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AT A GLANCE

2024 Issue 4 at a Glance:

Esteemed colleagues,

In the fourth issue of 2024, the Turkish Journal of Ophthalmology features six original articles, one review, two case reports, and a letter to the editor with the authors' reply.

In their article titled "An Investigation of the Psychosocial Outcomes of Dry Eye Disease Treatment in Children with Computer Vision Syndrome", Temeltürk et al. conducted a study with 38 individuals, mostly girls, and revealed that there was a significant decrease in anxiety levels and improvement in quality of life functionality scores after dry eye disease (DED) treatment in computer vision syndrome (CVS). These findings underline that pediatric patients with CVS-related DED experience substantial psychosocial problems that may be alleviated with appropriate DED treatment (See pages 183-189).

In a comparative study titled "Clinical Outcomes of Enhanced Monofocal (Mono-EDOF) Intraocular Lenses with the Mini-Monovision Technique versus Trifocal Intraocular Lenses: A Comparative Study", Can and Bayhan share the results of 48 eyes of 24 patients in two groups. They report that enhanced monofocal (mono-EDOF) lenses are not as effective as trifocals for near vision when targeting emmetropia, but when applied with the mini-monovision approach, they improved near vision while largely solving the problems of dysphotopsia and decreased contrast sensitivity seen with trifocal lenses (See pages 190-197).

Çakar Özdal et al. conducted a survey study titled "Treatment of Behçet Uveitis in Türkiye" with a web-based questionnaire sent to uveitis specialists in Türkiye by email. The survey contained 16 questions about the treatment approach to ocular involvement due to Behçet's disease. Determining the treatment approaches of our colleagues treating uveitis in Türkiye with this survey revealed that awareness could be raised regarding the early initiation of biologic agents in patients with Behçet uveitis, and there is also a need for more information sharing on subjects such as preparation for and safety monitoring of conventional immunosuppressive and anti-TNF-α therapy; drug use during pregnancy; and vaccination and surgery (See pages 198-204).

In their study titled "Emotional State Evaluation of Retinitis Pigmentosa Patients with the Beck Depression Inventory", Öner et al. assessed 134 people, including the control group, and found that the incidence and severity of depression was higher in patients with retinitis pigmentosa than in normal individuals. As a significant relationship was found between the patient's functional vision tests and the frequency and severity of depression, it was pointed out that depression can reduce the reliability of visual function tests and reduce the quality of life in these patients. Therefore, it is important to evaluate mental health in addition to functional tests in retinitis pigmentosa (See pages 205-211).

In their highly comprehensive retrospective observational study titled "Traumatic Brain Injury in Admitted Patients with Ocular Trauma", Zhang et al. showed that 184,124 (58.2%) of 316,485 patients presenting with ocular trauma also had traumatic brain injury. The authors noted that although the mortality rate is low, it should be taken into account that these patients face a difficult rehabilitation process and disability, and similar analytical studies may guide screening and rehabilitation studies (See pages 212-222).

In their retrospective study of 15 eyes of 14 patients titled "Surgical Outcomes of Rhegmatogenous Retinal Detachment Associated with Regressed Retinopathy of Prematurity", Özdemir Zeydanlı et al. reported that the failure rate of primary surgery was 53% overall, with rates of 33% in those who underwent scleral buckling (SB), 100% in those who underwent pars plana vitrectomy (PPV), and 40% in those who underwent combined SB-PPV as primary surgery. The authors emphasized the need to create a lifelong examination program aiming to timely identify and address potential complications, especially for non-verbal patients (See pages 223-227).

Age-related macular degeneration (AMD), which is one of the leading causes of vision loss in people older than 55 in Western countries, is also one of the main causes of blindness worldwide. In their review, Neri et al. discuss the different stages of AMD with a special focus on the changes that occur in the choriocapillaris. The choriocapillaris can now be examined in much more detail with imaging techniques such as optical coherence tomography (OCT) and OCT angiography, and its various roles in the different stages of AMD are of interest. Both the richness of the visuals and the comprehensive literature analysis of these competent authors make this review an invaluable reference in its field (See pages 228-234).

In their case series titled "Ocular Involvement in Patients with Infantile Nephropathic Cystinosis", Üzüm et al. evaluated the ocular involvement of 4 patients from 2 families with *in vivo* confocal microscopy (IVCM) and OCT findings and showed for the first time with IVCM that crystals accumulated in the corneal epithelium (See pages 235-239).

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AT A GLANCE

In a case report titled "Unilateral Papilledema with Bilateral Optic Nerve Sheath Distension", El-Gendy et al. presents a rare case of unilateral papilledema, which usually shows a fairly symmetrical bilateral pattern. They emphasized the necessity of early detection to prevent optic nerve damage in cases of unilateral papilledema and attempted to explain the unilaterality based on bilateral optic nerve sheath diameter measurements (See pages 240-245).

Mostafa Saadat wrote a letter to the editor regarding the article titled "The Role of *FOXP3* Polymorphisms in Graves' Disease with or without Ophthalmopathy in a Turkish Population" published in our journal, stating that the results reported by Yaylacıoğlu Tuncay et al. should be interpreted with caution considering the inclusion of individuals of both sexes. In their response letter, Yaylacıoğlu Tuncay et al. stated the results in their published article and the results of a re-analysis made by grouping the participants by sex were similar. However, as Mostafa Saadat emphasized in his letter, they agreed that polymorphic loci on the X-chromosome should be analyzed differently from loci on the autosomal chromosomes. The letter written by Mostafa Saadat and the detailed response from Yaylacıoğlu et al. will be a useful source of information for researchers investigating associations with X-linked polymorphic loci (See pages 246-250).

We believe that this issue, which blends directive original research findings, a reference-quality review, and striking, novel case reports, will be of considerable interest to our colleagues.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

Original Article

An Investigation of the Psychosocial Outcomes of Dry Eye Disease Treatment in Children with Computer Vision Syndrome

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Abstract

Objectives: Computer vision syndrome (CVS) is a common disorder among children and is often associated with dry eye disease (DED). While researchers have shown a higher prevalence of psychopathology in older patients with DED, the impact of CVS-induced DED on the psychological state of children is not well known. This study aimed to evaluate psychological outcomes before and after DED treatment in pediatric patients with CVS-related DED.

Materials and Methods: In this study, a total of 38 children (32 girls, 6 boys) with CVS-related DED were evaluated with the Schirmer test, tear break-up time (TBUT), ocular surface disease index (OSDI), and Oxford grading scale at the time of diagnosis and after treatment with artificial tear drops. Additionally, quality of life (QoL) and anxiety and depression symptoms were assessed using self-report scales for children.

Results: The mean age and mean daily screen exposure of the patients were 13.95±2.42 years and 5.65±2.31 hours, respectively. After treatment, TBUT and Schirmer test values of the patients increased significantly, while OSDI values decreased ($p<0.001$ for all). The anxiety and depression scores of the patients decreased, while QoL functionality scores increased ($p<0.05$ for all) following treatment. There were significant correlations between Schirmer test values and anxiety scores ($r=-0.32$, $p=0.045$) and QoL total scores ($r=0.38$, $p=0.016$).

Conclusion: Enhanced QoL and decreased anxiety and depression scores were associated with improved Schirmer test results, indicating that appropriate DED treatment may mitigate the psychosocial effects of CVS-related DED in pediatric patients.

Keywords: Dry eye disease, computer vision syndrome, children, quality of life, anxiety, depression

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Introduction

Computer vision syndrome (CVS) is defined as a collection of eye-related issues and visual disturbances that occur due to prolonged use of digital screens.[1] CVS is commonly associated with prolonged computer usage exceeding 3 hours per day, and it is often characterized by visual, ocular and musculoskeletal symptoms.[2] The exponential proliferation of digital devices has made them an integral part of daily life, putting millions of individuals across all age groups at risk of developing CVS. Individuals spend more time on computers, laptops, smartphones, tablets, and e-readers, which contribute to CVS. Compared to the last few decades, children also spend extensive time using digital screens for schoolwork, playing video games, and engaging in communication activities such as sending and receiving text messages.[3] According to previous studies, the prevalence of CVS in children and adolescents is estimated to range from 50% to 70%.[4,5]

The primary clinical manifestation of CVS is dry eye disease (DED), which occurs at a prevalence of approximately 60%.[6] DED is characterized by persistent symptoms such as tearing, burning or stinging sensations, ocular discomfort, blurred vision, and photophobia. These symptoms have been documented to have negative effects on quality of life (QoL), impacting not only vision-related daily life but also broader aspects of general well-being.[7,8,9] Additionally, studies have revealed a higher prevalence of psychiatric disorders in patients with DED.[10,11,12] Among psychiatric diagnoses, anxiety and depressive disorders were the

most frequently investigated, and findings consistently indicated that individuals with DED exhibited elevated levels of anxiety and depressive symptoms compared to those without DED.[13,14,15]

Treatment options for DED often involve the use of artificial tear substitutes, which aim to replenish the natural tear film and lubricate the eyes to alleviate symptoms.[16] Previous studies have reported that artificial tear therapy has been associated with improvement in QoL.[17] Additionally, the potential of artificial tears to alleviate symptoms of anxiety and depression in DED patients has also been described.[18,19]

Drawing from the aforementioned research, it can be inferred that DED treatment might positively impact the psychological well-being of children diagnosed with CVS-related DED. The primary objective of the present study was to assess the impact of DED treatment on health-related QoL, as well as levels of depression and anxiety, among pediatric patients with CVS-related DED.

Materials and Methods

Study Design and Participants

This prospective study was conducted in the ophthalmology and psychiatry departments of a secondary care hospital. The study was approved by the Haseki Training and Research Hospital Ethics Committee (approval number: 55-2022, date: 23.03.2022) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all children and their parents.

The study included 38 children between 9 and 18 years old who were diagnosed with CVS-related DED and presented to the ophthalmology outpatient clinic. CVS was diagnosed based on the presence of eye complaints such as eye fatigue, burning, irritation, redness, and blurred vision due to long-term computer or digital screen use. All patients complained of worsening symptoms during exposure to digital screen light. To assess average daily screen exposure, a questionnaire was employed to determine the duration of computer, laptop, and phone usage during the last 6 months, measured in hours per day. Total daily screen exposure time was calculated for each child before and after DED treatment.

Exclusion criteria were the presence of neurological disorders (e.g., cerebral palsy, epilepsy), systemic chronic illnesses (e.g., type 1 diabetes), and history of any psychiatric diagnosis. Ophthalmological exclusion criteria were as follows: presence of any other eye diseases (e.g., retinal disease, uveitis, glaucoma, congenital cataract, pterygium, conjunctivitis, keratitis, blepharitis, nystagmus, orbital pathology, or history of ocular trauma or surgery); previous diagnosis of dry eye; use of any ophthalmic medication or contact lenses; and spherical equivalent outside the range of ±0.5 diopters, intraocular pressure measurements exceeding 21 mmHg, best corrected visual acuity below 20/25, or non-cooperation during the initial ophthalmological examination.

Initially, 85 children with CVS-related DED were recruited for the study. Of these, we also excluded participants with other factors that may contribute to DED symptoms, such as exposure to sun, wind, or air conditioning (n=15), those without complete ophthalmologic examinations during follow-up (n=20), and those who were non-cooperative with psychiatric assessments (n=12). Finally, a total of 38 children were included in the analysis.

Ophthalmologic Evaluation

All participants underwent comprehensive ophthalmological assessments that included best corrected visual acuity measurement using the Snellen chart, biomicroscopic examination of the anterior segment, intraocular pressure measurement via non-contact tonometry, and dilated fundus examination. A single automatic refractor-keratometer device (RF-K2, Canon Inc., Tokyo, Japan) was utilized to measure spherical equivalent.

Ocular surface damage and signs of tear dysfunction were assessed using the tear break-up time (TBUT) test, Schirmer test, ocular surface disease index (OSDI), and Oxford grading scale before and one month after treatment. The OSDI questionnaire was completed by the children with the assistance of their parents and specialists. The question regarding night driving was deemed irrelevant for children and was consequently excluded from the final score calculation.[20] The reliability of the OSDI among children has been previously assessed and confirmed.[21] To evaluate TBUT, fluorescein was instilled in the lower conjunctival sac, and the tear film was examined with a blue filter. The appearance of the first dry spots on the cornea since the last blink was observed, and the average of three consecutive measurements was obtained in seconds. Schirmer's test was evaluated with topical proparacaine hydrochloride (Alcaine, Alcon, Fort Worth, USA) to test basal tear secretion using a specialized Schirmer's strip prepared from Whatman grade 41 filter paper. Symptomatic DED was diagnosed using the OSDI questionnaire, TBUT, and Schirmer tests. The criteria for diagnosis included an OSDI score of ≥13, a TBUT of ≤10 seconds, and a Schirmer test result of ≤10 mm. The Oxford grading scale was used to rate the grade of corneal and conjunctival staining.

Dry Eye Treatment

Treatment for DED consisted of preservative-free artificial tear drops containing dextran and hydroxypropyl methylcellulose (Tears Naturale Free, Alcon, Fort Worth, USA) to reduce the ocular irritation secondary to preservatives. The administration of topical drops (4 times daily) was to be supervised by parents at home and by teachers during school hours. Additionally, the 20-20-20 rule and digital screen limitation were recommended for all patients. This rule can be defined as taking a 20-second break to look at something 20-feet away every 20 minutes.[22]

Psychiatric Measures

Following the ophthalmologic examination, all participants were asked to complete the psychiatric scales in one session that lasted approximately 30 minutes. After one month of follow-up, the same questionnaires were repeated.

In the current study, the Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV) and Pediatric Quality of Life Inventory (PedsQL) were used to assess the children's psychiatric symptoms and QoL, respectively, based on children's own reports.

The PedsQL was developed by Varni et al.[23] to assess health-related QoL in children. The PedsQL 4.0 Generic Core Scales include 23 items in 4 subscales: (1) physical functioning, (2) emotional functioning, (3) social functioning, and (4) school functioning. A 5-point response scale with scores ranging from 0 to 4 was used to assess child self-reports. Items were reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100%, 1 = 75%, 2 = 50%, 3 = 25%, 4 = 0%), so that higher scores indicated better QoL. The score range was based on the percentage of the total summary and subscale scores on the PedsQL.[24] The Turkish version of the PedsQL was found to be valid and reliable for the age group of 7 to 18 years.[25,26]

The RCADS-CV was developed to screen for anxiety, depression, and obsessive-compulsive symptoms in children and adolescents. This self-report questionnaire consists of 47 items in 6 subscales: generalized anxiety disorder, separation anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), social phobia, and major depressive disorder. Additionally, there are two comprehensive subscales referred to as "total internalizing" and "total anxiety." Each item is scored between 0 and 3 (0 = never, 1 = sometimes, 2 = often, 3 = always).[27] The validity and reliability of the Turkish version were conducted by Gormez et al.[28]

Statistical Analysis

A statistical power analysis was conducted to estimate the required sample size. To achieve an 80% power level (alpha = .05) for the detection of a medium effect size, the anticipated sample size required, as determined by G*Power 3.1, was approximately 34.[29,30,31] Statistical analyses were performed using SPSS 24.0. The Shapiro-Wilk test was utilized to determine whether the data were normally distributed. Comparisons of psychiatric scale measures and dry eye evaluation tests between pre- and post-treatment were reported using paired-samples t-test due to the normal distribution of the data. Pearson's correlation analyses were conducted to determine the associations between the improvements in ophthalmic measurements and psychiatric scales.

Results

The demographic and clinical characteristics of the patients are summarized in Table 1. Of the 38 children diagnosed with CVS-related DED, 32 (84.2%) were female, and 6 (15.8%) were male. The mean age was 13.95±2.42 years. The mean duration between two consecutive assessments was 35.36±8.62 days.

According to the analysis of the children's dry eye tests, which included TBUT, Schirmer, and OSDI values before and after topical treatment, statistically significant differences were identified (Table 2). Mean TBUT and Schirmer test results were 7.45±3.43 s and 11.84±6.50 mm at the time of diagnosis and 9.92±2.89 s and 15.66±6.40 mm at the time of the follow-up examination, respectively. The mean OSDI score decreased from 45.99±15.47 to 25.46±13.37 with DED treatment (p<0.001). There was also a significant reduction in daily screen exposure time between the pre- and post-treatment evaluations (5.65±2.31 h vs. 4.88±2.56 h, p=0.004). When examining the pre- and post-treatment Oxford grading scale results, we observed that in the pre-treatment assessment, 6 children (15.8%) were classified as having an Oxford grade 1, whereas 32 of them (84.2%) were categorized as grade 0. Following the post-treatment evaluations, all children exhibited an Oxford grade of 0.

Table 1. Sociodemographic and clinical characteristics of the patients (n=38)

Characteristic	
Age (years)	13.95±2.42
Sex (male/female), n (%)	6 (15.8)/32 (84.2)
BCVA (Snellen decimal)	0.97±0.05
Spherical equivalent, D	-0.09±0.55
IOP, mmHg	15.7±3.1
Daily screen exposure (hours)	5.65±2.31

Values are presented as mean ± standard deviation unless otherwise noted. BCVA: Best corrected visual acuity, D: Diopter, IOP: Intraocular pressure

Additionally, significant improvements in QoL and anxiety, depression, and OCD symptoms were found among children with CVS-related DED following treatment. Pre-treatment scores and post-treatment outcomes are displayed in Table 2 with corresponding p-values. According to the results, a substantial improvement in QoL and a decrease in RCADS-CV subscales were observed.

At the time of the initial examination, daily screen exposure time was not associated with TBUT but was significantly correlated with OSDI score (r=0.401, p=0.025) and Schirmer test results (r=-0.366, p=0.049). Additionally, no significant correlation was detected between screen usage time and psychiatric measures (p>0.05 for all). At the follow-up examination, Schirmer test values were positively correlated with QoL scores (total and emotional functioning domain) and negatively correlated with generalized anxiety, total anxiety, and total internalizing scores. QoL scores were also negatively correlated with anxiety and internalizing scores (Table 3).

Discussion

In this study, we observed a decrease in anxiety and increase in functionality in association with reduced dry eye severity after dry eye treatment. This suggests that CVS-related DED may have detrimental psychosocial effects in pediatric patients that could potentially improve with appropriate DED treatment.

Given the widespread use of digital screens, the age at first exposure to screens is decreasing. Studies have reported digital screen usage rates of up to 92.7% in the pediatric population.[32] The widespread use of digital screens such as computers, tablets, and smartphones has significantly contributed to the spread of CVS-induced DED in children and adolescents.[33,34] A recent

Table 2. Comparison of dry eye test results and psychiatric scale scores before and after treatment for dry eye			
Dry eye tests	**Pre-treatment Mean ± SD**	**Post-treatment Mean ± SD**	**p***
TBUT, s	7.45±3.43	9.92±2.89	**<0.001**
Schirmer test, mm	11.84±6.50	15.66±6.40	**<0.001**
OSDI	45.99±15.47	25.46±13.37	**<0.001**
Scales			
PedsQL			
Physical functioning	72.44±19.28	82.15±14.40	**<0.001**
Emotional functioning	64.86±21.03	73.94±18.16	**0.006**
Social functioning	84.86±21.73	90.13±13.87	**0.04**
School functioning	68.28±18.82	75.65±17.09	**0.003**
Total	72.76±16.94	80.47±12.61	**<0.001**
RCADS-CV			
GAD	49.08±10.97	43.07±11.24	**0.002**
SAD	53.29±11.37	49.36±10.35	**0.03**
PD	57.24±13.07	52.44±10.91	**0.01**
OCD	53.21±11.52	47.78±10.94	**0.004**
SP	48.16±13.10	40.39±10.88	**0.001**
MDD	49.55±14.09	44.47±12.25	**0.003**
Total anxiety	52.94±13.22	45.05±12.25	**0.001**
Total internalizing	52.36±13.58	44.73±12.40	**0.001**

*Paired-samples t-test. Bold values indicate statistical significance (p<0.05). SD: Standard deviation, TBUT: Tear break-up time, OSDI: Ocular surface disease index, PedsQL: Pediatric Quality of Life Inventory, RCADS-CV: Revised Child Anxiety and Depression Scale-Child Version, GAD: Generalized anxiety disorder, SAD: Social anxiety disorder, PD: Panic disorder, OCD: Obsessive-compulsive disorder, SP: Social phobia, MDD: Major depressive disorder

Table 3. Correlations between psychiatric scale scores and Schirmer test						
		Schirmer	**RCADS-anxiety**	**RCADS-internalizing**	**RCADS-GAD**	**PedsQL-total**
RCADS-anxiety	**r** **p**	**-0.32*** **0.045**				
RCADS-internalizing	**r** **p**	-0.30 0.067	**0.99***** **<0.001**			
RCADS-GAD	**r** **p**	**-0.32*** **0043**	**0.89***** **<0.001**	**0.88***** **<0.001**		
PedsQL-total	**r** **p**	**0.38** **0.016**	**-0.48**** **0.002**	**-0.47**** **0.002**	**-0.39*** **0.014**	
PedsQL-emotional functioning	**r** **p**	**0.32*** **0.043**	-0.29 0.075	-0.30 0.066	-0.27 0.092	**0.79***** **<0.001**

Bold values indicate statistical significance (*p<0.05, **p<0.01, ***p<0.001). RCADS: Revised Child Anxiety and Depression Scale-Child Version, PedsQL: Pediatric Quality of Life Inventory, GAD: Generalized anxiety disorder, r: Pearson's correlation coefficient

study exploring the correlations between computer exposure time and dry eye tests, including Schirmer, TBUT, and OSDI, indicated that longer exposure time results in worse dry eye test results.[35] In line with this study, we found significant correlations with digital screen exposure time for OSDI score and Schirmer test results. However, the relationship was not significant for TBUT.

It is well known that DED has a detrimental impact on the patient's daily life. The unpleasant symptoms of dry eye, such as burning, stinging, ocular grittiness, foreign body sensation, blurred vision, and photophobia, could contribute to impaired QoL.[36] In addition to alterations in visual performance and ocular functioning, chronic pain may also play a role in the poor QoL of patients with DED.[8,9,37] Moreover, topical eye drops for DED were found to be associated with improved QoL compared to baseline, as a significant number of patients reported relief from symptoms.[38,39] Consistent with this, our study revealed statistically significant improvements in QoL across all domains at the post-treatment assessment. Furthermore, positive correlations were observed between QoL scores, particularly

emotional functioning and total summary scores, and the results of the Schirmer test. These results suggest that DED symptoms resulting from prolonged digital screen exposure can have detrimental effects on adolescents' QoL, and accurate treatment of CVS-related DED may lead to an increase in QoL for pediatric patients.

Dry eye symptoms can exacerbate or trigger symptoms of anxiety and depression. For instance, ocular pain and discomfort may lead to psychosocial stress, depression, and anxiety.[40,41] Conversely, depression, stress, and anxiety can influence subjective ocular symptoms and pain perception, contributing to the establishment of a cyclic relationship.[42,43,44] Anxiety may also arise from patients' concerns regarding their symptoms and the potential occurrence of DED.[15] Additionally, it has been proposed that individuals with depression may be more susceptible to DED due to elevated levels of proinflammatory cytokines,[45] as well as alterations in neurotransmitters and neuropeptides.[46]

Regarding the depression and anxiety levels of participants in this study, we observed statistically significant reductions in depression, all subtypes of anxiety, and total internalized symptoms following DED treatment compared to baseline scores. This underscores the notable association between the severity of DED and the presence of depression and anxiety symptoms, suggesting that successful management of DED may have a beneficial effect on alleviating symptoms of depression and anxiety.[18] In accordance with this thought, a recent study demonstrated an association between eye drop frequency and depression and anxiety scores, suggesting that topical eye drops potentially play a significant role in the psychosocial status of patients with DED.[19] In the current study, significant associations between the increase in Schirmer test values and the decreases in generalized anxiety and total anxiety scores were also detected. This is also in line with previous research indicating that the severity of DED symptoms impacts depressive symptoms in both younger and older populations.[37,38,39,42] In summary, CVS-related DED may increase depressive symptoms and anxiety levels in pediatric patients, suggesting it has detrimental effects not only on the ocular system but also psychiatric well-being.

Study Limitations

This study has several notable strengths and limitations. Primarily, it fills a crucial void in the existing literature by being the first study to delve into the QoL, depression, and anxiety levels of pediatric patients afflicted with CVS-related DED specifically. The prospective study design also allowed an evaluation of changes over time, thereby bolstering the reliability and credibility of the findings.

Nevertheless, it is imperative to delineate certain limitations inherent in the study. Foremost, the relatively modest sample size may limit the generalizability of the findings and impede the discernment of subtle yet clinically significant differences. To mitigate this limitation, future research endeavors should utilize a longitudinal design and larger cohort to validate and strengthen the conclusions drawn. Additionally, the short follow-up period employed in this study might fail to capture enduring changes in QoL and psychological outcomes. Therefore, conducting investigations with prolonged follow-up is warranted to elucidate the trajectory of these outcomes over time. However, it is pertinent to recognize that CVS-related DED typically does not necessitate protracted treatments, as it commonly resolves rapidly following topical interventions and adherence to recommendations concerning digital screen usage. Furthermore, the abbreviated follow-up period in our study may offer a more accurate depiction of psychological outcomes, given their susceptibility to fluctuations influenced by various social and environmental factors. Another limitation of the present study pertains to the absence of impression cytology within our methodology. Moreover, reliance on self-report measures to assess QoL, anxiety, and depression levels may introduce potential biases such as recall bias or subjective interpretation. To enhance the robustness and validity of the findings, future studies could integrate objective measures or clinical assessments. Additionally, it is conceivable that a notable placebo effect might be at play, potentially confounding the observed results. Lastly, the absence of a control group receiving no treatment for DED due to ethical considerations poses a limitation, as it precludes the ability to discern the specific effects of the intervention. Subsequent research with a more targeted approach toward this aspect are warranted to gain a comprehensive understanding of the associations under investigation.

Conclusion

In conclusion, there is a noticeable dearth of research focusing on the impact of topical treatment on QoL and psychosocial well-being, including anxiety and depression symptoms, in children with CVS-related DED in the available literature. The present study revealed a significant reduction in anxiety levels and improvement in QoL functionality scores following treatment for DED. These findings underscore the notion that pediatric patients with CVS-related DED experience considerable psychosocial effects that might be alleviated through appropriate treatment interventions for DED. Moreover, the study highlights the importance of further research endeavors aimed at elucidating the intricate relationship between psychiatric disorders and dry eye symptoms among children and adolescents afflicted with CVS-related DED. By delving deeper into these associations, future studies can contribute to a more comprehensive understanding of the multifaceted impact of DED on the psychosocial well-being of children and adolescents. Such investigations are crucial for informing tailored interventions and support strategies aimed at ameliorating the psychosocial burden experienced by this vulnerable population.

Ethics

Ethics Committee Approval: The study was approved by the Haseki Training and Research Hospital Ethics Committee (approval number: 55-2022, date: 23.03.2022) and conducted in accordance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all children their parents.

Authorship Contributions

Surgical and Medical Practices: A.M.K., E.Ö., Concept: R.D.T., A.M.K., Design: R.D.T., A.M.K., E.Ö., Data Collection or Processing: R.D.T., A.M.K., E.Ö., Analysis or Interpretation: R.D.T., A.M.K., Literature Search: R.D.T., A.M.K., E.Ö., Writing: R.D.T.

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Original Article

Clinical Outcomes of Enhanced Monofocal (Mono-EDOF) Intraocular Lenses with the Mini-Monovision Technique versus Trifocal Intraocular Lenses: A Comparative Study

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Abstract

Objectives: It was aimed to compare the clinical results of the mini-monovision technique (MMV) with enhanced monofocal intraocular lens (IOL) and trifocal IOL applications and to evaluate the intereye differences in the MMV group.

Materials and Methods: This retrospective observational study evaluated the results of cataract surgeries performed on 48 eyes of 24 patients. Surgeries in Group I were performed for MMV using the RayOne EMV IOL targeting emmetropia in dominant eyes (Group IA) and -0.70 diopter (D) myopia in non-dominant eyes (Group IB), while those in Group II were performed with the AcrySof® IQ PanOptix™ TNFT00 IOL targeting emmetropia. After the surgeries, uncorrected and corrected distance, intermediate, and near distance visual acuities, contrast sensitivity measurements, and defocus curves were determined. Subjective evaluation was made with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The groups were compared statistically.

Results: Postoperative refraction mean spherical equivalent was -0.25±0.22 D, -0.67±0.33 D, and -0.16±0.31 D in the three groups, respectively. A statistical difference was identified in favor of Group IA for uncorrected distance vision and in favor of Group IB for near vision ($p<0.05$). There was no difference in bilateral uncorrected visions in Groups I and II ($p>0.05$). While contrast sensitivity was better in Group I at all spatial frequencies ($p<0.05$), better vision was achieved in the defocus curve at distance in Group IA and at near in Group IB. In the binocular evaluation, it was seen that Groups I and II had similar results. In the subjective evaluation, NEI-VFQ-25 scores were 94.1±4.2/100 in Group I and 91.5±3.0/100 in Group II at 6 months ($p>0.05$). Photic complaints were significantly more common in Group II.

Conclusion: With the MMV technique, it was observed that enhanced monofocal lenses provided better visual acuity at all distances and less dysphotopsia than trifocal lenses, whereas trifocal lenses were better at providing independence from glasses.

Keywords: Presbyopia-correcting intraocular lenses, mini-monovision technique, enhanced monofocal IOLs, mono-EDOF IOLs

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Introduction

Today, cataract surgery has become extensively used to treat both cataract and presbyopia. While cataract was initially treated uneventfully in many aspects with monofocal intraocular lenses (IOLs),[1,2] when it came to the treatment of presbyopia, only partial success could be achieved with the monovision technique.[3] As a result, first bifocal and then trifocal IOLs became widely adopted for the treatment of presbyopia. Trifocal IOLs are reported to provide excellent near, intermediate, and distance visual acuities, allowing a very high rate of spectacle independence. However, it has also been observed that because of significant photic complaints and loss of contrast sensitivity, their areas of indication are limited, especially in relation to patients' lifestyles and concomitant ocular diseases.[4,5,6] Later, the "enhanced depth of focus" (EDOF) group of lenses was introduced to treat presbyopia. However, the first of these were hybrid EDOF IOLs, which combined an increased focal depth with multifocal optical properties, and it was determined that they did not offer adequate correction of presbyopia, while also causing the abovementioned problems of trifocal lenses at nearly the same rate.[7,8] Subsequently, another subgroup of focal depth enhancing lens were developed under the name of "monofocal plus" or "monofocal enhanced". As these lenses utilize spherical aberration (SA) to increase the depth of focus, they can also be called pure EDOF (non-diffractive, non-refractive).[9] Although this group was found to largely eliminate problems such as dysphotopsia and loss of contrast sensitivity, they could not

match the excellence of trifocal lenses in near vision.[10] To eliminate this last problem, it was recommended to use this group of lenses with the "mini-monovision" (MMV) technique, which targets emmetropia in the dominant eye and a myopic offset of -0.25 to -1.00 diopter (D) in the non-dominant eye.[11,12]

As a result, two popular IOL groups and approaches seem to predominate in the current treatment of pseudophakic presbyopia: 1) pure EDOF or enhanced monofocal (mono-EDOF) IOL implantation with the MMV approach, and 2) trifocal IOL implantation with a bilateral emmetropia approach. This study endeavored to compare these two groups. The study has two separate aims; the first is to determine and compare the clinical results obtained with both approaches, and the second is to investigate the MMV method in terms of intereye differences in functionality and reliability.

Materials and Methods

Study Design and Patients

This retrospective observational study included bilateral cataract and clear-lens surgical cases performed by two surgeons (İ.C. and H.A.B.) in two different centers.

The study protocol was approved by the Ethics Committee of Yozgat Bozok University (decision no: 2024-GOKA EK241_241_2024.03.27_12, date: 27.03.2024) and was carried out in accordance with the principles of the Declaration of Helsinki. The surgeries were performed with an interval of 7-21 days between fellow eyes.

All patients included in the study were over 50 years of age and had visual impairment due to cataract or had presbyopic complaints and desired spectacle independence. Patients with severe ocular pathology, uncontrolled diabetes and diabetic retinopathy, age-related macular degeneration, other retinal and macular diseases, uveitis, diseases affecting the pupil, severe dry eye, glaucoma, strabismus, amblyopia, or history of any ocular surgery or trauma were not included in the study. In addition, patients with axial length outside the range of 21.5-26.00 mm and corneal astigmatism greater than 0.75 D were excluded from the study. All patients underwent preoperative macular optical coherence tomography examination with an Optovue RTVue (Optovue, Fremont, CA, USA) device and the presence of retinal disease was ruled out. All included patients were informed about the study and a consent form was obtained.

Two separate groups were formed for the study. Patients in the first group (Group I) received the enhanced monofocal RayOne EMV IOL (Rayner Intraocular Lenses Limited, Worthing, United Kingdom) targeting emmetropia in the dominant eye (Group IA) and -0.70 D of myopia in the non-dominant eye (Group IB). Patients in the second group (Group II) received AcrySof® IQ PanOptix™ TNFT00 (Alcon Laboratories Inc., Fort Worth, TX, USA) IOLs with emmetropia targeted in both eyes. Each group included 24 eyes of 12 patients. Before the operations, detailed eye examinations including monocular and binocular corrected and uncorrected visual acuities, manifest refractions, corneal keratometric values, intraocular pressures, and biometric measurements obtained using the Lenstar LS 900 (Haag-Streit, USA) device were performed in all patients. Dominant and non-dominant eyes were determined. Tear functions were evaluated with the Schirmer and tear film break-up tests. The Barrett-II formula was used for IOL power calculations.

The surgeries were performed following a standard pupil dilatation regimen, under topical anesthesia, using a Centurion Vision System (Alcon Inc., Fort Worth, TX, USA) through a 2.2-mm main incision made on the steep keratometry axis or using a temporal approach. The same surgical phacoemulsification protocol was used in all cases, and all IOLs were placed in the capsule. Postoperatively, the patients received topical moxifloxacin (Vigamox ophthalmic solution, Novartis, Basel, Switzerland) for 1 week and prednisolone for 3 weeks.

Intraocular Lenses

The RayOne EMV is a one-piece hydrophilic acrylic lens with 26% water content. It has an optic diameter of 6.0 mm, total diameter of 12.5 mm, and biconvex optic shape. The refractive index is 1.46 and the Abbe number is 56. It has an aspheric anterior surface and closed-loop anti-vaulting haptics. The lens is implanted using a preloaded injector.

The PanOptix TNFT00 is a one-piece hydrophobic acrylic with an optic diameter of 6.0 mm, total diameter of 13.0 mm, and two open-loop modified L haptics. It has a 4.5-mm central non-apodized diffractive region with 15 diffractive rings and a peripheral refractive region between 4.5 and 6.0 mm. The refractive index is 1.55 and the Abbe number is 37. The lens has negative asphericity of -0.10 µm.

Postoperative Evaluation

The patients were operated between November 2021 and May 2023 and followed up for at least 6 months (mean 12±4.8 months) postoperatively. Examinations were performed at postoperative 1 day, 1 week, and 1, 3, and 6 months. At each examination, manifest refractions were recorded, followed by monocular and binocular corrected and uncorrected distance (4 m), intermediate (66 cm), and near (40 cm) visual acuity measurements made in photopic environment using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart for distance, the Colenbrander mixed contrast card set (Precision Vision, IL, USA) for intermediate, and the Jaeger chart for near. As the charts were designed for use at distances of 35 cm and 63 cm, the logarithm of the minimum angle of resolution (logMAR) values were corrected according to the distances of 40 cm and 66 cm used in this study.[13]

Defocus curves were determined at postoperative 6 months. The procedure was performed under photopic conditions, separately for the dominant and non-dominant eyes and binocularly for patients in Group I and binocularly in Group II, between +2.0 and -4.0 D at a distance of 4 m by adding -0.50 D lenses.

Contrast sensitivity tests were also performed at postoperative 6 months. Measurements were performed under photopic conditions (85 cd/m^2) with and without glare using the CSV-1000 (Vector Vision Co, Ohio, USA) device. Results were obtained at spatial frequencies of 3, 6, 12, and 18 cycles per degree (cpd) and translated to logCS using the table provided by Vector Vision.[14]

Subjective Assessment and Evaluation of Side Effects

The patients' satisfaction with their surgical outcomes was assessed by administering the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) twice, at postoperative 3 and 6 months.[15] This scale consists of questions in 12 domains: general vision, near vision, distance vision, driving, peripheral vision, color vision, ocular pain, general health and vision, role limitations, dependency, social functioning, and mental health. The highest score is 100 and represents an optimal functional state. In this study, patients were asked additional questions about halo (rings around lights), glare (trouble seeing street signs due to bright lights or oncoming headlights), double vision and ghosting, and color vision at 3 and 6 months after their second eye surgery. The patients were shown standard photographs showing examples of photic phenomena. If they answered yes, the type of symptom was noted and patients were asked to rate the extent to which these symptoms affected their daily lives. The act of driving at night was specifically questioned, and patients were also asked about their spectacle independence at near, intermediate, and distance and whether they would recommend the same IOL to family and friends. In addition, patients in the MMV group were asked whether they noticed a difference in vision between eyes in normal daily binocular viewing conditions. Responses to these additional questions were assessed independently of the NEI VFQ-25 questionnaire.

Statistical Analysis

All data were analyzed using SPSS software (version 22.0, IBM Corp., Armonk, NY, USA). Wilcoxon paired-samples test, chi-square test, and Mann-Whitney U tests were used for comparisons between the groups. Results were evaluated with a 95% confidence interval and a p value of <0.05 was considered statistically significant. Affirmative responses to the additional questions in the questionnaire were evaluated by percentage.

Results

A total of 48 eyes of 24 patients with complete follow-up were included in the study. The mean age of the 12 patients in Group I was 65.75 (±9.98) years and that of Group II was 63.25 (±7.46) years. Demographic characteristics and preoperative data of the groups are given in Table 1. There was no statistical difference between the groups.

All operations were performed without complications. The cumulative dissipated energy was 4.20±2.41 seconds in Group I and 4.95±3.05 seconds in Group II, while the mean power of the implanted lenses was 21.2±2.49 D in Group I and 21.1±2.04 D in Group II. There was no difference between the groups in terms of surgical parameters.

Visual Outcomes

Vision and refraction results obtained at postoperative 3 and 6 months were recorded and the most recent values obtained at month 6 were used in the study. Mean spherical equivalent (SE) values were -0.25±0.22 D in Group IA, -0.67±0.33 D in Group IB, and -0.16±0.31 D in Group II. In Group I, comparison of SE values between dominant and non-dominant eyes with the Wilcoxon paired-samples test revealed a statistically significant difference (p=0.022), whereas no significant difference was found between Group IA and Group II (p=0.101). In Group I, only one patient had a myopic outcome of -1.0 D in the non-dominant eye. The mean final visual acuities measured at postoperative 6 months are given in Table 2. Statistical evaluations were performed in the RayOne EMV group between dominant and non-dominant eyes monocularly and between the RayOne EMV group and PanOptix groups binocularly. In Group I, there was a difference between dominant and non-dominant eyes in favor of dominant eyes for uncorrected distance visual acuity and in favor of non-dominant eyes for uncorrected near visual acuity. When refractive errors were corrected in the non-dominant eyes, there was no significant difference between the groups (Table 2).

There were also no differences in any binocular uncorrected visual acuity measurements between the RayOne EMV MMV approach and the binocular PanOptix group measurements (p>0.05).

Comparison of defocus curves in Group I showed that dominant eyes provided better visual acuity between +2.00 and 0.00 D (corresponding to distance vision), while non-dominant eyes had better results between -1.50 and -4.0 D (corresponding to near vision). In binocular measurements, there was marked

Table 1. Demographic characteristics and preoperative and operative data of the patients

Parameter	RayOne EMV group	PanOptix group	p value
Mean age (years)	65.75±9.98	63.25±7.46	0.246*
Sex (female/male)	6/6	6/6	1.000**
Dominant eyes (right/left)	4/8	6/6	0.670**
Mean corrected distance visual acuity (logMAR)	0.12±0.22	0.16±0.31	0.567*
Mean corneal toricity (D)	0.48±0.23	0.43±0.29	0.212*
Mean kappa angle (mm)	0.20±0.22	0.22±0.19	0.809*
Mean axial length (mm)	23.53±1.10	23.22±1.99	0.555*
Mean cumulative dissipated energy (seconds)	4.20±2.41	4.95±3.05	0.460*
Mean implanted IOL power (D)	21.2±2.49	21.1±2.04	0.784*

*Mann-Whitney U test, **Chi-square test, logMAR: Logarithm of the minimum angle of resolution, D: Diopter, IOL: Intraocular lens

improvement in the areas where both subgroups were inadequate (Figure 1A). Although the RayOne EMV and PanOptix had very similar binocular defocus curves, it was noted that results for distance vision were slightly better in the RayOne EMV MMV group, while there was no difference for near and intermediate vision (Figure 1B).

The results of contrast sensitivity measurements are shown in Table 3. There was a significant difference in favor of the RayOne EMV MMV group in both glare and no-glare conditions ($p<0.05$).

Subjective Assessment, Dysphotopsia, and Spectacle Independence

Scores on the VFQ-25 used for subjective assessment were 94.1±4.2 out of 100 in Group I at 6 months (with no difference between 3 and 6 months). In Group II, the scores were 89.9±5.6 at 3 months and 91.5±3.0 at 6 months, which was not a significant difference ($p=0.234$). In addition, when problems such as halo, glare, starburst, and ghosting were described and shown as pictures to the patients, one patient in the RayOne EMV group reported glare in one eye (non-dominant) at 3 and 6 months (4.1%). In the PanOptix group, dysphotopsia was reported in both eyes by 5 patients (41.6%), including halo in 2 patients (16.6%), glare in 2 patients (16.6%), and starburst in 1 patient (8.3%). The patients stated that the severity of these symptoms decreased between 3 and 6 months. When asked whether they would recommend this surgery to their relatives, 100% of patients in both groups answered affirmatively. In terms of spectacle independence, a patient in Group I whose non-dominant eye had -1.0 D myopia expressed noticing an intereye difference in distant vision, especially while watching television. The patient was initially given distance glasses, then underwent corneal refractive surgery at postoperative 4 months, after which the myopia was reduced to -0.50 D and the problem was solved. Another patient with good near vision (J1 level) requested near glasses to read very small writing, and the problem was solved by providing +0.50 D reading glasses. As a result, 2 of the 12 patients were prescribed glasses (one for distant and one for near) and the spectacle independence rate was 83.3%. Group II had 100% spectacle independence.

At the patients' postoperative 6-month follow-up examination, no problems such as IOL tilt and decentration, posterior capsule opacity, or other concomitant ocular problems were encountered in either group.

Table 2. Postoperative visual acuity results (logMAR)

Visual acuities	Group I (RayOne EMV MMV) Monocular			Group I (RayOne EMV MMV) binocular	Group II (PanOptix) binocular	p value**
	Group IA Dominant eyes	Group IB Non-dominant eyes	p value*			
UDVA	0.00±0.03	0.05±0.08	**0.019**	0.00±0.03	0.01±0.10	0.789
UIVA	0.03±0.06	0.01±0.04	0.231	0.00±0.02	0.00±0.11	0.504
UNVA	0.04±0.06	0.01±0.04	**0.045**	0.01±0.02	0.02±0.05	0.231
CDVA	-0.01±0.02	-0.01±0.03	0.713	-0.01±0.03	0.02±0.13	0.546
DCIVA	0.02±0.04	0.01±0.04	0.812	0.00±0.01	0.01±0.11	0.812
DCNVA	0.05±0.06	0.04±0.07	0.433	0.00±0.03	0.00±0.15	0.909

*Comparison of dominant and non-dominant eye VA in the RayOne EMV group; Wilcoxon paired-samples test, **Comparison of binocular VA in RayOne EMV MMV and PanOptix groups; Mann-Whitney U test. logMAR: Logarithm of the minimum angle of resolution, MMV: Mini-monovision, UDVA: Uncorrected distance visual acuity, UIVA: Uncorrected intermediate distance visual acuity, UNVA: Uncorrected near visual acuity, CDVA: Corrected distance visual acuity, DCIVA: Distance-corrected intermediate distance visual acuity, DCNVA: Distance-corrected near visual acuity. Results given as mean and standard deviation. Significant differences are shown in bold

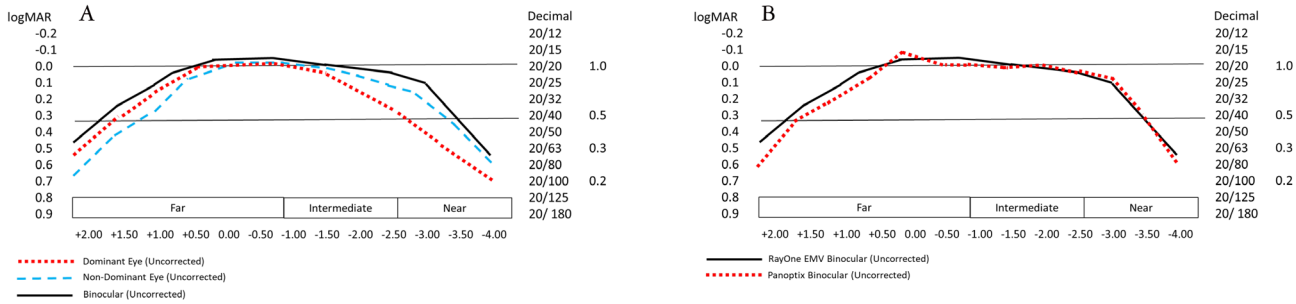

Figure 1. (A) RayOne EMV mini-monovision group: dominant eyes, non-dominant eyes, and binocular average defocus curves. (B) Average binocular defocus curves of the RayOne EMV and PanOptix groups. logMAR: Logarithm of the minimum angle of resolution

Table 3. Contrast sensitivity measurements (logCS)				
Spatial frequencies		**RayOne EMV MMV group**	**PanOptix group**	**p value***
No-glare condition	3 cpd	1.96±0.16	1.77±0.11	**0.045**
	6 cpd	1.99±0.23	1.71±0.56	**0.031**
	12 cpd	1.59±0.15	1.39±0.23	**0.009**
	18 cpd	1.21±0.19	1.01±0.09	**0.013**
Glare condition	3 cpd	1.81±0.15	1.55±0.17	**0.022**
	6 cpd	1.84±0.23	1.59±0.28	**0.017**
	12 cpd	1.41±0.07	1.25±0.19	**0.044**
	18 cpd	1.15±0.20	1.00±0.24	**0.034**
*Mann-Whitney U test, cpd: Cycles per degree. Results given as mean and standard deviation. Significant differences are shown in bold				

Discussion

This study sought to investigate two main issues. The first was to compare the visual outcomes obtained with enhanced monofocal lenses used with the MMV approach with those obtained with trifocal lenses and also determine to what extent enhanced monofocal group lenses provide solutions to common adverse effects of trifocal lenses. The second was to investigate the visual objective and subjective results of the intereye refractive difference created with MMV approach.

Numerous publications and meta-analyses in the literature have shown that trifocal lenses provide uncorrected visual acuities that can be considered perfect for near, intermediate, and far distances.[4,5,16,17] These publications report a mean binocular uncorrected distance visual acuity between -0.02 and 0.00 logMAR, binocular uncorrected intermediate distance visual acuity (80 cm) between 0.00 and 0.11, and binocular uncorrected near visual acuity (40 cm) between 0.00 and 0.18, and although different results were reported for spectacle independence, the results were close to 100%. However, we also see that dysphotopsia rates are reported at very high rates in the same studies. For example, in a study by Kohnen et al.[4] with PanOptix trifocal lenses, dysphotopsia was reported in 93% of the cases (89% halo, 11% glare, 7% double vision, 4% ghosting, and 4% distorted vision). In a meta-analysis published by Mencucci et al.[5], a high prevalence of halo (70%) and glare (50%) was seen with trifocal lenses. Loss of contrast sensitivity is another important problem with trifocal lenses. Rosen et al.[18] determined that significant contrast reduction with multifocal lenses was reported in two-thirds of the 195 studies examined in their meta-analysis. Again, Mencucci's et al.[5] study with two separate trifocal lenses reports a significant decrease from normal values, more prominently at higher spatial frequencies (18 cpd).

When the causes of dissatisfaction with multifocal lenses were investigated, dysphotopsia was identified as the second most important cause after blurred vision.[19,20] In addition, dysphotopsia was found to be the second most important cause after loss of contrast sensitivity among the reasons for surgical IOL exchange.[21] These two important adverse effects, as well as the limited indication areas in major ocular comorbidities, have led to research beyond trifocal lenses despite their excellent visual results. The first alternative developed was EDOF group lenses that combined refractive or diffractive optical properties and would later be called hybrid EDOF,[9] but these lenses were found to cause dysphotopsia and contrast loss to almost the same degree as trifocal lenses and yet could not match their performance for near vision.[7,22,23] Following the emergence of many lenses claiming to be EDOF in the market, the American Academy Task Force Consensus reports proposed four standard criteria delineating the definition of EDOF.[24,25] Thus, although the aim was to differentiate EDOF lenses from monofocal lenses, meeting the American National Standard Institute (ANSI)-III criterion in particular (median distance corrected monocular intermediate distance [66 cm] visual acuity should be at least 0.2 logMAR) is not possible without a very large comparative study. Therefore, many lenses that provide a substantial focal depth do not qualify as EDOF and are classified as enhanced monofocal or monofocal plus. New approaches have been proposed in response to this insufficiency and confusion, leading to the separate classification of hybrid EDOF lenses (refractive or diffractive EDOF lenses) and pure EDOF lenses (pinhole or SA-based). Here, according to the definitions of Kanclerz et al.[9], if the lens uses chromatic aberration, has diffractive physical properties, or is refractive and uses additional dioptric power to increase near vision, it is not pure EDOF. In a new classification published later, we see that non-diffractive lenses that increase the depth of focus through modifications to the central zone that provide a change from center to periphery are collected in the same group (type 5 in the publication), and depth of focus is mainly achieved with the addition of SA in this group.[26]

Although these lenses were classified as enhanced monofocal after the ANSI criteria, we think it would be appropriate to call them "non-diffractive/non-refractive EDOF", considering that the group does not contain multifocal optical properties and provides significant focal depth, and the ANSI criteria should be revised to define the enhanced monofocal groups. It would at least be more accurate to classify the enhanced monofocal group as a subgroup under EDOF lenses, because the current nomenclature ignores the increase in focal depth provided by this group of lenses. In many publications we also see the use of the term "mono-EDOF" for this group of lenses.[27,28]

In our opinion, the Ray-One EMV lens, which meets three of the four ANSI criteria, can also be referred to as non-diffractive EDOF until the ANSI standards are reconsidered or standard definitions are introduced for the enhanced monofocal lens group, as the monocular focal depth of the lens is reported as 1.49 D and 2.25 D in MMV (with -1.0 D offset in the non-dominant eye).[27,28,29] Nevertheless, in the present study, the Ray-One EMV lens is referred to as enhanced monofocal or mono-EDOF.

The RayOne EMV IOL, as a non-diffractive, positive SA-based lens, is considered as a solution to the known problems of trifocal lenses along with other predominantly negative SA IOLs in the same group, such as Eyehance, Vivity, and LuxSmart.

In studies targeting emmetropia in both eyes, excellent results were obtained in the range of -0.01 to 0.00 logMAR at distance and intermediate distance with the enhanced monofocal or mono-EDOF lenses Eyehance, Vivity, and RayOne EMV. Additionally, near vision that can be considered successful and satisfactory at the level of 0.1 logMAR at -2.0 D on the defocus curve was achieved with Vivity and RayOne EMV lenses, whereas this value was unsatisfactory with the Eyehance lens (0.4 logMAR).[10] However, in Kohnen's et al.[4] PanOptix studies, near vision (40 cm) was excellent at 0.00 logMAR at -2.0 D. In short, although enhanced monofocal lenses provide very good and satisfactory results in near vision, they do not achieve the same level of excellence as trifocal lenses. In the same study, it was noted that the proportion of cases without halo or glare was 95%-100% in the enhanced monofocal non-diffractive lens groups, while the contrast sensitivity results were nearly the same as in the monofocal lens group.

Hovanesian et al.[8] reported that 69% of the patients in the PanOptix group and 85% in the Vivity group reported no or minimal halo and glare, and this difference was significant. In the same study, the rate of complete spectacle independence was 83% in the PanOptix group but only 33% in the Vivity group, which was a highly significant statistical difference ($p<0.0001$). There was also a significant difference in patient satisfaction results, with 85% of patients in the PanOptix group and 57% in the Vivity group stating they were very satisfied.

In a study conducted by Asena et al.[30] targeting bilateral emmetropia, the visual difference in the PanOptix /Vivity comparison was in favor of mono-EDOF at distance and the trifocal lens at near. In that study, better near vision in the trifocal lens group despite postoperative SE results of -0.60 D in the Vivity group and -0.09 D in the PanOptix group indicates the superiority of the trifocal lens in this area, while to the contrary, the better distance vision in the mono-EDOF group may be a result of the superior contrast provided by non-diffractive lenses. In this context, the MMV approach emerges as a solution by targeting -0.25 to -1.00 D myopia to the non-dominant eye to ensure excellent outcomes despite the residual near visual acuity problem with enhanced monofocal lenses.

In our study, evaluation of the binocular uncorrected visual outcomes obtained using the RayOne EMV IOL with MMV targeting -0.70 D in the non-dominant eye shows that the results obtained (0.00±0.03 logMAR at distance, 0.00±0.02 logMAR at intermediate, and 0.01±0.02 logMAR at near) did not differ statistically from the visual results achieved in the PanOptix trifocal group ($p>0.05$). In addition, we observed that 95.9% of patients in the MMV group did not experience dysphotopsia, and contrast sensitivity results in glare and no-glare conditions were significantly better than in the PanOptix group (Table 3).

It is seen that the MMV approach provides a significant benefit, especially in the enhanced monofocal groups that we refer to as non-diffractive mono-EDOF. For example, Park et al.[11] investigated the differences between emmetropia and MMV groups using the Eyehance IOL, with -0.75 D targeted for non-dominant eyes in the MMV group, and reported that binocular UCVA increased from 0.33±0.13 logMAR to 0.06±0.06 logMAR, spectacle dependence for near vision decreased from 80% to 20%, and there was no difference between the groups in terms of dysphotopsia. In another study, Solomon et al.[12] compared emmetropia and MMV groups using the Vivity lens and reported a postoperative mean SE of -0.45 D in the MMV group and 0.01 D in the emmetropia group. Near visual acuity was 0.39 logMAR in the emmetropia group and 0.21 logMAR in the MMV group. The difference was significant ($p<0.001$). There was again no difference in dysphotopsia between the groups.

Our study corroborates previous studies in the literature conducted with other monofocal plus or mono-EDOF lenses, and to our knowledge, there is no other publication in the literature on the MMV method with RayOne EMV lenses.

At the same time, our study shows that spectacle independence reached 83.3% with the MMV approach. This is still below the 100% figure achieved with PanOptix. As a result, in the comparison of trifocal lenses and MMV using enhanced monofocal lenses, which was one of the two main objectives of our study, we can say that trifocal lenses are still superior in functional areas such as spectacle independence, whereas the use of mono-EDOF lenses with the MMV approach is superior in terms of avoiding adverse effects, providing patient satisfaction, and preventing possible unhappiness.

The second important issue is the problems that may be encountered with MMV. For example, there is a case report in the literature in which lens exchange was required due to patient intolerance after implementing MMV with Vivity lenses despite having only -0.50 D myopia in the non-dominant eye.[31] This is one of the reasons why dominant and non-dominant eyes were examined separately and compared in our study. Accordingly, uncorrected visual acuities in the dominant and non-dominant eyes respectively were 0.00±0.03 and 0.05±0.08 logMAR for distance ($p<0.05$), 0.03±0.06 and 0.01±0.04 logMAR for intermediate ($p>0.05$), and 0.04±0.06 and 0.01±0.04 logMAR for near ($p<0.05$). Thus, there was a significant difference in favor of the dominant eye for distance and the non-dominant eye for near vision. The mean SE obtained in the non-dominant eyes of our patients was -0.67±0.33 D. When the patients were asked whether they noticed an intereye difference in the postoperative questionnaire, only 1 of the 12 patients (who had postoperative refraction of -1.00 D in the non-dominant eye) said they noticed

a difference between the eyes and was uncomfortable. One of the important considerations when applying the MMV method is how much myopia should be targeted in the non-dominant eye. For example, a study conducted by van Amelsfort et al.[32] using Vivity lenses showed that when -0.25 D was targeted in the non-dominant eye and a postoperative mean SE of -0.13 D was obtained, binocular near vision remained at the level of 0.23 logMAR. As a result, we can say that setting a myopic target of at least -0.50 D for the non-dominant eye is effective in improving binocular near vision, and we found that the intereye difference was not perceived by patients, did not cause subjective complaints, and did not require glasses unless it exceeded -1.00 D.

Study Limitations

The limiting aspects of our study can be considered the small number of patients and its basis on subjective questionnaires for dysphotopsia assessment instead of more quantitative methods such as a halometer.

Conclusion

Enhanced monofocal (mono-EDOF) lenses implanted using the MMV approach largely eliminated dysphotopsia and severe contrast sensitivity reduction, which are important potential problems of trifocal lenses, and the MMV method provides a solution to the issue of these lenses being less effective than trifocals in near vision when emmetropia is targeted.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Yozgat Bozok University (decision no: 2024-GOKAEK241_241_2024.03.27_12, date: 27.03.2024) and was carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

Treatment of Behçet Uveitis in Türkiye

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Abstract

Objectives: Behçet uveitis (BU) is a potentially blinding disorder. The main determinant of visual prognosis is early and appropriate treatment that provides rapid suppression of inflammatory attacks, control of subclinical inflammation, and prevention of new attacks. Our study aimed to determine the Turkish uveitis specialists' approach regarding the treatment choices and management of special situations such as pregnancy, vaccination, and surgical planning in BU patients, and to increase information sharing and raise awareness of issues where knowledge is lacking.

Materials and Methods: A web-based survey including 16 questions about the treatment approach in ocular involvement of Behçet's disease was sent via e-mail to uveitis specialists in Türkiye. Based on the answers of 49 ophthalmologists who responded to the survey, we evaluated the approaches of uveitis specialists in our country to initiating treatment, selecting therapeutic agents, monitoring, switching and stopping treatment, and special situations such as surgical planning, vaccination, and pregnancy in BU patients.

Results: Uveitis specialists in our country mostly act in accordance with the guidelines in the decision to start treatment, selection of therapeutic agents, and monitoring the safety of treatment in BU. However, there is a lack of information about the therapeutic approach in pregnancy and vaccination practices. It was also observed that there is no consensus on the precautions to be taken before cataract surgery.

Conclusion: Our study has shown that there is a need for more detailed and widespread information sharing on treatment in preparation for ocular surgery, safety monitoring, drug use during pregnancy, and vaccination in BU patients.

Keywords: Behçet syndrome, uveitis, therapeutics, vaccination, pregnancy

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Introduction

Behçet's disease (BD) is a systemic vasculitis of unknown etiology characterized by chronic and recurrent oral aphthous ulcers, genital ulcers, skin lesions, and ocular, gastrointestinal, and central nervous system involvement. Ocular involvement is the most common organ involvement of the disease.[1,2,3,4] Epidemiologically, a multicenter national database study conducted in our country revealed that Behçet uveitis (BU) is the most common non-infectious cause of uveitis, with a rate of 25%.[5] Ocular involvement is characterized by non-granulomatous panuveitis attacks and retinal vasculitis. Attack frequency and severity vary among individuals and are the main determinant of visual prognosis.[1,2,3,4,6,7]

Fluorescein angiography (FA) is the gold standard for the early detection and evaluation of BU-related posterior segment involvement. The presence of optic disc (OD) leakage, macular edema, vasculitis-related leakage and occlusion, ischemia, and neovascularization are decisive in the choice of treatment. Appropriate treatment is critical to prevent future complications related to ocular involvement of BD. The aim of treatment in BU is to rapidly suppress intraocular inflammation, prevent relapses, and achieve clinical and angiographic remission. In treatment, systemic corticosteroids (CS) should be used short-term in the acute period to rapidly control inflammation. The use of CS long-term or as monotherapy has no place in current BU treatment. The efficacy of conventional immunosuppressive (CIS) drugs and biologic agents has been demonstrated by clinical trials. The use of these agents varies according to disease course and attack

severity, and is the most important determining factor for visual prognosis.[1,2,3,4,6,8]

We conducted a web-based survey study to evaluate treatment approaches to BU patients among ophthalmologists following uveitis patients in our country.

Materials and Methods

A survey consisting of 16 multiple-choice questions was prepared by the executive board of the Uvea-Behçet Division of the Turkish Ophthalmological Association (TOA). Via the TOA, this survey was sent by email in March 2023 to ophthalmologists actively following uveitis patients and they were asked to respond online. The 16 questions in the survey included 6 questions evaluating treatment preferences in different clinical presentations of BU, 4 questions about and tests to be ordered and precautions to be taken before initiating anti-tumor necrosis factor-alpha (TNF-α) agents and CIS treatment, 1 question about vaccination while using anti-TNF-α agents, 3 questions about drug selection before and during pregnancy, 1 question evaluating the steps of treatment discontinuation in BU patients, and 1 question evaluating pre-cataract surgery planning in BU patients. The survey questions and the participants' responses can be found in the Appendix 1.

We evaluated the distribution of the participants' responses to each question to determine the approaches of uveitis specialists in our country to the treatment of BU.

Results

A total of 62 ophthalmologists were invited to participate in the survey, and responses were received from 49 (79%). Based on the distribution of their responses to the survey questions (see appendix), we determined the following:

For patients presenting with a first ocular attack without vitreous haze but with OD staining with or without peripheral retinal capillary leakage on FA, azathioprine (AZA) was the most preferred therapeutic agent, and in cases with peripheral leakage, adding oral CS to treatment was preferred. However, in cases of diffuse FA leakage, intravenous (iv) pulse CS was most commonly preferred (39%), and the combination of adalimumab (ADA) + AZA was the most preferred additional treatment to iv pulse steroid (25%).

In a patient with OD staining and peripheral retinal capillary leakage detected on routine follow-up FA while under AZA therapy, the most preferred treatment options were adding ADA (53%) or cyclosporine-A (CSA) (31%).

In a patient with a panuveitis attack and diffuse capillary leakage on FA while under combined AZA + CSA therapy, the most frequently preferred approach was to start iv pulse CS and anti-TNF-α therapy with ADA or infliximab (IFX) (71%). In addition, 24% of the specialists preferred adding an anti-TNF-α agent without CS, so the total rate of anti-TNF-α preference for such cases was 95%.

The leading approach to a patient who developed a posterior uveitis attack while under ADA therapy at the standard dose (40 mg injection at 2-week intervals) was to switch to weekly ADA administration (69%). Only 12% of the specialists preferred to switch the anti-TNF-α agent.

In terms of routine laboratory examinations before the initiation of immunosuppressive therapy, the examinations selected by the participants were complete blood count (100%), liver and kidney function tests (100%), hepatitis markers and human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA) (88%), QuantiFERON test (QFT) (73%), syphilis serology (67%), and brain magnetic resonance imaging (MRI) (4%). For patients to be started on anti-TNF-α, QFT was selected by all participants (100%) and brain MRI was selected by 31% of the participants. While the majority of the participants (69%) responded that anti-TNF-α safety monitoring should be performed at 3-month intervals, 31% selected the option to be perform it at 6-month intervals.

For patients with an indication for anti-TNF-α therapy but positive QFT and exclusion of active tuberculosis, 96% of the participants preferred to start anti-TNF-α with isoniazid prophylaxis.

The majority of the participants stated that tetanus, coronavirus disease 2019, hepatitis, and pneumococcal vaccines could be administered while under biologic therapy. The live vaccine options were also selected by 10-14% of the participants.

Regarding the treatment approach during pregnancy, the most preferred options for patients with a unilateral posterior uveitis attack were intravitreal dexamethasone implantation and ADA therapy. A quarter of the participants selected certolizumab pegol for patients who had an attack after week 20 of pregnancy. For a patient planning to become pregnant, more than 70% of the participants preferred to discontinue AZA and CSA therapy 3 months in advance, but would continue ADA therapy.

The most important factor in the decision to reduce systemic therapy was the absence of OD staining and retinal vascular/capillary leakage on FA, which was selected by 86% of the participants.

For a patient under combined anti-TNF-α and CIS therapy, 43% of the participants preferred to add oral CS before elective cataract surgery, 31% considered it sufficient to start topical CS, and 23% would make no change to treatment.

Discussion

This study reveals the approaches taken in the treatment of BU by Turkish ophthalmologists actively following uveitis patients. We observed that the respondents initiated immunomodulatory therapy in patients with posterior segment involvement. AZA was the first-choice immunosuppressive agent for mild involvement, while ADA was preferred as the anti-TNF-α agent in cases of more severe involvement or non-response to CIS therapy, and increasing the frequency of ADA administration was preferred in case of non-response to the standard ADA regimen. It was understood that most of the specialists adhered to national guidelines regarding preparation for and safety monitoring of biologic therapy.

Due to the high incidence of BD-related uveitis in Türkiye and the potential risk of blindness, it is important that the treatment approaches of ophthalmologists who actively follow uveitis patients in our country are standard and adhere to current guidelines and the official Health Practices Communique. In 2018, the European League Against Rheumatism (EULAR) published updated evidence-based recommendations for the management and treatment of BD.[9] According to these recommendations, AZA, CSA, interferon alpha, or monoclonal anti-TNF-α antibody therapy should be initiated in all Behçet's patients with involvement of the posterior segment of the eye. Systemic CS should only be used in combination with AZA or other immunosuppressive drugs. An acute, vision-threatening uveitis attack should be treated with high-dose CS, IFX, or interferon alpha, and in unilateral attacks, intravitreal bolus CS injection should only be administered in addition to systemic therapy.[9] According to an expert committee of the American Uveitis Society, monoclonal anti-TNF-α agents should be used as the first choice in the treatment of BU.[10] Interferon alpha was used in the treatment of BU in Türkiye in the 2000s, and publications reported successful results in the treatment of refractory BU.[11,12,13,14,15,16] However, it is no longer used since being withdrawn from the market in 2020. Therefore, interferon was not included as an option in the survey questions.

Monoclonal anti-TNF agents were introduced in the 2000s,[17] but until recently they were used as an off-label treatment regimen in patients who were unresponsive or intolerant to CIS and interferon therapy. In Türkiye, ADA has been licensed for use in the treatment of non-infectious uveitis involving the posterior segment, including BU, since December 2018. The licensed use of ADA may have played a role in its high selection rate in the survey responses.

Recognizing posterior segment involvement is of prognostic significance in BU. FA is considered the gold standard in the detection and monitoring of posterior segment inflammation in BU.[3,18] It is known that posterior segment involvement can be detected by FA in patients with no clinical signs of intraocular inflammation.[19] OD staining and fern-like retinal capillary leakage are the most common FA findings of BU.[1,2,3,4] In their FA study, Keorochana et al.[20] reported OD hyperfluorescence at a rate of 73% and diffuse vascular leakage in most eyes of patients with BU. In another study by Mamdouh et al.[21], subclinical uveitis activity was detected with FA in 52.1% of 23 eyes with inactive BU. Kabaalioglu Guner et al.[22] showed in their recent study including 162 eyes that 90 of them were clinically inactive but considered active according to FA findings. In a clinically quiet eye between attacks, OD staining and retinal capillary leakage observed on FA are the main signs of persistent subclinical inflammation. This suggests that systemic treatment is indicated or that the current systemic treatment is inadequate.[1,2,3,4,13,14,15] Therefore, these FA findings were specifically included in the survey questions.

It is noteworthy that in the evaluation of the respondents' treatment preferences in three different case scenarios presenting without clinically significant posterior segment involvement but with subclinical involvement on FA, treatment was selected according to the FA findings. AZA is still used as the first choice in cases with relatively mild involvement because its efficacy in the treatment of BD was demonstrated in a randomized controlled trial, and patients who start AZA early are known to have a better visual prognosis in long-term follow-up.[23,24] On the other hand, combined immunosuppressive or anti-TNF-α treatment regimens are selected in patients presenting with diffuse capillary leakage on FA or in patients with peripheral leakage while receiving AZA therapy. In case of attacks involving the posterior segment and diffuse leakage while under combined immunosuppressive therapy, administering iv pulse CS and starting an anti-TNF-α agent are most preferred. Markomichelakis et al.[25] reported that in the treatment of BU attacks, a more rapid effect was obtained with a single IFX infusion compared to intravitreal triamcinolone acetonide or iv pulse CS administration. However, Turkish specialists still prefer iv pulse CS for the treatment of attacks in patients planned to start anti-TNF-α therapy. In clinical practice, the fact that tests must be performed before initiating anti-TNF-α and obtaining the results takes a few days may also play a role in this preference. The participants' answers suggest that they consider the need for rapid and strong suppression of the BU attack. Nearly all (95%) of the specialists who participated in this study preferred to start anti-TNF-α in a BU patient with severe involvement, especially if observed to be resistant to conventional treatment. This approach is consistent with literature data demonstrating the efficacy of both IFX and ADA therapy in patients resistant to conventional drugs.[17,26,27,28,29,30]

If an attack is observed while using an anti-TNF-α agent, the agent should be switched to another anti-TNF or its dose and frequency should be adjusted.[31,32,33,34,35] In our survey, the most preferred approach to a patient who has an attack during standard-dose ADA therapy was to increase the frequency of ADA administration. It has been reported that increasing the ADA dose via weekly injections may be sufficient to control inflammation in cases of non-infectious uveitis or scleritis after primary or secondary failure of biweekly ADA therapy.[35,36]

Before initiating treatment with CIS or biologic agents, all patients should be evaluated in terms of complete blood count, liver and kidney function tests, systemic comorbidities such as hepatitis and tuberculosis, history of malignancy, pregnancy/breastfeeding, and immunization history.[4,37] The adverse effects of CIS drugs include myelosuppression and hepatonephrotoxicity.[37] The majority of specialists in our study seem to perform examinations in accordance with standard norms.

Anti-TNF-α drugs also have potential adverse effects such as causing demyelinating disease, predisposing to infection (tuberculosis, hepatitis B-C, and HIV), inducing autoantibody production, and increasing the risk of malignancy.[6,31,34,37,38,39,40,41,42,43] In a study evaluating the results of IFX therapy in patients with BU, Ohno et al.[39] reported a 0.3% rate of tuberculosis and less than 1% prevalence of lupus-like syndrome, demyelinating disease, and malignancies during the 2-year study period. In our country, the use of anti-TNF-α

is reported to increase the risk of tuberculosis by 10-20 times.[43] In ophthalmology practice, the QFT screening test is frequently used in the evaluation of tuberculosis. All participants in our study marked the QFT for the systemic examination to be performed before anti-TNF-α therapy. The risk of demyelinating disease is evaluated by brain MRI. In our study, approximately one-third of the specialists selected the brain MRI option. This rate may be related to the lack of routine MRI for neuro-BD in asymptomatic Behçet patients. However, screening for demyelinating disease is imperative in patients with idiopathic intermediate uveitis before starting anti-TNF-α therapy. It is interesting that a small number of specialists selected HLA-B51 and pathergy tests among the systemic evaluation options in our study, because it is known that HLA-B51 positivity has no place in the uveitis diagnosis algorithm or treatment selection, and the pathergy test is not a determinant of treatment in the pre-treatment evaluation.[6,7]

The regulation on the safety of anti-TNF drugs provides a "Drug Safety Monitoring Form" and specifies that monitoring with this form is required at 3-month intervals. In response to the question in our survey regarding how often this follow-up form should be repeated, 69.4% of the participants answered 3 months and 30.6% answered 6 months.

According to the algorithms in the national guideline for tuberculosis diagnosis and treatment, for patients planned to start anti-TNF-α who have positive QFT results and no active tuberculosis infection, it is recommended to initiate prophylactic isoniazid therapy and continue for 9 months, while starting combined anti-tuberculosis therapy is not recommended.[43] Consistent with this, 96% of the participants stated that anti-TNF-α treatment could be initiated with isoniazid in a patient with positive QFT but no active tuberculosis.

In patients receiving anti-TNF-α, non-live vaccines can be administered without needing to discontinue treatment. In addition, if the clinical picture is suitable, performing vaccination after interrupting ongoing immunosuppressive therapy long enough for the pharmacokinetic elimination of the drug increases the efficacy of the vaccine. It is not recommended to administer live vaccines (BCG, measles/mumps/rubella, varicella, oral polio, yellow fever, rotavirus) during anti-TNF-α therapy. When a live vaccine is necessary for a patient receiving immunosuppressive therapy, the benefits should outweigh the possible risks and treatment should be interrupted taking into account the duration of the microbe and the half-life of the drug, with the live vaccine administered after an appropriate time interval.[44,45,46] The fact that up to 14% of the participants in our study marked live vaccine options when asked which vaccines they prefer to administer without interruption of biologic therapy suggests that there is a lack of knowledge on this subject.

The use and management of CIS or anti-TNF-α drugs before and during pregnancy differ. Data on this subject are limited. The EULAR recommendations on the use of anti-rheumatic drugs in pregnancy advise carefully weighing the risk of harm to the fetus with treatment against the harm to mother and fetus without treatment, as well as involving other relevant branches such as rheumatology and gynecology in the treatment decision and obtaining the mother's informed consent. AZA, CSA, and tacrolimus are among the few agents that can be used for maintenance or attack suppression during pregnancy.[47] The 2020 American College of Rheumatology (ACR) guideline states that AZA is the safest CIS drug that patients with rheumatism and musculoskeletal system can use during pregnancy, while CSA and tacrolimus are recommended conditionally.[48] In both the EULAR and ACR recommendations, methotrexate, mycophenolate mofetil, leflunomide, and cyclophosphamide are listed as CIS agents that should not be used.[47,48] Guidelines on the use of anti-TNF-α in pregnancy indicate that ADA, IFX, and golimumab can be used in the first trimester, and certolizumab pegol can be used throughout pregnancy.[47,48,49,50] Certolizumab pegol, a monoclonal fragment antigen-binding "Fab" region antibody fragment, is the safest anti-TNF-α agent to use during pregnancy as it cannot cross the placenta due to its lack of the Fc segment.[47,48,49,50] In addition, intravitreal CS injections can be used as an adjunct agent during pregnancy, in unilateral cases, and in the presence of refractory macular edema.[6,51,52,53] In our study, intravitreal dexamethasone implant (51%) and ADA (32.6%) were the most preferred treatment preferences for a Behçet's patient in the first 20 weeks of pregnancy with bilateral ocular involvement but presenting with a unilateral uveitis attack, while intravitreal dexamethasone implant (34.7%), ADA (34.7%), and certolizumab pegol (25%) were selected for such patients at 21 weeks of pregnancy or later. These results suggest that further information is needed on the safety of certolizumab pegol in pregnancy. The most accurate and reliable approach is to schedule drug use in advance for patients planning to conceive. Guidelines recommend becoming pregnant during a period of rheumatological disease inactivity. In patients using AZA and CSA, discontinuing treatment is recommended 3 months before pregnancy planning. Discontinuing ADA and IFX is not recommended according to the guidelines.[47,48,49,50] While most participants did not consider it necessary to discontinue ADA therapy, they stated that they would discontinue AZA and CSA treatment 3 months in advance.

In BU patients, a relationship between FA findings and visual prognosis and increased risk of recurrent uveitis attacks in the presence of persistent angiographic leakage have been demonstrated.[20,54] Clinical remission is not sufficient in the decision to terminate treatment. Remission is said to be complete if a "dry angiogram" is obtained; i.e., there is no staining of the OD or retinal vascular/capillary leakage on FA.[4,8,55] The high selection rate of the angiographic remission condition in the survey question about the decision to terminate treatment indicates that the specialists take the right approach in this regard.

Cataract development is one of the most common complications seen in BU, reported at rates of 31-77% in large series.[56,57,58,59] When planning cataract surgery in Behçet's patients, issues of concern are the possibility that visual acuity may not increase in eyes with permanent structural damage in the posterior segment, and the risk of developing severe

postoperative inflammation and triggering a uveitis attack. It has been reported that Behçet's patients have good cataract surgery outcomes, provided that preoperative inflammation is well controlled.[60,61,62,63,64,65] A meta-analysis study examining the results of uveitic cataract surgery indicated that visual results were worse in eyes with active inflammation during surgery and highlighted the importance of controlling inflammation for more than 2 months preoperatively.[66] Matsuo et al.[63] reported that a history of uveitis attack within 1 year preoperatively in Behçet's patients was associated with risk of postoperative attacks, so the disease should be inactive for at least 6 months preoperatively. The questions in our survey provided no specific information about preoperative attack history or duration of remission; only the preoperative prophylaxis approach was questioned for a patient who was in remission under combined biologic and immunosuppressive treatment regimen and not receiving CS. Although several studies have reported the use of perioperative iv, oral, topical, or intravitreal CS in uveitic cataract surgery, there is no standard prophylaxis protocol.[67,68] It is reported to be safe to perform cataract surgery within one week after the last IFX infusion in Behçet's patients who are in remission under the IFX treatment regimen, with no need for another prophylactic approach.[60,61] In our study, 22% of the participants did not consider any prophylaxis necessary in a patient receiving anti-TNF-α and immunosuppressive therapy, while 43% deemed it necessary to initiate oral steroids and 31% topical steroids. These results show that there is no standard approach.

Study Limitations

One of the most important limitations of our study is that the ophthalmologists participating in the survey were of different seniority, so their experiences with uveitis differed. Another limitation is that the clinical vignettes created for the survey do not include all possible scenarios. Furthermore, the survey questions were multiple-choice, and the respondents were not given the opportunity to give different answers. Therefore, the results obtained may not represent a general approach.

Conclusion

The management and treatment of BU pose serious challenges due to the different clinical aspects. Despite the rapid development of new imaging methods in recent years, FA remains the gold standard in the diagnosis, treatment selection, and follow-up of the disease. Treatment options should be determined according to the patient's general health status and the severity of their clinical findings. Although previously our goal in treatment was to suppress attacks and provide clinical remission, thanks to current biologic agents, our goal is now to prevent attacks by suppressing subclinical inflammation and to achieve a permanent remission in which vision is preserved. Whether clinical or subclinical, posterior segment involvement is an absolute indication for the initiation of immunosuppressive therapy in BU. The visual prognosis can be markedly improved by starting directly with biologic agents in severe cases, switching to biologics in cases unresponsive to CIS agents, changing biologic agents when necessary, and waiting for a period of uveitis inactivity for all surgical procedures except emergencies. Determining the treatment approaches of Turkish uveitis specialists will make it possible to increase their awareness about the early initiation of biologic agents in BU and to share the knowledge and experience that will enable better management of BU patients. This study showed that more detailed and widespread information sharing is needed on the topics of CIS and anti-TNF-α therapy preparation, safety monitoring, drug use during pregnancy, vaccination, and surgery in BU.

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Ethics

Ethics Committee Approval: Not necessary.

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Authorship Contributions

Concept: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Design: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Data Collection or Processing: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Analysis or Interpretation: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Literature Search: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Writing: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y.

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Original Article

Emotional State Evaluation of Retinitis Pigmentosa Patients with the Beck Depression Inventory

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Abstract

Objectives: To evaluate the incidence and severity of depression in patients with retinitis pigmentosa (RP).

Materials and Methods: The Beck Depression Inventory (BDI) was administered to 74 patients with RP and 60 healthy controls. Biomicroscopic anterior segment and fundus examination, visual field, optical coherence tomography, and full-field electroretinography tests were performed in all cases. Variables were evaluated with bivariate, multiple linear, and ordinal logistic regression analyses.

Results: The RP group included 40 (54%) male and 34 (46%) female patients, while the control group included 23 (38%) male and 37 (62%) female subjects. The patient group had a mean age of 39.20±12.4 years, median best corrected visual acuity (BCVA) of 0.10 decimal (1.0 logarithm of the minimum angle of resolution [logMAR]; range, 1.3-0.7 logMAR), and median visual field mean deviation (MD) score of -28.00 decibels (dB) (range, -1.00 to -34.00 dB). The median BDI score was statistically significantly higher in the patient group (19 points) than in the control group (12 points) ($p<0.001$). Moderate to severe depression (BDI ≥20) was detected in 61% of patients, while this rate was 25% in healthy controls. BCVA and visual field MD values were identified as predictors of depression score and severity level. The patients' age and gender did not affect total depression score or severity.

Conclusion: The prevalence and severity of depression were found to be higher in RP patients than in healthy controls. There was a significant relationship between the patient's functional vision tests and the frequency and severity of depression. Depression reduces the reliability of visual function tests and impairs patients' quality of life. Therefore, assessing mental health as well as functional tests is important in patients with RP.

Keywords: Retinitis pigmentosa, depression, Beck Depression Inventory

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Introduction

Retinitis pigmentosa (RP) is a group of hereditary and progressive degenerative retinal diseases that first affect rods and later cone cells. The disease causes symptoms such as reduced night vision, impaired dark adaptation, and narrowing of the peripheral visual field. In advanced cases, decreased central vision and complete vision loss may occur.[1,2]

The lack of treatment for the disease, its chronic course, and potential to progress to blindness can lead to adverse psychological effects in patients and their families.[3] The deterioration in visual function along with the concomitant mood disorder can severely impair the patient's quality of life.[4]

As the disease progresses, the results of tests based on patient performance and compliance, such as visual acuity and visual field, may become more variable and less reliable.[5] As a result, in advanced cases, researchers work with questionnaires and quality of life scales that may have better reliability. The questionnaires are based on the individual's assessment of their current level of functional vision.[6] Reliable questionnaires are also used in the follow-up of the natural course of hereditary retinal dystrophy and in clinical trials of emerging new treatment methods.[7]

An individual's perceptions related to functional status and disability may be altered as a result of the depression that can occur in association with their disease. In summary, depression can both reduce the reliability of clinical test results and negatively affect responses to quality of life scales.

Although there are many studies involving anatomic and functional assessments of patients with RP, studies on depression and anxiety disorder in these patients are insufficient. Due to the rare occurrence of the disease, the studies include limited numbers of patients. Moreover, the prevalence and severity of depression may vary between populations due to cultural, environmental, and socioeconomic factors. In this study, we aimed to investigate the prevalence and severity of depression among patients with RP. We evaluated the relationship between depression prevalence and severity and the patients' age, sex, visual acuity, and visual field test results. For this purpose, we evaluated patients and controls using the previously validated Turkish version of the Beck Depression Inventory (BDI).[8]

Materials and Methods

This cross-sectional study was conducted between January and December 2023. The patient group comprised individuals diagnosed with RP who were followed up in our clinic, and the control group consisted of patients who were examined in our clinic during the same period. All participants underwent best-corrected visual acuity (BCVA) measurement and slit-lamp anterior segment and fundus examinations. BCVA was assessed by Snellen chart and recorded in decimal, then converted to logarithm of the minimum angle of resolution (logMAR). Visual field test was performed using the 30-2 program on a Humphrey Field Analyzer (Carl Zeiss Meditec AG, Germany) and optical coherence tomography examination was performed (Topcon, Japan). In addition, full-field electroretinography (ERG; Monpack 3, Metrovision, France) was performed in the RP patients. The patients' BCVA and their mean deviation (MD) values on the visual field test were recorded. Data from a single eye were used for patients whose vision levels and MD values were equal in both eyes, while data from the better eye were used in cases where they were unequal. The visual field test results of 29 patients who had low reliability parameters and impaired fixation were not included in the study.

Inclusion criteria for the patient group were: age over 18 years, no history of systemic disease, no ocular pathology (e.g., glaucoma, amblyopia) other than RP, fundus examination findings such as pigmentary changes consistent with bilateral RP, bone spicules, retinal and retinal pigment epithelium atrophy, narrowing of the visual field, and attenuated scotopic responses on ERG. Participants in the control group were over 18 years of age, had perfect BCVA, and had no history of systemic comorbidities.

The BDI was administered to all participants in the patient and control groups. The participants were asked to complete the questionnaire in the clinic or bring it to their next visit. For patients with low vision, the questionnaires were completed with assistance from their relatives or our clinical staff.

Acıbadem University Ethics Committee approval was obtained for the study (decision no: ATADEK 2022-20/08, date: 30.12.2022). The study procedures were carried out in accordance with the Declaration of Helsinki. An informed consent form was obtained from each participant.

Beck Depression Inventory

The BDI is a questionnaire used to evaluate an individuals' mental state. It consists of 21 questions that the individual answers according to their current state. Each question has 4 response options scored from 0 to 3. Total scores of 0-13 are interpreted as no depression, 14-19 as mild depression, 20-28 as moderate depression, and 29-63 as severe depression. The Turkish validity and reliability study was conducted.[8]

Statistical Analysis

The data were analyzed with the SPSS version 21.0 program (IBM Corp, Armonk, NY, USA). The normality of the data was tested with the Shapiro-Wilk test. Continuous data were represented as median, range, and interquartile range and compared using the Mann-Whitney U test. Categorical data were represented as frequencies and percentages and compared using Pearson's chi-square or Fisher exact test. Bivariate regression analysis of depression score and severity level was performed according to age, sex, visual acuity, and MD value.

Results

A total of 134 participants were included in our study. Of these, 60 were healthy controls with normal visual acuity and visual field, and 74 were RP patients with visual impairment and visual field narrowing. Age, sex, marital status, education level, and parental consanguinity were recorded for the patient group. There were 40 (54%) males and 34 (46%) females in the RP group and 23 (38%) males and 37 (62%) females in the control group. The mean age was 39.20±12.4 years in the patient group and 36.70±9.2 years in the control group. There was no statistically significant difference between the two groups in terms of age or sex. The demographic data of the patients are shown in Table 1.

The median visual acuity of the patient group was 0.10 decimal (1.0 logMAR; 1.3-0.7 logMAR range). Patients were grouped according to the classification defined by the World Health Organization and International Classification of Diseases, which was also used in previous studies.[9,10] Thirty-six (48.6%) patients were below 0.05 decimal (1.3 logMAR) and at the level of legal blindness. In the remaining cases, visual acuity level was 0.05 to 0.3 decimal (1.3-0.5 logMAR) in 14 patients (19%), 0.3 to 0.7 decimal (0.5-0.2 logMAR) in 17 patients (22.9%), and better than 0.7 decimal (0.2 logMAR) in 3 patients (4.1%). According to this, the patient group consisted predominantly of advanced cases. The 45 patients with visual field data had a median MD of -28.00 decibels (dB) (range: -1.00 to -34.00 dB), and 90% had an MD below the overall median of -5.63 dB. There were no participants in the control group with a visual field lower than -5 dB (Table 2).

The median BDI score was statistically significantly higher in the patient group than in the control group (19 vs. 12; $p<0.001$). In the patient group, 9.5% had no depression while the other 90.5% were found to have some degree of depression. The prevalence of moderate to severe depression was higher in the patient group than in the control group (61% vs. 25%). In

the control group, 68% of the individuals had mild to moderate depression (Table 2).

Visual acuity level was determined to be a predictor of depression score and severity. Each Snellen line increase in visual acuity was associated with a 0.85-point decrease in depression score (B=-0.85, p<0.001) and 18% lower odds of moderate to severe depression (odds ratio [OR]: 0.82, p<0.001). Patients with visual acuity higher than 0.7 had similar depression scores to the control group and low odds of moderate to severe depression (OR: 0.13, p<0.001) (Table 3).

Visual field MD values were also found to be predictive of depression score and severity. Each 10-unit reduction in MD was associated with a 2.5-point increase in depression score and a 1.8-fold increase in the odds of severe depression. Especially among patients with MD values below -30 dB, depression scores increased by over 8 points (B=8.7, p<0.001) while the odds of moderate to advanced depression were more than 6 times higher (OO=6.60, p<0.001) (Table 3).

Depression scores and depression severity tended to increase significantly with age. However, when adjusted for sex, visual acuity, and visual field, it did not have a significant effect on depression score. Sex was not found to impact depression score or severity.

Table 1. Demographic data of the patients

	RP, n=74
Age (years)	
Mean ± SD	39.20±12.4
Range	(18-71)
Sex	
Male	40 (54%)
Female	34 (46%)
Education level	
Primary school	32 (43%)
Secondary school	27 (37%)
University	15 (20%)
Marital status	
Married	47 (64%)
Single	23 (31%)
Divorced	4 (5%)
Parental consanguinity	
None	19 (25%)
First degree	28 (38%)
Second degree	16 (22%)
Third degree	11 (15.0%)

RP: Retinitis pigmentosa, SD: Standard deviation

Discussion

Potentially chronic and progressive ocular pathologies such as dry eye, glaucoma, age-related macular degeneration, and uveitis have been shown to be accompanied by depression.[11,12,13,14,15] RP differs from these pathologies in that it has distinct hereditary features, starts at an earlier age, and has no standard treatment protocol. For these reasons, the frequency and severity of depression may differ from those in the aforementioned disease groups. In this study, we evaluated the frequency and severity of depression in RP patients. We examined the relationships between depression score and severity and the patients' age, sex, and results of functional tests such as visual acuity and visual field. We found that depression was more common and more severe among patients with RP than healthy controls.

Several scales can be used to assess the presence and severity of depressive symptoms.[16] The tests that have been most frequently used in studies of RP patients are the hospital anxiety and depression scale (HADS), BDI, patient health questionnaire, and Zung depression scale (ZDS). In this study we used the BDI, which was validated with university students in our country and has a high sensitivity and specificity when a cut-off value of 13 points is used.[8]

When the stages of RP were evaluated, 85.2% of the patients in this study had intermediate or advanced disease. Nearly half (49%) of the patients had a visual acuity worse than 0.05 decimal (1.3 logMAR) and were legally blind. According to BDI results, depression was detected in 90.5% of the patients and was moderate or severe in 61% of them. Previous studies have reported depression rates varying between 15.5% and 34.8% in patients with RP.[17,18,19,20,21,22] The much higher frequency of depression in our study may be due to reasons such as the high mean age of the patients and the fact that most patients had intermediate to advanced stage RP. In addition, differences in the scales and cut-off values used to identify depression may have been a factor in the high variability of the results. Again, cultural and geographic factors may also contribute to this result.

In a study conducted in Greece, which has similar geographic and cultural characteristics to our country, the frequency of depression in RP patients was found to be 76.5% and the frequency of moderate depression was 26.5%.[23] The results obtained in that study are closer to our results, supporting the idea that cultural and geographic factors may influence the prevalence of depression. Another noteworthy finding of our study was that the rate of moderate depression was as high as 25% in the control group. This may indicate that we as a society have a strong inclination for depression. Although not within the scope of this study, socioeconomic, cultural, and geographic differences may have contributed to the higher rate of depression in the control group compared to other studies.

When the data related to age and sex were evaluated, we determined that although older patients showed a higher frequency and severity of depression, older age was not

Table 2. Comparison of BCVA, visual field MD scores, and depression scores and severity between the groups				
	Control, n=60	**RP, n=74**	**Total, n=134**	**p**
BCVA (Snellen decimal)				-
Median (IQR)	1.00 (1.00, 1.00)	0.10 (0.05, 0.25)	0.65 (0.08, 1.00)	
Range	1.00, 1.00	0.001, 0.90	0.001, 1.00	
BCVA quartile, decimal				-
0.001-0.05	0 (0)	36 (49)	36 (27)	
>0.05-0.70	0 (0)	35 (47)	35 (26)	
>0.70-<1.00	0 (0)	3 (4.1)	3 (2.2)	
1.00 (normal)	60 (100)	0 (0)	60 (45)	
MD (dB)				<0.001[1]
Median (IQR)	-3 dB (-3, -4)	-28 dB (-18, -32)	-6 dB (-3, -30)	
Range	-2, -5 dB	-1, -34 dB	-1, -34 dB	
MD Quartile*, dB		**n=45**	**n=105**	<0.001[2]
-0.83 to -3.00	40 (67)	3 (6.6)	43 (41)	
-3.00 to -5.63	20 (33)	4 (8.8)	24 (23)	
-5.63 to -30.2	0 (0)	21 (46.6)	21 (20)	
-30.2 to -34.0	0 (0)	17 (37.7)	17 (16)	
Total BDI score				<0.001[1]
Median (IQR)	12 (8, 17)	19 (13, 25)	16 (11, 22)	
Range	1, 28	0, 44	0, 44	
Depression severity				<0.001[2]
None (BDI 0-13)	19 (32)	7 (9.5)	26 (19)	
Mild (BDI 14-19)	26 (43)	22 (30)	48 (36)	
Moderate (BDI 20-28)	15 (25)	31 (42)	46 (34)	
Severe (BDI 29-63)	0 (0)	14 (19)	14 (10)	

*Visual field results from 29 patients with low reliability or poor fixation were excluded from the analysis. [1]Mann-Whitney U test, [2]Fisher's exact test. BCVA: Best corrected visual acuity, MD: Mean deviation, RP: Retinitis pigmentosa, IQR: Interquartile range, dB: Decibel, BDI: Beck Depression Index

significantly associated with depression scores in multiple regression analyses. Similarly, there was no relationship with sex. When the literature is examined, there are studies showing no correlation between the presence of depression and patients' age, sex, and socioeconomic and education levels.[18,20,22] However, other publications reported that depression is more common among female patients over the age of 35 years.[17,21] This discrepancy may be related to these studies being retrospective, including patients from different racial and ethnic backgrounds, and not involving functional vision tests.[17,21]

There is consensus among most studies of RP patients conducted to date that the frequency and severity of depression increases with deterioration of visual function.[18,20,22,23,24,25] A study in which 34 patients were assessed using the ZDS showed that advanced age and BCVA were correlated with depression scores.[23] Similarly, in a larger series of 112 cases evaluated with the HADS, depression scores were significantly correlated with BCVA and functional vision score (FVS).[18] In the evaluation of depression, Hahm et al.[20] also used the BDI, as in our study, but observed no correlation between BDI score and FVS. In our study, there was a negative relationship between the patient's visual acuity and visual field MD values and the frequency and severity of depression. The reasons for this result could include different disease severity in the studied groups, different BDI cut-off values, and their use of the FVS as a functional test.

In our study, visual acuity and visual field were used as functional vision tests. It is known that visual acuity and visual field are the two most important factors affecting patients' activities of daily living, quality of life, and emotional state.[25] One study showed that a significant deterioration in quality of life and emotional state occurred when visual acuity decreased below 0.3 decimal and the visual field narrowed beyond the central 20 degrees. In addition, FVS, which is obtained by evaluating these two measurements together, was correlated with the patients' results on quality of life questionnaires.[26] When the visual field results were examined in our study, we observed that the central 20 degrees was preserved in 23 patients (31%), while the other 51 patients (69%) had a visual field smaller than the central 20 degrees. We believe that severe visual field loss in our patients contributed to the high frequency and severity of depression.

Table 3. Bivariate regression of total depression score and presence of moderate to severe depression by age, sex, visual acuity, and mean deviation value

	n	BDI score			Moderate/severe depression		
		B	95% CI	p	OR	95% CI	p
Age (per 1 year increase)	134	0.09	-0.02, 0.20	0.104	1.01	0.99, 1.04	0.233
Age (per quartile), years	134			0.011			0.091
18-26	37	0.00	-	-	1.00	-	0.091
>26-36	33	0.71	-3.4, 4.8	0.735	0.87	0.37, 2.03	0.741
>36-48	36	4.8	0.79, 8.9	0.019	2.34	1.04, 5.38	0.044
>48-71	28	3.1	-1.2, 7.4	0.154	1.37	0.53, 3.54	0.519
Sex	134			0.525			0.541
Male	63	0.00	-	-	1.00	-	-
Female	71	1.0	-2.1, 4.0	0.525	1.21	0.65, 2.26	0.541
Mean MD value (per 10 dB increase)	105	2.5	1.4, 3.6	<0.001	1.81	1.39, 2.36	<0.001
Mean MD quartile, dB	105			<0.001			<0.001
-0.83 to -3.00	43	0.00	-	-	1.00		-
-3.00 to -5.63	24	1.1	-3.0, 5.3	0.588	0.82	0.32, 2.11	0.685
-5.63 to -30.2	21	4.3	0.51, 8.0	0.026	2.72	1.19, 6.30	0.020
-30.2 to -34.0	17	8.7	5.0, 12	<0.001	6.60	2.74, 16.5	<0.001
Mean BCVA (per 0.10 decimal increase)	134	-0.85	-1.2, -0.54	<0.001	0.82	0.76, 0.88	<0.001
Mean BCVA quartile, decimal	134			<0.001			<0.001
1.00 (normal)	60	0.00	-	-	1.00	-	-
>0.70 - <1.00	3	0.02	-9.4, 9.5	0.997	0.13	0.06, 0.29	<0.001
>0.05 - 0.70	35	4.8	1.4, 8.2	0.006	0.15	0.01, 1.43	0.099
0.001 - 0.05	36	8.9	5.6, 12	<0.001	0.52	0.21, 1.26	0.152
Study group	134			<0.001			<0.001
Control	60	0.00	-	-	1.00	-	-
RP	74	6.6	3.8, 9.4	<0.001	5.13	2.64, 10.3	<0.001

BDI: Beck Depression Inventory, CI: Confidence interval, OR: Odds ratio, MD: Mean deviation, dB: Decibel, BCVA: Best corrected visual acuity, RP: Retinitis pigmentosa

In the follow-up and evaluation of new treatment methods in patients with hereditary retinal dystrophy, quality of life measures were revised to make a tool more specific to retinal dystrophy.[26] This assessment, which is based on the patient's perceptions and responses concerning their eye health, was shown to correlate with functional tests.[27,28] In one study using this assessment, the results were shown to be associated with visual acuity and ellipsoid zone area.[28] As standard visual tests can be difficult to perform in patients with hereditary retinal dystrophy, the applicability of new tests is important.[28,29] The presence of a mood disorder increases the variability and decreases the reliability of standard clinical tests and reduces quality of life.[5,29] Therefore, depression that occurs in association with the patient's disease should not be overlooked.

Study Limitations

RP is among the rare diseases, so case numbers are limited. Studies with more participants are needed. At the same time, the frequency and severity of depression may have been high because most of the patients in our study had intermediate to advanced disease. Studies conducted in homogeneous groups with better representation of the early stages may yield different results. Education level and marital status, which may indirectly affect depression, were not exactly matched in the control and patient groups and thus could not be included in the analysis. Visual acuity was evaluated with a decimal chart and converted to logMAR. Therefore, there may have been differences between the measurements. Additionally, visual field data from patients whose test results indicated low reliability could not be included in the study. We evaluated patients' functional tests such as visual acuity and visual field, but did not perform an anatomic evaluation. Most patients had attenuated rod and cone responses in the full-field ERG test, but wave morphology could not be evaluated and included in the study. For patients with no response on full-field ERG, a multifocal ERG test can be added

if fixation is adequate. In those with poor fixation, the newer full-field stimulus threshold test can be applied.[30] The participants in our study did not undergo a psychiatric evaluation; the results are based on a questionnaire that can be considered a screening test. As questionnaires are based on patient reports, the objectivity of the data decreases and bias may occur. Most of the patients could not provide reliable information about the duration of their disease. Therefore, disease duration could not be evaluated in the study. Finally, different racial and ethnic groups were not studied.

Conclusion

Patients with RP, especially those with intermediate to advanced disease, have an increased incidence and severity of depression. There was no relationship between depression status and factors such as age and sex. The strongest predictors of depression were the results of functional tests such as visual acuity and visual field. However, depression reduces the reliability of visual function tests and reduces patients' quality of life. In these cases, various mental health screening tools can be applied in clinical practice in addition to visual function tests. RP patients require a multidisciplinary approach involving branches such as low vision rehabilitation and psychiatry. By treating the underlying depressive symptoms and developing strategies to cope with the disease, the patient's quality of life may improve, functional test performance may increase, and the results of these tests may be more meaningful.

Ethics

Ethics Committee Approval: Acıbadem University Ethics Committee approval was obtained for the study (decision no: ATADEK 2022-20/08, date: 30.12.2022). The study procedures were carried out in accordance with the Declaration of Helsinki.

Informed Consent: Obtained.

Authorship Contributions

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

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Original Article

Traumatic Brain Injury in Admitted Patients with Ocular Trauma

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Abstract

Objectives: To characterize the epidemiology of simultaneous traumatic brain injury (TBI) and ocular trauma.

Materials and Methods: In this retrospective, observational study, de-identified data from patients admitted with ocular trauma and TBI was extracted from the National Trauma Data Bank (2008-2014) using International Classification of Diseases 9th Revision, Clinical Modification diagnostic codes and E-codes relating to injury circumstances. Mechanisms, types of ocular and head injuries, intention, and demographic distribution were determined. Association of variables was calculated with Student's t and chi-squared tests and logistic regression analysis.

Results: Of 316,485 patients admitted with ocular trauma, 184,124 (58.2%) also had TBI. The mean (standard deviation [SD]) age was 41.8 (23) years. Most were males (69.8%). Race/ethnicity distribution was 68.5% white, 13.3% black, and 11.4% Hispanic patients. The mean (SD) Glasgow Coma Score (GCS) was 12.4 (4.4) and Injury Severity Score (ISS) was 17 (10.6). Frequent injuries were orbital fractures (49.3%) and eye/adnexa contusions (38.3%). Common mechanisms were falls (27.7%) and motor vehicle-occupant (22.6%). Firearm-related trauma (5.2%) had the greatest odds of very severe injury (ISS >24) (odds ratio [OR]: 4.29; p<0.001) and severe TBI (GCS <8) (OR: 5.38; p<0.001). Assault injuries were associated with the greatest odds of mild TBI (OR: 1.36; p<0.001) and self-inflicted injuries with severe TBI (OR: 8.06; p<0.001). Eye/adnexal contusions were most associated with mild TBI (OR: 1.25; p<0.001). Optic nerve/visual pathway injuries had greater odds of severe TBI (OR: 2.91; p<0.001) and mortality (OR: 2.27; p<0.001) than other injuries. Of associated head injuries, the odds of severe TBI were greatest with skull base fractures (OR: 4.07; p<0.001) and mortality with intracerebral hemorrhages (OR: 4.28; p<0.001). Mortality occurred in 5.9% of patients.

Conclusion: TBI occurred in nearly two-thirds of ocular trauma admissions. The mortality rate was low with implications for challenging rehabilitation and long-term disability in survivors.

Keywords: Demographic disparity, falls, intention, motor vehicle accidents, ocular trauma, traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is defined as brain injury resulting from blunt force to the head or body, or penetration of the brain or skull.[1] The Centers for Disease Control and Prevention (CDC) categorized TBI into groups based on International Classification of Diseases (ICD) classifications, which include skull fractures, various intracranial injuries, optic nerve/visual pathway injuries, and shaken baby syndrome.[2] TBI is a leading cause of disability and death in the United States and has been shown to predispose children to developmental delay and adults to dementia.[3,4,5] The United States has the highest incidence of TBI in the world,[6] and it causes a disproportionately large financial burden comprising costs from acute medical care to long-term rehabilitation and associated disability.[7,8] The annual burden of TBI has been estimated to be $13 billion, with a further $64.7 billion from lost productivity.[7]

Mild TBI has been associated with deficits in visual fields, accommodation, vergence, and versions, while more severe TBI may result in additional signs of structural damage. Fifteen percent of those who experience visual symptoms acutely subsequently develop chronic visual deficits.[9] TBI also may lead to chronic psychological and neurocognitive deficits

including attention, visuospatial association, and executive function.[10] Table 1 summarizes the types and ophthalmic consequences of TBI. The proximity and contiguity of the eye to the brain increases the likelihood of simultaneous injuries. While ocular injury is the most common cause of monocular blindness in the United States, the majority survive their injuries. However, mortality in patients with ocular trauma most commonly is associated with concurrent TBI.[11] While several reports have detailed the spectrum of ophthalmic manifestations of TBI,[9,10,12,13,14,15,16,17] few studies have studied simultaneous ocular trauma and TBI, with most reports detailing combat-related blast injuries.[18,19,20,21,22,23] We used a national database to characterize epidemiologic patterns of non-combat injury in the United States. Identification of at-risk groups and

Table 1. Summary of types of traumatic brain injury and ophthalmic consequences

Types of TBI	Mild (concussion or GCS 13-15) most common
	Moderate (GCS 9-12)
	Severe (GCS <8)
Primary TBI (initial injury)	Direct (blunt, penetrating)
	Indirect (rotational and acceleration/deceleration forces, pressure waves)
Types of primary TBI	Diffuse axonal injury
	Hematoma
	Contusion
Secondary TBI (cascade of events following initial injury) • Most recover from mild TBI (mTBI) within 30 days • Few mTBI proceed to secondary axonopathy even years after initial injury. Most vulnerable are the developing brains of children and the brains of older adults	
Pathophysiology of secondary TBI	Diffuse cerebral edema
	Vascular/cellular dysregulation
	Hypoxia/anoxia
	Hypotension
	Inflammation
	Metabolic dysfunction
Ophthalmic consequences	Traumatic optic neuropathy • Decreased acuity • Dyschromatopsia • Contrast sensitivity deficits
	Visual field defects
	Ocular motor nerve palsies (III, IV, VI) → strabismus/impaired ductions
	Accommodation insufficiency
	Saccade and anti-saccade deficits
	Smooth pursuit deficits
	Convergence insufficiency
	Nystagmus
	Pupillary reaction abnormalities
	Stereopsis reduction
	Sympathetic pathway disruption - Horner's syndrome
	Brain stem injuries • Internuclear ophthalmoplegia • Dorsal midbrain syndrome
	Higher order dysfunctions
	• Photophobia
	• Visual memory deficits
	• Reaction time deficits
	• Reading deficits

Table constructed with information derived from references detailing visual consequences in TBI.[12,13,14,15,16] TBI: Traumatic brain injury, GCS: Glasgow Coma Score

the circumstances surrounding their injuries may help guide clinical practice, develop preventative measures, and provide a foundation for further research.

Materials and Methods

The institutional review board of the Albert Einstein College of Medicine approved this evaluation of the National Trauma Data Bank (NTDB) (approval no: #2015-4769, date: 04.08.2015). All data in the NTDB is de-identified and patient consent was deemed unnecessary. The NTDB is one of the world's largest trauma registries and is maintained by the American College of Surgeons. It contains de-identified data from over 900 centers of all levels.[24] Patients included in this study were admitted with ICD Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 800.00 to 959.9. Details of our methodology and the specific codes used are outlined in a previous publication.[19] The definition of TBI was based on CDC ICD-9-CM criteria: factures of the vault and base of skull (800.0-801.9); multiple fractures of the skull (803.0-804.9); intracranial injuries including concussion, laceration, hemorrhage, and contusion (850.1-850.5, 850.9, 851.0-854.1); injury of the optic nerve and pathway (950.1-950.3); shaken baby syndrome (995.55); and unspecified head injury (959.01).[2] ICD-9-CM codes of ocular injuries were extracted and the associated E-codes (external circumstances of injury) are summarized in Supplementary Table 1. The specific ocular injury categories based on Birmingham Eye Trauma Terminology System[25] and Ocular Trauma Score (OTS)[26] used by ocular trauma surgeons for unified terminology and prediction of visual outcome are not available in the NTDB and were not used in this study.

For each patient, the injury type, mechanism, intent, and location; demographic data including gender, age, race, and ethnicity; and information about the hospital course, including the year of admission, trauma center level (1-4), and length of stay, were documented. Both Injury Severity Score (ISS) and Glasgow Coma Score (GCS) were collected to classify injury severity. ISS is the numerical assignation given to all major trauma, based on parts of the body involved and the degree of injury. These numbers have been found to correlate with hospital stay, morbidity, and mortality. For logistic regression analysis, continuous variables were categorized. ISS was categorized according to NTDB subgroups as minor (1-8), moderate (9-15), severe (16-24), and very severe (>24). GCS, an index of degree of TBI, was categorized as mild (13-15), moderate (9-12), and severe (≤8) brain injury. Age was divided into three groups: pediatric (<21 years), adult (21-64 years), and older adult (≥65 years). Mortality was determined by disposition data, which included discharged home; transferred to another hospital, nursing home, or rehabilitation facility; left against medical advice; transferred to hospice; and death.

Statistical Analysis

All data calculations were performed using SPSS version 24 software (IBM Corp, Armonk, NY, USA). The mean, standard deviation (SD), median, and interquartile range were calculated for all continuous variables. Associations between variables were determined using Student's t-test and chi-squared test. Univariate logistic regression was used to calculate odds ratios (OR) to determine the relative strength of the association between demographic groups, mechanisms of injury, and degree of TBI and injury severity. Statistical significance was set at $p<0.05$. Data categorized as undetermined or unknown were excluded from analyses.

Results

General Characteristics

Of 316,485 patients admitted with ocular trauma, 184,124 (58.2%) were also diagnosed with TBI. The mean (SD) age was 43 (23.1) years. Most patients were in the 21-64 year age group (111,494; 60.6%). Males comprised 128,580 (69.8%) and were, on average, younger than females (40.4 vs. 49.1 years; $p<0.001$). Males outnumbered females in all groups except the ≥80 years age group (Figure 1). By race, 126,090 patients (68.5%) were white, 24,445 (13.3%) were black, and Hispanics represented

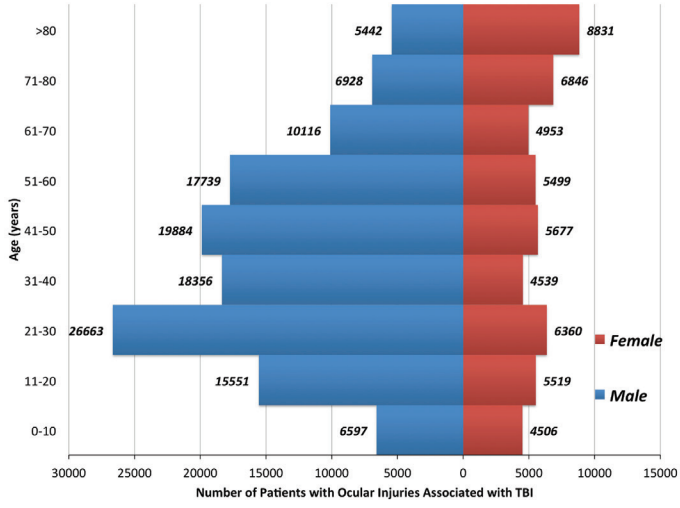

Figure 1. Frequency of ocular trauma associated with traumatic brain injury (TBI) in different age groups. The patients in the most productive years of life, 21-64 years old, comprised the largest group with concurrent ocular trauma and TBI (60.6%)

21,025 (11.4%). The most common mechanisms of trauma were falls (51,041; 27.7%), motor vehicle traffic-occupant (MVTO) (41,629; 22.6%), and struck by/against (SBA) (27,942; 15.2%). Blunt force traumas (159,414; 86.6%) outnumbered penetrating traumas (5,884; 3.2%). Frequent locations of injury were the street (82,092; 44.6%) and home (45,631; 24.8%). Most injuries were unintentional (137,454; 74.7%), followed by assault (35,281; 19.2%) and self-inflicted (3,056; 1.7%) (Table 2).

Common ocular injuries were orbital (80,914; 43.9%), contusions of eye/adnexa (70,545; 38.3%), and open wound of ocular adnexa (35,752; 15.1%) (Figure 2A). Retinal injuries were documented in 11,413 patients (6.2%). Of these, the

Table 2. Findings and demographic data of patients with ocular injury and traumatic brain injury, National Trauma Data Bank (2008-2014) (N=184,124)

Characteristic	Number	Percent	Characteristic	Number	Percent	Mean (SD)	Median (IQR)
Year			**Age (years)**			43 (23.1)	41 (24-60)
2008	22584	12.3	0-10	11103	6		
2009	25152	13.7	11-20	21070	11.4		
2010	25396	13.8	21-30	33023	17.9		
2011	25168	13.7	31-40	22895	12.4		
2012	28375	15.4	41-50	25561	13.9		
2013	27806	15.1	51-60	23238	12.6		
2014	29643	16.1	61-70	15069	8.2		
Total	184124	100.0	71-80	13774	7.5		
			>80	14273	7.8		
Gender			Unknown	4118	0.2		
Female	55544	30.2					
Male	128580	69.8	**Hospital stay**			7.5 (11.4)	4 (2-8)
			1 day	35046	19		
Race			2-3 days	52854	28.7		
Black	24445	13.3	4-6 days	38837	21.1		
White	126090	68.5	>6 days	57140	31.0		
Other	33589	18.2	Unknown	247	0.1		
Hispanic	21025	11.4	**Mortality**	10787	5.9		
Hospital			**ISS**			17 (10.6)	14 (9-22)
Level I	69799	37.9	1-8 (mild)	32354	17.6		
Level II	34447	18.7	9-15 (moderate)	58941	32.0		
Level III	3198	1.7	16-24 (severe)	47413	25.8		
Level IV	252	0.1	>24 (very severe)	36644	19.9		
Not applicable	76428	41.5	Unknown	8772	4.7		
			GCS			12.2 (4.2)	14 (11-15)
Locations			<8 (severe)	23862	13		
Street	82092	44.6	9-12 (moderate)	10859	5.9		
Home	45631	24.8	13-15 (mild)	83849	45.5		
Public building	10294	5.6	Unknown	65554	35.6		
Recreation	7190	3.9					
Residential institution	6260	3.4	**Mechanisms**				
Industry	3203	1.7	Fall	51041	27.7		
Farm	1043	0.6	MVT-occupant	41629	22.6		
Mine	99	0.1	Struck by/against	27942	15.2		
Other	9014	4.9	MVT-motorcyclist	11575	6.3		
Unspecified	14226	7.7	MVT-pedestrian	8168	4.4		
Unknown	5072	2.8	Firearms	5634	3.1		
			Other	10274	5.6		
			Unknown	7340	4		

Table 2. Continued								
Characteristic	**Number**	**Percent**		**Characteristic**	**Number**	**Percent**	**Mean (SD)**	**Median (IQR)**
US regions				**Intention**				
Midwest	37043	20.1		Assault	35281	19.2		
Northeast	37066	20.1		Self-inflicted	3056	1.7		
South	63874	34.7		Unintentional	137454	74.7		
West	42356	23		Other	46	0.0		
Not applicable	875	0.5		Undetermined	947	0.5		
Unknown	2910	1.6		Unknown	7340	4		

SD: Standard deviation, IQR: Interquartile range, ISS: Injury Severity Score, GCS: Glasgow Coma Score, MVT: Motor vehicle traffic, US: United States of America

majority were listed as retinal edema (11,132; 6%); retinal hemorrhages, retinal holes, and vitreous hemorrhages each occurred in <1% of cases. Cranial nerve and visual pathway injuries occurred in 8,553 patients (4.6%). Of these, optic nerve/visual pathways injuries (2,762; 32.3%) were most common, followed by facial nerve (2,443; 28.6%) and abducens nerve (986; 11.5%) (Figure 2B). Frequent head injuries were facial fractures (118,863; 64.6%), subarachnoid hemorrhage (32,766; 17.8%), and subdural hemorrhage (32,632; 17.7%) (Figure 2C). Most patients had moderate ISS (58,941; 32%) and mild GCS (126,107; 68.5%). The mean (SD) ISS was 17 (10.6) and mean (SD) GCS was 12.4 (4.4). The mean (SD) hospital stay was 7.5 (11.4) days and the mortality rate was 5.9% (10,787 patients).

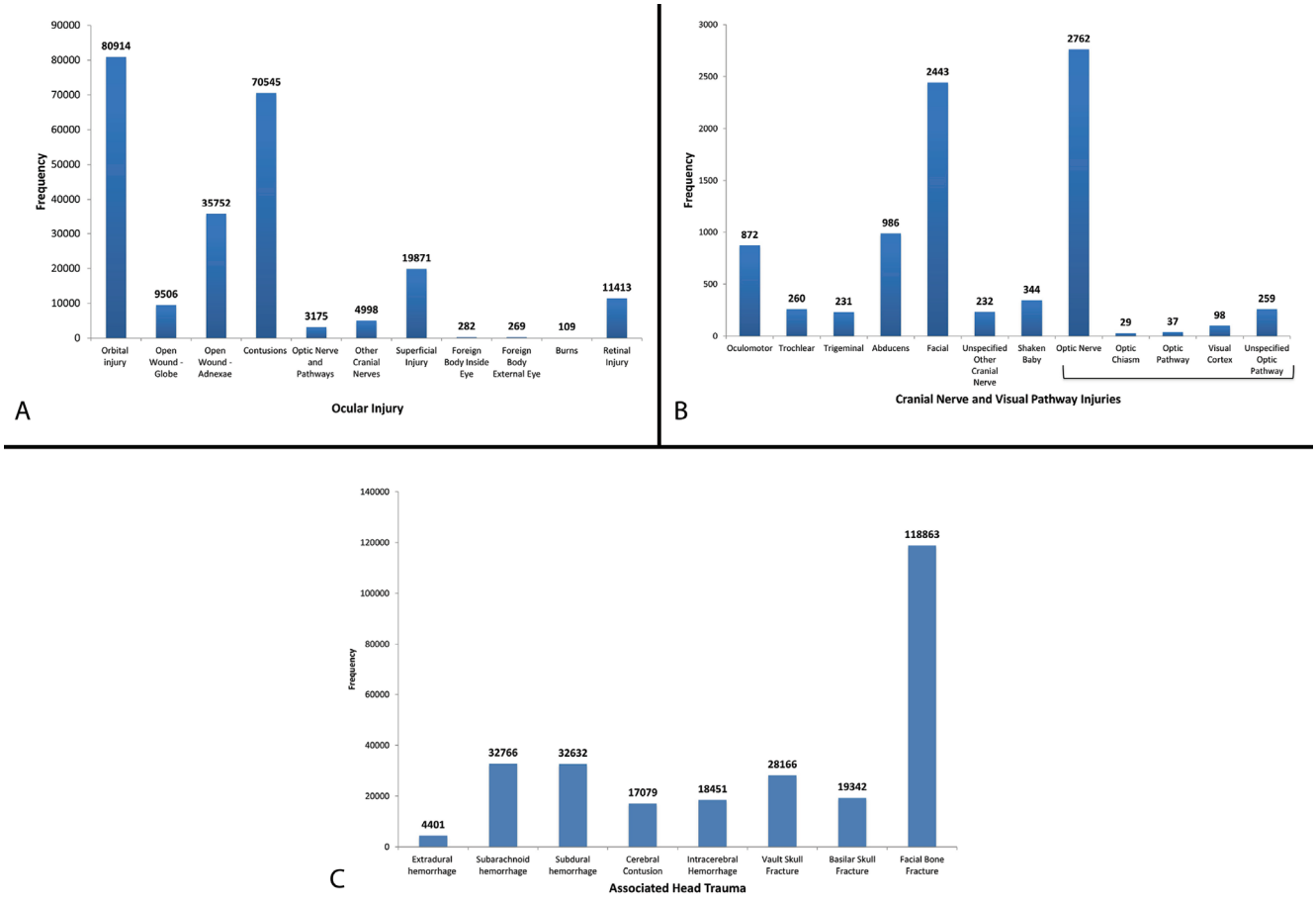

Figure 2. (A) Spectrum of ocular trauma associated with traumatic brain injury (TBI). The most common injuries seen include orbital (34.2%), contusions (29.8%), and open adnexal injuries (15.1%). (B) Cranial nerve injuries in ocular trauma associated with TBI. The most frequent cranial nerves affected were the optic, facial, and abducens nerves. Of visual pathway injuries (indicated by bracket), the optic nerve was most frequently injured. (C) Associated head injuries in ocular trauma associated with TBI. Facial bone fractures far outnumbered other head injuries

Comparative Analysis

Demographic Differences

Patients younger than 21 years of age had the greatest odds of trauma by MVTO (OR: 1.88; 95% confidence interval [CI], 1.83-1.93; p<0.001), while the 21-64 year group had greater odds of trauma due to motor vehicle traffic-motorcyclist (MVTM) (OR: 4.98; 95% CI, 4.70-5.27; p<0.001) than the other age groups. Patients 65 or older had greater odds of sustaining injury from falls (OR: 15.12; 95% CI, 14.71-15.54; p<0.001) (Figure 3A). Regarding intention, the highest odds of unintentional injury were in patients younger than 21 (OR: 1.07; 95% CI, 1.04-1.10; p<0.001) and 65 or older (OR: 7.81; 95% CI, 7.43-8.22; p<0.001), while patients 21-64 years old had the greatest odds of assault (OR: 2.91; 95% CI, 2.83-2.99; p<0.001) and self-inflicted injuries (OR: 1.98; 95% CI, 1.83-2.16; p<0.001). The youngest group had higher odds of injury in recreational facilities than other locations (OR: 2.93; 95% CI, 2.79-3.08; p<0.001), the 21-64 year group, in the street (OR: 1.96; 95% CI, 1.92-2.00; p<0.001), and those 65 or older, at home (OR: 4.42; 95% CI, 4.31-4.53; p<0.001).

Females were more likely to have unintentional injury (OR: 3.15; 95% CI, 3.06-3.25; p<0.001) and injury by fall (OR: 2.77; 95% CI, 2.71-2.84; p<0.001) or MVTO (OR: 1.37; 95% CI, 1.34-1.40; p<0.001). Females also had greater odds of

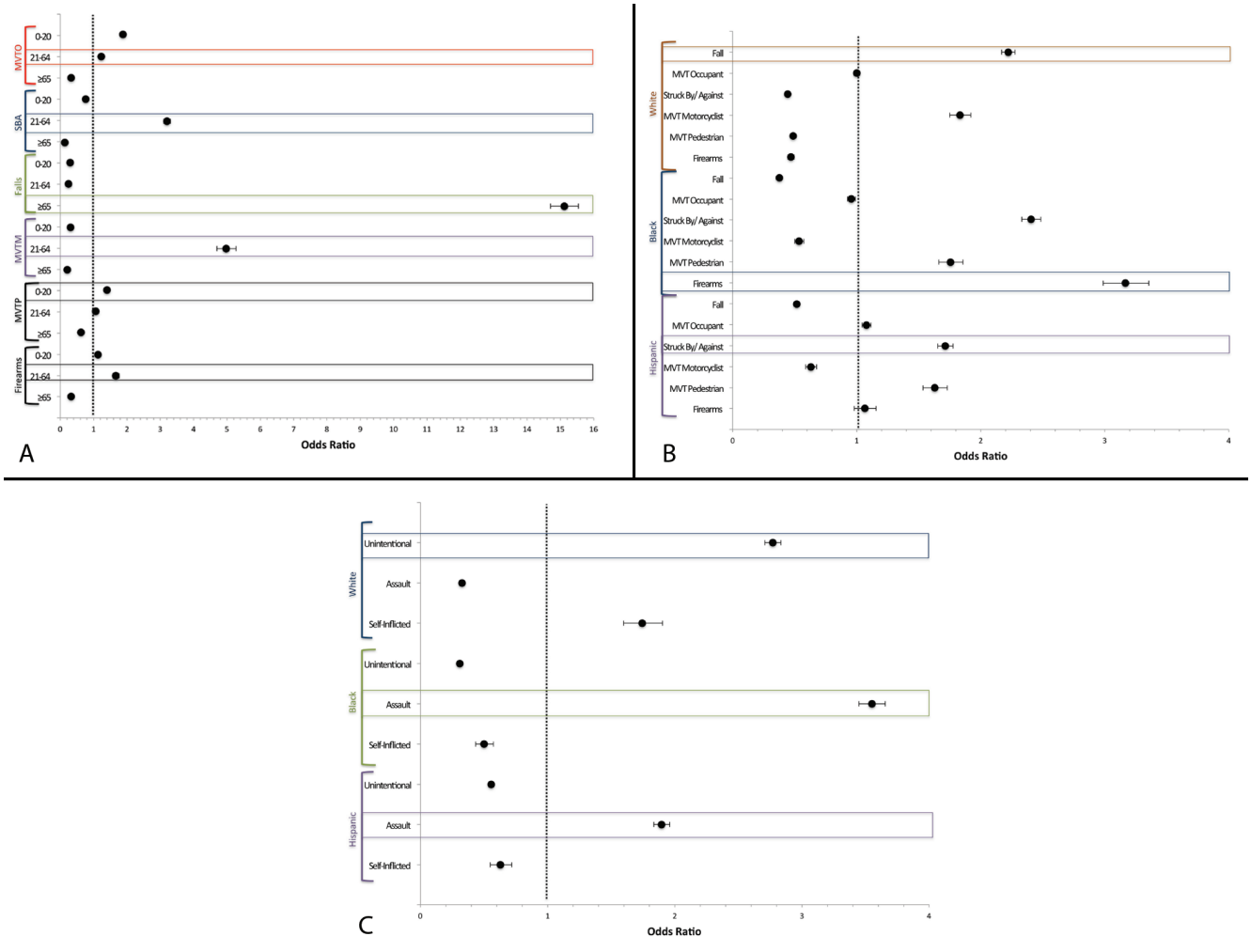

Figure 3. (A) Summary of the simple logistic regression analysis of mechanisms of injury and different age groups in ocular trauma associated with TBI. The odds of falls were 15 times higher in patients aged 65 and older compared to other age groups, while MVTM, SBA, and firearms were most likely in the 21-64 year age group. (B) Summary of the simple logistic regression analysis of mechanisms of injury and race/ethnicity in ocular trauma associated with TBI. White patients had the greatest odds of injury from falls and MVTM, black patients from firearms and SBA, and Hispanics from SBA and MVTP. (C) Summary of the simple logistic regression analysis of intention of injury and race/ethnicity in ocular trauma associated with TBI. White patients had the greatest odds of unintentional injury and were also most likely to suffer self-inflicted injury. Blacks and Hispanics were most likely to suffer injury by assault

TBI: Traumatic brain injury, MVTO: Motor vehicle traffic-occupant, SBA: Struck by/against, MVTM: Motor vehicle traffic-motorcyclist, MVTP: Motor vehicle traffic-pedestrian

injury at home (OR: 2.11; 95% CI, 2.06-2.15; p<0.001) and in residential facilities (OR: 2.26; 95% CI, 2.15-2.38; p<0.001). Males were more likely to sustain injury from assault (OR: 3.20; 95% CI, 3.10-3.30; p<0.001) and self-inflicted injury (OR: 2.23; 95% CI, 2.02-2.45; p<0.001). Males also had greater odds of injury by SBA (OR: 3.87; 95% CI, 3.73-4.02; p<0.001), MVTM (OR: 3.28; 95% CI, 3.10-3.47; p<0.001), and firearms (OR: 2.72; 95% CI, 2.52-2.93; p<0.001), and were more likely to sustain injury in the street (OR: 1.24; 95% CI, 1.21-1.27; p<0.001) than females.

White patients were older than black or Hispanic patients, with the greatest odds of being 65 years or older (OR: 2.84; 95% CI, 2.75-2.92; p<0.001). Black patients had the greatest odds of being 21-64 years old (OR: 1.59; 95% CI, 1.54-1.64; p<0.001) and slightly lower odds of being younger than 21 (OR: 1.29; 95% CI, 1.25-1.34; p<0.001). Hispanic patients had greater odds of being younger than 21 years old (OR: 1.56; 95% CI, 1.51-1.61; p<0.001) and lower odds of being 21-64 years old (OR: 1.31; 95% CI, 1.27-1.35; p<0.001) than non-Hispanics. White patients were most likely to be injured by falls (OR: 2.22; 95% CI, 2.17-2.28; p<0.001) and black patients by firearms (OR: 3.17; 95% CI, 2.99-3.36; p<0.001) compared to other races. Hispanic patients also had the greatest odds of injury by SBA (OR: 1.71; 95% CI, 1.65-1.78; p<0.001) and similarly high odds of motor vehicle traffic-pedestrian (MVTP) (OR: 1.63; 95% CI, 1.53-1.73; p<0.001) (Figure 3B). Regarding intent, white patients had the highest odds of unintentional injury (OR: 2.77; 95% CI, 2.71-2.84; p<0.001), while black (OR: 3.55; 95% CI, 3.45-3.66; p<0.001) and Hispanic patients (OR: 1.90; 95% CI, 1.84-1.96; p<0.001) had the greatest odds of injury from assault (Figure 3C).

Mechanism of Trauma

Injury severity varied with the mechanism of injury. SBA (OR: 2.25; 95% CI, 2.18-2.32; p<0.001) had the greatest odds of being associated with minor injury (ISS 1-8), while falls (OR: 1.27; 95% CI, 1.25-1.30; p<0.001) were most associated with moderate injury (ISS 9-15), and MVTO (OR: 1.68; 95% CI, 1.64-1.76; p<0.001) and firearms (OR: 4.29; 95% CI, 4.06-4.53; p<0.001) had greater odds of being associated with very severe injury (ISS >24) than with other severities. GCS also varied with mechanism of injury. Injuries from falls (OR: 2.28; 95% CI, 2.21-2.34; p<0.001) and SBA (OR: 2.43; 95% CI, 2.34-2.52; p<0.001) had the greatest odds of being associated with minor trauma (GCS 13-15). MVTP (OR: 1.32; 95% CI, 1.21-1.44; p<0.001) was most often associated with moderate trauma (GCS 9-12). MVTO (OR: 1.62; 95% CI, 1.57-1.66; p<0.001), MVTM (OR: 1.20; 95% CI, 1.91-2.08; p<0.001),

Table 3. Simple logistic regression analysis of common mechanism of injury and Glasgow Coma Score in traumatic brain injury with ocular trauma

Glasgow Coma Score	Injury (total)	Frequency (% of total)	p value	Odds ratio	95% confidence interval
13-15 (mild TBI)	Fall (n=46110)	38955 (84.5)	<0.001	2.277	2.214-2.342
	MVT-occupant (n=39150)	26749 (68.3)	<0.001	0.666	0.649-0.682
	Struck by/against (n=25324)	21869 (86.4)	<0.001	2.427	2.338-2.521
	MVT-motorcyclist (n=10994)	6863 (62.4)	<0.001	0.544	0.522-0.566
	MVT-pedestrian (n=7775)	4585 (59.0)	<0.001	0.473	0.451-0.495
	Firearms (n=5273)	2016 (38.2)	<0.001	0.199	0.188-0.210
9-12 (moderate TBI)	Fall (n=46110)	2546 (5.5)	0.372	0.979	0.934-1.026
	MVT-occupant (n=39150)	2167 (5.5)	0.506	0.983	0.936-1.033
	Struck by/against (n=25324)	1197 (4.7)	<0.001	0.811	0.762-0.863
	MVT-motorcyclist (n=10994)	615 (5.6)	0.968	0.998	0.918-1.086
	MVT-pedestrian (n=7775)	557 (7.2)	<0.001	1.320	1.208-1.442
	Firearms (n=5273)	337 (6.4)	0.011	1.156	1.033-1.294
≤8 (severe TBI)	Fall (n=46110)	4609 (10)	<0.001	0.355	0.343-0.366
	MVT-occupant (n=39150)	10234 (26.1)	<0.001	1.617	1.574-1.661
	Struck by/against (n=25324)	2258 (8.9)	<0.001	0.348	0.333-0.364
	MVT-motorcyclist (n=10994)	3516 (32.0)	<0.001	1.998	1.915-2.083
	MVT-pedestrian (n=7775)	2633 (33.9)	<0.001	2.151	2.049-2.258
	Firearms (n=5273)	2920 (55.4)	<0.001	5.381	5.090-5.690

TBI: Traumatic brain injury, MVT: Motor vehicle traffic

MVTP (OR: 2.15; 95% CI, 2.05-2.26; p<0.001), and firearms (OR: 5.38; 95% CI, 5.09-5.69; p<0.001) were all most likely to be associated with severe trauma (GCS ≤8) (Table 3).

Injury Severity and Degree of Traumatic Brain Injury

Assault injuries were mostly associated with minor injury (OR: 1.67; 95% CI, 1.63-1.72; p<0.001) while self-inflicted injuries (OR: 5.24; 95% CI, 4.87-5.64; p<0.001) were mostly associated with very severe injury according to ISS. Similarly, assault injuries had the greatest odds of association with minor TBI (OR: 1.36; 95% CI, 1.32-1.40; p<0.001) and self-inflicted injuries, with severe TBI (OR: 8.06; 95% CI, 7.45-8.72; p<0.001) (Figure 4A).

Optic nerve and visual pathway injuries were associated with greater odds of severe TBI than other injuries (OR: 2.91; 95% CI, 2.70-3.14; p<0.001). Eye/adnexal contusions (OR: 1.25; 95% CI, 1.22-1.28; p<0.001) were most associated with minor TBI. Open globe injuries were most associated with severe TBI compared to lower levels of TBI (OR: 1.76; 95% CI, 1.68-1.85; p<0.001) (Figure 4B). Traumatic optic neuropathy was more associated with mortality (OR: 2.27; 95% CI, 2.02-2.55; p<0.001) than other visual pathway injuries. Of ocular motor nerve palsies, third nerve palsy had greatest association with severe TBI (OR: 4.32; 95% CI, 3.76-4.96; p<0.001), while sixth nerve palsy was most associated with moderate TBI (OR: 2.00; 95% CI, 1.62-2.48; p<0.001). There was no strong relation between fourth nerve palsy and any TBI category. Of the related head injuries, skull base fractures had the greatest odds of severe TBI (OR: 4.07; 95% CI, 3.95-4.21; p<0.001), while intracerebral hemorrhages (OR: 4.28; 95% CI, 4.10-4.48; p<0.001) and skull base fractures (OR: 3.74; 95% CI, 3.57-3.91; p<0.001) had similarly high odds of mortality-related trauma.

Discussion

TBI has received the most attention in relation to sport and combat-related injury, but is now increasingly recognized in other forms of trauma. Numerous studies have examined the visual and ocular sequelae of TBI.[9,10,12,13,14,15,16,17] However, few have evaluated the concurrence of ocular trauma and TBI and the circumstances of injury.[18,19,20,21,22,23] It is important for physicians to understand this association and identify at-risk populations, as they will frequently encounter patients with these comorbidities and may be a part of multidisciplinary teams managing the acute care and long-term rehabilitation.

We found that a majority of patients admitted with ocular injuries had associated TBI. These patients were predominantly male, white, between 21 and 64 years old, and from the southern United States. Most injuries resulted from blunt force trauma and were unintentional. Although falls were the most common mechanism for the whole group, mechanisms varied amongst different demographic groups. Males were more often injured by SBA, MVTM, and firearms, and females by falls and MVTO. Furthermore, males were more likely to suffer assault or self-inflicted injury, while females were more likely to suffer unintentional injury. Scruggs et al.[27] in their study of ocular injuries in trauma patients using weighted NTDB data also found that patients were more likely to be male and white. However, their average age was 38.2 years, which is younger than the average of 41.8 years in our study. Also, they found MVTO to be the most frequent mechanism of injury among patients with ocular injury of any type, with falls being the next most frequent. These differences likely resulted from sourcing different datasets and our subgroup focus, which may have skewed our findings towards an older group more prone to falls.

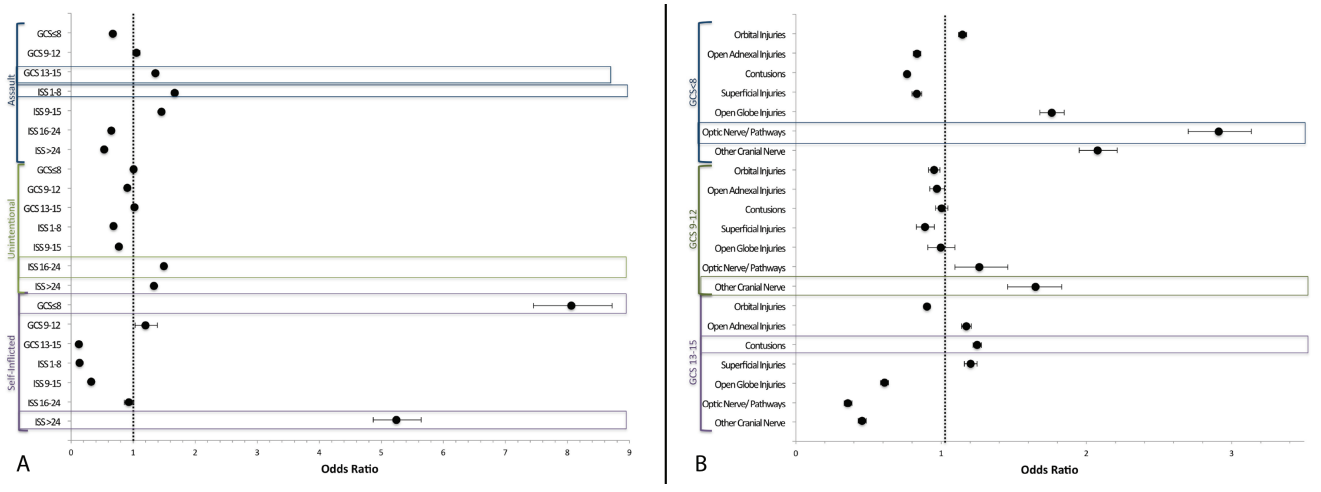

Figure 4. (A) Summary of the simple logistic regression analysis of injury intention and injury severity. Assault was most associated with minor TBI (GCS 13-15) and ISS (1-8) (p<0.001), while self-inflicted injury had 9 times greater odds of association with severe TBI (GCS ≤8) and 5 times greater odds of very severe ISS (>24). (B) Summary of the simple logistic regression analysis of ocular trauma and severity of TBI. Of all injuries, optic nerve/visual pathway injuries had the highest odds of association with severe TBI (GCS ≤8), other cranial nerve injuries with moderate TBI (GCS 9-12), and contusions with mild TBI (GCS 13-15)

GCS: Glasgow Coma Score, ISS: Injury Severity Score, TBI: Traumatic brain injury

Falls were often associated with moderate injury severity and minor TBI, and occurred most at home and in residential facilities. However, GCS has been shown to be a poor predictor of mortality in older adults, as they tend to present with higher GCS (lower TBI level) relative to injury severity compared to younger patients.[28] Furthermore, the mortality from falls among older adults in the United States has been shown to be very high.[29] Han et al.[30] examined ethnic and racial differences in falls in adults older than 65 years and found that falls and consequent mortality was highest amongst white patients compared to black and Hispanic patients. This is consistent with our findings that falls were most common among white patients. Although previous literature has addressed both diagnoses separately, to our knowledge, there have not been any studies of concurrent TBI and ocular injury resulting from falls.

Gardner et al.[31] conducted a scoping review to examine TBI in older adults and found that over 50% of those aged 65-74 years had TBI from falls, which increased to over 70% in the 75-84 years group and over 80% in those 85 and older. Furthermore, they found that most patients with TBI tended to be white females. Results are similar in studies examining ocular injury alone. McGwin et al.[32] used the National Hospital Ambulatory Medical Care and National Hospital Discharge surveys to evaluate eye injuries in the United States. Of 422,604 patient visits, they found that falls were highest in females older than 60 years of age. These findings concur with our results of fall-related eye injuries being most frequently observed in women and in patients 65 and older. In a study of isolated orbital fractures, Toivari et al.[33] also found that falls were the most frequent mechanism of injury in the older age group.

With respect to racial variations, we found that young black patients represented an especially vulnerable population. Our study revealed that black patients incurred their injuries mostly from assault and were at highest risk for firearm-related injury than another race/ethnicity. Firearm-related injuries were mostly associated with very severe injury and severe TBI, carrying implications for poor outcomes for this group. Our findings are supported by McGwin et al.[34], who identified young, male, black patients to be at highest risk of gun-related eye injury. Bertisch et al.[35] examined 399 survivors of firearm brain injury and found that black patients were disproportionately affected and often victims of assault. In our study, unintentional injuries outnumbered other intentions among white patients, although white and male patients were more prone to self-inflicted injuries than other group. These injuries had the highest ISS and levels of TBI, a finding that comports with other studies.[36,37] Most of these patients survived their injuries and represent an at-risk group that can be targeted to prevent further attempts.

Orbital injuries and eye/adnexal contusion were the most frequently identified ocular injuries concurrent with TBI, while open-globe injuries were less common. Weichel et al.[18] studied combat-related ocular trauma and found that TBI was present in 66.4% of cases. Closed-globe injuries were more frequent than open-globe injuries. Their study also revealed that TBI ranged evenly from mild to severe. Although our study revealed a similar preponderance of ocular injuries, TBI was mostly mild. This might reflect the relative severity of combat-related versus civilian injuries. Despite these differences, we noted that concurrent open-globe injury and TBI were mostly associated with severe TBI rather than other levels of TBI (Figure 4B). This implies greater injury severity that might impact management planning by ophthalmic surgeons as part of the multidisciplinary trauma team.

Retinal injuries occurred in 6.2% of all patients with TBI in this population. Several reports have associated retinal findings in patients with TBI.[23,38,39,40] In a recent study that looked specifically at ocular injuries in children with documented abusive head trauma, Weiss et al.[40] used the same NTDB source and found that retinal edema was more associated with severe TBI (GCS <8) (OR: 1.19; p=0.051) and severe ISS: 16-24 (OR: 1.21; p=0.030) than other categories of injury severity. In the present study, retinal hemorrhages also had the greatest association with severe ISS (OR: 1.69; p=0.005), but there was no propensity for association with any category of TBI.

Traumatic optic neuropathy represented 1.5% of all ocular injuries with TBI and had the highest association with mortality. Warner and Eggenberger[41] estimated that traumatic optic neuropathy occurred in 0.5-5% of closed head injuries and up to 10% of craniofacial fractures, which comports with our findings. Contrary to other studies, we found that abducens (sixth) nerve injuries outnumbered oculomotor (third) and trochlear (fourth) nerve injuries. Gise et al.[19], who found similar relative frequencies in pediatric ocular motor nerve injuries with TBI, suggested this is likely due to observer bias. Emergency department physicians evaluating patients in the context of acute major trauma may find it easier to identify the adducted eye of sixth nerve palsy than other ocular motor nerve palsies which might require more patient cooperation and a skilled examiner. Heo and Lambert[22] used claims data (2007-2016) and assessed rates of muscle transposition surgery and chemodenervation in third, fourth, and sixth nerve palsy in patients with TBI. They found that out of 2,606,600 patients with TBI, 1,851 patients (0.071%) had ocular motor nerve palsy and fourth nerve palsies were most frequent (37.7%). They also noted that third nerve palsy was most associated with moderate to severe TBI. We similarly found a stronger association between severe TBI and third nerve palsies compared to other ocular motor nerve palsies.

Study Limitations

This study has several strengths, including the large dataset which allows a detailed analysis. Also, the availability of grades of GCS and ISS enabled analysis of associations between mechanisms, intentions, and various injuries with grades of TBI and global body injury. However, important limitations include the retrospective, database-sourced design. The NTDB is submitted by trauma teams and the spectrum of reported ocular injuries may represent underestimations. Ophthalmic injury details were grouped in broad categories without details that usually are subsequently outlined by ophthalmic surgeons.

Citirik et al.[23] detailed clinical and ancillary findings in patients with Terson's syndrome and TBI, and visual outcomes following pars plana vitrectomy. Vision improved in all patients, all of whom were operated on more than 6 months post-injury. These findings are useful and might help guide ophthalmic surgeons managing this ocular trauma. Similar specific clinical, management, and outcome details are not available in the NTDB.

OTS, a system of grading the degree of ocular trauma using injury variables (initial vision, ruptured globe, endophthalmitis, perforating injury, retinal detachment, and afferent pupillary defect), to predict final visual outcome is not available in this database.[26] Ophthalmic outcomes are also missing from the NTDB. In a recent paper, Sia et al.[20] reported visual outcomes of 88 patients at Walter Reed National Military Medical Center admitted following combat-related trauma. They found that patients with ocular trauma alone had better vision-related quality of life than those with ocular trauma and TBI.

Lastly, this data also employed ICD-9-CM codes used between 2008-2014, which are not as specific as new ICD-10-CM codes. We did not use more recent data using the ICD-10-CM to ensure uniformity of code style for consistent analysis. With respect to the most documented retinal injury of "retinal edema", commotio retinae/Berlin's edema is classified under the non-specific ocular contusion/concussion with the ICD-9-CM code 921.3. The current ICD-10-CM is similarly non-specific. The American Academy of Ophthalmology has recommended using H35.81 for "other specified retinal disorders; retinal edema for commotio retina", with the addition of a mechanism of injury.[42]

Despite these limitations, the findings disclosed herein are worthy of consideration. A recent meta-analysis reviewed ocular trauma publications over the last 20 years and found reported ocular trauma with concomitant TBI in 38-64% of open-globe injuries and 39-47% in closed-globe cases. In the Walter Reed Ocular Trauma Database, 40% of patients with ocular trauma had concomitant TBI.[21] Although the reviewed reports all detail combat-related injuries, they comport with our findings of TBI in 58% of all ocular trauma of all mechanisms. Physicians managing trauma need to be aware of the frequent concurrence of TBI and ocular trauma and be acquainted with the spectrum of ophthalmic sequelae of TBI that may require long-term rehabilitation after acute surgical intervention.

Conclusion

TBI was a frequent finding in admitted trauma patients with ocular injury. Males and patients in their productive years were most frequently affected. Mechanisms and intentions of injuries varied with demographic groups. Similar analytical studies that confirm our findings will not only help inform providers of the frequent concurrence of ocular trauma and TBI in the general population but may help guide screening and rehabilitation efforts and help policy makers develop focused interventional strategies that measurably reduce ocular trauma.

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Ethics

Ethics Committee Approval: The institutional review board of the Albert Einstein College of Medicine approved this evaluation of the National Trauma Data Bank (NTDB) (approval no: #2015-4769, date: 04.08.2015).

Informed Consent: All data in the NTDB is de-identified and patient consent was deemed unnecessary.

Authorship Contributions

Concept: T.T., C.H.H., J.N.M., Design: T.T., C.H.H., J.N.M., Data Collection or Processing: K.Z., T.T., C.H.H., A.P., J.N.M., Analysis or Interpretation: K.Z., T.T., C.H.H., A.P., J.N.M., Literature Search: K.Z., J.N.M., Writing: K.Z., T.T., C.H.H., A.P., J.N.M.

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

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Original Article

Surgical Outcomes of Rhegmatogenous Retinal Detachment Associated with Regressed Retinopathy of Prematurity

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Abstract

Objectives: To evaluate the characteristics and surgical outcomes of late-onset rhegmatogenous retinal detachment (RRD) associated with regressed retinopathy of prematurity (ROP) and the status of fellow eyes.

Materials and Methods: Retrospective review of consecutive cases undergoing surgery for regressed ROP-related RRD and the fellow eyes between 2012-2022. Demographic data, fundus findings, retinal detachment characteristics, surgical procedures, and anatomic and functional outcomes were analyzed. Anatomic success was defined as retinal attachment after silicone oil removal at final follow-up.

Results: Fifteen eyes of 14 patients with a history of regressed ROP underwent surgical repair for RRD at a mean age of 12 (range, 3-26) years. Primary surgical intervention yielded a 53% failure rate overall. This rate was 33% for scleral buckling (SB), 100% for pars plana vitrectomy (PPV), and 40% for combined SB-PPV surgery. Eyes with posterior cicatricial changes and/or proliferative vitreoretinopathy (PVR) demonstrated a higher tendency for recurrence. The final anatomic success rate was 73% after a mean number of 2.3 (range, 1-5) surgeries. The chances of restoring useful vision diminished with repeated surgery despite the improvement in anatomic success. In the fellow eyes, peripheral retinal pathologies were universally observed, with posterior cicatricial changes noted in 33%.

Conclusion: The study reveals a significant initial failure rate in surgical treatment of cases with late-onset RRD associated with regressed ROP, particularly in eyes with posterior cicatricial changes or PVR, suggesting the need for a combined surgical approach as an initial strategy in such high-risk cases. The consistent presence of retinal abnormalities in fellow eyes calls for proactive monitoring and potential prophylactic intervention.

Keywords: Retinopathy of prematurity, ROP, retinal detachment, regressed ROP, cicatricial ROP

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Introduction

Retinopathy of prematurity (ROP) is a developmental vasoproliferative disorder of the retina that affects premature infants. As a result of advances in neonatal care and improved survival rates of extremely premature infants with low birth weights, the incidence of ROP has markedly increased over recent decades.[1] Most cases of ROP regress either spontaneously or after treatment with laser photocoagulation, anti-vascular endothelial growth factor (VEGF) injections, or vitreoretinal surgery.[2] Following the resolution of the acute phase of ROP, premature retinas generally undergo regression stages.[2,3] However, until recently, the classification and treatment of ROP have predominantly concentrated on the acute phase, with limited attention given to regression. The third edition of the International Classification of ROP recently provided a comprehensive delineation of the long-term sequelae associated with regressed ROP, including retinal detachment (RD), retinoschisis, and peripheral avascular retina, which is predisposed to lattice-like retinal degenerations and tears.[4] Previous large-scale studies have reported retinal tear rates ranging from 11% to 31% and RD rates from 15% to 39% in ROP survivors.[5,6,7] Once a rhegmatogenous RD (RRD) occurs, it brings unique challenges to the surgeon because of the nature of the disease, which involves a thinned, avascular, and hence fragile retina, and the pathological vitreoretinal interface in these eyes. Management strategies include scleral buckling (SB), pars plana vitrectomy (PPV), or a combination of both. Nevertheless, the prognosis remains guarded, with success rates typically lower than those observed in adult RRD without a history of ROP.[5]

In this report, we present the characteristics and surgical outcomes of eyes with spontaneous or treatment-induced regressed ROP that developed late RRD, also providing an overview of the status of fellow eyes. Herein, we aim to investigate the optimal surgical strategy in these eyes, specifically exploring the efficacy of PPV, SB, or combined surgery (SB and PPV) based on fundus characteristics.

Materials and Methods

We conducted a retrospective review of medical records at Gazi University Medical Faculty Hospital from 2012 to 2022. The focus of the investigation was on individuals who underwent vitreoretinal surgery for late RRD associated with a history of regressed ROP, whether spontaneously or following laser treatment. The study received approval from the Gazi University Local Ethics Committee with a protocol number of E.867614 (meeting date: 23.01.2024) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients or their parents.

Patients were excluded if their gestational age at birth exceeded 32 weeks, birth weight was over 2000 grams, or if they presented clinical findings or had a family history indicative of familial exudative vitreoretinopathy, incontinentia pigmenti, or other Wnt-associated vitreoretinopathies.

Data collected for each case included patient demographics (age and sex), gestational age and weight at birth, duration of postnatal incubation, systemic and ocular comorbidities, any previous treatment for ROP during the neonatal period, RD details with descriptions and age at onset, type and size of retinal tear(s), surgical procedure(s) performed, tamponade used, anatomical and functional results, and follow-up periods. To objectively analyze cicatricial findings in each eye, we utilized the staging system previously described by Kaiser et al.[5] Eyes without posterior cicatricial changes but with peripheral retinal abnormalities such as lattice-like degeneration, vitreoretinal abnormalities at the former ridge area, or peripheral avascular retina were classified as stage 1. Those with changes in the posterior pole, particularly macular dragging and ectopia, were classified as stage 2. The presence of a retinal fold indicated stage 3, tractional RD or retinoschisis indicated stage 4, and phthisis was classified as stage 5. The condition of the fellow eyes was also investigated, focusing on fundus findings, prophylaxis administered, and spherical equivalent refraction. Anatomic success was defined as retinal attachment at the final follow-up after silicone oil removal.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences v22.0 (IBM Corp.; Armonk, NY, USA) and statistical significance was set as a 2-tailed p value <0.05. Snellen visual acuities were converted to logarithm of the minimum angle of resolution (logMAR) units for analyses. Continuous data were tested for normality using the Shapiro-Wilk test. The Wilcoxon signed ranks test was used to compare paired non-parametric data when evaluating the significance of differences in initial and final visual acuity.

Results

Twenty-eight eyes of 14 patients were included in the study. Ten (71%) were male, 4 (29%) were female. The patients' birth weights ranged from 720 to 2000 g, with a mean of 1324 g. Their gestational ages at birth ranged from 24 to 32 weeks, with a mean of 28.6 weeks. All patients had a history of incubator care with oxygen therapy ranging from 1 week to 3 months. Half of the patients had intellectual disabilities, accompanied by varying degrees of motor disturbance and a tendency toward self-mutilation in some patients. Two patients had a history of laser photocoagulation treatment in both eyes for type 1 ROP, while the remaining eyes did not receive any treatment in the neonatal period.

Fifteen eyes developed late RRD, with 13 patients experiencing RRD in one eye and one patient having bilateral RRD with a 5-year interval between eyes. The age at RD development ranged from 3 to 26 years, with an average of 12 years. Two eyes had prior prophylactic treatment with SB. Two eyes had prior phacoemulsification and intraocular lens implantation an average of 3 years (30 and 42 months) before RD development.

In terms of RD characteristics, all eyes presented with macula-off RD. Nine eyes (60%) had total RD, while 6 eyes (40%) had subtotal RD, mainly involving the temporal and inferior quadrants. Types of retinal breaks included multiple retinal holes and tears (n=10, 67%), dialysis (n=3, 20%), giant retinal tear (n=1, 7%), and a tear that could not be visualized in one eye (7%). Six eyes (40%) had peripheral retinal pathologies only, such as peripheral avascular retina, lattice-like degeneration, and vitreoretinal interface abnormalities at the former ridge area, without apparent cicatricial changes. Three eyes (20%) had stage 2 cicatricial changes, showing macular ectopia without apparent peripheral retinal traction. The remaining 6 eyes (40%) had a significant tractional component, including retinal folds or tractional RD, consistent with stage 3 and 4 fundus changes. Two-thirds of the eyes (n=10, 67%) had proliferative vitreoretinopathy (PVR) on presentation.

Six eyes (40%) underwent primary SB surgery, 6 eyes (40%) underwent PPV (including 2 eyes that had prior prophylactic SB), and the remaining 3 eyes (20%) underwent combined SB and PPV surgery. Additional procedures during the primary surgery included lensectomy (n=6, 40%) and retinotomy-retinectomy procedures (n=3, 20%). Silicone oil tamponade was employed in all eyes where vitrectomy was performed.

Overall, 8 eyes (53%) had failure of the primary repair, necessitating further surgery. Specifically, the primary failure rate was 33% in eyes treated solely with SB surgery. This subgroup comprised eyes with stage 1 (n=4) and 2 (n=2) fundus changes without a significant tractional component. Two eyes experiencing repair failure after SB had PVR (n=1) or posterior cicatrization (n=1). Notably, the remaining 4 eyes had no posterior pole pathology or PVR and did not show recurrence after primary SB surgery.

In contrast, eyes treated with primary PPV showed a 100% primary failure rate. All eyes in this subgroup presented with PVR at baseline. Among them, 2 eyes (25%) had stage 3-4, 1 eye (25%) had stage 2, and 1 eye (25%) had stage 1 fundus changes.

Among eyes treated with combined surgery, including the 2 eyes previously treated with prophylactic buckle, the primary failure rate was 40%. Of these 5 eyes, 4 (80%) displayed stage

3-4 cicatrization with significant peripheral traction, and 4 (80%) had PVR.

In the entire cohort, RD recurrence was more common in eyes with PVR (70%) than in those without PVR (20%) and in eyes with posterior cicatricial changes with or without peripheral traction (67%) compared to those with peripheral abnormalities only (33%). However, these differences did not reach statistical significance because of the low number of patients (p=0.06 and p=0.44, respectively). In two eyes, RD recurrence was related to macular holes secondary to posterior tractional membranes, and they were successfully repaired with an amniotic membrane graft (Figure 1).

Following repeat surgeries, the final anatomical success rate reached 73% (n=11), with an average of 2.3 surgeries (range: 1-5) required per eye. The mean follow-up time was 47 months, ranging from 10 to 126 months. At the final follow-up, 3 eyes (20%) retained silicone oil, while 1 eye (7%) developed hypotonia and phthisis bulbi. Overall, there was a significant improvement in visual acuity after surgery (p=0.011), with an initial mean visual acuity of 2.1±0.6 logMAR (equivalent to 20/2500 Snellen) and subsequent improvement to a final mean visual acuity of 1.4±0.8 logMAR (equivalent to 20/500 Snellen). Further investigation of the visual outcomes based on the recurrence of RD revealed notable differences. In eyes that did not experience a recurrence and were successfully treated with primary surgery, the improvement in functional vision was statistically significant (-0.89 logMAR, p=0.04). Conversely, in eyes that did experience recurrent RD, despite achieving anatomic reattachment by the final follow-up, the improvement in visual acuity was not statistically significant (-0.31 logMAR, p=0.1).

Fellow Eyes

Of the 14 patients, one patient had bilateral late-onset RD and the fellow eye of another patient was already in a phthisic state. Among the remaining 12 fellow eyes, peripheral avascular retina was noted in 4 eyes (33%), visible vitreous membranes and interface abnormalities at the former ridge area in 3 eyes (25%), lattice peripheral retinal degeneration in 6 eyes (50%), atrophic retinal holes in 4 eyes (33%), macular ectopia and dragging in 3 eyes (25%), macular fold in 1 eye (7%), and tractional retinoschisis in 1 eye (7%). To address these conditions, prophylactic 360-degree laser photocoagulation was performed in 8 of these eyes. Furthermore, a prophylactic encircling buckle was placed in 2 eyes. Refraction data, available for 8 of these eyes, revealed a mean spherical equivalent error of -3.2 diopters with a range of -6.50 to +1.00 diopters.

Discussion

The management of ROP extends beyond the treatment of acute disease, demanding lifelong attention. Our study adds to the growing evidence highlighting the imminent threat to useful vision in ROP survivors due to late rhegmatogenous complications, particularly RD. Previous research has documented concerning rates of surgical failure (23% to 60%) in this population, coupled with a generally poor visual prognosis once a RRD occurs.[3,5,6,8,9] Consistent with these findings, we observed a high rate of reoperation (53%) and poor visual outcomes.

Previously, Kaiser et al.[5] revealed a susceptibility to RRD even in patients without severe retinal cicatrization. Subsequent research has corroborated this, demonstrating a higher-than-expected prevalence of peripheral degenerations (54%), atrophic holes (35%), and tears (31%) in the peripheral avascular retina, significantly contributing to late RRD.[6,7] Our findings align, with half of the fellow eyes exhibiting lattice-like degenerations,

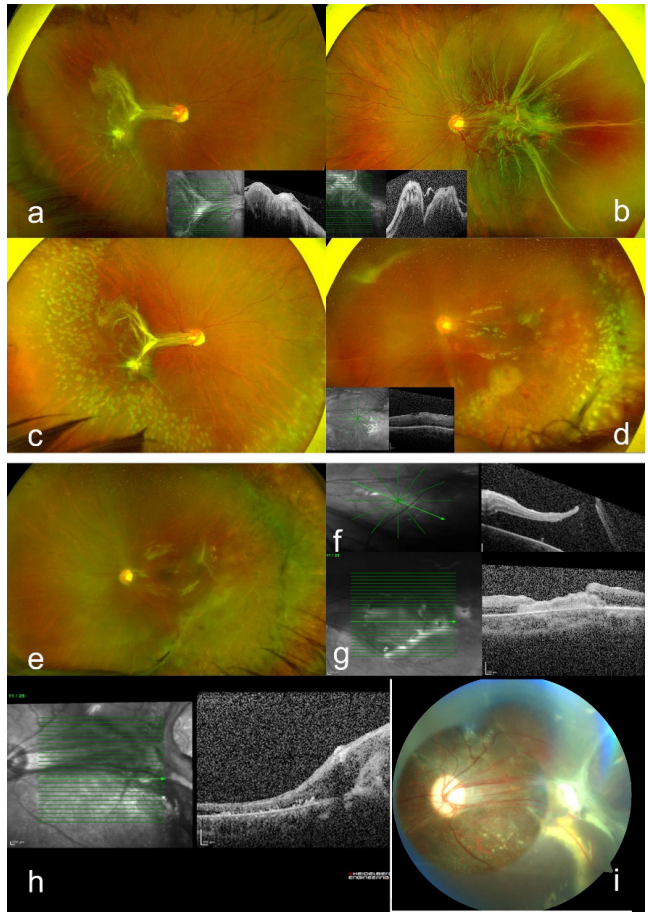

Figure 1. A 12-year-old male patient born at 32 weeks of gestation with a birth weight of 2000 grams who did not receive any treatment for retinopathy of prematurity as an infant was referred with sudden decline in vision in his left eye. His visual acuity was 20/400 in the right eye and counting fingers at a distance of 1 meter in the left eye. The baseline examination revealed bilateral macular dragging and peripheral avascular retina (a, b), along with rhegmatogenous retinal detachment in the left eye caused by a retinal break in the upper temporal quadrant (b). Prophylactic laser photocoagulation was applied to the pigmented lattice degenerations present in the avascular retina of the right eye (c). Combined surgery involving scleral buckling and pars plana vitrectomy was performed in the left eye (d). One month postoperatively, the retina was successfully reattached (e). However, a subsequent recurrent retinal detachment occurred due to the formation of a secondary macular hole within a period of one month (f). This complication was managed by the placement of an amniotic membrane graft, which facilitated the closure of the hole (g). After the third surgical intervention, anatomic success was confirmed, with the retina remaining attached during an 8-month follow-up period after silicone oil removal (h, i). The patient's visual acuity in the left eye remained counting fingers at 1 meter despite anatomic reattachment

and one-third presenting with retinal holes or tears, indicating a sustained risk.

Notably, the mean age for RD development in our cohort (12 years) echoes the findings of Tufail et al.[10] and Sen et al.[9] who observed RRD predominantly in the first to third decades of life (Table 1). While RRD more commonly occurred in late childhood to adolescence, it is crucial to consider the high prevalence of mental retardation and intellectual disabilities in this demographic, as seen in our cohort where half of the patients presented with these conditions, often leading to delayed detection of RD. Furthermore, self-mutilation behavior, commonly observed in this group, heightens the risk of trauma-induced RRD, emphasizing the critical need for proactive preventative strategies to protect these vulnerable eyes. Given the risks, prophylactic treatments such as laser ablation of the persistent avascular retina, or SB in rare cases with significant peripheral retinal pathologies or evident traction, can be considered. Notably, in our cohort, two eyes treated with prophylactic buckle still developed late-stage RRD. This suggests that wider buckles supporting more posteriorly located degenerations or tractions may be necessary to effectively protect areas at risk. The need for further research is evident, particularly to determine the indications and benefits of prophylactic treatment for high-risk eyes and to better understand the implications of persistent avascular retina.

Beyond the challenges of delayed recognition, the inherent complexity of RD within the context of ROP significantly impacts surgical outcomes and complicates the choice of an optimal surgical approach. Existing literature indicates a higher success rate for SB over PPV or combined approaches.[6,9,10] Tufail et al.[10] reported a single surgery success rate of 73% with SB in ROP patients with late RRD, compared to 57% with PPV. Similarly, Hamad et al.[6] reported a primary success rate of 64% with SB, as opposed to 36% with PPV or combined procedures. In our cohort, the primary success rate after SB was 67%, which was higher than PPV or combined surgery (0% and 60%, respectively). This disparity likely stems from the careful patient selection for each technique. SB appears to be particularly effective for isolated RRD in phakic eyes when the retinal break(s) are identifiable and located in mid-zone 2 or anterior zones. However, its efficacy as a stand-alone procedure decreases in the presence of significant posterior cicatrization and tractional components such as retinal folds or tractional RD, which were observed in 40% of our cases. These eyes typically presented retinal tears near areas of traction, where a regressed fibrovascular ridge created a taut vitreoretinal interface with fibrotic membranes. Our experience shows that PPV poses its own set of challenges in such eyes, particularly the difficulty in separating the vitreous cortex, which tends to adhere strongly to both the detached retina and the former ridge area. Achieving complete vitreous removal up to the periphery is often elusive, making an encircling band a useful adjunct to PPV for supporting the residual peripheral vitreous. Notably, while all eyes in the primary PPV group initially failed in our cohort, only 40% in the combined PPV and SB group required further surgery. Despite the high prevalence of PVR (80%) and tractional component (80%) in the combined surgery group, the primary failure rate was nearly comparable to those with milder cicatricial changes who underwent primary SB repair (33%). However, it is important to note that while surgery often more effectively releases anteroposterior traction, it may not fully alleviate tangential traction. The persistence of this traction can lead to recurrences and the formation of new breaks, necessitating repeat surgeries, including relaxing retinectomies in some instances, or the use of some novel sealing materials such as amniotic membrane grafts, as demonstrated in Figure 1.

Study Limitations

There are several limitations to this study. The retrospective nature and the small patient cohort limit its scope, preventing the derivation of incidence or prevalence data. Additionally, referral selection bias is inherent, as the research was conducted at a tertiary institution, which typically attracts more severe

Table 1. Literature review of ROP-related RRD outcomes

Author[ref]	Year	N of cases	Mean GA at birth (weeks)	Mean birth weight (g)	Age at RD development (years)	Mean number of surgeries	Primary anatomic success (%)*			Final anatomical success (%)**
							Primary SB	Primary PPV	Combined SB-PPV	
Kaiser et al.[5]	2001	31	27.9	1136	26.6	1.25	73	100	100	96
Park et al.[3]	2004	5	29.8	1252	8.2	1.6	0	0	100	20
Tufail et al.[10]	2004	40	28.8	1100	22.3	-	72	57	75	97
Sen et al.[9]	2019	22	29.6	1300	10.4	1.4	71	47	-	73
Hamad et al.[6]	2019	88	26.2	832	35	1.5	86	75	26	76
Our study	2024	15	28.6	1324	12	2.3	67	0	60	73

*Primary anatomic success is defined as complete retinal reattachment following the initial surgical procedure, without additional interventions, **Final anatomic success is defined as retinal attachment maintained after silicone oil removal, as assessed at the final follow-up. ROP: Retinopathy of prematurity, RRD: Rhegmatogenous retinal detachment, GA: Gestational age, SB: Scleral buckling; PPV: Pars plana vitrectomy

and complex cases. This may lead to an observation of a disproportionately high rate of primary failure compared to the general population. Despite these constraints, the study gathered long-term follow-up data on ROP-related late RRD and fellow eyes, contributing valuable insights to the relatively sparse literature on late complications in regressed ROP and its management strategies. Overall, our findings support the use of SB as the initial approach for isolated RRD with limited posterior cicatrization. For cases involving significant posterior cicatrization, along with considerable traction and/or posterior breaks, a combination of PPV and SB appears to be the most effective initial approach. While anatomic success can be achieved even after multiple surgeries, the chances of restoring useful vision diminish correspondingly.

Conclusion

As we confront the growing global challenge of ROP due to increased survival rates of extremely premature neonates and the use of anti-VEGF therapy, our focus should pivot towards a deeper understanding, proactive prevention, and effective management of its late complications. It is imperative to establish a rigorous lifelong examination schedule, particularly for non-verbal patients, to timely identify and address potential complications. Further research is essential not only to determine effective prophylactic and surgical strategies but also to customize these approaches for the unique risk profiles of individual patients.

Ethics

Ethics Committee Approval: The study received approval from the Gazi University Local Ethics Committee with a protocol number of E.867614 (meeting date: 23.01.2024) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Obtained.

Authorship Contributions

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

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Review

Choriocapillaris in Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is a multifactorial disease characterized by progressive alterations of different retinal structures ultimately leading to vision loss. Among these, the choriocapillaris (CC) has been found to be affected in different stages of AMD. In this review we provide a discussion on the different stages of AMD, focusing particularly on the alterations involving the CC. This has been possible thanks to the introduction of optical coherence tomography-angiography, a recently developed imaging technique which allows the detection of blood flow in choroidal vessels. Therefore, the aim of this review is to provide a description of the various alterations involving the CC in the different stages of AMD.

Keywords: Age-related macular degeneration, choriocapillaris, optical coherence tomography angiography, AMD classification

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Introduction

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is one of the principal causes of blindness worldwide and the leading cause of visual loss in western countries in people older than 55 years of age.[1] This disorder is estimated to affect 196 million people globally, among which 8.4 million suffer from a moderate to severe visual impairment.[2] The exact pathophysiologic process leading to the development of AMD is still incompletely understood. However, a combination of non-modifiable and modifiable risk factors has been implicated in the pathogenesis. The former include genetic predisposition, with the genes *CFH*, *C3*, *C2*, *ARMS2*, *FB*, *CFHR4*, *CFHR5*, and *F13B* having the strongest correlation,[1] as well as age, northern-European ancestry, and a positive family history.[2] Among the latter, only smoking is a known risk factor, although cardiovascular disease, a high body mass index, a high-fat diet, and low intake of antioxidants have also been hypothesized.[3,4]

AMD is characterized by the accumulation of uncleared cellular debris coming from the retinal pigment epithelium (RPE), called drusen, between the RPE and the inner collagenous layer of Bruch's membrane (BM). Drusen are constituted of lipids with esterified and unesterified cholesterol, as well as proteins and carbohydrates.[5]

Numerous classifications have been proposed for AMD.[4,6,7] However, the classification proposed by Ferris et al.[8] is the most widely used. This classification identifies five clinical stages: no apparent aging changes, normal aging changes, and early, intermediate, and late AMD. Grading is based on the presence of drusen and pigmentary abnormalities within the space of two disc diameters from the fovea. The first two stages are non-pathologic, early AMD is characterized by the presence of medium drusen (>63 µm and <125 µm) and the absence of pigmentary alterations, intermediate AMD (iAMD) by large drusen (>125 µm) and/or pigmentary abnormalities, and late

AMD corresponds to the presence of macular neovascularization (MNV) and/or geographic atrophy (GA).[8] Patients with early AMD are usually asymptomatic or may complain of mild central vision distortion, while later forms present with a more marked vision loss that can progress more or less rapidly in the neovascular or GA forms, respectively.[4]

In the past, the AMD diagnosis was mostly based on clinical examination. Nowadays, imaging techniques including structural optical coherence tomography (OCT) and OCT angiography (OCTA) may allow for an earlier and faster diagnosis.[4,5,6,7,8,9] In AMD the choriocapillaris (CC) can also undergo several alterations which can reflect the different stages of the disease. In iAMD, a lower number of signal voids, larger signal void average size, and greater signal void total area may be observed on OCTA.[10,11] In neovascular AMD (nAMD) and GA, the signal void size is even larger, suggesting that an impairment of the CC can lead to the development of these pathologies.[12]

The Choriocapillaris

The choroid is located between the sclera and the retina and receives blood from three branches of the ophthalmic artery.[13] The choroid is composed of three layers in the macular region: Haller's layer, Sattler's layer, and the CC.[14]

The CC, initially documented in 1702, forms the innermost layer of the choroid and consists of fenestrated capillaries situated just beneath BM. The CC represents the structure with the highest capillary density in the human body, allowing a high rate of exchange.[15]

The configuration of the CC varies across different regions of the eye. In the equatorial area, the capillaries exhibit a polygonal shape; at the periphery, they form an elongated network; in the posterior pole, they resemble a dense honeycomb structure; whereas in the peripapillary and submacular areas, they appear as a continuous aggregation of capillaries.[14,16]

Histologically, the CC typically exhibits an average height of 6.8±2.5 µm. Endothelial cells form the innermost membrane and primarily facilitate molecular exchange between BM and the blood, predominantly through fenestrations, although occasionally via intracellular transportation. Various molecules are involved in the biochemical pathways of CC cells, including transthyretin, heparin, and fibronectin. It is also important to highlight the role of vascular endothelial growth factor (VEGF) in the physiological choroidal development, as it is also involved in the neovascular form of late AMD.[14] The CC has numerous other functions in addition to paracellular fluid exchange through fenestrations. The hydrostatic and oncotic pressures inside its vessels help maintain retinal attachment and can influence intraocular pressure. Additionally, CC flow can vary throughout the day, typically peaking in the morning and responding to postural changes.[14]

Several previous studies have investigated the CC histologically, especially in eyes with GA. McLeod et al.[17] analyzed postmortem choroids from 11 subjects, including controls, GA patients, and individuals with nAMD. They utilized methacrylate embedding and sectioning to assess structural changes, revealing that while GA regions exhibited evident loss of RPE, the CC could remain intact. This led the authors to propose that the primary insult in GA likely begins at the RPE level, followed by subsequent CC degeneration. Seddon et al.[18] investigated postmortem choroids from 36 subjects, including controls and AMD patients with varying disease stages, including GA. They employed *Ulex europaeus* agglutinin (UEA) lectin staining and confirmed a significant reduction in the CC in eyes with GA, particularly in regions of RPE atrophy. Despite some persistence of CC vessels within GA regions, their diameter was notably reduced, indicating both morphological and functional changes in these surviving vessels. Lastly, Edwards et al.[19] conducted a recent analysis on postmortem choroids from eight subjects, including controls and individuals with GA, with available imaging data prior to death for clinicopathologic correlations. Using UEA lectin staining, they observed severe CC dropout directly corresponding to areas of RPE atrophy in GA eyes. Surviving CC vessels in these regions appeared constricted. Conversely, CC vessels in regions with intact RPE resembled those in healthy controls.

OCTA to Assess the CC

OCTA offers several advantages over fluorescein angiography (FA) and indocyanine green angiography (ICGA), including its non-invasive nature which eliminates the need for contrast agent injections and reduces the risk of allergic reactions.[20,21] Additionally, OCTA provides higher resolution visualization of deeper layers. However, it lacks the ability to dynamically interpret blood transit and visualize leakages. Interpretation of OCTA images may be challenging in the presence of pathological alterations such as retinal neovascularization or drusen, as these can interfere with the passage of the laser beam.[22,23] Furthermore, small vessels may not be clearly identifiable on OCTA due to slow blood flow, and any eye movement can result in artifacts, complicating image interpretation.[24]

OCTA is an imaging technique used to visualize blood flow in retinal and choroidal vessels. It works by acquiring multiple B-scans of the same area to generate three-dimensional volumetric data, providing a representation of the vascular lumen.[22] OCTA images of the CC typically have a granular appearance, which helps distinguish this vascular layer from the underlying layers.[25,26,27,28] To improve image quality and enhance visualization of CC vessels,[28,29,30] image averaging can be employed, transforming the granular pattern into a meshwork and rendering vessel segments more continuous.[14,31]

OCTA images of the CC typically display "flow voids", which manifest as small dark regions that possibly represent intercapillary spaces, alongside brighter areas indicative of blood flow within the CC.[11,21] Interestingly, there's been a suggestion to rename "flow voids" as "signal voids", as it's challenging to distinguish blood flow below the decorrelation threshold.[32] Also interestingly, there exists a mathematical power law relationship between the number and size of these voids, with a constant correlated to factors such as age, hypertension, and the presence of late AMD in the fellow eye.[10] Studies have indicated that the

increase in flow deficits with aging is more pronounced in the fovea.[33] This is probably due to the higher production of waste metabolites in the foveal region, which puts the CC under greater stress.[14]

Overall, there are some limitations in studying the alterations of the CC in different stages of AMD. These include several artifacts that may limit the assessment of the CC.[21]

CC in Intermediate AMD

In AMD, the CC can undergo various alterations, which differ according to the stage of the disease.[34] In iAMD, drusen are predominantly found in areas of the choroid with a reduced perfusion of the CC. This has been extensively confirmed by OCTA studies showing that flow deficits are heightened in regions where drusen and reticular pseudodrusen are located (Figure 1).[14,35] This observation has led to the hypothesis that the degeneration of endothelial cells can contribute to drusen formation.[14]

In one of the first investigations on this subject, 42 patients (42 eyes) diagnosed with iAMD were compared with 20 healthy controls (20 eyes).[32] The analysis involved quantifying the area of the CC with non-detectable perfusion, indicating total dropout of CC vessels, and determining the average signal void size in the CC with an OCTA device. To ensure accurate analysis, areas directly beneath drusen and major retinal vessels were excluded to minimize the influence of shadowing and projection artifacts. Additionally, patients with iAMD were categorized based on fellow eye status, resulting in two groups: patients affected by bilateral iAMD and those affected by unilateral iAMD with nAMD in the other eye. The study revealed no disparities in the area of non-detectable CC perfusion among the three groups. However, patients with unilateral iAMD exhibited a significant increase in average CC signal void size compared to both bilateral iAMD cases and healthy individuals. Given that eyes affected by iAMD are more likely to progress to nAMD if the fellow eye has nAMD,[36] these findings support the presence of an ischemic choroidopathy that may predispose to neovascularization development. Consequently, alterations in the CC seem to play a crucial role in nAMD pathogenesis. A notable limitation of that study was the inability to assess the CC beneath drusen due to the use of a spectral domain device for image analysis. Nonetheless, previous histopathological research has indicated that drusen tend to form in areas of altered vascularization,[6] suggesting that OCTA might reveal areas with different CC perfusion among patients with iAMD.

To investigate potential topographical discrepancies in CC perfusion among patients with iAMD, a follow-up study utilized a swept source OCTA device.[37] This device offered enhanced assessment capabilities under drusen due to its longer wavelength, which improves penetration through the RPE.[11,38,39] In this study, 30 eyes with iAMD and 30 healthy controls were prospectively included. Notably, CC images were examined in three distinct regions to enable a topographical analysis: (i) within the region with drusen, (ii) within a 150 µm-wide ring surrounding the margin of drusen, and (iii) in drusen-free regions. Comparative analysis with controls revealed that iAMD eyes exhibited a lower number of signal voids, larger average signal void size, and larger total signal void area. Particularly significant differences in these parameters were observed in regions underneath and adjacent to drusen, supporting earlier findings suggesting that drusen tend to form over areas of altered vascularization.[6]

Imaging of the retina has been utilized to study dysfunction of the outer retina resulting from CC impairment in iAMD eyes. A histopathological study by Curcio et al.[40] revealed an important decrease in the number of photoreceptors in eyes with drusen.

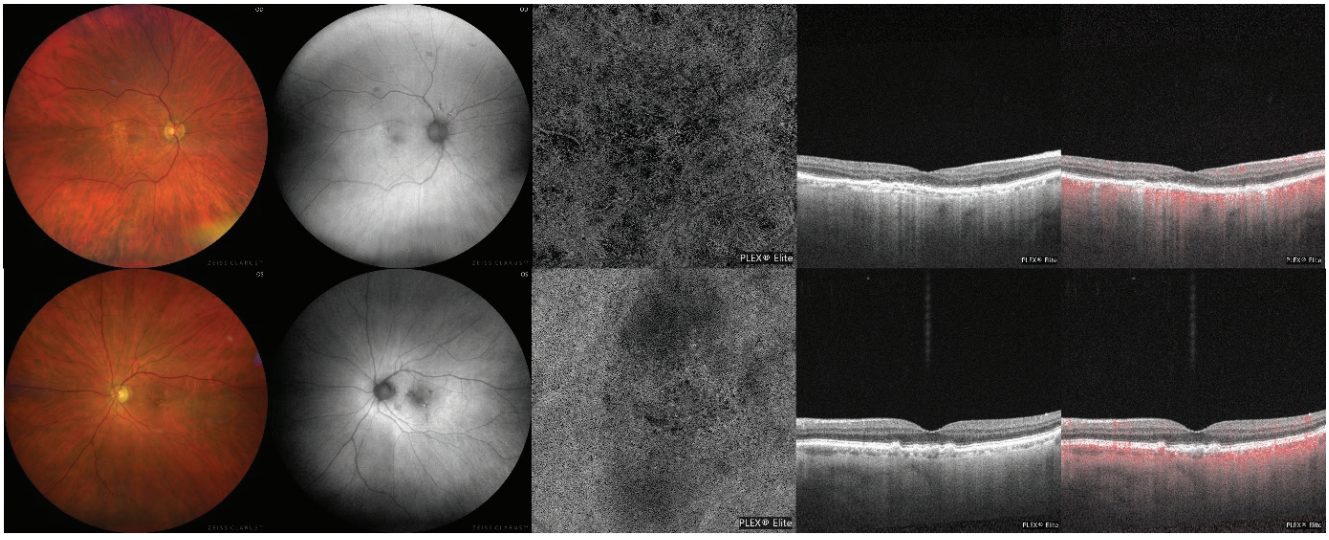

Figure 1. Multimodal imaging from a patient with intermediate age-related macular degeneration: fundus photography (left), green autofluorescence (left-middle), *en face* optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). Drusen larger than 125 µm can be observed on structural OCT, and the *en face* OCTA image segmented at the level of the CC demonstrates areas of hypoperfusion in this vascular layer

Additionally, Boretsky et al.[41], using adaptive optics scanning laser ophthalmoscopy, demonstrated a progressive decline in the density of photoreceptors across different AMD stages. Given the importance of CC flow for sustaining photoreceptors, the reduced CC perfusion in AMD eyes may potentially contribute to photoreceptor damage through an ischemic mechanism. Consequently, multimodal imaging techniques were used to investigate the correlation between CC alterations and photoreceptor disfunction in iAMD eyes.[42] Photoreceptor damage was quantitatively evaluated through analysis of the reflectivity of *en face* OCT images obtained at the ellipsoid zone (EZ). The signal from the EZ originates from ellipsoids in the most internal segment of photoreceptors, which are densely filled with mitochondria.[43] Since both photoreceptor damage and dysfunction can manifest as areas with decreased reflectivity on *en face* images, several studies have evaluated EZ reflectivity as a surrogate for photoreceptor dysfunction.[44,45] However, several patient characteristics (e.g., cataracts) can greatly influence structural brightness, which poses a significant challenge in using *en face* structural OCT to assess the reflectivity of photoreceptors and complicates cohort comparisons. To address this issue, several studies have "normalized" the images.[44,45]

A study involving 35 patients with iAMD and 35 healthy controls utilized swept source OCT and OCTA imaging to establish a topographical correlation with photoreceptor and CC impairment, respectively.[42] This investigation revealed that in eyes with iAMD, the "normalized" EZ reflectivity was notably reduced even in areas devoid of drusen. These findings indicate an important and widespread alteration of photoreceptors. Notably, a positive association was observed between the "normalized" EZ reflectivity and CC perfusion in drusen-free regions. However, no such relationship was identified in regions with drusen or in healthy eyes. Consequently, these results suggest a pathological connection between photoreceptor impairment and CC perfusion in AMD, particularly in regions devoid of drusen.

Another study assessed the association between photoreceptor dysfunction and CC vascularization using multifocal electroretinogram (mfERG) and OCTA, respectively, in 17 eyes of 17 patients with iAMD.[46] Overall, the findings revealed a direct relationship between N1 implicit time and both total signal void area and average signal void size. The N1 wave is believed to stem from post-receptor signals after cones, whereas the P1 wave is derived from the inner retina. Therefore, it was hypothesized that changes in the CC mostly impact post-photoreceptor function. Moreover, the correlation between CC changes and mfERG implicit time, rather than the amplitude of the response, suggests a connection with neuroretinal functional alterations instead of actual cell loss.[47]

CC in Neovascular AMD

nAMD represents a form of late AMD characterized by angiogenesis stimulated by various proinflammatory and proangiogenic cytokines, including VEGF. These cytokines can be secreted by immune cells infiltrating the macula or, more importantly, by RPE cells.[48] Pathologic vessels can originate from either the choroidal or retinal circulation.[8] Hence, the term MNV is preferred over choroidal neovascularization. Three types of MNV have been identified: type 1, type 2, and type 3.[49]

Both types 1 and 2 involve vessel growth from the CC: type 1 manifests beneath the RPE layer, while type 2 penetrates BM and the RPE, proliferating into the subretinal space. In contrast, type 3 MNV originates from the retinal circulation.[49] Histologically, macrophage infiltration near MNV areas, deposits in BM, and ghost CC are commonly observed.[14] Newly formed vessels usually present without fenestrations[14] and the leakage of proteinaceous material occurs mostly through transendothelial channels.[17]

The CC has been extensively studied using OCTA in patients with nAMD (Figure 2).[34] In type 1 MNV, the presence an area

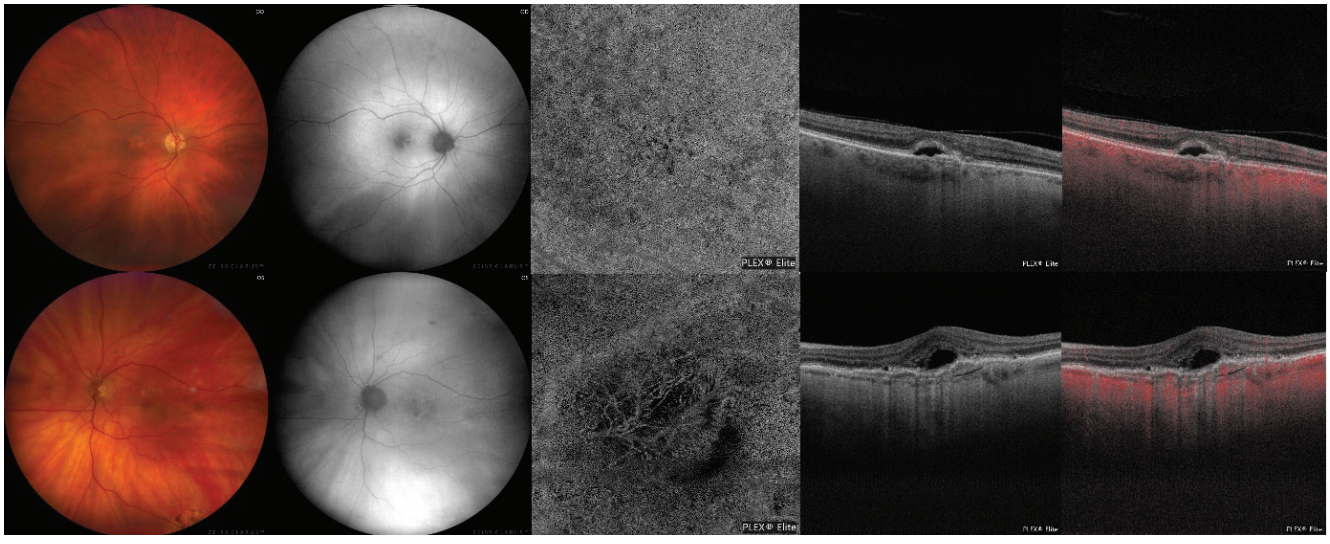

Figure 2. Multimodal imaging from a patient with neovascular age-related macular degeneration: fundus photography (left), green autofluorescence (left-middle), optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). On the *en face* OCTA image, macular neovascularization is evident around a region of CC hypoperfusion

of CC non-perfusion around the lesion has been demonstrated, which was termed "dark halo". It is still not clear if this darkening effect is due to the presence of blood or subretinal or intraretinal fluid, and it is also not fully understood whether the dark halo area indicates ischemia of the CC or is a shadowing effect.[35,50]

The emergence of type 3 MNV is believed to be linked to an alteration in the balance between VEGF and other cytokines coming from the RPE.[51] Studies have demonstrated that untreated nAMD eyes with type 3 MNV exhibit significantly higher levels of VEGF in the aqueous humor compared to eyes with MNV of type 1 or 2, which arise from the choroid instead of the retina. [51] Consequently, it has been proposed that outer retinal ischemia plays a crucial role in driving the development of this MNV subtype. This theory finds support in structural OCT studies, which have revealed a thinning in the choroid in individuals with AMD and type 3 MNV.[52,53]

Given the pivotal function of the CC in nourishing the outer retina and RPE, several OCTA studies have delved into the characteristics of the CC in eyes affected by type 3 MNV. In an OCTA investigation, the CC was quantitatively assessed in eyes with type 3 MNV and the unaffected (i.e., having no signs of MNV) fellow eyes of 21 patients.[54] Furthermore, these unaffected eyes were compared with the unaffected fellow eyes of 20 patients with unilateral type 1 or 2 MNV. The OCTA analysis revealed that eyes with type 3 MNV had significantly higher total signal void area and average CC signal void size (representing CC hypoperfusion) when compared with unaffected fellow eyes. These findings suggest that CC hypoperfusion may lead to ischemic abnormalities of the RPE, ultimately contributing to the development of type 3 MNV. Importantly, the unaffected fellow eyes of patients with unilateral type 3 MNV exhibited more pronounced CC impairment compared to the unaffected fellow eyes of patients with unilateral type 1/2 MNV. These results hint at a potential bilateral effect of CC hypoperfusion in patients with unilateral type 3 MNV, which could partly elucidate the heightened risk of these unaffected eyes eventually developing type 3 MNV.

Another study utilizing swept source technology and image compensation with structural information reaffirmed previous observations of decreased CC perfusion in eyes with type 3 MNV.[55] This investigation included 26 eyes with type 3 MNV (21 patients) and 26 eyes with iAMD (17 patients). Compared to eyes with iAMD, both the total signal void area and the average CC signal void size were elevated in eyes with type 3 MNV. Collectively, findings from OCTA studies support the notion that CC alterations may indeed play a significant role in the development of type 3 MNV, potentially even more so than in eyes with type 1/2 MNV.

Choriocapillaris in Geographic Atrophy

GA is a form of late, non-exudative AMD characterized by atrophy of the RPE and outer retina, along with significant impairment of the CC (Figure 3).[56]

OCTA images have revealed impaired CC perfusion primarily within areas of RPE atrophy in GA.[56,57,58,59] However, some hypoperfusion has been observed in regions with intact RPE, particularly along the GA border. Importantly, perfusion levels at the GA border serve as a significant biomarker for GA progression. Specifically, reduced perfusion in the GA border has been linked to faster GA progression over time. Finally, the CC was demonstrated to be impaired in regions of nascent GA, further suggesting that CC changes may precede a definite atrophy of the RPE.[60]

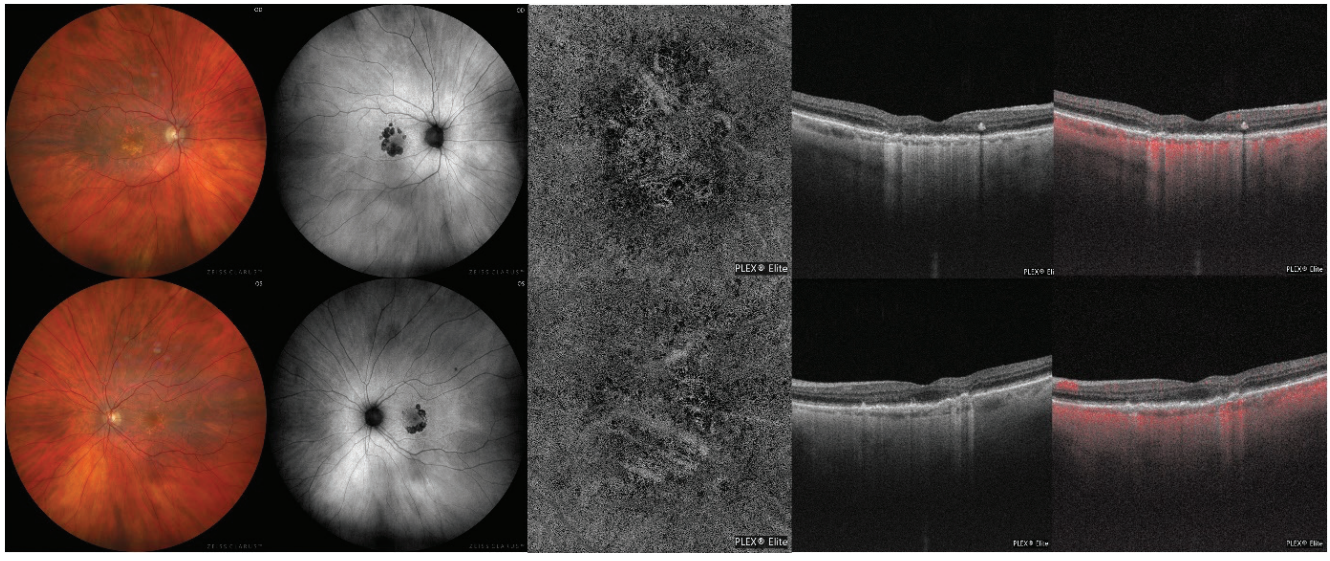

Figure 3. Multimodal imaging from a patient with geographic atrophy: fundus photography (left), green autofluorescence (left-middle), *en face* optical coherence tomography angiography (OCTA) image segmented at the level of the choriocapillaris (CC) (middle), structural OCT B-scan image through the fovea (right-middle), and structural OCT B-scan image with overlaid flow (right). In the *en face* OCTA image segmented at the level of the CC, there is a noticeable diffuse hypoperfusion of the CC, primarily co-localizing with the region exhibiting geographic atrophy. Interestingly, the absence of the CC causes a better visualization of the outer choroidal vessels, which are usually not visible in physiological conditions

Conclusion

AMD is a leading cause of visual impairment worldwide, impacting various structures within the eye. The CC is significantly affected in AMD, with pathologic changes varying across disease stages. The advent of OCTA has notably enhanced our understanding of these alterations, offering advantages over conventional FA and ICGA. This review aimed to underscore the newfound insights into the role of the CC in AMD, which are vital for elucidating its pathogenesis and facilitating the delivery of optimal therapy for affected patients.

Ethics

Authorship Contributions

Concept: All authors, Design: All authors, Literature Search: G.N., Writing: G.N., E.B.

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

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Case Report

Ocular Involvement in Patients with Infantile Nephropathic Cystinosis

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Abstract

Cystinosis is a rare autosomal recessive lysosomal storage disease associated with high mortality and morbidity rates. The most distinctive ocular manifestations of cystinosis are photophobia, tearing, and blurred vision. Herein, we assessed the ocular involvement of four patients from two families diagnosed with infantile nephropathic cystinosis using optical coherence tomography (OCT) and *in vivo* confocal microscopy (IVCM). Anterior segment OCT demonstrated multiple hyperreflective punctate deposits, and IVCM revealed needle-shaped bright crystal deposits in the corneal stroma in all patients. Three patients also had crystal deposits in the epithelium, where epithelial cell disruption was observed. Crystal deposits around the subepithelial nerve plexus were noted in some sections. In one patient, round and needle-shaped bright deposits along with inflammatory cells were observed in the limbal region of the conjunctiva. Infrared fundus images of two female siblings revealed hyperreflective crystal-like deposits around the optic disc, macula, and peripheral retina, and enhanced depth imaging OCT showed accumulation of crystals in all layers of the retina.

Keywords: Infantile nephropathic cystinosis, *in vivo* confocal microscopy, optical coherence tomography

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Introduction

Cystinosis is a rare lysosomal storage disease with autosomal recessive inheritance and high mortality and morbidity.[1,2] It is caused by a mutation in the *CTNS* gene, which is located on chromosome 17p13.2 and encodes cystinosin, a membrane transport protein that transports cystine from lysosomes to the extracellular space.[1,3]

Cystinosis has three clinical forms: infantile (early-onset) nephropathic cystinosis, juvenile (late-onset) nephropathic cystinosis, and adult (ocular) cystinosis. Infantile nephropathic cystinosis accounts for approximately 95% of cases and is the most severe form.[1] Cystine crystals can accumulate in various organs, including primarily the eyes and kidneys, as well as the nervous system, thyroid gland, bones, muscles, bone marrow, pancreas, liver, lungs, and gonads.[4] These deposits can lead to numerous problems such as Fanconi syndrome, renal failure, rickets, retarded growth and development, learning disabilities, muscle atrophy, gastrointestinal symptoms, dysphagia, and hypothyroidism.[5,6]

In the eye, deposition can be seen in the cornea, conjunctiva, limbus, iris, anterior chamber, iridocorneal angle, lens capsule, ciliary body, choroid, and rarely in the retinal pigment epithelium and optic disc.[1] Clinically, it causes symptoms such as photophobia, tearing, and blurred vision.[7,8] Corneal deposition starts in the periphery and superficial layers and later progresses centrally and into the deeper corneal layers.[9] Gahl et al.[1] defined a scoring system to objectively evaluate the density of cystine deposits in the cornea. This corneal cystine crystal score (CCCS) ranges from 0 (no deposits) to 3 (full of deposits) with 0.25-unit intervals. In advanced cases, pathologies such as recurrent corneal epithelial erosions, corneal thinning, band keratopathy, filamentary keratitis, peripheral corneal neovascularization, posterior synechia, secondary pupillary block, glaucoma, papilledema, and reduced color and night vision may occur.[1,2,3]

In this case report, we discuss the ocular involvement of four patients from two families diagnosed with infantile nephropathic

cystinosis and present their *in vivo* laser confocal microscopy (IVCM) and anterior segment optical coherence tomography (OCT) findings.

Case Reports

Family 1

A couple with two children and no history of consanguineous marriage presented for photophobia in their sons, aged 6 and 9 years. Both boys had best corrected visual acuity (BCVA) of 20/20 in both eyes, and intraocular pressures (IOP) were approximately 12-15 mmHg bilaterally. On biomicroscopic examination, bilateral diffuse cystine crystal deposits in the cornea were observed in both patients (Figure 1). CCCS was 3 in both eyes in the younger sibling and 2 in both eyes in the older sibling. In Scheimpflug-Placido disc-based corneal tomographic imaging (Sirius®, CSO, Italy), central corneal thicknesses (CCT) in the right and left eyes were measured as 548 and 545 µm in the younger sibling and 580 and 570 µm in the older sibling, respectively. In manual measurements performed with anterior segment OCT (Topcon®, Japan), right and left CCT values were 560 and 546 µm in the younger sibling and 575 and 574 µm in the older sibling, respectively. No retinal involvement was observed. The patients exhibited physical growth retardation. It was learned that both patients had been diagnosed with cystinosis 4 years earlier and had since received systemic and topical cysteamine (Cystamin® 0.55%, Tobio Pharmaceuticals, 3 times daily) therapy. However, they had been unable to use topical cysteamine for the last 6 months because it was not available in our country. No mutation in the *CTNS* gene could be detected by clinical exome sequencing. In the deletion/duplication analysis, homozygous duplication of *CTNS* exons 6-8 was detected.

Family 2

A couple with two children and a history of consanguineous marriage presented for photophobia in their two daughters, aged 14 and 18 years. In both patients, BCVA ranged from 16/20 to 20/20 and IOP ranged from 14 to 16 mmHg. On biomicroscopic examination, both patients had cystine crystal deposits in the corneas of both eyes. CCCS was 3 in both eyes in the younger sibling and 2 in both eyes in the older sibling. On corneal tomographic imaging, CCT in the right and left eye was measured as 530 and 536 µm in the younger sibling and 524 and 518 µm in the older sibling, respectively. Manual CCT measurements obtained with anterior segment OCT in the right and left eye were 532 and 546 µm in the younger sibling and 534 and 533 µm in the older sibling, respectively. Both patients also had retinal cystine deposits surrounding the optic disc, around the vascular arcades, and in the peripheral regions that were more pronounced on infrared images (Spectralis®, Heidelberg Engineering, Germany) (Figure 2). OCT sections obtained in enhanced depth imaging mode (EDI-OCT; Spectralis®, Heidelberg Engineering, Germany) revealed cystine deposits in the ganglion cell layer (GCL), inner nuclear layer (INL), inner plexiform layer (IPL), and outer plexiform layer (OPL), but no involvement in the choroid (Figure 3).

It was learned that both of the patients had received systemic and topical cysteamine therapy for a diagnosis of cystinosis and underwent kidney transplantation (the older sibling in 2013 and the younger in 2017). A homozygous c.18_21del/p.Thr7PhefsTer7 rs786204501 variant in exon 3 of the *CTNS* gene was detected by clinical exome sequencing.

Anterior Segment OCT and IVCM Imaging

On anterior segment OCT, all of the patients had diffuse hyperreflective punctate deposits in the stromal layer (Figure 4). On IVCM (Rostock Cornea Module®, Heidelberg Engineering, Germany), diffuse bright needle-shaped crystal deposits were observed in the stroma in all patients. Three patients had crystal deposits in the epithelium, and epithelial cell disruption was observed in these regions. Crystal deposits around the subepithelial nerve plexus were observed in some sections. In one patient, bright round and needle-shaped deposits and inflammatory cells were observed in the limbal region of the conjunctiva (Figure 5).

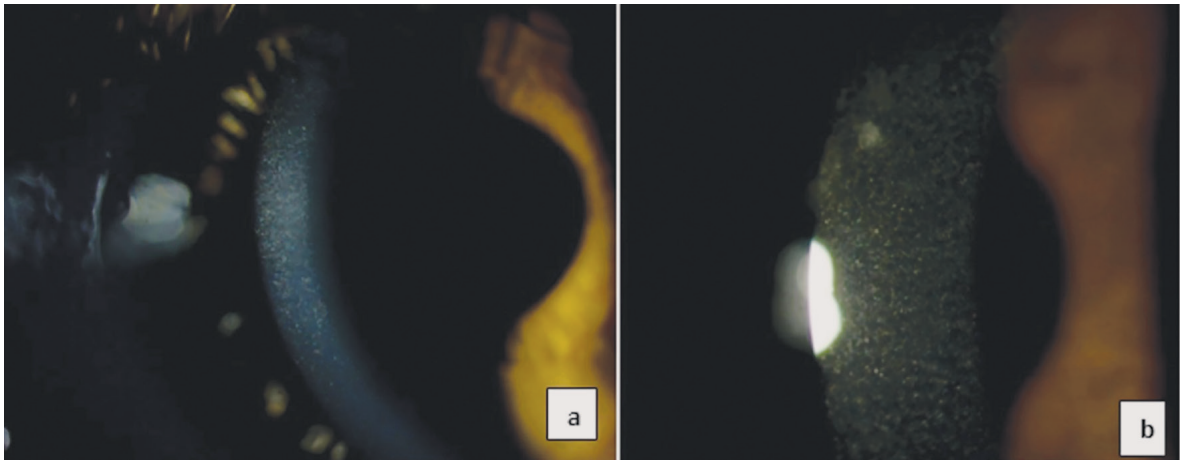

Figure 1. Anterior segment photographs of the diffuse cystine crystal deposits in the cornea taken at 10x (a) and 16x (b) magnification

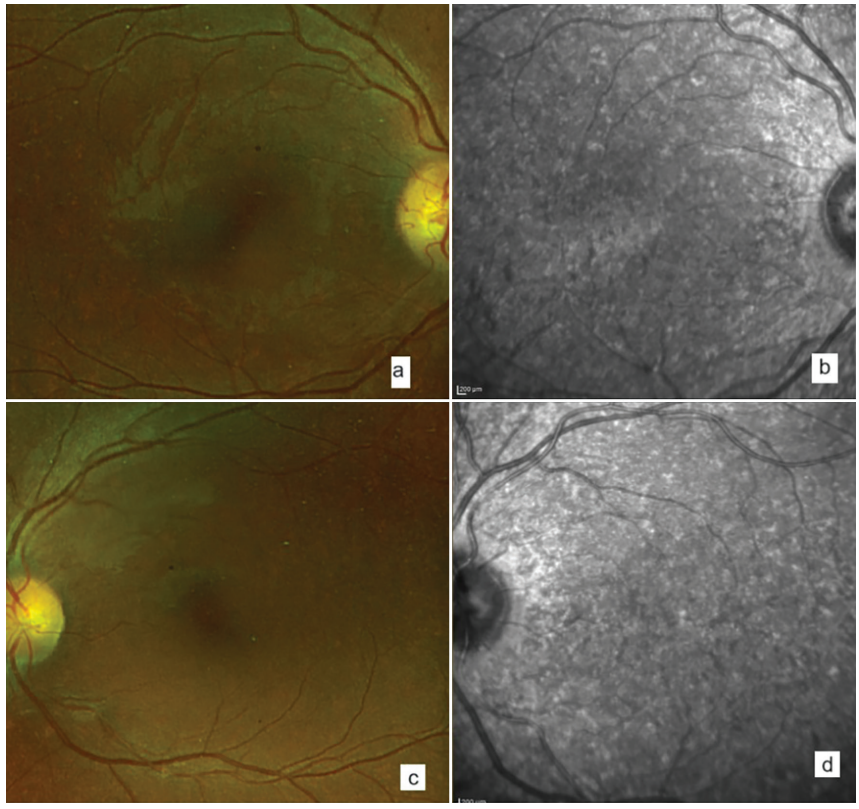

Figure 2. Color and infrared fundus photographs of the right eye (a, b) and left eye (c, d) showing cystine crystal deposits in the macula and optic disc pallor

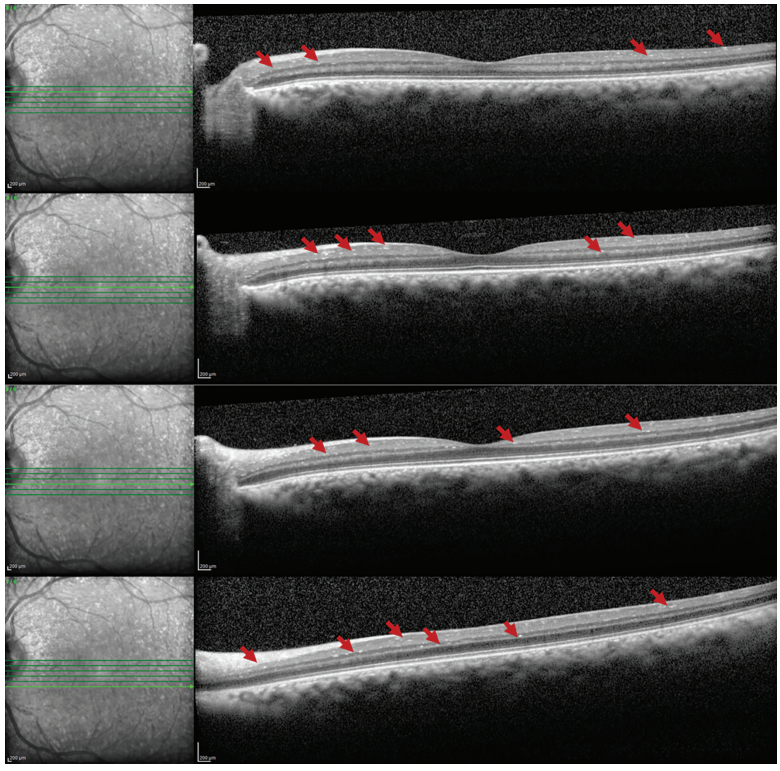

Figure 3. Cystine crystal deposits (red arrows) in the different retinal layers shown on optical coherence tomography sections obtained in enhanced depth imaging mode

Discussion

Ocular involvement is among the most common causes of symptoms and morbidity in patients with cystinosis.[1] The most prominent feature of ocular involvement in cystinosis is diffuse crystal deposition in the cornea. IVCM and OCT enable a detailed assessment of the depth and morphology of these crystals.[10,11] Ozdemir et al.[10] demonstrated the presence of needle- and fusiform-shaped crystal structures in the anterior and posterior stroma using anterior segment OCT and IVCM imaging in a 36-year-old male patient diagnosed with cystinosis. No cystine deposits were detected in the corneal epithelial and endothelial layers. Keidel et al.[11] revealed widespread crystal deposition in all levels of the stroma using anterior segment OCT in 88 eyes of 45 patients. We also observed diffuse stromal deposits in all 4 patients in this study, but there were also deposits in the epithelium in 3 patients. Disruptions in the epithelial cells were noted in areas of dense crystal deposition.

In addition to the cornea, cystine crystals may also accumulate in the retina and choroid in cystinosis. Al Abdulsalam[12] reported OCT findings of dome-shaped crystal deposits in the outer retinal layers in the subfoveal region in a 19-year-old female patient with cystinosis. Keidel et al.[13] detected cystine crystals

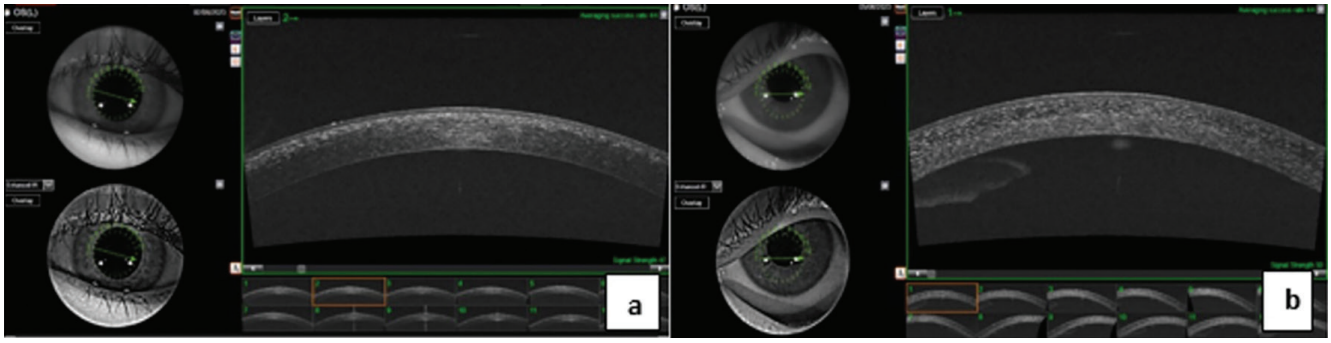

Figure 4. Anterior segment optical coherence tomography images showing cystine crystal deposits in the (a) epithelium and anterior stroma and (b) anterior, middle, and posterior stroma

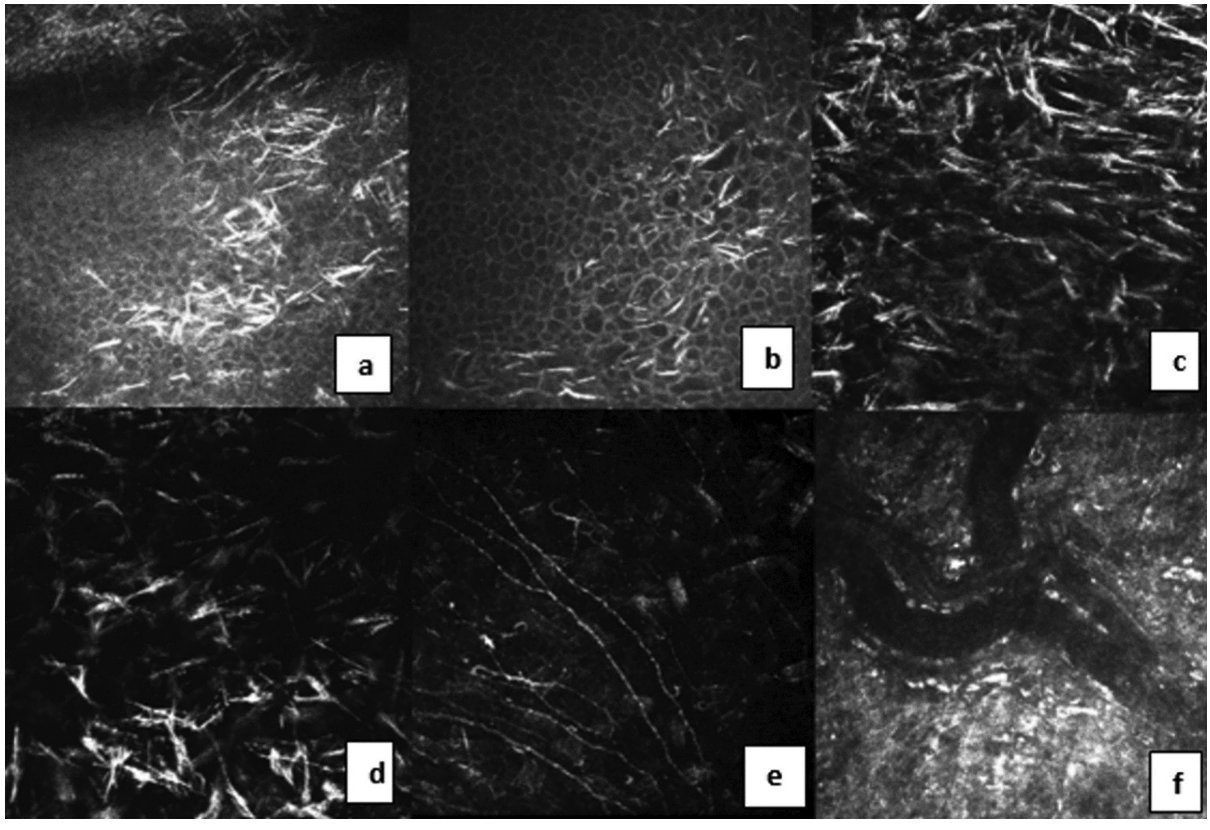

Figure 5. *In vivo* confocal microscopy images showing (a) hyperreflective crystals in the epithelium, (b) disruption of epithelial cells, (c, d) stromal deposits, (e) cystine crystal deposits around the subepithelial nerve plexus, and (f) punctate and linear hyperreflective deposits in the conjunctiva and limbal region

in the fovea on fundus examination and stated that on OCT imaging, these deposits were densest in the choriocapillaris, followed by the GCL, INL, IPL, and choroid. Among our patients, no significant retinal pathology was observed in the boys, while the girls had widespread cystine crystals in the GCL, IPL, INL, and OPL on posterior segment OCT sections and fundus autofluorescence.

Cystinosis is treated with cysteamine, which is available in oral and topical form. Oral cysteamine therapy may slow the progression of renal and retinal findings, but its effect on the cornea is limited because of its avascular structure. In contrast, topical cysteamine both relieves symptoms and helps dissolve crystals in the cornea.[1,14] Early-onset, long-term cysteamine therapy delays end-stage renal failure, reduces the risk of extrarenal complications, and improves survival rates.[15] Among our cases, we believe the diagnosis of the boys at age 2 and 5 and the resulting early initiation of treatment prevented the occurrence of renal complications.

Calculations based on IVCM and OCT deposit analysis have been shown in the literature to offer a more objective and accurate assessment during disease progression and may serve as biomarkers in the future.[11,16] Vercauteren et al.[17] compared corneal thickness measurements taken by anterior segment OCT and corneal tomography in patients with cystinosis and found that corneal tomography measurements were much higher. Therefore, they suggested that anterior segment OCT should be taken as a basis for prognosis and evaluation of treatment response. In our patients, CCT measurements performed with anterior segment OCT did not show a marked deviation from corneal tomography measurements.

In the literature, studies of cystinosis patients consist of limited cases series. Our study demonstrated for the first time with IVCM that crystals accumulated in the corneal epithelium. In conclusion, cystinosis is a rare lysosomal storage disease with autosomal recessive inheritance, and the morphology, extent, and depth of cystine crystals deposited in the cornea and retina can be objectively demonstrated at the tissue and cellular level with IVCM and OCT.

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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

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Case Report

Unilateral Papilledema with Bilateral Optic Nerve Sheath Distension: A Case Report

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Abstract

Bilateral edematous optic disc swelling from papilledema is caused by elevated intracranial pressure (ICP). Idiopathic intracranial hypertension (IIH), a clinical syndrome with elevated ICP of unclear etiology, is a frequent cause of this condition. IIH typically affects obese middle-aged females. Papilledema usually has a fairly symmetrical bilateral pattern. Unilateral papilledema is a rare disorder that must be detected early to avoid optic nerve damage. However, the etiology of unilateral papilledema remains unclear. Based on bilateral optic nerve sheath diameter measurements, we aimed to find an explanation for the unilaterality in this rare case.

Keywords: Idiopathic intracranial hypertension, optic nerve sheath diameter, unilateral papilledema

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Introduction

Papilledema is bilateral and nearly symmetrical optic disc swelling attributed to increased intracranial pressure (ICP).[1] One of the common causes of ICP is idiopathic intracranial hypertension (IIH), a clinical syndrome of increased ICP of unknown etiology that usually occurs in obese middle-aged females.[2] Unilateral papilledema is a rare condition, reported in 4% of all IIH patients, and may be misdiagnosed as local ocular pathology, making IIH diagnosis difficult.[3,4,5] In the presented case, we attempted to assess optic nerve swelling using fundus photography, optical coherence tomography (OCT), and ultrasound (US) measurement of optic nerve sheath diameter (ONSD) to establish the diagnosis despite the unilateral condition. Lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure was done to confirm increased ICP and confirm the diagnosis of unilateral papilledema. The cause of unilateral papilledema is still unclear. Based on the data obtained, including bilateral increased ONSD, we aimed to identify the etiology of the unilaterality in these rare cases.

Case Reports

A 35-year-old obese woman presented to our clinic with transient visual obscuration in both eyes that persisted for a few seconds. The patient denied any other visual complaints, redness, itching, ocular pain, or discharge. She complained of frequent one-sided headaches but denied having diplopia, tinnitus, neck stiffness, and weakness or numbness of the limbs. The patient reported no allergy or drug reactions, and she was a non-smoker, non-alcoholic, non-diabetic, and non-hypertensive, with no history of using oral contraceptives, corticosteroids, or other drugs or positive family history of autoimmune or neurological diseases.

The patient had no complaints of chest pain or shortness of breath. On physical examination, she was found to be obese (body mass index of 30 kg/m^2) with no other detected abnormalities. Body temperature and blood pressure (110/70 mmHg) were normal. Laboratory results indicated normal cell counts and random blood glucose, with no vitamin or iron deficiency.

Visual and optic nerve function tests revealed bilateral 20/20 visual acuity and normal color vision and contrast sensitivity with no evidence of red color desaturation. Pupillary reaction was normal on both sides. Anterior segment examination was normal, with no evidence of conjunctival injection, congestion, cells, or flares in the anterior chamber. Ocular motility was normal and painless in all directions. Intraocular pressure (IOP) was within normal range (18 mmHg). There were no signs of proptosis or eyelid swelling.

Fundus examination revealed a normal right fundus with no disc swelling, while the left eye exhibited disc swelling at both the nasal and temporal margins with circumferential halos and obscuration of some blood vessels upon leaving the disc. Paton lines were observed with absent venous pulsations bilaterally. There was no evidence of vasculitis, retinitis, vitritis, or optociliary shunts. Fundus photography and fluorescein angiography of the right eye showed well-defined disc margins and no evidence of optic disc swelling, early dilated capillaries, or late dye leakage. The left eye had a swollen disc with blurred margins, partially obliterated cupping, Paton lines, and no evidence of anomalous blood vessel bifurcations. Fundus fluorescein angiography showed early dilated capillaries with late optic disc leakage (hot disc; Figure 1).

OCT showed a completely normal right disc with preserved cupping, no evidence of peripapillary fluid, and normal retinal nerve fiber thickness (RNFLT; average 109 µm) with normal double hump pattern and minimum rim width (MRW). However, OCT of the left eye showed peripapillary fluid with hyporeflective triangles, a partially obliterated disc cup, increased RNFLT (average 179 µm), an elevated double hump curve, and a thickened MRW with an elevated curve. Macular scanning revealed no evidence of macular thickening or macular intraretinal fluid. Bilateral enhanced depth image OCT (EDI-OCT) demonstrated no evidence of disc drusen (Figure 2).

Blue-light fundus autofluorescence revealed no optic disc drusen, well-defined disc margins in the right eye, and blurred margins in the left eye (Figure 3). Furthermore, US measurements of ONSD demonstrated thickening bilaterally, with a right ONSD of 6.61 mm and a left ONSD of 6.9 mm (Figure 4). Neuroimaging including magnetic resonance imaging (MRI) and magnetic resonance venography revealed no evidence of space-occupying lesions, inflammation, transverse sinus stenosis, or occlusion. However, MRI indicated flattening of the globe and tortuous optic nerve in the left eye with prominent CSF around the optic nerve bilaterally (Figure 5).

The patient was then eligible to undergo lumbar puncture and was referred to the neurological department. The opening pressure was 35 cmH_2O and CSF analysis was normal. Accordingly, the case was diagnosed as IIH according to the Dandy criteria. The patient received 500 mg of acetazolamide twice daily and 25 mg topiramate once daily with diet therapy, and instructions for weight reduction and follow-up after one month were recommended.

After 1 month, the patient reported resolution of the visual obscuration and a decrease in headache attacks, which disappeared completely after 4 months. The results were confirmed by fundus photography, which showed the disappearance of previously observed peripapillary intraretinal fluid. OCT revealed a significant reduction in RNFLT in the left eye with a reduction in the double hump curve and MRW (Figure 6). However, there was only a slight decrease in ONSD (average 6.2 mm).

Discussion

Unilateral optic disc swelling may be caused by several conditions, including anterior ischemic optic neuropathy (AION), optic neuritis, disc drusen, compressive and infiltrative optic neuropathy, disc tumors, papillophlebitis, diabetic papillopathy, neuroretinitis, and rarely, papilledema.[6] Whenever confronted with a case of unilateral papilledema, it is recommended to obtain a comprehensive medical and familial history, conduct a thorough evaluation of visual function and pupillary reactions, and consult with an ophthalmologist to assess IOP, perform slit-lamp and fundus examinations, and utilize diagnostic techniques including OCT, fundus photos and autofluorescence

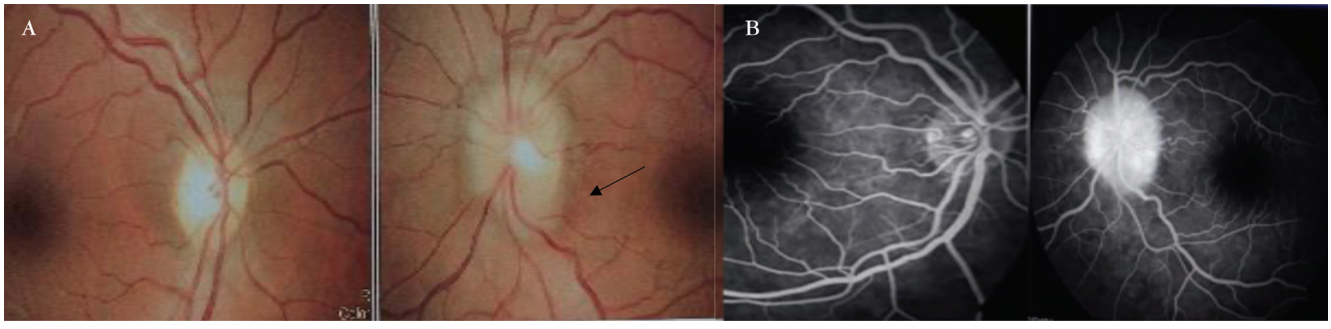

Figure 1. (A) Fundus photography shows the right normal optic disc and left swollen disc with Paton lines (black arrow). (B) Fluorescein angiography shows no evidence of late leakage on the right and significant late disc leakage on the left

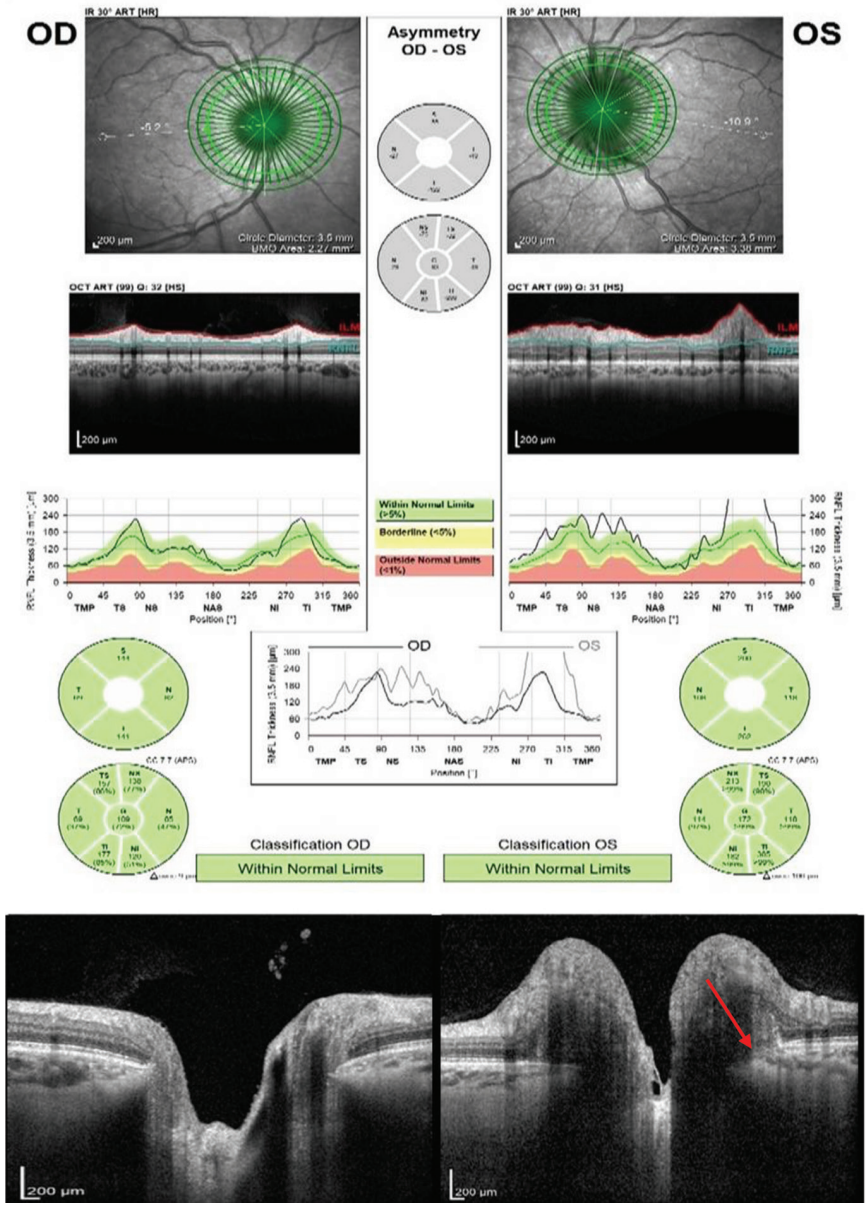

Figure 2. Optical coherence tomography showing retinal nerve fiber thickness in both eyes (top panels) and line scans (bottom panels) demonstrates a normal right eye and peripapillary fluid with a hyporeflective triangles and increased disc height in the left eye. Notice the superior displacement of Bruch's membrane described in papilledema (red arrow)

for excluding optic disc drusen. MRI of the brain and orbits and venography should be performed to reveal compressive lesions, optic nerve tumors, space-occupying lesions, and signs of increased ICP, if present.[7]

In our case, normal visual acuity, color vision, and pupillary reactions ruled out AION while optic disc drusen and optic neuritis were excluded through blue-light autofluorescence and EDI-OCT. The patient was non-diabetic and non-hypertensive, with MRI showing no compressive lesions. However, ONSD measured by US indicated bilateral thickening, raising high suspicion of increased ICP. This was confirmed by elevated lumbar puncture and a good response to medical treatment, with complete resolution. In our case, we used different modalities to detect the unilaterality of the condition. Some prior case reports of unilateral papilledema depended only on fundoscopy, which may miss subtle edema in the other less edematous eye. Others only used OCT to assess optic disc edema.[8,9] Swinkin et al.[9] assessed optic nerve sheath distension using fundus photography, OCT optic nerve scanning, and MRI. To the best of our knowledge, our report is the first to use US to measure ONSD in a case of unilateral papilledema, demonstrating that the sheath was relatively dilated in the right eye despite appearing normal in all other modalities.

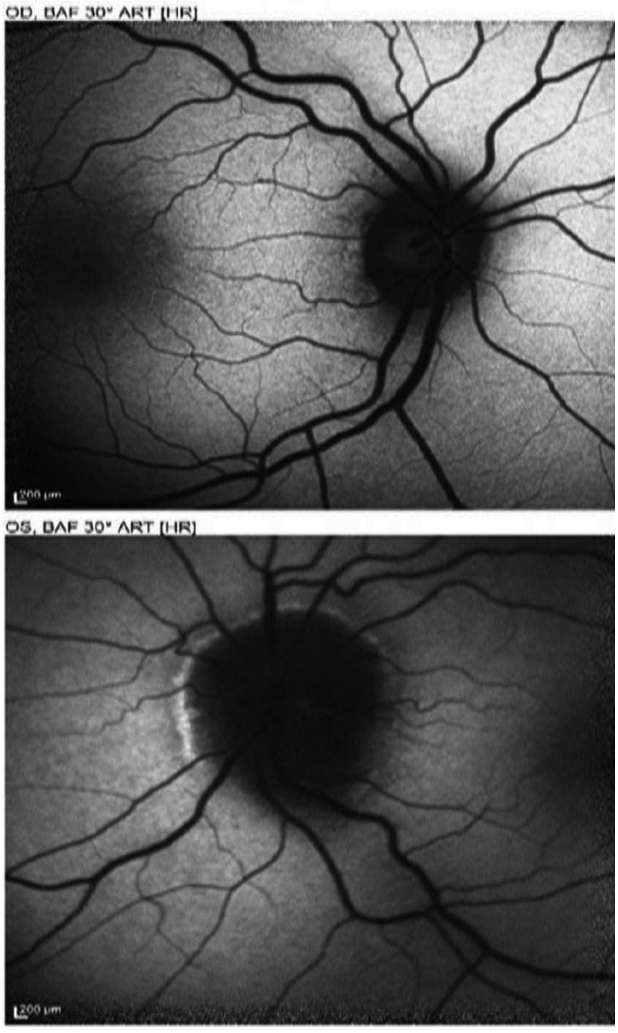

Figure 3. Blue autofluorescence shows well-defined disc margins in the right eye (top) and ill-defined margins in the left eye (bottom)

Measurement of ONSD using US is a generally accepted and documented procedure in the assessment of patients with increased ICP. Recently, it has been recommended, possibly routinely, in all cases suspected of IIH.[10] Nevertheless, its application is not very widespread, and in fact the modified Dandy criteria, which include clinical, laboratory, and radiographic data for the diagnosis of IIH, do not describe US or ONSD measurement. Regrettably, the B-scan has several drawbacks, including the blooming effect and distortions that can skew the results. To overcome that, we had to be cautious to average at the lowest feasible gain when utilizing mode B.[11,12]

There are hardly any situations in which unilateral papilledema is observed. In patients with pre-existing unilateral optic atrophy, only the normal eye experiences papilledema if ICP is later elevated, as in Foster-Kennedy syndrome. Differences in venous drainage between the eyes, differences in structural disc characteristics (including lamina cribrosa abnormalities), and unilateral highly myopic cases with significant differences in the anatomical path of the optic nerve are other proposed causes of unilateral papilledema documented in the literature.[4,13]

Many theories have been proposed to explain the occurrence of unilateral papilledema, but the reasons remain unclear. The relationship between CSF pressure, IOP, and systemic blood pressure is thought to play a role in papilledema occurrence. Whenever CSF pressure increases, IOP decreases, or perfusion pressure becomes lower. This is thought to cause axoplasmic flow stasis and optic disc edema.[14] Although the patient in our case showed bilateral normal IOP, she was non-hypertensive with normal systemic blood pressure. Accordingly, the only possible cause would be increased CSF pressure at the optic disc. However, ONSD was increased bilaterally and decreased after lumber puncture, indicating successive treatment and reduction in ICP.[15] Another theory was that a smaller bony canal on the side of the normal nerve might have a role in preventing transmission of CSF pressure along the optic nerve, resulting in less edema.[16] Conversely, Farrokhi et al.[17] found that the optic nerve bony

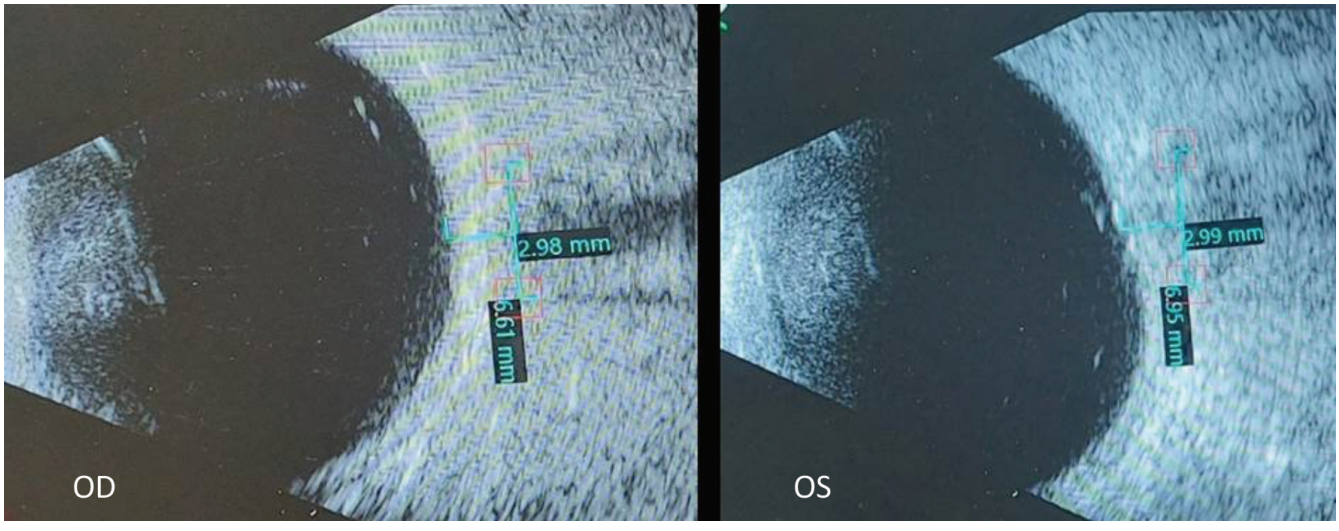

Figure 4. Ultrasound measurement of optic nerve sheath diameter at 3 mm behind the globe shows thickening and dilatation

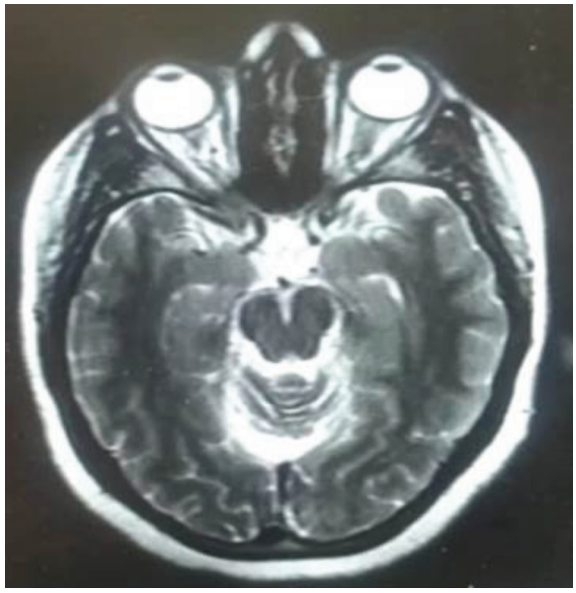

Figure 5. Magnetic resonance imaging of the orbit shows flattening of the left sclera with tortuous left optic nerve and prominent surrounding cerebrospinal fluid

canal was nearly the same in both eyes in cases of bilateral, very asymmetric papilledema using computed tomography, which is more accurate in assessing the bony canal than MRI used by Bidot et al.[16] In our case, the bilaterally distended ONSD makes this theory unsuitable to explain this unilateral condition.

The subarachnoid spaces of the optic nerve are supposed to be inhomogeneous, containing trabeculae, septa, and pillars that might affect CSF dynamics and may have a role in unilateral papilledema.[18] On the other hand, orbital compartmentalization due to decreased communication between the intracranial and intraorbital subarachnoid spaces occurs in IIH and has been implicated as a cause of unilateral papilledema.[19]

Increased collagen in the lamina cribrosa and decreased elasticity, especially with aging, has been suggested as another explanation for unilaterality. Hayreh[20] explained that the optic nerve sheath comprises fibrous tissues that can expand and unfold so that it may expand in both eyes despite only one eye showing higher pressure to cause papilledema. Although many factors may play a role in the unilaterality of papilledema, the most acceptable theory in our case may be orbital compartmentalization. This theory was supported by MRI findings of a tortuous optic nerve on the affected side despite bilateral prominent subarachnoid

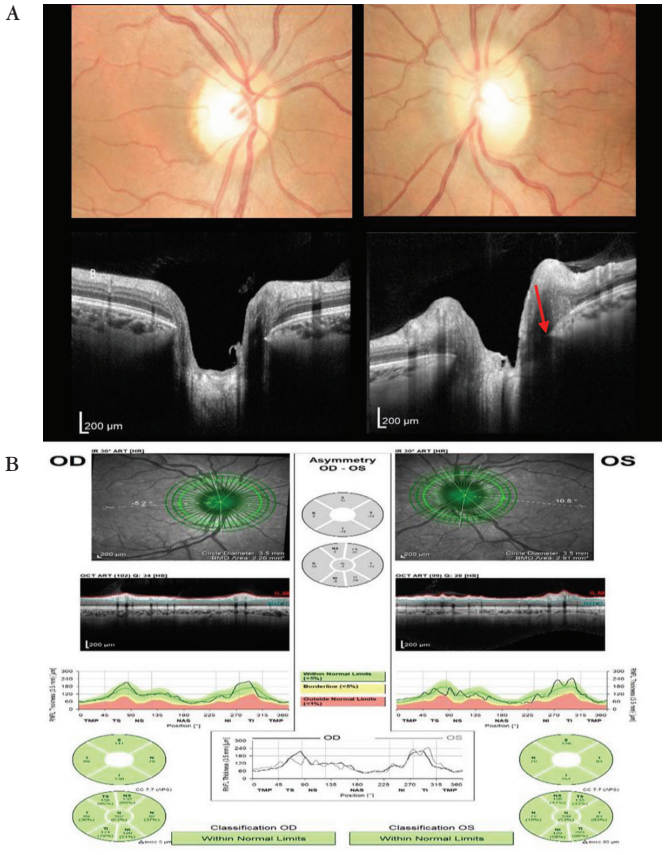

Figure 6. Follow-up images after 4 months. (A) Fundus photography shows improved definition of the disc margins after regression of the previously observed peripapillary fluid. (B) Optical coherence tomography (OCT) line scans of the disc demonstrate peripapillary fluid regression and reduced optic disc height in the left eye. Notice the inferior displacement of Bruch's membrane after resolution (red arrow). The bottom panel shows OCT disc imaging demonstrating a significant reduction in left retinal nerve fiber thickness (RNFLT) and near-normal double hump curve. Right RNFLT appears more or less normal

CSF and increased ONSD on both sides. Another explanation may be an altered response of the optic disc collagen fibers to back pressure or optic nerve head ischemia. Consequently, further studies are required to elucidate these findings.

Unilateral papilledema is a rare condition with unknown pathogenesis, making it challenging to diagnose. However, it should be recognized early to begin prompt treatment to save the optic nerve. Measurement of ONSD may have a role in identifying increased ICP and distinguishing it from other causes of unilateral disc swelling.

Ethics

Informed Consent: Obtained.

Authorship Contributions

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

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

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Letter to the Editor Re: How to Estimate Allele Frequencies and Make Statistical Comparisons in Case-Control Studies of Polymorphic X-Linked Loci

Mostafa Saadat

Shiraz University College of Sciences, Department of Biology, Shiraz, Iran

Keywords

Allele frequency, Hardy-Weinberg equilibrium, polymorphisms, X-linked

Dear Editor,

It was with great interest that I read the article by Yaylacıoğlu Tuncay et al.[1] entitled "The role of *FOXP3* polymorphisms in Graves' disease with or without ophthalmopathy in a Turkish population" recently published in the *Turkish Journal of Ophthalmology.* The authors compared three *FOXP3* polymorphisms (rs3761549, rs3761548 and rs3761547) between Graves' disease patients with or without ophthalmopathy and between Graves' disease patients and controls.

As mentioned by the authors, the forkhead box P3 (*FOXP3*, MIM: 300292) gene has been mapped to human chromosome Xp11.23. Considering that males and females have one and two X chromosomes, respectively, the genotypic patterns are quite different between the two sexes. Females have three genotypes (including two homozygotes and one heterozygote) and males have only two hemizygous genotypes. Therefore, it is impossible to pool the genotypes of the sex groups. Unfortunately, the authors made a fatal mistake by pooling the genotypes of both sexes. I have already discussed this point in a debate.[2] However, I think it is necessary to explain the following points: 1) how we should estimate allele frequencies, and 2) how we should make statistical comparisons in case-control studies for such loci.

According to the STrengthening the REporting of Genetic Association studies statement, in genetic association studies, researchers should compare the observed and expected genotypic values based on Hardy-Weinberg equilibrium (HWE).[3]

Suppose we have two alleles A_1 and A_2, at an X-linked polymorphic locus. If the frequencies of A_1A_1, A_1A_2, and A_2A_2 genotypes in females are "a", "b" and "c", respectively, and the frequencies of A_1 and A_2 hemizygous genotypes in males are "d" and "e", then the allele frequency can be calculated by the counting method. The number of females and males is equal to n_1 (=a+b+c) and n_2 (=d+e), respectively.

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DOI: 10.4274/tjo.galenos.2024.55507

The allele frequencies of A_1 and A_2 are denoted by p and q, respectively, and are estimated using the following formulas:

$$p=(2a+b+d)/(2n_1+n_2)$$
$$q=(b+2c+e)/(2n_1+n_2)$$

Then, the expected values for the A_1A_1, A_1A_2, and A_2A_2 genotypes in the female samples, calculated using the estimated p and q, are equal to p2, 2pq, and q2, respectively. Finally, the observed and expected values for the genotypes should be compared using the chi-squared test. The degree of freedom is 1.

Because the number of X chromosomes differs between the sexes of the participants, to compare cases with controls (in case-control studies), participants should be stratified by sex. However, when allelic frequency is estimated in the manner described above, it is possible to compare allelic frequencies (and not genotypic frequencies) between all cases and controls, regardless of their sex.

Considering that Yaylacıoğlu Tuncay et al.[1] included both sexes among their participants, the reported results should be interpreted with caution. It is recommended that the authors present their data on the genotypes of each polymorphism according to the sex of the participants and reanalyze their data to address the major issues mentioned above. As emphasized elsewhere,[3,4,5] the researchers should also show that the frequencies of the observed genotypes are not significantly different from their expected frequencies based on HWE. I wish the esteemed authors all the best in their research.

Ethics

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

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Reply

First of all, we thank the author for evaluating our article.[1] As the author and we pointed out in our article, the Forkhead box P3 (*FOXP3*) gene is on the X chromosome. As far as we know, ten different reports in the literature have investigated the association between *FOXP3* polymorphisms and the development of Graves' disease (GD).[2,3,4,5,6,7,8,9,10,11] Seven of those reports presented the genotype and allele frequencies by pooling both sexes,[2,3,4,5,6,7,8] and the rest stratified the participants by sex and reported the genotype and allele frequencies separately in females and males.[9,10,11] In our article, we aimed to evaluate the frequency of *FOXP3* polymorphisms in GD with or without ophthalmopathy in a Turkish population.[1] Since the number of participants in each group was limited in our study and there were no corrections for the previously published articles,[2,3,4,5,6,7,8] we did not stratify the groups by sex and used the results of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) directly to analyze genotype and allele frequencies.[1] In the PCR-RFLP method, the results were shown by band patterns and those patterns do not indicate whether the sample had one or two alleles of the gene of interest. Additionally, using the same analysis method, we could compare our results with those seven reports that did not stratify the groups by sex.

However, as mentioned by the author, as males have one and females have two X chromosomes, the genotypic patterns differ between the two sexes. There are three genotypes (two homozygotes and one heterozygote) in females but only two hemizygous genotypes in males. Therefore, it will be better to stratify the groups by sex and define the genotype and allele frequencies separately in females and males for X-linked genes. Moreover, the author emphasized the importance of comparing the observed and expected genotypic values based on Hardy-Weinberg equilibrium (HWE) in his letter and explained the formula for an X-linked polymorphic locus. According to the concerns reported by the author, in this reply, we reported our additional analysis by stratifying the groups by sex as shown in Tables 1, 2, 3, and 4.

Firstly, we did the HWE analysis in both the controls and study groups, as suggested by the author. The frequencies of the observed genotypes were not significantly different from their expected frequencies based on HWE for all single nucleotide polymorphisms (SNPs) in female control groups (rs3761547, p=0.926; rs3761548, p=0.881; and rs3761549, p=0.926).

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Table 1. Genotypic and allelic distribution of *FOXP3* SNPs in female study and control groups				
Genotype	**Control group n=68**	**Study group (non-GO/GO) n=130**	**p value**	**OR (95% CI)**
rs3761548 -3279 C/A				
CC	39 (57%)	30 (23%)	-	1.0[a]
AC	26 (38%)	74 (57%)	**<0.0001**	3.7 (1.9-7.1)
AA	3 (5%)	26 (20%)	**<0.0001**	11.26 (3.1-40.8)
Allele				
C	104 (76%)	134 (51%)	-	1.0[a]
A	32 (24%)	126 (49%)	**<0.0001**	3.05 (1.9-4.8)
rs3761549 -2383 C/T				
CC	58 (85%)	89 (68%)	-	1.0[a]
CT	10 (15%)	35 (27%)	**0.03**	2.28 (1.04-4.9)
TT	0 (0%)	6 (5%)	-	-
Allele				
C	126 (93%)	210 (81%)	-	1.0[a]
T	10 (7%)	50 (19%)	**<0.0001**	3 (1.4-6.1)
rs3761547 -3499 A/G				
AA	58 (85%)	103 (79%)	-	1.0[a]
AG	10 (15%)	26 (20%)	0.34	1.4 (0.65-3.24)
GG	0	1 (1%)	-	-
Allele				
A	126 (93%)	232 (89 %)	-	1.0[a]
G	10 (7%)	28 (11%)	0.27	1.5 (0.71-3.23)

[a]The first allele or genotype (CC for -3279 C/A, CC for -2383 C/T, AA for -3499 A/G) is considered the reference value. SNP: Single nucleotide polymorphism, GO: Graves' ophthalmopathy, OR: Odds ratio, n: Number, CI: Confidence interval. Frequencies of genotypes and alleles were compared using chi-square test. Bold values indicate statistical significance

Table 2. Genotypic and allelic distribution of *FOXP3* SNPs in non-GO and GO female patients				
Genotype	**Non-GO**	**GO**	**p value**	**(95% CI)**
	n=56	**n=74**		
-3279 C/A				
CC	10 (17.9%)	17 (23.0%)	0.47	1.38 (0.5, 3.2)
AC	34 (60.7%)	40 (54.0%)	0.44	0.8 (0.38, 1.5)
AA	12 (21.4%)	17 (23.0%)	0.84	1.09 (0.4, 2.5)
Allele			0.77	1.07 (0.65, 1.7)
A	54 (48.2%)	74 (50%)		
C	58 (51.8%)	74 (50%)		
-2383 C/T				
CC	42 (75.0%)	47 (63.5%)	0.16	0.58 (0.26, 1.25)
CT	10 (17.9%)	25 (33.8%)	0.06	2.4 (0.98, 5.41)
TT	4 (7.1%)	2 (2.7%)	0.07	0.24 (0.05, 1.24)
Allele			0.46	0.78 (0.42, 1.50)
C	94 (81.0%)	119(80.4%)		
T	18 (19.0 %)	29 (19.6%)		
-3499 A/G				
AA	44 (78.6%)	59 (79.7%)	0.52	1.1 (0.46, 2.52)
AG	12 (21.4%)	14 (18.9%)	0.71	0.86 (0.36, 2.02)
GG	0	1 (1.4%)	-	-
Allele			0.57	0.99 (0.4, 2.19)
A	100 (86.2%)	132 (89.2%)		
G	12 (13.8%)	16 (10.8%)		

SNP: Single nucleotide polymorphism, GO: Graves' ophthalmopathy, OR: odds ratio, n: number, CI: confidence interval. Frequencies of genotypes and alleles were compared using chi-square test

Table 3. Allelic distribution of the male study and control groups				
Allele	**Control group n=32**	**Study group (non-GO/GO) n=44**	**p value**	**OR (95% CI)**
rs3761548				
C	27 (84%)	20 (45%)	-	1.0[a]
A	5 (16%)	24 (55%)	**<0.0001**	6.8 (2.1-19)
rs3761549				
C	30 (94%)	42 (95%)	-	1.0[a]
T	2 (6%)	2 (5%)	0.74	2.3 (1.2-4.2)
rs3761547				
A	30 (94%)	44 (100%)	-	-
G	2 (6%)	0 (0%)	-	-

[a]The first listed allele is considered the reference value. GO: Graves' ophthalmopathy, OR: Odds ratio, n: Number, CI: Confidence interval. Frequencies of alleles were compared using chi-square test. Bold values indicate statistical significance

Table 4. Allelic distribution of the study and control groups regardless of their sex				
Allele	**Control group n=168**	**Study group (non-GO/GO) n=304**	**p value**	**OR (95% CI)**
rs3761548				
C	131 (78%)	154 (51%)	-	1.0[a]
A	37 (22%)	150 (49%)	**<0.0001**	3.4 (2.24-5.2)
rs3761549				
C	156 (93%)	252 (83%)	-	1.0[a]
T	12 (7%)	52 (17%)	0.0025	2.3 (1.2-4.2)
rs3761547				
A	156 (93%)	276 (91%)	-	1.0[a]
G	12 (7%)	28 (9%)	0.43	1.31 (0.65-2.67)

[a]The first listed allele is considered the reference value. GO: Graves' ophthalmopathy, OR: Odds ratio, n: Number, CI: Confidence interval. n=2 x number of females + number of males. Frequencies of alleles were compared using chi-square test. Bold values indicate statistical significance

Secondly, when the groups were stratified by sex, we found that the frequency of the AC and AA genotypes of -3279 (rs3761548) and the CT genotype of -2383 (rs3761549) were significantly increased in our female study group (Table 1). Additionally, the A allele of -3279 had a significantly increased frequency both in the female (Table 1) and male study groups (Table 3) when compared separately or when compared between controls and patients regardless of sex (Table 4). The frequency of the T allele of -2383 was significantly increased both in our female study group when compared separately (Table 1) and in the whole study sample when compared regardless of sex (Table 4). However, the frequency of the T allele of -2383 was not significantly increased in our male study group when compared separately (Table 3). For polymorphism -3449 (rs3761547), allele and genotype frequency distribution were not significantly different in any comparisons between the control and study groups (Table 1, Table 3, and Table 4).

Thirdly, comparing the genotypic and allelic distributions of each of the three *FOXP3* SNPs between female patients with Grave's ophthalmopathy (GO) and GD without ophthalmopathy (non-GO) showed no statistically significant difference (Table 2).

Consequently, the results in our published article and the analysis made by stratifying the participants by sex were similar. However, as the author emphasized in his letter, polymorphic loci on X-chromosome should be analyzed differently than the loci on autosomal chromosomes. Therefore, his letter and our reply will be helpful for researchers who will investigate associations with X-linked polymorphic loci.

Ethics

Authorship Contributions

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

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