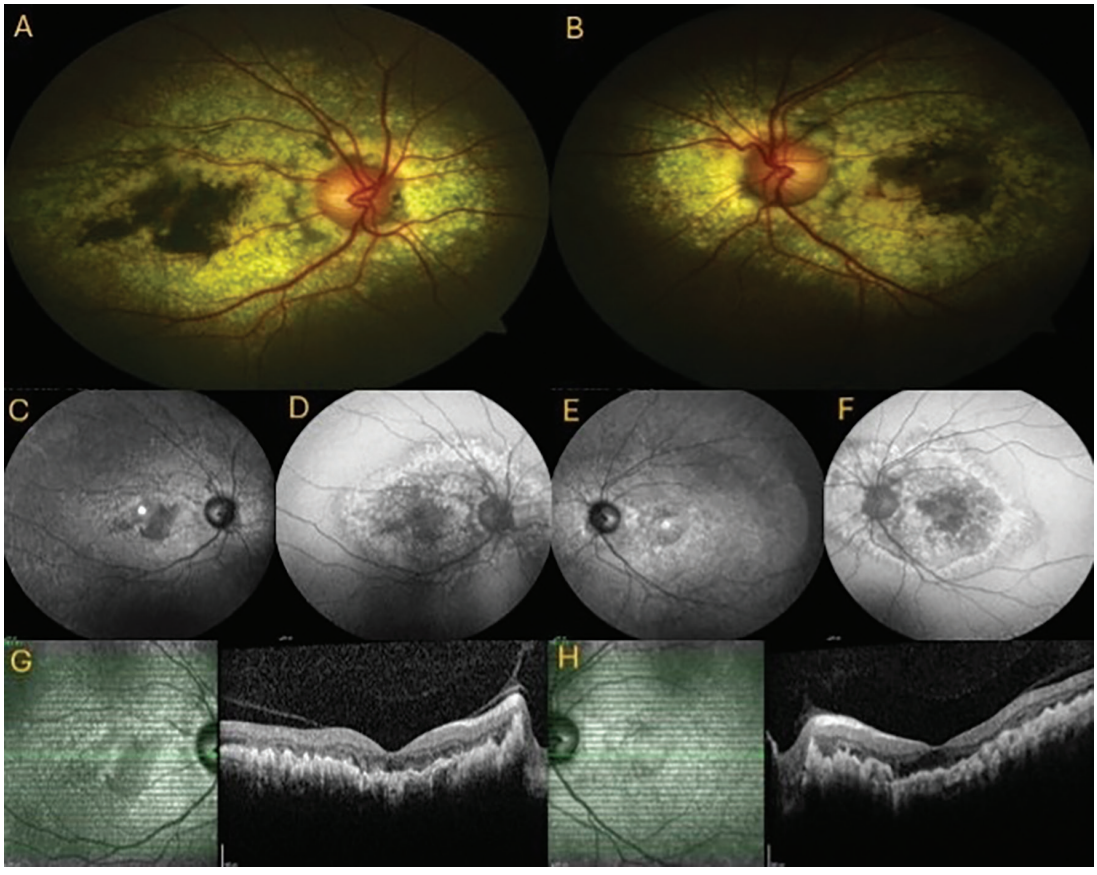

Figure 4. Color fundus examination of Case 3 demonstrates numerous drusen in the macular and peripapillary regions of the right (A) and left (B) eyes, arranged in a radial pattern with a tendency to coalesce. Fundus autofluorescence imaging shows extensive hyperautofluorescent areas in both the right (C, D) and left (E, F) eyes. Optical coherence tomography reveals widespread sub-retinal pigment epithelium deposits in both eyes, along with disrupted ellipsoid zone integrity (G, H)
RPE: Retinal pigment epithelium

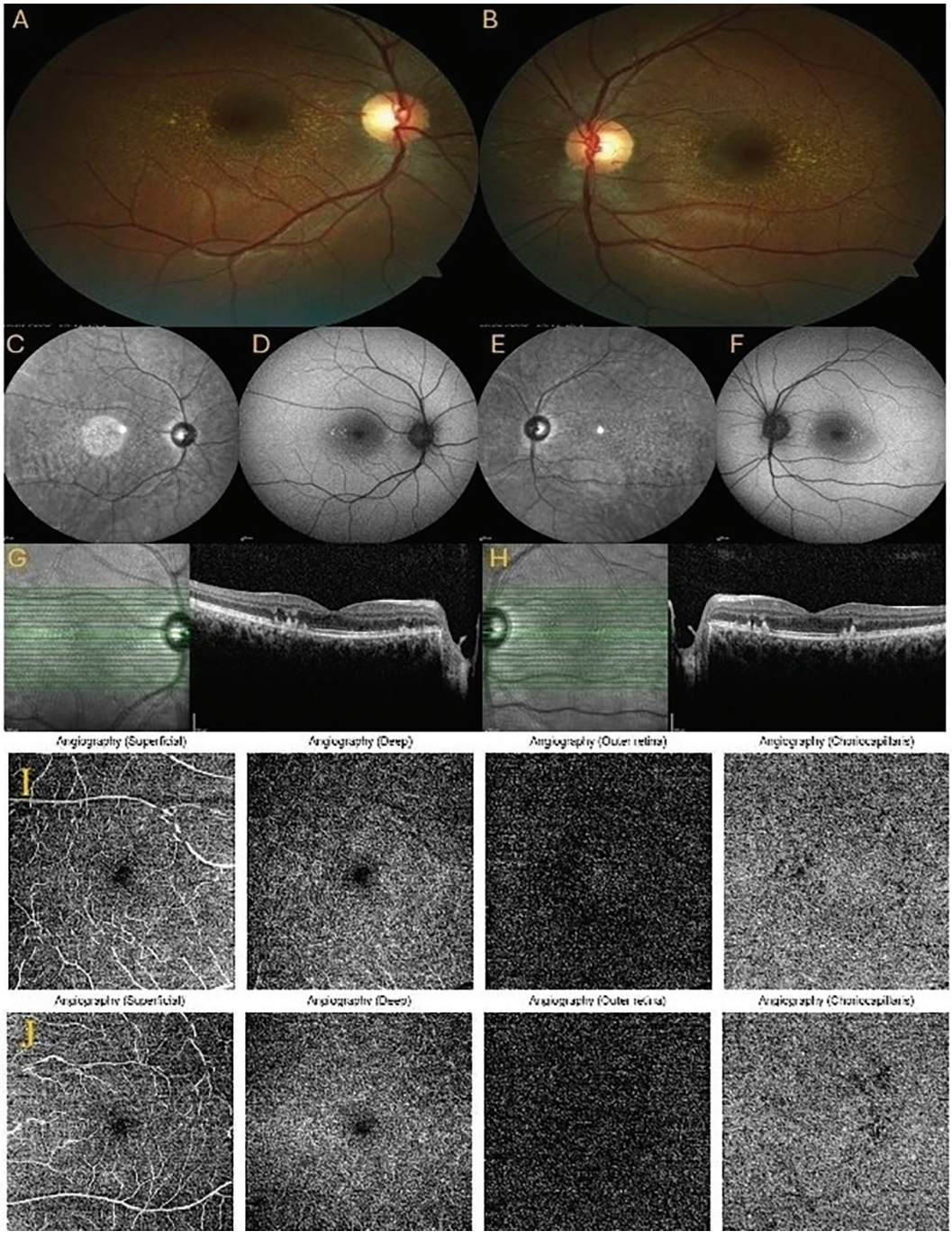

Figure 5. Color fundus photographs of Case 4 show a small number of small, radially arranged drusen in the macular region, along with a few small drusen located nasal to the optic disc in both the right (A) and left (B) eyes. Fundus autofluorescence images of the right (C, D) and left (E, F) eyes demonstrate a few small hyperautofluorescent areas in the parafoveal region. Optical coherence tomography images of the right (G) and left eyes (H) reveal a small number of drusen located in the parafoveal region bilaterally. Optical coherence tomography angiography images of the right (I) and left eyes (J) show a preserved foveal avascular zone in both the superficial and deep capillary plexuses, with mild microvascular irregularities in the perifoveal region. The deep capillary plexus appears largely unremarkable. At the level of the choriocapillaris, focal flow deficits and mild heterogeneity are observed, which are more limited and less pronounced compared to the index case. No abnormal vascular network suggestive of macular neovascularization is detected

Table 2. Clinical comparison of Malattia Leventinese/Doyne honeycomb retinal dystrophy and age-related macular degeneration

Clinical presentation	Malattia Leventinese	Age-related macular degeneration
Age at onset	Usually the 3rd-4th decade	Advanced age (>50 years)
Inheritance pattern	Autosomal dominant	Multifactorial/Sporadic
Genetic basis	Strong association with the *EFEMP1* p.Arg345Trp mutation	Polygenic (e.g., *CFH*, *ARMS2*, *HTRA1*)
Drusen morphology	Presence of drusen located nasal to the optic disc Presence of drusen in the macula exhibiting a typical radial arrangement Drusen can become large, dense, and confluent in advanced stages, frequently accompanied by juxtapapillary nodular drusenoid lesions	A drusen pattern where both hard and soft drusen can be seen together; soft drusen are generally large, confluent, and prominent in the macula
Multimodal imaging	FAF: Hyper/hypoautofluorescent areas corresponding to drusen located in the macula and around the optic disc OCT: Sub-RPE deposits FFA: Large central drusen have poorly defined borders and a hypofluorescent appearance, whereas small radial drusen are well-defined and prominently hyperfluorescent OCTA: Relatively preserved superficial and deep capillary plexuses, mild perifoveal microvascular irregularities, and a heterogeneous mottled appearance with focal flow deficits at the choriocapillaris level. MNV is not common in the early stage	FAF: Irregular autofluorescence patterns, hypoautofluorescent areas in regions of atrophy OCT: Drusen, RPE irregularities, geographic atrophy, subretinal and intraretinal fluid FFA: Early hyperfluorescence in drusen, leakage in the presence of MNV OCTA: Decreased choriocapillaris density, focal flow deficits, and MNV (type 1, 2, 3)
Macular neovascularization	Can develop with varying frequency (6-24%)	Common (especially in the neovascular type)
Progression pattern	Slow onset, with atrophy and/or MNV in the advanced stage	Progressive; progression from dry type to neovascular type or geographic atrophy

FAF: Fundus autofluorescence imaging, OCT: Optical coherence tomography, RPE: Retinal pigment epithelium FFA: Fundus fluorescein angiography, OCTA: OCT angiography, MNV: Macular neovascularization

early stages, as in our fourth case, but vision loss becomes pronounced in the advanced stages. The primary causes of this loss are drusen confluence, RPE atrophy, and MNV development.[9] Regular OCTA imaging is recommended during follow-up for the early detection of MNV.[10] OCTA was performed in all of our cases, but MNV was not detected in any of the patients. MNV and subretinal hemorrhage are rarely seen in ML/DHRD, and when they do develop, they are the most important complications that can lead to severe vision loss.[12,13,14] Although anti-vascular endothelial growth factor (anti-VEGF) therapy has been reported to be effective in cases developing MNV in the literature, there is no specific treatment for the macular atrophy that develops over time. In cases where MNV is not detected, the treatment approach is directed toward visual rehabilitation and preservation of functional vision.[12,15] In contrast, another study examining inherited macular diseases reported that despite consecutive intravitreal anti-VEGF injections in an ML/DHRD patient that developed MNV, there was no significant change in the MNV on OCTA measurements, and their visual acuity continued to decline.[16]

Our cases highlight the distinctive importance of multimodal imaging findings in the diagnosis of ML/DHRD. This disease can easily be confused with AMD and other dystrophies. In the advanced stages of ML/DHRD, drusen coalesce to form a homogeneous area, and atrophy develops in these regions. This differs from the lifecycle of drusen in AMD, which mostly disappear with outer retinal atrophy.[17] A comparison of the clinical findings of ML/DHRD and AMD is summarized in Table 2.[5,10,14,18,19,20,21,22] Sorsby retinal dystrophy generally presents with reticular drusen and is characterized by hypoautofluorescence on FAF and deposits above the RPE on OCT.[23] Pattern dystrophy is characterized by typical hyperautofluorescent lesions in the center of the macula

and subretinal hyperreflective deposits on OCT, and it is among the retinal dystrophies requiring differential diagnosis from ML/DHRD.[24] The radially arranged and honeycomb-like drusen appearance in ML/DHRD serves as a distinguishing feature.[14] The p.Arg345Trp variant identified in this study is the classic *EFEMP1* mutation most frequently associated with ML/DHRD and forms the molecular basis of the disease. The independent reporting of this variant in different populations in the literature supports its strong causal relationship with the disease. This demonstrates a high genotype-phenotype correlation, increasing the diagnostic value of targeted genetic analyses in cases where ML/DHRD is suspected clinically.

Apart from the ML/DHRD diagnosed in our cases, *EFEMP1* gene mutations have also been associated with juvenile open-angle glaucoma, sporadic cuticular drusen, and myopia. Furthermore, *EFEMP1* was reported to make polygenic contributions to common ophthalmic diseases such as primary open-angle glaucoma, and *EFEMP1*-related signaling pathways have been linked to AMD. However, despite the available evidence, it is not yet fully understood how *EFEMP1* is involved in this broad spectrum of clinically distinct diseases.[25]

ML/DHRD should be kept in mind for young patients presenting with drusen. Anti-VEGF injections and regular follow-ups are important for patients who develop MNV. NV was not detected in any of our cases, demonstrating that family screening is of critical importance in the diagnosis of this rare and sight-threatening disease. This study documents the first ML/DHRD cases in Türkiye diagnosed through both clinical and genetic analyses. This rare disease must be considered in the differential diagnosis of patients with drusen at a young age, as well as older patients who present with fundus and OCT images distinct from the typical AMD drusen pattern.

Ethics

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

Declarations

Authorship Contributions

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

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Letter to the Editor

Inherited Retinal Dystrophies in the Differential Diagnosis of Uveitis: Clinical Clues from a Case

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Dear Editor,

Inherited retinal dystrophies (IRD) may present with inflammatory findings in some cases, which complicates the differential diagnosis and can lead to misdiagnosis as uveitis. We would like to emphasize that accurate clinical differentiation plays a decisive role not only in establishing appropriate treatment strategies but also in the timing and planning of re/habilitative approaches.

A 27-year-old female patient was evaluated at two separate centers for suspected intermediate uveitis and was subsequently referred to our clinic due to the lack of a typical response to treatment. Her medical history revealed that she initially presented with complaints of stinging and ocular discomfort. Following the detection of vitreous cells and macular edema, she received two bilateral intravitreal triamcinolone acetonide (Kenakort-A®; Deva Holding A.Ş., İstanbul, Türkiye) injections, followed by the initiation of systemic corticosteroid (methylprednisolone, Prednol®; Gensenta İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) therapy at a dose of 64 mg/day. At the second center, azathioprine (Imuran®; Excella GmbH & Co. KG, Feucht, Germany) at a dose of 150 mg/day was added to this treatment.

No pathology was detected on systemic evaluations and her personal/family history was unremarkable except for a positive QuantiFERON-TB Gold test, for which she had been started on 300 mg/day isoniazid (I.N.H.®; Koçak Farma İlaç ve Kimya Sanayi A.Ş., Kapaklı, Tekirdağ, Türkiye). On ophthalmological examination, visual acuity (Snellen decimal) was 1.0 in the right eye and 0.8 in the left eye. Anterior segment examination revealed no findings suggestive of active or prior uveitis. Intraocular pressure was measured as 20 mmHg bilaterally via applanation tonometry. No vitreous reaction was observed on fundus examination, but the presence of a peripapillary white gliotic appearance bilaterally and waxy pallor of the optic disc, arteriolar attenuation, and perivascular white gliotic sheathing in the left eye was noted. In addition, granular pigmentary changes were detected in the mid-peripheral retina (Figure 1A, B).

Fundus fluorescein angiography (FFA) was evaluated with a confocal scanning laser ophthalmoscopy system

Keywords: CC2D2A, differential diagnosis, electroretinography, fundus autofluorescence, fundus fluorescein angiography, inherited retinal dystrophies, low vision re/habilitation, optical coherence tomography, uveitis, visual field

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(Heidelberg Retina Angiograph 2, Heidelberg Engineering, Germany). Optic disc margins and vascular structures were normal bilaterally, with no leakage observed. Transmission (window) defects secondary to retinal pigment epithelial (RPE) changes were present in the mid-peripheral areas. The macula and peripapillary region appeared relatively spared (Figure 1C, D).

Fundus autofluorescence (FAF) images were obtained by confocal scanning laser ophthalmoscopy (Spectralis HRA + OCT, Heidelberg Engineering, Germany). A symmetrical, well-defined hyperautofluorescent ring was observed in the macula. The characteristic appearance of peripapillary hyperautofluorescence with preserved autofluorescence around the optic disc was noted (Figure 1E, F).

Optical coherence tomography (OCT) images were acquired using spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, Germany). Irregularities and focal disruptions were observed bilaterally in the perifoveal region of the ellipsoid zone (EZ), while the subfoveal EZ band was preserved (Figure 1G, H). Bilateral cystoid macular edema (CME) was present. Involvement of the inner retinal layers with the presence of retinoschisis cavities was observed bilaterally. It was noted that the retinal layers had lost their characteristic laminated appearance.

Visual field testing was performed using the SITA-Standard 24-2 program (Humphrey Field Analyzer II, Carl Zeiss Meditec, USA). Bilateral concentric constriction was detected (Figure 2A, B).

Electroretinography (ERG) was performed in accordance with the 2022 ISCEV (International Society for Clinical Electrophysiology of Vision) standards (MonPack One, Metrovision, Perenchies, France). Scotopic responses were completely extinguished, and photopic responses were significantly reduced. This combination was interpreted as consistent with advanced rod-cone dystrophy (Figure 2C).

As the findings were compatible with IRD, azathioprine was discontinued, while systemic corticosteroid treatment was tapered and stopped. Topical brinzolamide (Britil®; World Medicine İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) was added for the management of CME. Genetic analysis identified a homozygous c.1028G>T (p.Trp343Leu) missense variant in the *CC2D2A* gene. According to the American College of Medical Genetics and Genomics criteria, the variant was classified as a variant of uncertain significance (VUS).

The demonstration of microinflammatory processes and altered immune responses in some subtypes of IRD suggests that clinical presentations resembling inflammation may have a pathophysiological basis.[1,2] However, this biological foundation indicates that inflammatory findings should not be interpreted as primary uveitis.[3] Cases have been reported in the literature where IRD was misdiagnosed as

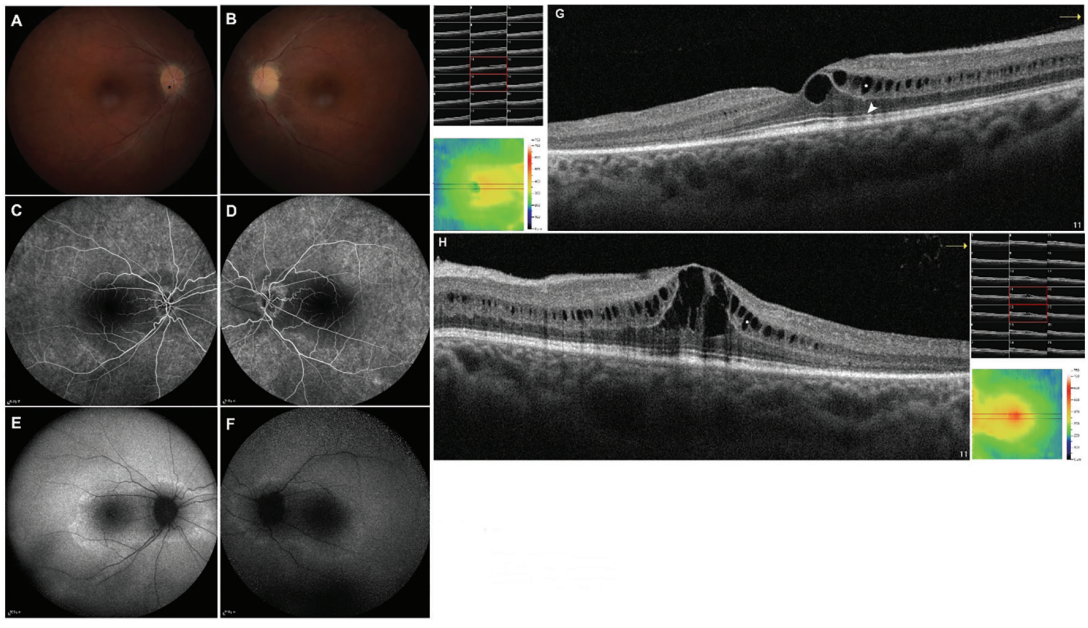

Figure 1. Color fundus photographs of the right (A) and left (B) eyes. Perivascular sheathing was observed over the optic disc (A, black asterisk). Fundus fluorescein angiography frames of the right (C) and left (D) eyes. Fundus autofluorescence images of the right (E) and left (F) eyes. Optical coherence tomography scans of the right (G) and left (H) eyes. Irregularities and focal disruptions in the EZ (G, white arrow) and retinoschisis cavities (G/H, white asterisks) were observed

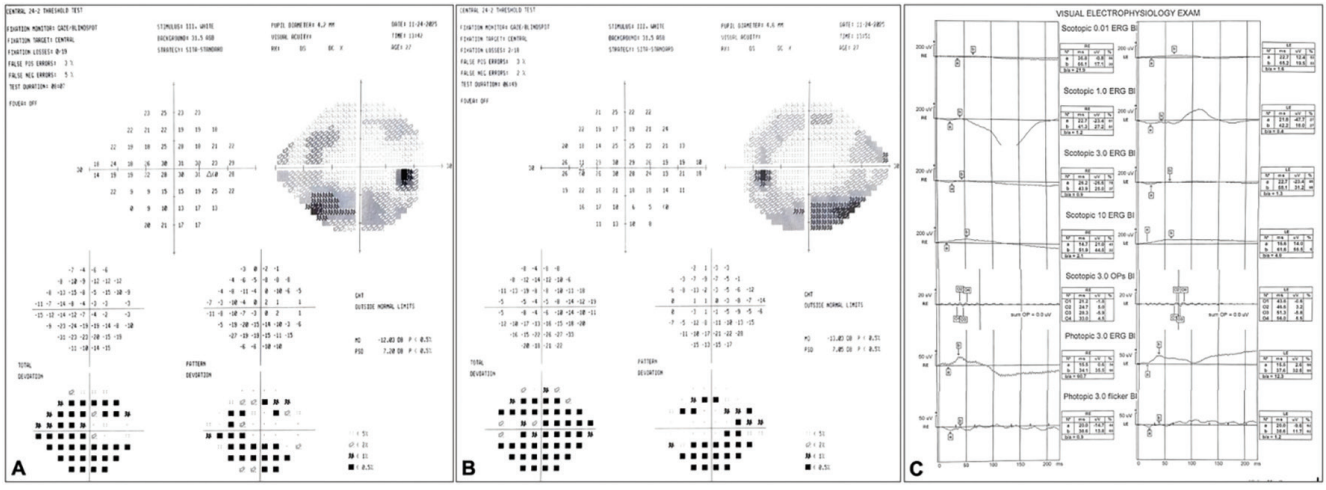

Figure 2. Visual fields of the right (A) and left (B) eyes and the electroretinogram (C)

uveitis, leading to the development of ocular and systemic complications secondary to long-term corticosteroid use.[4] Although there is currently no curative treatment for IRD, early diagnosis is important for the timely initiation of re/habilitative care, the planning of supportive approaches, and the evaluation of gene-targeted treatment options in applicable cases.[5]

In clinical practice, recognizing the clinical and imaging findings suggestive of IRD is essential. In this patient group presenting with uveitis-like findings, the absence of sudden visual loss, the lack of clues favoring IRD in the medical history, and the inability to identify an etiology for uveitis are common characteristics.[3] In our case, vision was preserved, posterior pole findings were detected incidentally during a routine examination, and no guiding information was obtained from the personal or family history.

On ophthalmological examination, the inflammatory phenotype associated with IRD typically exhibits bilateral and symmetrical involvement. A pronounced discrepancy between the severity of inflammation and visual function is an important clinical clue that may suggest an underlying dystrophic process.[6] Anterior chamber inflammation is absent in most cases. The accompanying presence of perivascular sheathing can be a misleading finding in favor of uveitis. In the presented case, the absence of inflammatory cells in the anterior chamber, the bilateral and symmetrical nature of the findings, and their restriction to the posterior segment supported a diagnosis of IRD.

In the early stages of the disease, FFA may have limited specificity in the differential diagnosis. In the advanced stages of the degenerative process, optic disc or retinal vascular leakage can be observed in late-phase (6-8 minutes) FFA frames.[3] The primary notable finding in the presented case was the observation of extensive RPE loss, excluding a limited preserved area between the optic disc and the macula. The absence of leakage in the optic disc and retinal vascular structures was interpreted as consistent with an early-stage inflammatory pattern.

In cases of IRD associated with uveitis, FAF imaging offers important clues for differential diagnosis. While a sharply demarcated, bilateral, and symmetrical parafoveal hyperautofluorescent annulus (ring sign) is frequently observed in the macular region in IRD, a patchy and asymmetrical distribution is generally seen in uveitis.[7,8] Furthermore, the presence of preserved autofluorescence around the optic disc (peripapillary sparing) is considered a characteristic finding of IRD. The "speckled pattern" consisting of hyperautofluorescent mottling observed around degenerative areas is another finding considered indicative of IRD.[3] In our case, the parafoveal hyperautofluorescent ring and the area of preserved peripapillary autofluorescence strongly supported the diagnosis of IRD. Additionally, this autofluorescence pattern correlated with the limited area of preserved RPE between the fovea and optic disc on FFA (Figure 1C-F).

In the literature, irregularities or focal disruptions in the EZ are described as characteristic OCT findings for IRD. CME is a frequent component of IRD-associated inflammation, and involvement of the inner retinal layers, particularly retinoschisis areas in the inner nuclear layer, constitutes another commonly observed structural change in this disease group. Reports indicate that sectoral thickening (microedema) of the retinal nerve fiber layer (RNFL) can also occur.[9] Although the OCT findings in our case were consistent with the literature, no significant sectoral thickening was detected on RNFL analysis.

In functional evaluations, the discrepancy between the ERG and visual field in very early stages is a valuable clinical parameter for differentiating IRD from uveitis.[10] The

relative preservation of the visual field despite significantly diminished electrophysiological responses is interpreted as consistent with early-stage IRD, where photoreceptor outer segment involvement is limited. In our case, the extinguished scotopic ERG responses indicate that the rod system was affected. Furthermore, the development of concentric constriction of the visual field suggests that the disease was at an advanced functional stage.

In cases where the possibility of IRD is overlooked during the diagnostic process, the pattern of response to treatment can provide important clues for the differential diagnosis.[3] Inflammatory findings accompanying IRD may show partial and transient improvement with systemic or local corticosteroid therapy, tending to recur shortly thereafter. This transient response-relapse behavior has been reported in misdiagnosed IRD cases.[2] Therefore, careful evaluation of the treatment response is diagnostically significant.

Given that the *CC2D2A* variant identified in our patient was classified as a VUS, its causal relationship with the clinical phenotype has not yet been established with certainty. Nevertheless, biallelic *CC2D2A* variants have been reported to be associated with isolated rod-cone dystrophy, and the CC2D2A protein has been shown to localize to the photoreceptor connecting cilium/transition zone and to play a role in outer segment protein trafficking.[11,12] These findings suggest a potential biological link between the inflammatory presentation in our patient and ciliary dysfunction and indicate that the inflammatory phenotype in CC2D2A-associated retinal dystrophies may not yet be sufficiently characterized.

In conclusion, keeping IRD in mind in the differential diagnosis of unusual clinical presentations mimicking inflammation enables not only diagnostic accuracy but also the appropriate planning of the patient's long-term follow-up and management. Diagnostic delays can negatively impact not only clinical decisions but also the timing of re/habilitative and psychosocial support processes, thereby leading to a decline in the patient's quality of life.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of the clinical findings and visual materials included in this study for scientific purposes.

Declarations

Author Contributions

Surgical and Medical Procedures: N.Y., P.Ö., Concept: D.Y., N.Y., Design: D.Y., N.Y., Data Collection or Processing: D.Y., P.Ö., E.Ş., N.Y., Analysis or Interpretation: D.Y., P.Ö., E.Ş., N.Y., Literature Search: D.Y., N.Y., Writing: D.Y., P.Ö., E.Ş., N.Y.

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Letter to the Editor

Coexistence of Retinitis Pigmentosa and Coats-Like Vitreoretinopathy

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Dear Editor,

This letter shares the multimodal imaging findings, genetic profile, and therapeutic approach of a case of retinitis pigmentosa (RP) presenting with signs of Coats-like retinopathy. RP is a hereditary, progressive degenerative disease of the retina. The disease initially manifests with night blindness and peripheral visual field loss, while severe central vision loss may develop in later stages.[1] Although RP is generally observed as an isolated ocular condition, it may also be associated with systemic diseases and other ophthalmologic pathologies. A well-known example is Usher syndrome, in which RP is accompanied by hearing loss.[2] Another ophthalmologic pathology reported in association with RP is Coats-like vitreoretinopathy, a combination referred to as Coats-like RP.

Coats-like RP can present with abnormal telangiectatic vessels in the retina and subretinal lipid exudation. Although the exact etiology and genetic background of Coats-like RP have not been fully elucidated, it has been reported to be associated with mutations in various genes, such as Norrie disease protein and Crumbs cell polarity complex component 1 (*CRB1*).[3] While several cases of Coats-like RP have been reported from Türkiye and worldwide, data regarding the genetic background and treatment approaches of such cases remain limited.

A 38-year-old woman presented to our clinic with complaints of bilateral low vision since childhood. The patient reported also having hearing loss since childhood, but no other known systemic disease. There was no parental consanguinity or family history of similar complaints.

The patient underwent a detailed ophthalmologic examination. Her best-corrected visual acuity (BCVA) according to Snellen chart was 3/20 in the right eye, while vision in the left eye was limited to light perception. Intraocular pressures and anterior segment examination findings were normal in both eyes. Fundus examination revealed a blunted macular reflex, peripheral retinal atrophy, and bone spicules bilaterally. Additionally, bilateral subretinal lipid exudation and telangiectatic changes were noted inferior to the optic disc and along the inferior arcuate vessels (Figure 1).

Swept-source optical coherence tomography (OCT) (Topcon, Tokyo, Japan) demonstrated a central macular thickness of 507 µm in the right eye and 363 µm in the left eye, as well as bilateral diffuse intraretinal cystic spaces and disruption of the ellipsoid zone (Figure 2). Wide-field fundus fluorescein angiography (Optos, USA) revealed bilateral telangiectatic vessels and vascular leakage in the inferior retina (Figure 3). The patient's findings were consistent with Coats-like RP, and a variant of Usher syndrome was suspected due to her concomitant hearing loss. Whole-exome sequencing identified a homozygous *USH2A* mutation (c.12706T>G). Audiological evaluation confirmed sensorineural hearing loss.

Keywords: Retinitis pigmentosa, Coats-like vitreoretinopathy, telangiectasia, photocoagulation

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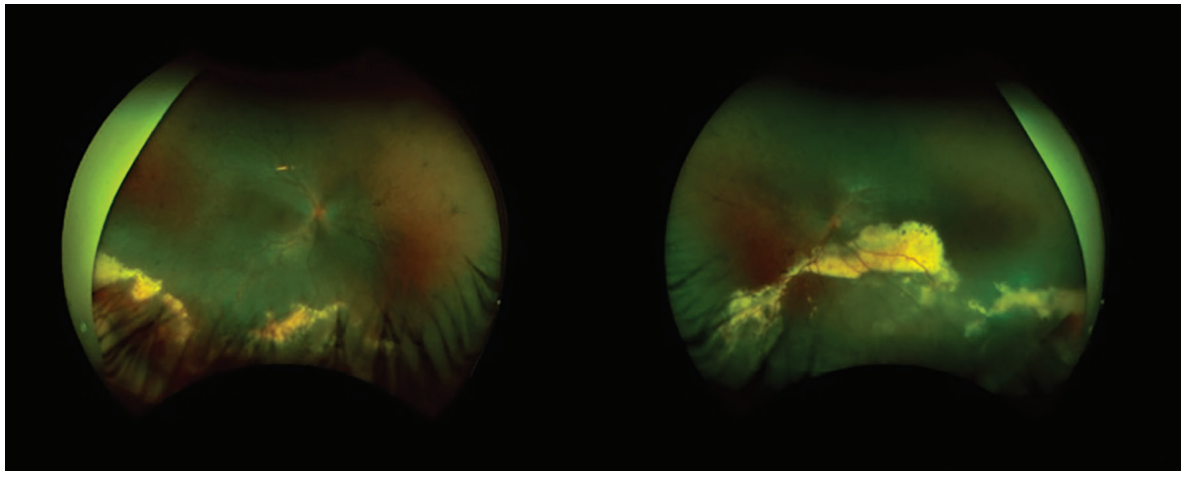

Figure 1. Bilateral subretinal lipid exudation and telangiectatic changes in the inferior retina and bone spicules in the peripheral retina were observed. The exudation extended to the macula in the left eye (left)

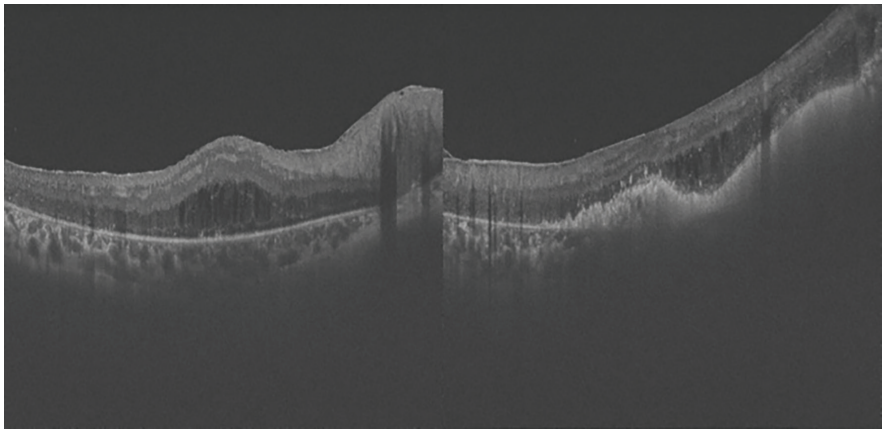

Figure 2. Swept-source optical coherence tomography revealed bilateral diffuse cystic cavities, atrophy of the outer retinal layers, and deposition consistent with subretinal lipid exudation on the left

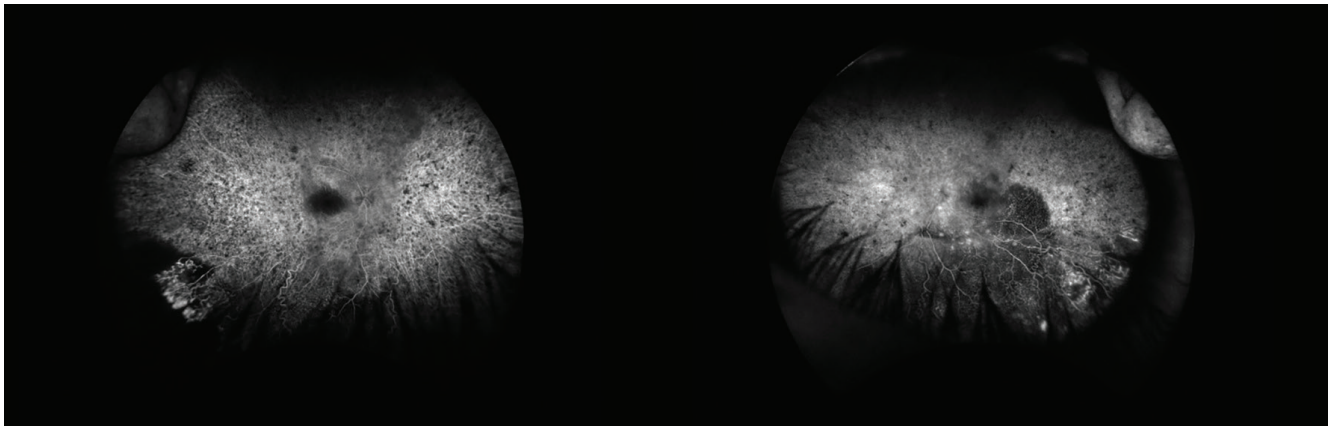

Figure 3. Wide-field fundus fluorescein angiography demonstrated telangiectasia and vascular leakage in the inferior retina bilaterally

Monthly injections of intravitreal bevacizumab (Avastin; Genentech, USA) were administered three times to the right eye and twice to the left eye. Fifteen days after the injections, photocoagulation was applied bilaterally to areas with telangiectatic vessels and vascular leakage in the inferior quadrants and ischemic areas in the superior quadrants.

At the 1-month follow-up after photocoagulation, bilateral serous retinal detachment was detected in the inferior quadrants, with elevated areas of persistent telangiectatic vessels. Consequently, 180-degree transscleral cryotherapy was applied to the inferior retinal quadrants of both eyes in a single session. Cryotherapy was applied to the affected areas using a double freeze-thaw technique in a single session per eye.[4]

At the one-month follow-up after cryotherapy, Snellen BCVA was still 3/20 in the right eye and light perception in the left eye. On fundus examination, photocoagulation and cryotherapy scars were present in addition to the initial findings, and subretinal exudation was observed inferior to the optic disc. Photocoagulation was performed on the retinal area between the inferior arcuate vessels and the ischemic zone in the right eye (Figure 4).

At the patient's most recent examination, after two years of follow-up, BCVA remained unchanged at 3/20 in the right eye and light perception in the left eye. Fundus examination revealed persistent exudation. Central macular thickness was 524 µm in the right eye and 291 µm in the left eye, and OCT findings were similar to those observed in the initial examination (Figure 5).

Aflibercept was considered as an alternative anti-vascular endothelial growth factor (anti-VEGF) agent during follow-up. However, it could not be administered because the patient could not afford the medication. Furthermore, follow-up and treatment intervals could not be optimized because the patient was unable to attend scheduled examinations regularly due to socioeconomic limitations.

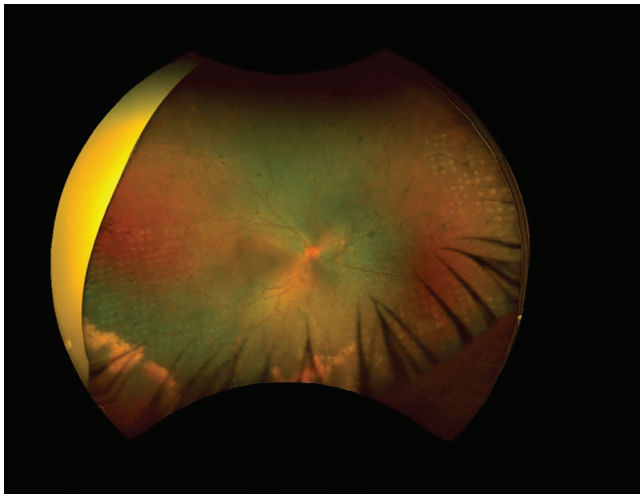

Figure 4. Wide-field fundus image of the right eye following photocoagulation

RP can coexist with a variety of systemic and ocular pathologies. When associated with systemic disease, the coexistence is referred to as syndromic RP. The association of RP with Coats-like lesions was first described in 1988.[5] Coats disease typically affects males in early childhood and is usually unilateral.[4] In contrast, Coats-like lesions associated with RP are usually detected in adulthood, exhibit bilateral involvement, and present with telangiectatic changes and lipid exudation in the inferior retina.[3] Consistent with previous reports in the literature, our patient was an adult woman with RP who exhibited telangiectasia and exudation involving the inferior retina.

Although our patient's retinal findings resembled those in previously reported cases, the presence of sensorineural hearing loss suggested the possibility of a syndromic condition such as Usher syndrome. In a cohort study conducted by Daich Varela et al.[6], Coats-like retinopathy associated with hereditary retinal diseases was reported to have a considerably heterogeneous genetic basis, occurring in the context of various gene mutations. The most common associations were with *CRB1*, *RHO*, and *USH2A* mutations, respectively.[6]

To the best of our knowledge, there are limited data on the underlying genetic mutations and treatment approaches in similar cases reported from Türkiye. Demirel et al.[7] reported a case with clinical findings similar to ours but provided no information regarding the genetic basis, and the patient was managed conservatively with preservation of visual acuity. Another three-case series from Türkiye reported clinical findings similar to ours but stated that genetic testing could not be performed.[8] In our patient, a homozygous *USH2A* mutation was identified, although it was classified as a variant of uncertain significance. Given the consistency between the mutation and the clinical findings, we believe the patient may have a variant of Usher syndrome with associated Coats-like RP. However, broader genetic analyses including the patient's parents or confirmation through experimental animal model studies, would be required to establish this mutation as a novel variant. Another case report described Coats-like RP findings in a patient with nanophthalmos.[9] These reports suggest that Coats-like RP may occur in association with systemic syndromes as well as other ocular pathologies, which complicates both the diagnosis and the management of the disease.

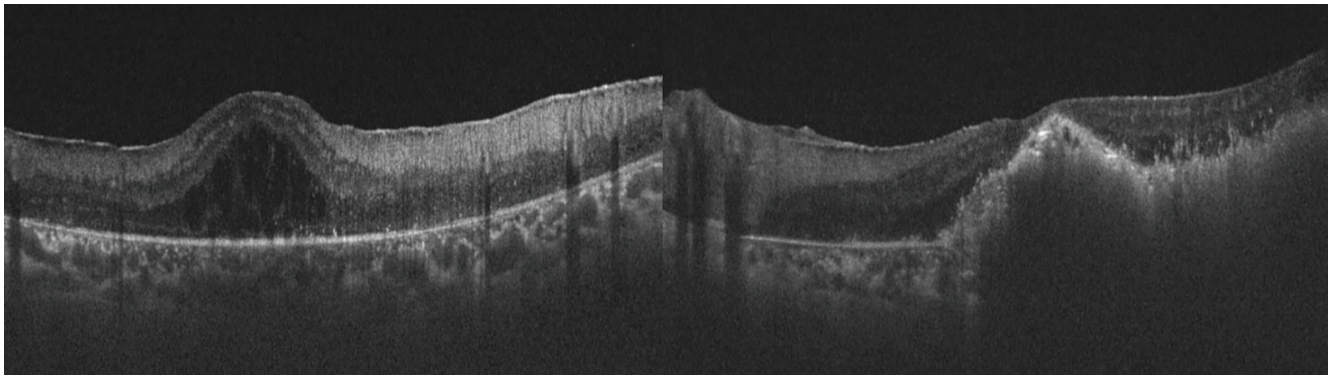

Figure 5. At the patient's final follow-up examination, swept-source optical coherence tomography images of the right (right) and left (left) eyes appear similar to the initial findings

The mainstay of treatment in RP patients with Coats-like retinopathy is ablation of all telangiectatic vessels and ischemic retina, sparing the parafoveal region. For this purpose, laser photocoagulation may be applied to non-elevated retinal areas, whereas cryotherapy is preferred for areas with extensive subretinal fluid and dense exudate. Anti-VEGF agents may be used as adjunctive therapy. Vitreoretinal surgery may also be required in patients with massive serous retinal detachment.[8] Although anatomical improvement following treatment has been reported in some cases, functional recovery remains limited.[3] In our case, treatment consisted of laser photocoagulation, intravitreal anti-VEGF injections, and cryotherapy. Over the two-year follow-up, no significant functional improvement was achieved due to retinal damage from both RP and the associated vascular pathology. Nevertheless, potential complications secondary to the vasculopathy were prevented, and anatomic integrity was preserved.

In conclusion, we report a case of Coats-like RP and sensorineural hearing loss associated with a homozygous *USH2A* gene mutation. However, larger case series and more detailed genetic analyses are needed to corroborate the pathogenicity of this mutation. Although such cases pose diagnostic challenges due to their relative rarity, they may carry a poor prognosis due to the multifactorial retinal damage involved. In similar cases, accurate diagnosis requires detailed multimodal imaging assessment, evaluation for additional systemic pathologies, and effective genetic counseling. It should also be kept in mind that combined treatment modalities may be necessary to halt disease progression.

Ethics

Informed Consent: Informed consent was obtained from the patient for all findings, genetic and laboratory results, and images related to this case.

Declarations

Authorship Contributions

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

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Bilateral Ocular Hypotony Secondary to Severe Dehydration and Uremia

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Dear Editor,

Ocular hypotony, defined as a sustained intraocular pressure (IOP) below approximately 6 mmHg, is a pathological condition that may compromise ocular structure and function. Prolonged hypotony can result in irreversible visual impairment through mechanisms such as corneal edema, choroidal effusion, retinochoroidal folds, and hypotonic maculopathy. Although surgical, traumatic, and inflammatory causes are most frequently encountered, systemic disturbances may also impair aqueous humor dynamics. Rare cases have been reported in association with severe dehydration, hypovolemia, and uremia, in which reduced aqueous humor production appears to play a central role.[1,2,3,4]

Herein, we report a case of bilateral ocular hypotony following severe systemic dehydration secondary to gastrointestinal bleeding. A 73-year-old man presented with bilateral ocular pain and decreased vision. Best-corrected visual acuity, assessed using a Snellen chart and subsequently converted to logarithm of the minimum angle of resolution (logMAR) units, was 1.00 logMAR (20/200) in the right eye and 0.30 logMAR (20/40) in the left eye. Goldmann applanation tonometry revealed an IOP of 5 mmHg in both eyes. Slit-lamp examination showed conjunctival hyperemia, Descemet membrane folds, and +2 anterior chamber cells bilaterally (Figure 1). Gonioscopy demonstrated open angles without evidence of cyclodialysis cleft or angle recession, with blood observed within Schlemm's canal (Figure 2). The right eye exhibited a dense corticonuclear cataract, whereas nuclear sclerosis was noted in the left. Fundus examination was limited in the right eye because of lens opacity but revealed normal optic discs and maculae, with attached retina and choroid in both eyes. No clinical signs of hypotonic maculopathy were identified. B-scan ultrasonography and optical coherence tomography showed a normal posterior segment in both eyes (Figure 3). Despite the presence of an anterior chamber reaction, no keratic precipitates, fibrin formation, posterior synechiae, or posterior segment inflammatory findings were observed.

The patient had experienced an upper gastrointestinal hemorrhage approximately 2 weeks earlier. Emergency endoscopy revealed a Forrest IIa gastric ulcer, and endoscopic hemostasis was performed. During subsequent follow-up, marked fluid loss and deterioration in hematological parameters necessitated intensive care admission. Laboratory findings demonstrated severe dehydration, anemia, and uremia secondary to acute kidney injury. Values (with normative ranges) were as follows: hemoglobin 7.8 g/dL (13.5-16.9), hematocrit 24.4% (40.0-49.4), serum creatinine 1.51 mg/dL (0.7-1.3), urea 83.46 mg/dL (19-49), and estimated glomerular filtration rate (eGFR) 45.18 mL/min/1.73 m^2 (>90). Serum sodium level was 142 mmol/L at presentation and remained stable during follow-up. Calculated serum osmolarity at presentation

Keywords: Ciliary ischemia, dehydration, hypovolemia, ocular hypotony

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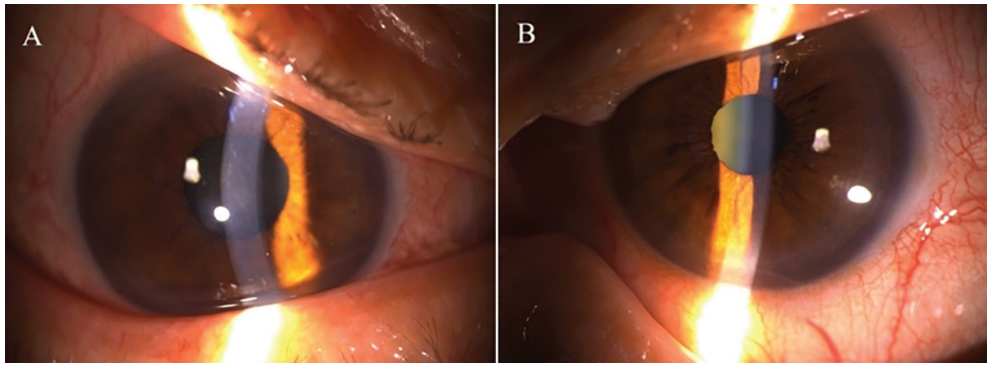

Figure 1. Anterior segment examination showed bilateral conjunctival hyperemia, corneal Descemet membrane folds, and +2 anterior chamber cells (A: right eye, B: left eye)

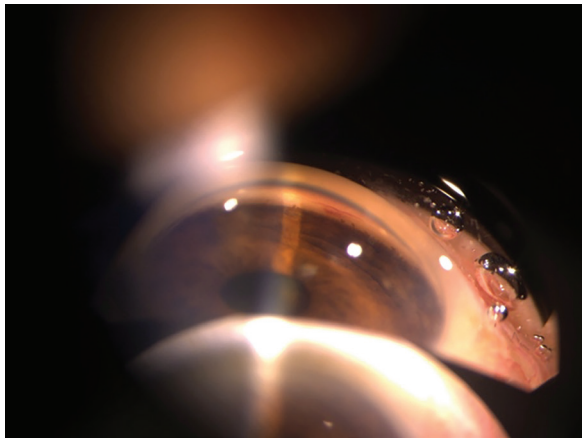

Figure 2. Gonioscopic examination revealed open angles in both eyes, with notable visualization of blood within Schlemm's canal in the left eye

was approximately 307 mOsm/kg, consistent with hyperosmolarity related to dehydration and uremia. The patient received intravenous fluid replacement, erythrocyte suspension transfusion, a proton-pump inhibitor (PPI), and intravenous iron supplementation. He was discharged after gradual systemic improvement on oral PPI and iron therapy.

No topical or systemic medications known to reduce aqueous humor production or to precipitate ocular hypotony were identified before or during the hypotony episode. Accordingly, the bilateral ocular hypotony was primarily attributed to hypovolemia-induced impairment of ciliary body perfusion. In addition, uremia-related osmotic alterations may have further exacerbated the hypotony. Topical dexamethasone 0.1% (Maxidex®, Novartis, Puurs, Belgium) was administered hourly together with atropine sulfate 1% (Atropin Sülfat®, Biofarma, İstanbul, Türkiye) three times daily. Systemic corticosteroids were withheld because of the recent gastrointestinal bleeding.

After 1 week, systemic and ocular findings improved, with IOP values of 8 mmHg and 11 mmHg, respectively. Conjunctival hyperemia, corneal folds, and anterior chamber inflammation decreased markedly. At the 1-month follow-up, IOP stabilized at 10-11 mmHg in both eyes. Endothelial pigment deposition diminished, and corneal folds and inflammatory cell infiltration resolved completely. Topical medications were gradually tapered and discontinued. Final laboratory tests confirmed systemic recovery, with hemoglobin 11.4 g/dL, hematocrit 38.2%, serum creatinine 1.10 mg/dL, urea 45.36 mg/dL, and eGFR 66.26 mL/min/1.73 m^2.

This case illustrates a fully reversible episode of bilateral ocular hypotony secondary to systemic dehydration and hypovolemia, further exacerbated by uremia associated with acute kidney injury. The concurrence of volume depletion and azotemia likely resulted in transient ciliary body hypoperfusion and suppression of aqueous humor production. The marked reduction of IOP to 5 mmHg, in the absence of prior ocular surgery, trauma, or hypotony-inducing medications, together with gradual normalization following systemic rehydration and renal recovery, supports transient aqueous hyposecretion due to ciliary ischemia as the principal mechanism.

In states of profound dehydration or hypovolemia, reduced perfusion of the ciliary circulation and altered plasma osmolality may impair aqueous production.[1,2,4] As described by Wang et al.[1], hypotony may arise from reduced aqueous production or increased aqueous outflow. In this patient, normal gonioscopic findings without cyclodialysis or angle recession favored a production-deficient mechanism. The presence of blood in Schlemm's canal was interpreted as a reflux phenomenon caused by a relative pressure gradient in the setting of marked hypotony, whereby episcleral venous pressure exceeded IOP, rather than a primary elevation of episcleral venous pressure. Similar cases reported by Schleis and Atanasoff[2] demonstrated IOP normalization

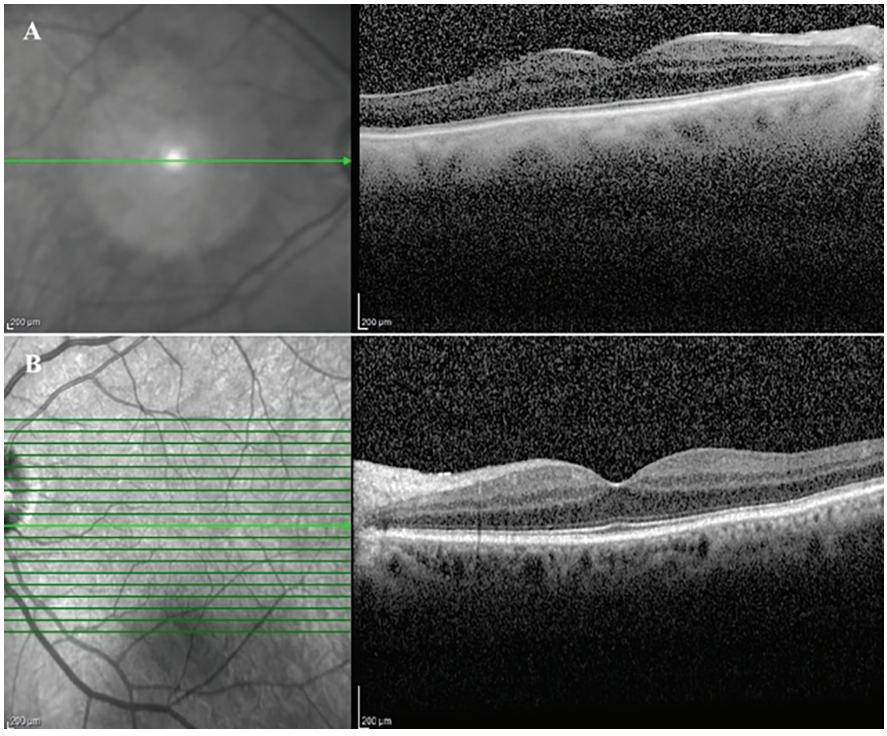

Figure 3. Macular optical coherence tomography. A) Right eye: Reduced image quality due to dense cataract, with preserved retinal architecture and no hypotony maculopathy. B) Left eye: Normal foveal contour and retinal layers, with no hypotony maculopathy

following intravenous fluid therapy, supporting this pathophysiologic explanation.

Although prolonged hypotony carries a risk of hypotonic maculopathy and visual loss,[4,5,6] early recognition and prompt systemic correction likely prevented structural macular changes in this patient. In hypovolemia-associated cases, restoration of intravascular volume and hemodynamic stability remains the cornerstone of management. In our case, systemic rehydration was considered the primary therapeutic intervention responsible for restoration of IOP. Topical therapy was used as an adjunctive treatment to mitigate ciliary body ischemia-related ocular inflammation and to support recovery of aqueous humor production.

In conclusion, dehydration-associated ocular hypotony may be fully reversible when promptly recognized and appropriately managed. Routine IOP monitoring should be considered in systemically compromised patients, particularly those with acute volume depletion or renal dysfunction. Timely diagnosis and systemic correction are essential to preserve visual function and prevent irreversible hypotonic complications.

Ethics

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

Declarations

Authorship Contributions

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

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Glaucoma Management in High Myopia: A Case of Hypotony-Related Serous Retinal Detachment Following Trabeculectomy and Successful Treatment with Intravitreal SF6 Gas

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Dear Editor,

Glaucoma management in highly myopic eyes presents significant diagnostic and therapeutic challenges.[1,2] Surgical intervention, particularly trabeculectomy, carries an increased risk of complications in this population, including hypotony and subsequent hypotony maculopathy or serous retinal detachment (SRD).[3,4]

A 22-year-old female patient with a known diagnosis of degenerative myopia and primary open angle glaucoma presented for follow-up. Her axial length was measured at 27.04 mm in the right eye, classifying her as highly myopic. She had no family history of glaucoma. In the right eye, her best-corrected visual acuity (BCVA) was 0.7 (with full correction) and initial intraocular pressure (IOP) was 31 mmHg. Gonioscopy revealed open angles (Shaffer grade 4). Fundus examination showed bilateral tilted discs and tigroid retinas, consistent with high myopia. The left eye had a BCVA of 1.0 with full correction, and its IOP remained stable between 18-21 mmHg throughout the follow-up period, with no vision loss. The optical coherence tomography (OCT) image illustrating the thickness of the right and left retinal nerve fiber layers is shown in Figure 1.

In December 2023, initial medical treatment was commenced with a fixed combination of dorzolamide/timolol (Tomec; Abdi İbrahim, Türkiye) and brimonidine (Brimogut; Bilim İlaç, Türkiye). Three weeks later, the patient showed an excellent response to the medical therapy, with her IOP dropping to 8 mmHg in the right eye.

In October 2024, ten months later, the patient presented with an acute increase in IOP after admitting that she had discontinued her medication for one week. Her IOP had acutely elevated to 44 mmHg in the right eye. Slit-lamp examination of the right eye revealed follicular conjunctivitis. The medical treatment was discontinued, and pattern scan laser trabeculoplasty (Topcon Medical Laser Systems, Santa Clara, CA, USA) was performed. Despite the laser treatment, the IOP remained high and uncontrolled, indicating a failure of conservative management and the need for more definitive intervention. Given the acute and significant IOP elevation and the patient's young age, which often correlates with more aggressive glaucoma, proceeding directly to surgical intervention was deemed necessary to prevent irreversible vision loss. Consequently, a trabeculectomy with 5-fluorouracil (5-FU) was performed

Keywords: Glaucoma, myopia, trabeculectomy

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in November 2024. Her preoperative IOP was 38 mmHg and BCVA was 0.2.

On postoperative day 1, she developed acute ocular hypotony, with an IOP of 5 mmHg. Clinical examination revealed a shallow anterior chamber, Descemet's membrane folds in the cornea, and a formed, diffuse bleb with a negative Seidel test. There was no iridolenticular touch. She was immediately started on cyclopentolate hydrochloride 1% (Sikloplejin; Abdi İbrahim, Türkiye) twice daily and a tight bandage was applied on the bleb region.

On postoperative day 2, SRD was detected as a complication, confirmed by OCT (Figure 2). Given the persistent hypotony and the presence of SRD, an intervention was planned. On postoperative day 4, an

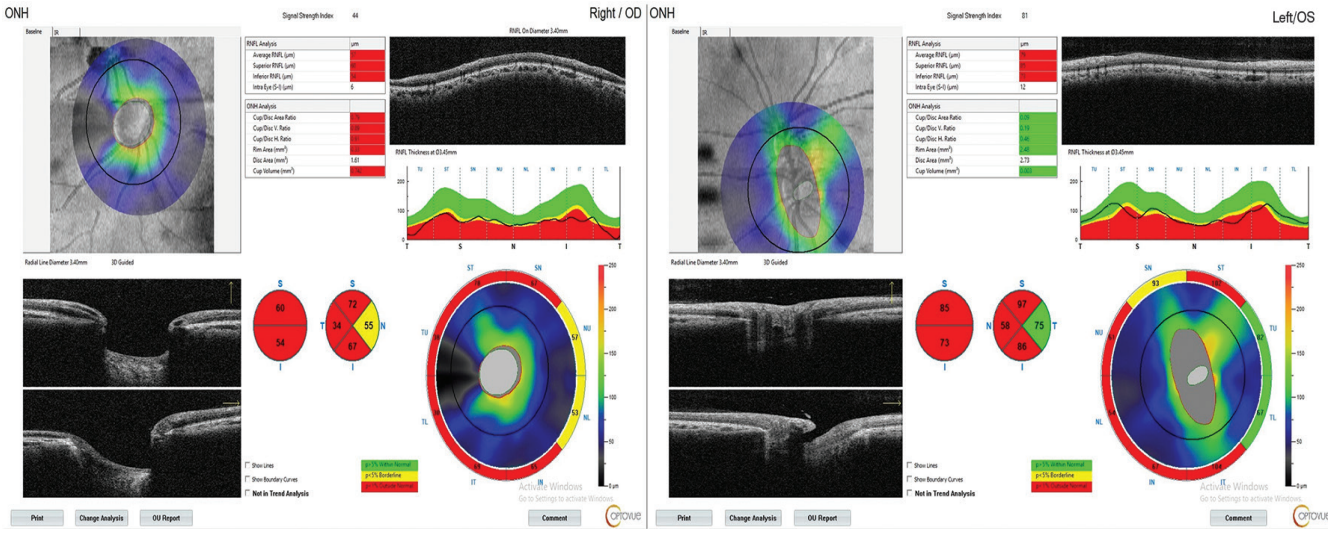

Figure 1. Combined preoperative optical coherence tomography images of the right and left eyes showing the optic nerve head and retinal nerve fiber layer analysis. Note: Color fundus photographs were not available due to clinical limitations

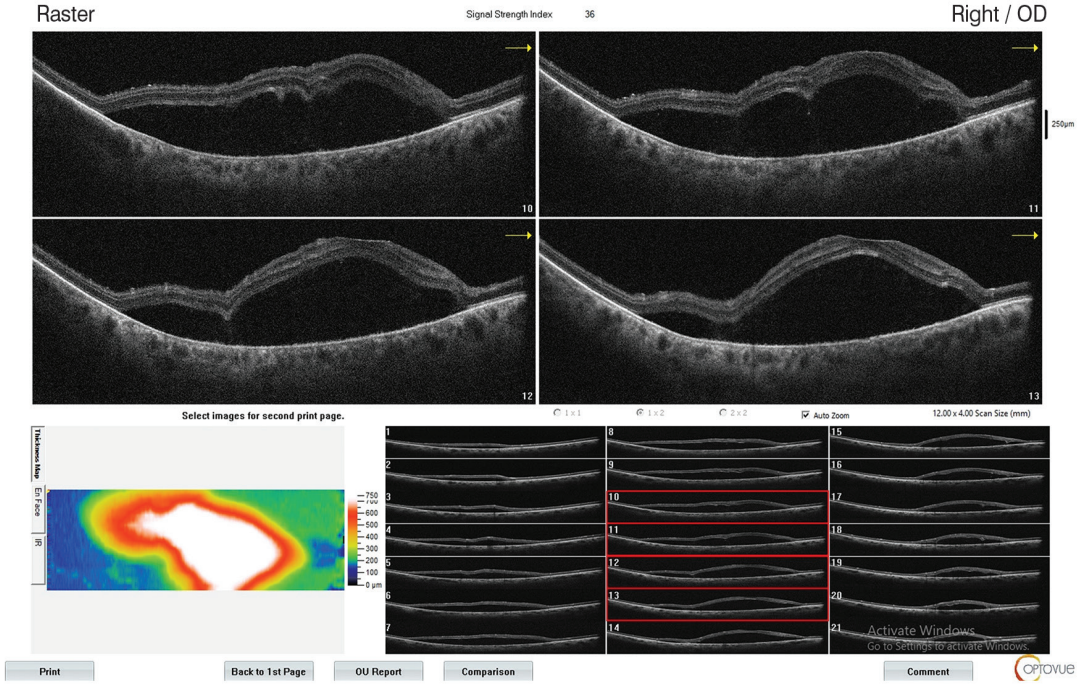

Figure 2. Optical coherence tomography image of the right eye on day 2 postoperatively, confirming the presence of subretinal serous fluid due to hypotony

intravitreal injection of 0.4 mL of SF_6 gas was administered and the patient was instructed to maintain a prone position.

She showed rapid improvement. On day 1 post-SF_6 injection, the retina was reattached, and the IOP was 10 mmHg. On day 3, the retina remained attached, and the IOP was 14 mmHg. At the final follow-up in February 2025, her BCVA was 0.1. OCT demonstrated complete resolution of the SRD (Figure 3). IOP was stable at 13 mmHg. The anterior chamber was formed (Figure 4), and the retina remained attached with no peripheral tears detected.

The management of glaucoma in highly myopic eyes is a complex clinical scenario, primarily due to the diagnostic difficulties and the increased risk of surgical complications. Our case highlights these challenges, particularly the development of acute ocular hypotony and subsequent SRD following trabeculectomy with 5-FU, and the successful management of this complication with intravitreal SF_6 gas injection. The occurrence of SRD after trabeculectomy is a known, although rare, complication that is typically associated with profound hypotony.[3,4]

The literature reports various approaches for managing post-trabeculectomy SRD. Many cases, particularly those without underlying high myopia or other predisposing factors, resolve spontaneously with conservative management (e.g., topical steroids and cycloplegics) as IOP normalizes.[5,6] For instance, Aydin et al.[7] reported a case of SRD following trabeculectomy for traumatic glaucoma, which was managed conservatively. However, in cases of persistent or severe hypotony, surgical intervention is often required. It is important to note that for early hypotony cases, techniques such as transconjunctival flap suturing can also be an effective and less invasive solution, as supported by published literature.[8] Our case is distinct from previous reports. Roy and Padhy[3] reported a case of SRD following trabeculectomy for angle recession glaucoma, which was successfully managed conservatively with steroids. These cases, while sharing the complication of post-trabeculectomy SRD, are rooted in a traumatic etiology, which may introduce confounding factors such as pre-existing angle damage or inflammation.

The most notable difference is the aggressive and rapid intervention with an intravitreal injection of 0.4 mL of SF_6 gas.[9,10,11] While intravitreal gas injection is generally considered safe, a potential concern is the exacerbation of anterior chamber shallowing. However, careful patient

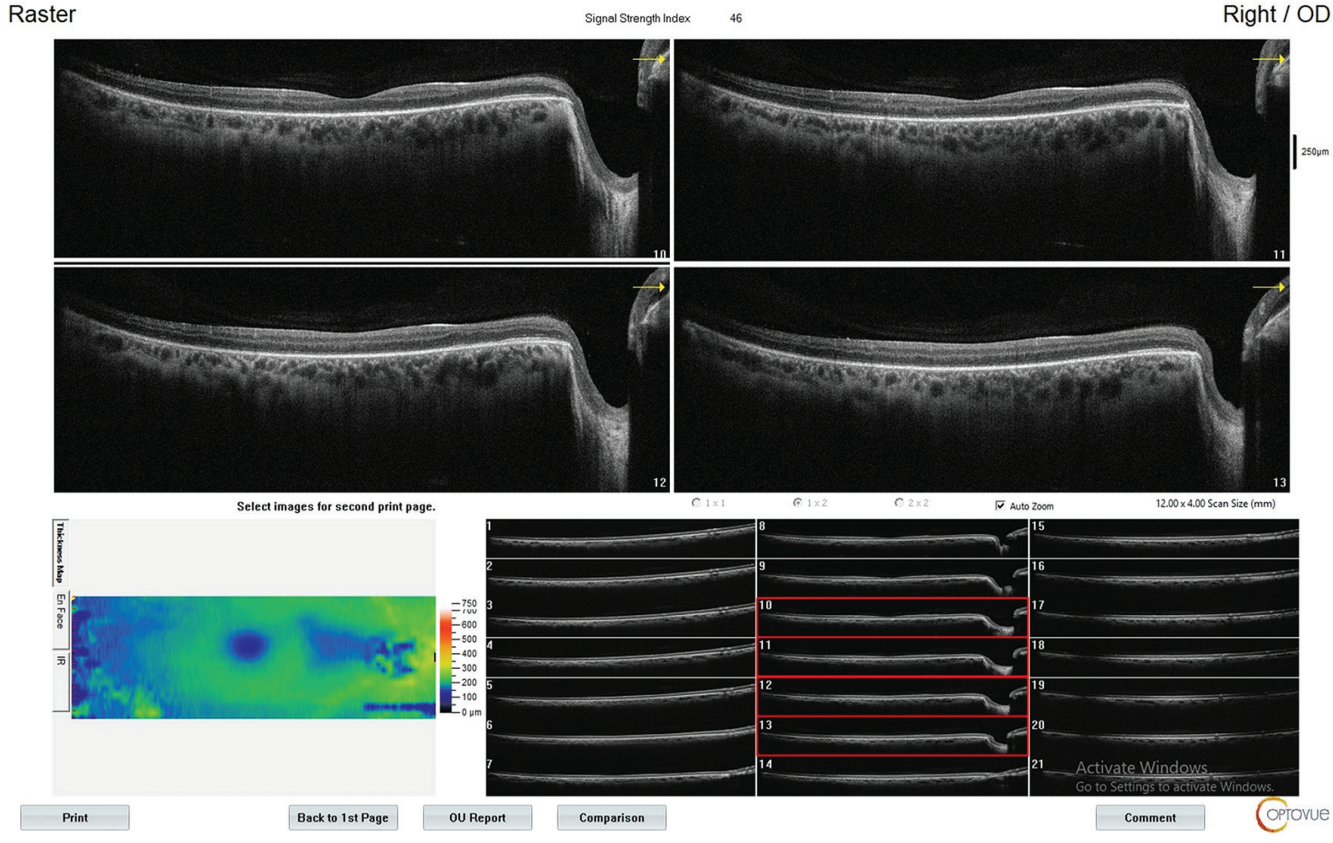

Figure 3. Optical coherence tomography image of the right eye after the intravitreal SF6 gas injection, showing the reattached retina

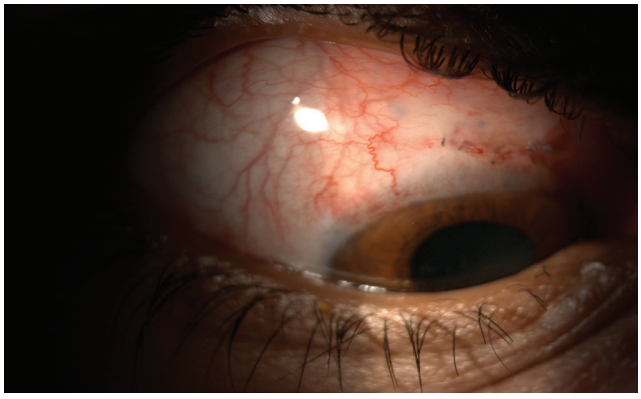

Figure 4. Final follow-up anterior segment photograph of the right eye. Note: An additional photograph demonstrating anterior chamber depth with a narrow-slit beam was not available due to clinical limitations

positioning and monitoring can mitigate this risk, and the rapid resolution of hypotony often outweighs this concern. The rationale for using an expansile gas is two-fold: first, the gas bubble mechanically increases the IOP, which helps to re-establish the pressure gradient and push the subretinal fluid back into the choroid; and second, the increased pressure is thought to reactivate the retinal pigment epithelium (RPE) pump mechanism, promoting the reabsorption of the subretinal fluid. The rapid resolution of the SRD (within 24 h) and the stabilization of the IOP following the SF_6 injection underscore its effectiveness as a minimally invasive and rapid intervention for hypotony-related SRD, especially in high-risk eyes like those with high myopia, where prolonged hypotony could lead to irreversible vision loss.

Finally, while the OCT images in our case did not clearly demonstrate an RPE tear, the possibility of an occult or small RPE tear could not be entirely excluded, especially given the high myopic status and the acute, profound hypotony. The mechanical stress on the thinned RPE layer in a highly myopic eye, combined with the acute pressure drop, may predispose the eye to a micro-tear, which would further impair the RPE's ability to pump fluid out of the subretinal space. The rapid resolution of the SRD after the SF_6 injection, which mechanically increased the IOP, suggests that the primary issue was the pressure gradient failure, but the possibility of a concurrent, small RPE defect remains a point for discussion and further investigation in similar cases.

This case report emphasizes the need for a high index of suspicion for glaucoma in young, highly myopic patients and the critical role of patient compliance in medical management. Furthermore, it demonstrates that while trabeculectomy in high myopia carries a significant risk of hypotony and SRD, this complication can be effectively and rapidly managed with an intravitreal injection of SF_6 gas, leading to anatomical and functional recovery.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Declarations

Authorship Contributions

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

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