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Original Articles

Review

Case Reports

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STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

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EDITORIAL

2016 Issue 2 at a Glance;

Dear readers,

This issue includes six original research articles, three case reports and a review chosen from among the valuable research being conducted by the ophthalmologic community of Turkey. We believe the contents will benefit our readers and contribute to the field nationally and internationally.

Photorefractive keratectomy (PRK) and small-incision lenticule extraction (SMILE) are two flapless refractive surgical techniques used to treat myopia. In their retrospective study, Yıldırım et al. investigated changes in corneal biomechanical characteristics after PRK (22 patients) and SMILE (23 patients) for low and medium myopia. They report that both procedures resulted in lower corneal biomechanical strength at postoperative 6 months, with a more pronounced change in SMILE patients. It was emphasized that this effect is associated with the amount of stromal tissue removed and amount of refractive error corrected (see pages 47-51).

In a retrospective analysis of clinical and demographic characteristics of Fuchs' uveitic syndrome (FUS) in the Turkish population, Nalçacıoğlu et al. found the most common complaints at presentation were declining visual acuity or blurred vision and floaters. Findings at presentation included small round white keratic precipitates (KP), anterior chamber reaction, various degrees of vitreous cells, heterochromia and iris nodules. Elevated intraocular pressure was observed in 18.1% of eyes, and the most frequent complication was cataract, seen in 52% of eyes. The authors emphasized that in their series, typical KP, low-grade anterior chamber reaction and variable viteous reaction were observed more often than heterochromia and were more diagnostically useful clinical findings (see pages 52-57).

Güngör et al. investigated retinal nerve fiber layer (RNFL) thickness in three optic nerve head (ONH) size groups as determined by optical coherence tomography (OCT). The study included 253 eyes of 253 healthy patients classified as having small, medium or large ONH. Siginifcant differences between the groups emerged in superior (p=0.008), inferior (p=0.004) and average (p=0.001) RNFL thickness, and ONH size weakly positively correlated with inferior and average RNFL thickness (r=0.150, p=0.017 and p=0.157, p=0.013, respectively). They suggest that these correlations may be due to the variable distance between the ONH margins and the measurement circle in ONH of different sizes (see pages 58-61).

Ophthalmologic findings may arise in acute leukemia patients either as a result of primary leukemic infiltration or secondary to disease and treatment. Orhan et al. determined the incidence of ocular findings in children with acute leukemia among a total of 120 patients, 83 (69.2%) with acute lymphoblastic leukemia (ALL), 35 (29.1%) with acute myeloblastic leukemia (AML), and 2 (1.7%) with mixed leukemia. They observed ophthalmologic findings in 41 (34.2%) of the patients, 12 at the time of leukemia diagnosis and 46 during treatment and follow-up. The incidence of ocular findings increased with age and was higher in AML than in ALL patients (see pages 62-67).

Tunay et al. included 150 partially-sighted children between the ages of 6 and 18 in their study aiming to determine the diagnostic distribution and clinical characteristics of school-aged children presenting for low vision rehabilitation, share the low vision rehabilitation methods applied and emphasize the importance of referring partially-sighted children to low vision rehabilitation. Hereditary visual impairment was the most common diagnosis with 36%, with cortical visual impairment accounting for 18% of this group. The most commonly used low vision aids were telescopic glasses for distance (91.3%), and magnifiers (38.7%) and telemicroscopic systems (26.0%) for near. Significant improvements in vision level were achieved for both near and distance using low vision aids. The study emphasizes the importance of the referral of children to low vision rehabilitation by both pediatricians and ophthalmologists (see pages 68-72).

A remarkable finding from Kurt et al.'s study conducted among 451 individuals aged 50 or over with binocular B class driving licenses was that more than 1 in 5 older drivers were not in compliance with the binocular B class driving license criteria for vision, usually due to senile cataract, but that a large proportion of these individuals continued to drive. Therefore, the authors concluded that individuals over 50 years old should be required to undergo periodic ophthalmologic examinations (see pages 73-76).

Despite advances in diagnosis and treatment, uveitis can become a serious problem with complications as severe as blindness, especially in pediatric patients. Juvenile idiopathic arthritis (JIA)-associated uveitis comprises a major subgroup of pediatric uveitis. Oray and Tuğal-Tutkun's review of therapeutic approaches to JIA-associated uveitis addresses medical treatment options, side effect profies and surgical interventions for complicated cases in the context of current literature and their clinical experience (see pages 77-82).

Sızmaz et al. present the clinical presentation and treatment of a case of contact lens-related polymicrobial keratitis. Pseudomonas auriginosa and Alcaligenes xylosoxidans were isolated from the patient's conjunctiva, cornea, contact lens storage case and lens solution, and polymerase chain reaction analysis of corneal scrapings was positive for Acanthameoba (see pages 83-86).

Güngör et al. share the clinical course and medical and surgical treatments applied in a Behçet's patient who developed herpetic keratouveitis and subsequent trabeculectomy failure 6 months after starting treatment with infliximab due to resistance to immunosuppressive treatment options. Their study highlights the possibility of systemic or ocular infections, including herpes simplex virus infection or reactivation, in patients using immunosuppressive or biologic agents, and raises awareness of the importance of keeping these patients under close medical surveillance (see pages 87-90).

Occult macular dystrophy is a hereditary macular dystrophy that presents with bilateral progressive vision loss while fundus appearance, fluorescein angiography and full-field electroretinogram are normal. In their report, Muslubaş et al. describe the clinical features and diagnostic methods used in a patient diagnosed with occult macular dystrophy (see pages 91-94).

Respectfully on behalf of the Editorial Board,

Özlem Yıldırım, MD

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Turk J Ophthalmol 2016;46:47-51

Original Article

Comparison of Changes in Corneal Biomechanical Properties after Photorefractive Keratectomy and Small Incision Lenticule Extraction

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Summary

Objectives: To compare the postoperative biomechanical properties of the cornea after photorefractive keratectomy (PRK) and small incision lenticule extraction (SMILE) in eyes with low and moderate myopia.

Materials and Methods: We retrospectively examined 42 eyes of 23 patients undergoing PRK and 42 eyes of 22 patients undergoing SMILE for the correction of low and moderate myopia. Corneal hysteresis (CH) and corneal resistance factor (CRF) were measured with an Ocular Response Analyzer before and 6 months after surgery. We also investigated the relationship between these biomechanical changes and the amount of myopic correction.

Results: In the PRK group, CH was 10.4±1.3 mmHg preoperatively and significantly decreased to 8.5±1.3 mmHg postoperatively. In the SMILE group, CH was 10.9±1.7 mmHg preoperatively and decreased to 8.4±1.5 mmHg postoperatively. CRF was significantly decreased from 10.8±1.1 mmHg to 7.4±1.5 mmHg in the PRK group whereas it was decreased from 11.1±1.5 mmHg to 7.9±1.6 mmHg in the SMILE group postoperatively. There was a significant correlation between the amount of myopic correction and changes in biomechanical properties after PRK (r=-0.29, p=0.045 for CH; r=-0.07, p=0.05 for CRF) and SMILE (r=-0.25, p=0.048 for CH; r=-0.37, p=0.011 for CRF).

Conclusion: Both PRK and SMILE can affect the biomechanical strength of the cornea. SMILE resulted in larger biomechanical changes than PRK.

Keywords: Photorefractive keratectomy, small incision lenticule extraction, myopia

Introduction

Photorefractive keratectomy (PRK) has been implemented effectively and reliably for many years in the treatment of myopia.[1,2] In the PRK procedure, the laser is applied directly to the anterior corneal stroma without creating a flap.[2] Small incision lenticule extraction (SMILE) is a newer procedure being utilized to treat myopia.[3,4] In the SMILE technique, myopia is corrected by creating a corneal lenticule and extracting it through a small incision, also without creating a flap.[3,4]

It is known that corneal refractive surgery affects corneal biomechanical properites.[5] There are many studies demonstrating that procedures involving flaps in particular have a negative impact on corneal biomechanical properties.[6,7]

The Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA) is a non-invasive instrument that assesses the corneal biomechanical properties corneal hysteresis (CH) and corneal resistance factor (CRF).[8]

Basically, the ORA takes two pressure measurements: the applanation pressure during the inward flexion of the cornea (P1) and the applanation pressure as the cornea returns to normal (P2). The difference between these two pressure measurements is the CH, reflecting the viscous resistance of the cornea.[9] The CRF value expresses the mean corneal mechanical resistance including viscous and elastic components, and is calculated with the formula: k1 (P1-P2)+0.3*k1*P2+k2. The k1 and k2 values are calibration constants.[9] CH and CRF are known to decrease in glaucoma, keratoconus and after corneal refractive surgery.[10,11,12]

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The aim of this study was to compare the changes in corneal biomechanical properties after PRK and SMILE in the treatment of low and moderate myopia.

Materials and Methods

This retrospective study was conducted in the Refractive Surgery Unit of the Beyoğlu Eye Training and Research Hospital. The study was approved by the institutional ethics board and adhered to the tenets of the Helsinki Declaration. Myopic patients with spherical values between -2.00 and 6.00 diopters (D) and astigmatism of less than 0.50 D who underwent SMILE or PRK were included in the study. Other inclusion criteria of the study were a mesopic (4 lux) pupil diameter ≤6.5 mm and a residual stromal thickness >300 µm. Patients with previous ocular surgery, concurrent ocular disease, concurrent systemic disease (diabetes mellitus, collagen tissue disease, etc.) or contraindication to refractive surgery were excluded from the study. Patients who developed intra- or postoperative complications were also excluded.

Corneal biomechanical properties were evaluated preoperatively and 6 months postoperatively. The amount of myopic correction achieved with the procedure was recorded. In addition, the maximum ablation amount in the PRK group and the maximum lenticule thickness in the SMILE group were recorded as the amount of stromal tissue removed.

Emmetropia was the aim for all patients.

Forty-two eyes of 23 patients (12 female, 11 male) in the PRK group and 42 eyes of 22 patients (12 female, 10 male) in the SMILE group were evaluated retrospectively. The mean ages of the PRK and SMILE groups were 27.6±5.2 years and 29.0±5.9 years, respectively (p=0.23). The PRK and SMILE groups had comparable amounts of refractive correction (p=0.25). The amount of stromal tissue removed was significantly greater in the SMILE group compared to the PRK group (p=0.04). The patients' demographic and preoperative corneal characteristics are shown in Table 1.

Surgical Procedure

All surgical procedures were performed by the same surgeons (A.A., A.D. and E.B.Ö.). The Visumax (Carl Zeiss Meditec) femtosecond laser system was used for the SMILE procedure. Spot size was 3 µm for the lamellar cut and 2 µm for the side cut; the energy level was adjusted to 140 nanojoules (nJ). The lenticule side cut was 15 µm thick with an angle of 120° and the optical zone was 6.5 mm. The side cut was 3 mm in all eyes.

The PRK procedure was performed by first marking an area of 9 mm diameter on the anterior corneal surface and debriding the epithelium with an axe blade, followed by laser application with the AMARIS excimer laser (SCHWIND eye-tech-solutions GmbH&Co. KG, Mainparkstrasse, Kleinostheim, Germany) to a 6.5 mm optical zone. In all patients, 0.02% mitomycin C (MMC) was applied for 30 seconds following laser application.

Measurement of Biomechanical Properties

All ORA measurements were taken preoperatively and 6 months postoperatively in a specially designated room by an experienced clinician. For each patient, three measurements close in value were taken. Unreliable atypical signals were not included in the analysis. Mean CH and CRF values were used in the analysis.

Statistical Methods

Mean, standard deviation, median, minimum-maximum, rate and frequency values were used as descriptive statistics. Distribution of the variables was analyzed with Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze quantitative data. Spearman correlation analysis was used to assess correlations. The Wilcoxon test was used to analyze repeated measures. Analyses were conducted using Statistical Package for the Social Sciences version 22.0 software.

Results

In the PRK group, mean CH values were 10.4±1.3 mmHg (range, 8.0-14.3 mmHg) preoperatively and 8.5±1.3 mmHg (range, 5.4-12.1 mmHg) 6 months postoperatively; CH was significantly lower at postoperative 6 months (p<0.001). In the SMILE group, preoperative CH was 10.9±1.7 mmHg (range, 7.6-14.6 mmHg) and 6 months postoperative CH was 8.4±1.5 mmHg (range, 7.6-12.6 mmHg); this difference was also statistically significant (p<0.001) (Table 2).

In the PRK group, preoperative and 6 months postoperative CRF values were 10.8±1.1 mmHg (range, 8.0-13.0 mmHg)

Table 1. Comparison of demographic characteristics, preoperative corneal characteristics and amount of tissue removed during the procedure between the patient groups

	PRK group	SMILE group	p
Age	27.6±5.2 (21-42)	29.0±5.9 (22-43)	0.23
Gender, % male	45	43	0.74
Manifest spherical equivalent, D (Refractive correction)	-3.6±0.6 (-2.00 to -5.00)	-3.5±1.0 (-2.00 to -5.50)	0.25
Central corneal thickness, µm	517.6±24.6 (494-564)	528.1±23.6 (503-601)	0.23
Amount of stromal tissue removed, µm	56.0±23.2 (37-108)	64.2±21.8 (45-110)	**0.04***
Corneal hysteresis, mmHg	10.4±1.3 (8.0-14.3)	10.9±1.7 (7.6-14.6)	0.78
Corneal resistance factor, mmHg	10.8±1.1 (8.0-13.0)	11.1±1.5 (7.7-14.9)	0.71

PRK: Photorefractive keratectomy, SMILE: Small incision lenticule extraction, D: Diopter
p* Mann-Whitney U test

and 7.4±1.5 mmHg (range, 4.4-10.5 mmHg), respectively (p<0.001). The SMILE group had CRF values of 11.1±1.5 mmHg (7.7-14.9) preoperatively and 7.9±1.6 mmHg (5.2-11.5) at postoperative 6 months (p<0.001) (Table 3).

The pre- to postoperative changes in CH and CRF values were significantly larger in the SMILE group compared to the PRK group (CH, p=0.03; CRF, p=0.048).

Maximum ablation amount was significantly correlated with changes in corneal biomechanical properties in both the PRK and SMILE groups (PRK: CH, r=0.24, p=0.036; CRF, r=0.28, p=0.04; SMILE: CH, r=0.19, p=0.008; CRF, r=0.39, p=0.007). In both groups, the amount of correction was negatively correlated to change in CH and change in CRF (PRK: CH, r=-0.29, p=0.045; CRF, r=-0.07, p=0.05; SMILE: CH, r=-0.25, p=0.048; CRF, r=-0.37, p=0.011) (Table 4).

None of the patients exhibited iatrogenic ectasia during the 6-month postoperative follow-up period.

Discussion

The impact of corneal refractive surgeries on the biomechanical properties of the cornea has been the focus of many studies to date.[7,10,13,14,15,16,17] Several studies have evaluated the changes in biomechanical properties resulting from laser-assisted in situ keratomileusis (LASIK) and PRK, which have been employed for many years to treat myopia, as well as the SMILE procedure, a more current treatment method.[7,10,13,14,15,16] Although there are studies comparing LASIK with PRK and with SMILE in terms of their effects on corneal biomechanical properties,[7,16,17] our study is the first to compare corneal biomechanical aspects of the SMILE and PRK procedures in the treatment of myopia. In the current study, CH and CRF were used to evaluate corneal biomechanical properties.

In a study by Kamiya et al.[7] comparing PRK and LASIK, corneal biomechanical parameters (CH and CRF) were significantly lower postoperatively in both the PRK and LASIK groups, with larger decreases observed in the LASIK group. The

Table 2. Changes in corneal hysteresis

	PRK group		SMILE group		p[a]
	Mean ± SD	**(Min-Max)**	**Mean ± SD**	**(Min-Max)**	
Preoperative CH, mmHg	10.4±1.3	8.0-14.3	10.9±1.7	7.6-14.6	0.104
Postoperative 6 month CH, mmHg	8.5±1.3	5.4-12.1	8.4±1.5	7.6-12.6	0.145
Change	1.9±1.2	1.0-4.6	2.5±1.1	0.6-5.7	**0.03**
Change p[b]	**0.000**		**0.000**		

CH: Corneal hysteresis, PRK: Photorefractive keratectomy, SMILE: Small incision lenticule extraction, SD: Standard deviation, Min: Minimum, Max: Maximum
p[a] Mann-Whitney U test
p[b] Wilcoxon test

Table 3. Changes in corneal resistance factor

	PRK		SMILE		
	Mean ± SD	**(Min-Max)**	**Mean ± SD**	**(Min-Max)**	**p[a]**
Preoperative CRF, mmHg	10.8±1.1	8.0-13.0	11.1±1.5	7.7-14.9	0.08
Postoperative 6 month CRF, mmHg	7.4±1.5	4.4-10.5	7.9±1.6	5.2-11.5	0.103
Change	2.7±1.1	-0.8-4.9	3.3±1.1	0.3-6.1	**0.048**
Change p[b]	**0.000**		**0.000**		

CRF: Corneal resistance factor, PRK: Photorefractive keratectomy, SMILE: Small incision lenticule extraction, SD: Standard deviation, Min: Minimum, Max: Maximum
p[a] Mann-Whitney U test
p[b] Wilcoxon test

Table 4. Associations between pre- to postoperative changes in corneal hysteresis and corneal resistance factor and amounts of refractive correction and stromal tissue removed

PRK		**ΔCH**	**ΔCRF**	**SMILE**		**ΔCH**	**ΔCRF**
Maximum ablation amount	r p	0.237 **0.036**	0.280 **0.046**	Maximum lenticule thickness	r p	0.196 **0.008**	0.398 **0.007**
Correction	r p	-0.293 **0.045**	-0.073 **0.050**	Correction	r p	-0.254 **0.048**	-0.369 **0.011**

ΔCH: Change in corneal hysteresis, ΔCRF: Change in corneal resistance factor, PRK: Photorefractive keratectomy, SMILE: Small incision lenticule extraction
Spearman correlation analysis

larger effect in the LASIK group was attributed to the creation of a corneal flap. Hamilton et al.[10] also compared PRK and LASIK and found lower CH and CRF values postoperatively, though there was no significant difference between the two procedures. Consistent with these studies, in the current study the PRK group had significantly lower CH and CRF values.

In the current study, MMC was applied postoperatively in all patients in the PRK group. It has been demonstrated that MMC application during the PRK procedure does not cause additional changes in biomechanical properties.[13,14] In a study by Wang et al.[15] comparing SMILE and LASIK, CH values were significantly lower after SMILE. They found that the difference in CH was especially large when correcting myopia of -6.00 D or more. The current study included patients with myopia between -2.00 and -6.00 D. Similarly, Wu et al.[16] compared SMILE and LASIK and found reduced CH following both procedures. Agca et al.[17] observed negative effects of both SMILE and LASIK on corneal biomechanical properties, but did not find any differences between groups in the reduction of CH and CRF. Consistent with the literature, in the current study we found significantly lower CH and CRF values in the SMILE group.

Studies have demonstrated that in LASIK and PRK, the amount of refractive error corrected is related to the changes in corneal biomechanical properties.[7,15] In the current study we also found significant correlations between amount of refractive correction and values for CH and CRF in both groups.

Unlike other studies, in the current study the amount of stromal tissue removed was quantified as the maximum lenticular thickness in the SMILE group and as the maximum ablation depth in the PRK group, and correlation analysis was performed using these values. In both groups, the amount of tissue removed from the stroma correlated with CH and CRF values.

In the SMILE procedure, the intracorneal lenticule is removed through a small side cut (2-3.5 mm). Because no flap is created, the SMILE procedure is considered more advantageous than LASIK in terms of the conservation of corneal biomechanical stability.[16] PRK is also used to correct myopia without the creation of a flap. Despite both procedures being 'flap-less', in our study we observed larger changes in the corneal biomechanical properties of the SMILE group.

In the current study, larger changes in CH and CRF were observed in the SMILE group compared to the PRK group. Studies have demonstrated that the biomechanical resistance of the cornea is greatest in its anterior third because the collagen fibrils there are denser and more tightly linked.[18,19] In the current study, the amount of refractive correction was comparable in the PRK and SMILE groups, whereas the amount of stromal tissue removed was significantly greater in the SMILE group ($p=0.04$). Therefore, the larger decreases in CH and CRF we observed in the SMILE group may be related to the presence of lamellar cuts in the anterior stroma and the greater amount of stromal tissue removed in the SMILE group compared to the PRK group.

The larger changes found in the SMILE group may be due to the fact that the method involves the removal of a piece of tissue from the stroma; even without creating a flap, making a cut within the stroma disrupts the linkage of collagen fibers. This is supported by several studies comparing SMILE and flapped corneal refractive procedures in which no significant differences were detected between the changes in corneal biomechanical properties of the two groups.[15,17]

The limitations of this study are that it was not designed prospectively and did not include a comparison with a LASIK group.

Conclusion

In summary, our study demonstrates that the PRK and SMILE procedures result in reduced corneal biomechanical strength in low and moderate myopia patients. With both procedures, this effect is associated with the amount of stromal tissue removed and the amount of refractive error correction.

Ethics

Ethics Committee Approval: The study was approved by the institutional ethics board, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yusuf Yıldırım, Cengiz Alagöz, Concept: Ali Demircan, Engin Bilge Özgürhan, Design: Alper Ağca, Onur Ölçücü, Data Collection or Processing: Abdurrahman Başcı, Yusuf Yıldırım, Analysis or Interpretation: Yusuf Yıldırım, Cengiz Alagöz, Literature Search: Abdurrahman Başcı, Ahmet Demirok, Writing: Onur Ölçücü, Yusuf Yıldırım.

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

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Original Article

Clinical Characteristics of Fuchs' Uveitis Syndrome

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Summary

Objectives: To evaluate the clinical and demographic properties of Fuchs' uveitis syndrome (FUS) in Turkish patients.

Materials and Methods: The medical records of 161 patients with FUS followed in the Uveitis Division of Ulucanlar Eye Hospital between 1996 and 2014 were respectively reviewed. The mean age at diagnosis, sex, the number of affected eyes, follow-up period, clinical findings at presentation, complications during the follow-up period, medical and surgical treatments, and best corrected visual acuity at the initial and final visits were recorded.

Results: The study included 171 eyes of 161 patients diagnosed with FUS. Of the patients, 94 (58.4%) were female and 67 (41.6%) were male. The mean age at presentation was 35.2±11.0 (11-65) years. The mean follow-up period was 23.5±32.8 (2-216) months. Ten (6.2%) patients had bilateral involvement. The most common symptoms at presentation were decreased visual acuity or blurred vision in 63 (39.1%) and floaters in 19 (11.8%) patients. Clinical findings at presentation included diffuse small, round, white keratic precipitates in 128 (74.8%) eyes, anterior chamber reaction in 82 (47.9%), vitreous cells in 122 (71.3%), heterochromia in 47 (27.4%) and iris nodules in 32 (18.7%) eyes. During the follow-up period, elevated intraocular pressure occured in 31 (18.1%) eyes and the most common complication was cataract development (89 eyes, 52.0%).

Conclusion: Heterochromia was observed in 27.4% of patients in our study. However, the diffuse small, round keratic precipitates, low-grade anterior chamber reaction and varying degrees of vitreous reaction are more common clinical characteristics that are helpful in making the diagnosis.

Keywords: Fuchs' uveitis syndrome, intraocular pressure, heterochromia, cataract, complications

Introduction

Fuchs' uveitis syndrome (FUS) accounts for 1-6% of all uveitis cases.[1,2] This syndrome is diagnosed based on clinical findings, without any laboratory testing. The clinical features of FUS have been described extensively in many studies.[3,4,5] However, there are data in the literature indicating that the clinical findings of FUS vary between different populations.[3,6,7,8] Despite the clinical signs being well known, the incorrect and/or delayed diagnosis of FUS is still a frequent occurrence.

The aim of this study was to evaluate the findings at time of presentation, the clinical and demographic characteristics, medical and surgical approaches used and complications during follow-up in Turkish patients diagnosed with FUS presenting to a reference hospital.

Materials and Methods

Of the 1,084 patients who presented to the Uvea unit of the Ulucanlar Eye Hospital, the medical records of the 161 patients (14.8%) diagnosed with FUS were analyzed retrospectively. FUS diagnosis was based on clinical findings as previously described in the literature.[5,9,10,11] Accordingly, cases exhibiting typically unilateral, chronic, low-grade anterior chamber reaction with varying degrees of vitreous opacity, widespread small- or medium-sized keratic precipitates (KP) in the corneal epithelium, diffuse iris atrophy and/or heterochromia but without acute exacerbations, posterior synechiae or cystoid macular edema were clinically diagnosed with FUS. All patients' diagnosis and follow-up visits were conducted in the uvea unit by the same physician (P.Ç.Ö.).

A detailed history was obtained from each patient followed by a thorough ophthalmologic examination. Each follow-up

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visit included best corrected visual acuity (BCVA) assessment, slit-lamp examination of the anterior segment in both eyes, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, and dilated fundus examination using a 90 diopter (D) lens. Patients with IOP ≥21 mmHg underwent angle assessment using gonioscopy. Glaucoma was defined as IOP ≥21 mmHg with optic disc cupping and/or glaucomatous visual field loss, or as the presence of glaucomatous visual field loss despite IOP <21 mmHg.

In order to aid differential diagnosis, erythrocyte sedimentation rate, whole blood count, tuberculin skin test, chest radiograph, angiotensin converting enzyme test, syphilis serology, and cranial magnetic resonance imaging (MRI) were performed as necessary. Fundus fluorescein angiography (FFA) was done in cases with retinal vasculitis findings. Visual field evaluation and ultrasonography were also conducted in selected patients when necessary.

Patients who had sight-limiting KP and cells and were scheduled for surgery were treated with topical corticosteroid for one week prior to the procedure. Patients with severe vitreous haze that significantly limited their vision were treated with posterior sub-Tenon's triamcinolone injection prior to planning the surgical approach.

Analysis included patients' age at diagnosis, gender, clinical findings at disease onset, follow-up duration, systemic diseases, BCVA at initial and final visits, complications, and medical and surgical treatments.

Data were analyzed with Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Mean values and percentages were obtained for analysis.

Results

The present study included 171 eyes of 161 patients diagnosed with FUS. Ninety-four (58.4%) of the patients were female, 67 (41.6%) were male. Mean age at diagnosis was 35.2±11.0 years (range, 11-65 years). Five patients (3.1%) were under the age of 16. Mean follow-up time was 23.5±32.8 months (range, 2-216 months). Four (2.4%) of the patients had rheumatoid arthritis, 1 (0.6%) had type 1 diabetes mellitus, 1 (0.6%) had epilepsy, and 1 (0.6%) had thyroid disease. The right eye was involved in 84 patients (52.1%) and the left eye was involved in 67 patients (41.6%), while 10 patients (6.2%) had bilateral involvement.

Blurred vision or decreased visual acuity was the most common complaint at presentation (63 patients, 39.1%). Sixty-eight patients (42.2%) had no symptoms, and the condition was noticed incidentally during routine examinations in the outpatient clinic. Symptoms at presentation are summarized in Table 1.

BCVA at the initial visit was ≥0.6 in 98 eyes (57.3%), between 0.2 and 0.5 in 38 eyes (22.2%), and ≤0.1 in 35 eyes (20.4%). At the final visit, BCVA distribution was ≥0.6 in 137 eyes (80.1%), between 0.2 and 0.5 in 15 (8.7%), and ≤0.1 in 19 (11.1%). Of the patients with a final BCVA ≤0.1, 1 eye (0.6%) was aphakic, while glaucomatous optic atrophy was observed in 4 eyes (2.4%), cataract in 8 (4.9%), cataract plus vitreous condensation in 4 (2.4%), and vitreous condensation alone in 2 eyes (1.2%).

KP was observed in 168 eyes (98.2%) at initial presentation, while 3 eyes (1.8%) did not exhibit KP. During follow-up, KP occasionally disappeared and reappeared or fluctuated in severity. In the majority of cases (143 eyes, 85.1%) KP were small to medium-sized, round, thin, white precipitates diffusely scattered over the entire posterior corneal surface (Figure 1). At initial visit the anterior chamber reaction was usually mild to moderate (reaction ≤ [1+] in 67 eyes [39.2%]). Although the severity of vitreous cells and opacity could not be evaluated in some of the involved eyes due to cataract, inflammatory cell reaction between (1+) and (3+) in the vitreous was observed in 120 eyes (70.2%). Forty-seven eyes (27.4%) exhibited heterochromia with varying degrees of iris depigmentation. The iris was atrophic at the pupillary margin in 80 eyes (46.7%), while flattening of iris crypts was observed in 41 eyes (23.9%) (Figure 2). Small multi-

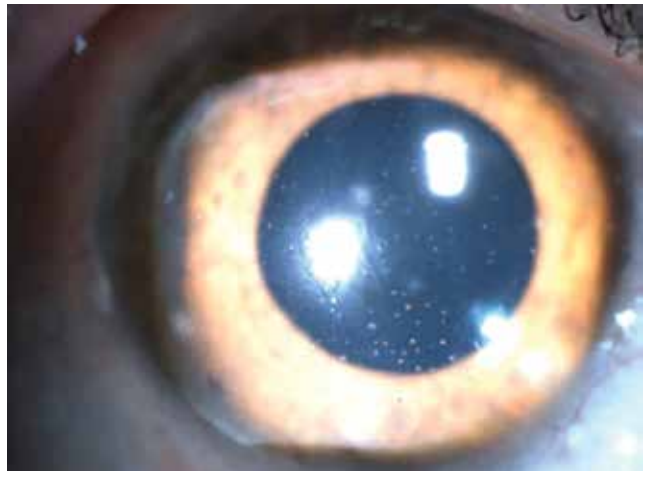

Figure 1. Diffuse, medium-sized, white, round keratic precipitates in a case of Fuchs' uveitis syndrome

Figure 2. Iris atrophy is more pronounced in the pupillary margin

focal Koeppe nodules localized to the pupillary margin were present in 32 eyes (18.7%); both Koeppe and Busacca nodules were present in 4 eyes (2.4%) (Figure 3). Posterior synechia was observed in 1 patient (0.7%) who had an IOL implant.

At diagnosis, 89 eyes (52%) had cataract. Of these, 2 (2.2%) were nuclear, 5 (5.6%) were mature, and 82 (92.1%) were posterior subcapsular cataract (Figure 4). Twenty-six eyes (15.2%) were pseudophakic. Findings at presentation are summarized in Table 2.

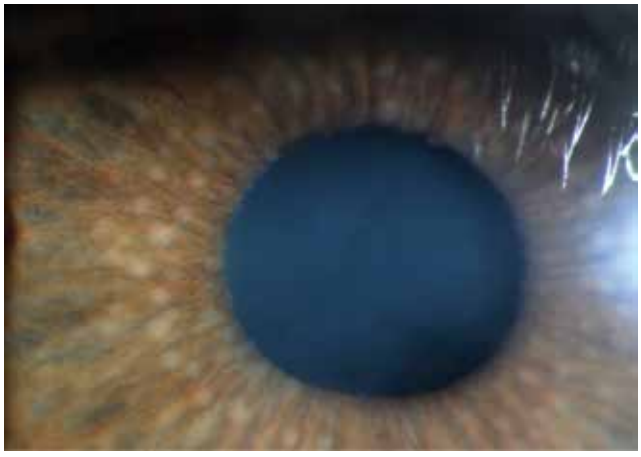

Figure 3. Koeppe nodules at the pupillary border and Busacca nodules in the iris stroma in a Fuchs' uveitis syndrome patient

Figure 4. A Fuchs' uveitis syndrome patient with posterior subcapsular cataract development

Table 1. Patients' symptoms at presentation	
Symptom*	n (%)
No symptoms	68 (42.2%)
Decreased visual acuity or blurred vision	63 (39.1%)
Floaters	19 (11.8%)
Irritation	14 (8.6%)
*Some patients had more than one symptom	

At final visit, 60 eyes (35.0%) were pseudophakic and 1 (0.6%) was aphakic. IOP was within normal limits in 134 patients (83.2%), whereas medical treatment for glaucoma was administered in 31 eyes (18.1%) of 27 patients (16.8%).

The most common complication during follow-up was cataract (89 eyes, 52.0%), followed by glaucoma (31 eyes, 18.1%), vitreous condensation (27 eyes, 15.7%) and secondary cataract (24 eyes, 14.0%). Complications observed are presented in Table 3.

Topical steroid therapy was administered in 26 eyes (15.2%) and periocular steroid injection was administered in 6 eyes (3.5%) due to severe inflammation in the vitreous. Thirty-one eyes (18.1%) received topical antiglaucomatous medication.

Table 2. Ocular findings in 171 eyes of 161 patients at time of presentation	
Finding	**n (%)**
Keratic precipitates	168 (98.2%)
Iris atrophy	
Heterochromia	47 (27.4%)
Loss of iris crypts	41 (23.9%)
Atrophy at the pupillary margin	80 (46.7%)
Iris nodules	
Koeppe nodules	32 (18.7%)
Koeppe ve Busacca nodules	4 (2.3%)
Anterior chamber reaction	
≤+1	67 (39.2%)
+1< x ≤+2	15 (8.7%)
Vitreous reaction	
≤+1	63 (36.8%)
+1< x ≤+2	52 (30.4%)
+2< x ≤+3	5 (2.9%)
+4 (severe vitritis)	2 (1.2%)
Lens opacity	
Posterior subcapsular opacity	82 (47.9%)
Mature cataract	5 (2.9%)
Nuclear opacity	2 (1.2%)

Table 3. Complications observed in patients with Fuchs' uveitis syndrome	
Complication*	**n (%)**
Cataract	89 (52%)
Glaucoma	31 (18.1%)
Vitreous condensation	27 (15.7%)
Secondary cataract	24 (14.0%)
Iris pigmentation on the IOL	19 (11.1%)
Glaucomatous optic disc	12 (7.0%)
Epiretinal membrane	4 (2.3%)
Peripheral vascular sheathing	4 (2.3%)
Chorioretinal scar	4 (2.3%)
Intravitreal hemorrhage	1 (0.6%)
Corneal endothelial plaque	1 (0.6%)
*In some eyes there were multiple complications; n: Number of eyes affected, IOL: Intraocular lens	

The visual acuity of 35 eyes (20.4%) worsened during the follow-up period; these eyes were treated with phacoemulsification (phaco) and intraocular lens (IOL) implantation. Trabeculectomy was performed on 8 eyes (4.7%) with uncontrolled IOP despite maximum medical treatment. Posterior capsule opacification developed in 34 eyes (19.8%) and was treated with YAG laser capsulotomy. Pars plana vitrectomy was performed in a total of 3 eyes (1.8%), 2 (1.2%) due to severe vitreous condensation and 1 (0.6%) due to vitreous hemorrhage. All surgical procedures performed are summarized in Table 4.

Discussion

FUS, which was first described in 1906 by Fuchs,[4] cannot be diagnosed by any laboratory test; its diagnosis is based solely on clinical findings. Despite these clinical findings being well defined in many studies, an accurate diagnosis is often delayed.[9,12] Misdiagnosis results in unnecessary tests and ineffective treatment.[5,7,9,10,11,12,13] The condition is usually unilateral, with only 5-10% of cases showing bilateral involvement.[10,14] One of the classic findings is KP, which have been described as diffuse, small, nonpigmented stellate precipitates that are usually nongranulomatous and tend not to aggregate. The vast majority of our patients (93.7%) exhibited unilateral involvement with small to medium white KP diffusely scattered over the corneal endothelium as well as mild anterior uveitis. Tugal-Tutkun et al.[10] described most of the KPs in their study (74.6%) as medium-sized. Descriptions of the clinical features of FUS have focused on findings related to anterior uveitis, while inflammatory findings in the posterior segment were assigned less importance.[7,9,13,15,16] However, this plays a major role in the misdiagnosis of FUS. Failure to realize that heterochromia, described as a primary clinical sign of FUS, does not occur in all cases or that inflammatory reaction in the vitreous is a sign of FUS has been reported as the main causes of misdiagnosis.[12,17] Consistent with these reports, in the current study heterochromia was present in 27.4% of cases at presentation, while inflammatory reaction in the vitreous was observed in 71.3% of cases. Bouchenaki and Herbort[17] reported that among 105 FUS patients, 77.1% with posterior segment manifestation had been referred with incorrect diagnoses (intermediate uveitis, 56.8%; posterior uveitis, 8.1%; panuveitis, 12.2%) and that their diagnosis were delayed by 3 years on average. Various studies have reported this diagnostic delay ranging from 3 to 6.7 years.[9,12] The clinical and demographic characteristics of studies in the literature are summarized in Table 5.

The most common complaint at presentation among the patients in the current study was decreased visual acuity or blurred vision (39.1%). Similarly, Yang et al.[3] reported that decline in visual acuity or blurred vision were the most common symptoms (in 82.6%) of the patients in their study. A large proportion of our patients had no additional symptoms (42.2%) and FUS was detected incidentally during routine outpatient follow-up visits. This is attributable to the disease course characterized by chronic, low-grade inflammation.

FUS usually manifests unilaterally, though the reported rate of bilateral involvement varies in the literature (0-21%).[3,6,7,10]

Table 4. Surgical procedures performed in patients with Fuchs' uveitis syndrome

Surgery*	n (%)
Phaco-IOL	35 (20.4%)
YAG laser capsulotomy	34 (19.8%)
Trabeculectomy	8 (4.6%)
Pars plana vitrectomy	3 (1.7%)

*Some eyes underwent more than one surgical procedure; n: Number of eyes, phaco-IOL: Phacoemulsification and intraocular lens implantation

Table 5. Demographic and clinical characteristics of patients with Fuchs' uveitis syndrome as reported in the literature

Characteristic	Yang et al.[3]	Arellanes-García et al.[6]	Norrsell and Sjödell[12]	Tugal-Tutkun et al.[10]	La Hey et al.[18]	Liesegang[16]	The current study
Patient number (n)	104	68	54	172	51	54	161
Mean age (years, min-max)	39.5 (16-78)	31 (5-80)	37 (19-57)	29.5 (10-75)	40 (17-71)	44.5	35.2 (11-65)
Gender (Male:Female)	1:1.1	1:0.8	1:1.6	1:1.3	1:0.7	1:1.3	0.7:1
Bilateral involvement	13.5%	10.3%	5.5%	5.2%	4%	0%	6.2%
Keratic precipitates	99.2%	90%	100%	96.7%	88%	96%	98.2%
Aqueous cells*	68.7%	86%	--	74%	60%	74%	47.9%
Vitreous cells	73.8%	46.7%	92.6%	71.8%	84%	53.7%	71.3%
Heterochromia	12.7%	25.3%	75.9%	39.7%	82%	77.8%	27.4%
Iris atrophy	100%	53.3%	100%	88.4%	100%	98%	46.7%
Iris nodules	28%	47.8%	--	32%	10%	1.9%	14.0%
Cataract and IOL	70.7%	69.3%	92.6%	69.1%	82%	90.7%	66.6%
Elevated IOP and Glaucoma	23.1%	34.6%	11.1%	12.7%	22%	59%	18.1%
Chorioretinal lesion	0%	1.3%	11.1%	7.7%	8%	3.7%	2.3%

*In some studies, evaluation of aqueous cells was done by laser flare photometry. --: Was not included in analysis, IOL: Intraocular lens, IOP: Intraocular pressure

In the current study, both eyes were involved in 6.2% of our cases. Norrsell and Sjödell[12] found that patients with bilateral involvement had more progressive disease, developed glaucoma more frequently, and required surgical approaches such as pars plana vitrectomy and cataract surgery more often. Of the bilateral FUS cases in our study, 2 developed glaucoma and another 2 formed epiretinal membrane associated with posterior segment involvement.

Iris changes are a typical finding of FUS. Hypochromia in the affected eye resulting from diffuse pigment loss is the key feature of FUS.[4,7,18,19] Heterochromia, characterized by color differences between the two eyes, is more apparent in light colored eyes than in dark eyes; therefore, the reported frequency of heterochromia varies widely between populations (12.7-82%).[3,5,6,7,10,12,13,18] In this study, we found heterochromia at a rate of 27.4%. This finding has long been considered a principal sign of FUS and even lead to it being called 'Fuchs' heterochromic iridocyclitis'. However, due to its varying rate of presentation it is important to remember, especially during diagnosis, that heterochromia is not observed in all cases.

Other findings of FUS include iris edema, iris nodules, abnormal iris blood vessels, and more rarely peripheral anterior adhesions and filiform hemorrhage of the anterior chamber angle during paracentesis.[20] Tugal-Tutkun et al.[10] analyzed a large case series and emphasized that medium-sized round KP and iris nodules were more common findings than heterochromia in the Turkish population. They observed iris nodules in 32% of the cases in their study, compared to 21% in our study population. This low rate may be due to these nodules, which are small and few in number in the majority of cases, not being recorded.

Many studies have emphasized cataract development as the most common complication observed in FUS patients.[3,7,10,16,19] Tugal-Tutkun et al.[10] found a 56% risk of cataract formation in patients not receiving steroid treatment over their 8-year follow-up period. Yang et al.[3] also emphasized cataract as the most common (70.7%) complication in their study. Similarly, cataract development was the most common complication observed in our study, at 52%. The variation reported in different studies may be related to disease duration and the chronic nature of the disease. Cataract develops due to changes in lens permeability resulting from recurrent uveitis attacks.[21] Unnecessary steroid therapy also increases the risk of cataract formation.

Today, successful visual outcomes can be achieved with modern cataract surgical techniques and IOL implantation. The most common surgical approach utilized during follow-up in our study was phaco-IOL implantation (20.4%). Following cataract surgery, 85.2% of the patients had a final BCVA of 0.6 or better.

Glaucoma is another of the main complications seen in FUS. Its reported frequency varies widely in the literature (11-59%).[3,7,9,16,18] Glaucoma was detected in 18.1% of our cases. IOP could not be controlled with medical treatment in 25.8% of those patients, necessitating trabeculectomy. IOP was controlled postoperatively with or without medication in all patients who underwent surgery.

There are reports in the literature of posterior segment findings in FUS patients such as chorioretinal scars associated with ocular toxoplasmosis infection, epiretinal fibrosis, and peripheral vascular changes.[7,9,18] Posterior segment findings observed in the current study included chorioretinal scar (2.3%), peripheral vascular sheathing (2.3%) and intravitreal hemorrhage (0.6%).

Conclusion

In this study we investigated clinical findings in FUS patients. Most of our patients exhibited diffuse, small to medium, white, round or large, stellate KP, low-grade anterior chamber reaction, and vitreous cells and/or vitreous opacity and/or vitreous degeneration with no marked involvement of the posterior pole. We found that vitreous involvement and KP pattern were more prominent diagnostic features than heterochromia. The most common complications during follow-up were cataract, posterior capsule opacification after cataract surgery, glaucoma and vitreous condensation. Based on our data, we believe that a diagnosis of FUS should be considered in cases that are generally unilateral with no marked iris depigmentation but with diffuse small white KP and low-grade anterior chamber reaction, where the fundus is visible and there are no other inflammatory findings except vitreous cells, opacity and/or changes in the vitreous collagen fibers.

Ethics
Ethics Committee Approval: It was taken from Yıldırım Beyazıt University Yenimahalle Research and Training Hospital,
Informed Consent: It was taken.
Peer-review: Externally peer-reviewed.
Authorship Contributions
Surgical and Medical Practices: Pınar Çakar Özdal, Concept: Pınar Nalçacıoğlu, Pınar Çakar Özdal, Design: Pınar Nalçacıoğlu, Data Collection or Processing: Pınar Nalçacıoğlu, Mert Şimşek, Analysis or Interpretation: Pınar Nalçacıoğlu, Literature Search: Pınar Nalçacıoğlu, Mert Şimşek, Writing: Pınar Nalçacıoğlu.
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Original Article

Retinal Nerve Fiber Layer Thicknesses in Three Different Optic Nerve Head Size Groups Measured by Cirrus Spectral Domain Optical Coherence Tomography

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Summary

Objectives: To compare the retinal nerve fiber layer (RNFL) thicknesses in three different optic nerve head (ONH) size groups measured by Cirrus spectral domain optical coherence tomography (OCT).

Materials and Methods: Between January and March 2013, 253 eyes of 253 healthy subjects were enrolled in this study (mean age: 42.7±7.4 years [28-62 years]; 121 men and 132 women). The patients were divided into 3 groups according to ONH size: 77 patients in the "small ONH" group (ONH area <1.63 mm^2), 90 patients in the "medium ONH" group (ONH area 1.63-1.97 mm^2), and 86 patients in the "large ONH" group (ONH area >1.97 mm^2).

Results: There were significant differences in superior (p=0.008), inferior (p=0.004) and average RNFL thickness (p=0.001) between the small, medium and large ONH groups. Positive correlations between ONH size and inferior/average RNFL thicknesses were significant but very weak (r=0.150, p=0.017 and r=0.157, p=0.013 respectively).

Conclusion: RNFL thickness as measured by Cirrus OCT is positively correlated with ONH size and the differences in RNFL thickness were statistically significant between groups. This correlation and difference may be the result of a varying distance between the circular scan and the ONH margin.

Keywords: Retinal nerve fiber layer, optic nerve head, optical coherence tomography

Introduction

Although the assessment of peripapillary retinal nerve fiber layer (RNFL) thickness is essential in the diagnosis and management of glaucoma, its objective evaluation remains a challenge in clinical practice.[1] Quantitative measurements of RNFL thickness have become possible with the development of imaging technologies such as optical coherence tomography (OCT).

Several authors have shown that the Cirrus HD Spectral Domain OCT has very good intra-observer repeatability in both healthy and glaucomatous eyes.[2,3,4] The principle involved in image acquisition is similar for all the devices and involves a scan with a diode laser that collects information of RNFL thickness in a 3.4-mm-diameter circle centered on the optic nerve head (ONH).

Several investigators have reported that a larger ONH had more optic nerve fibers as determined histologically in human eyes.[5,6] However, another histological study on human eyes could not detect a correlation between axon count and scleral canal area.[7] Some studies using Stratus OCT (time domain OCT) have shown that eyes with large disc area have a thicker RNFL,[8,9] whereas others did not find such a correlation.[10] This study was undertaken to compare the RNFL thicknesses in three different ONH size groups as measured by Cirrus spectral domain OCT.

Materials and Methods

Between January and March 2013, 253 eyes of 253 subjects were enrolled in this study (mean age: 42.7±7.4 years [28-62 years], 121 men and 132 women). The study population consisted of consecutive patients with minor refractive disorders. All individuals underwent a complete ophthalmological examination, including visual acuity measurement, intraocular pressure measurement, slit-lamp biomicroscopy, and indirect ophthalmoscopy, to determine eligibility. Inclusion criteria were: best corrected visual acuity above 20/25, spherical refractive error between -5 and +5 diopters, cylindrical refractive error between -2 and +2

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diopters, normal intraocular pressure ≤21 mmHg, normal appearance of the optic disc, no significant ocular disease found by routine ophthalmological examination, no history of glaucoma in the family, and no systemic diseases with possible ocular involvement, such as diabetes mellitus.

All participants gave their informed consent. The study was conducted according to the Declaration of Helsinki principles and was approved by the internal review board of the Başkent University Faculty of Medicine.

The patients were divided into 3 groups according to ONH area: 77 patients were in the 'small ONH' group (ONH area smaller than 1.63 mm^2), 90 patients were in the 'medium ONH' group (ONH area between 1.63 mm^2 and 1.97 mm^2), and 86 patients were in the 'large ONH' group (ONH area larger than 1.97 mm^2). These groups were classified according to the normal values and limits of the optic ONH parameters presented in Cirrus HD spectral domain OCT software.

Optical Coherence Tomography Measurements

Cirrus HD spectral domain OCT (Carl Zeiss Meditec, Dublin, CA, USA) was used to measure both the peripapillary RNFL thickness and ONH area. The examination was performed under mydriasis by two experienced operators (S.G. and A.A.).

After pupil dilation, 6x6 mm cube optic disc scans, which were formed from 200 A scans for each of 200 B scans, were obtained. From this cube of data, the machine automatically identified the center of the disc and created a 3.4 mm calculation circle around the disc. The RNFL thickness along this peripapillary circle was analyzed and compared to normative data.

Ultimately, the signal strength had to be 6 or higher.

Statistical Analysis

Statistical significances of RNFL thicknesses in ONH size groups (classified as small, medium and large) were analyzed with one-way ANOVA. Tukey's post hoc test was used to identify which RNFL quadrants resulted in significant mean thickness differences between ONH size groups. Possible correlations between the RNFL thickness and ONH parameters were analyzed with Pearson correlation coefficient. All statistical analysis was done with Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL, USA). The level of significance was taken as 0.05 in all statistical tests.

Results

The mean age was 40.12±8.49 years (range, 35-55 years) in the 'small ONH' group, 43.21±4.43 (range, 35-54 years) in the 'medium ONH' group and 41.07±12.42 years (range, 36-55 years) in the 'large ONH' group. There were no significant age differences between the groups (p=0.98). The male/female distribution was similar in all groups (p=0.69). There was no statistically significant difference in the mean refractive error between groups (p=0.87).

Significant differences in superior (p=0.008), inferior (p=0.004) and average RNFL thickness (p=0.001) were detected between the small, medium and large ONH groups. Mean values and standard deviations of all RNFL thickness parameters in each ONH size group are shown in Table 1. In general, larger ONH size corresponded to increased RNFL thicknesses in all quadrants.

The results of the correlation analysis of RNFL thickness and ONH size are reported in Table 2. Inferior and average RNFL thicknesses were positively correlated with ONH size; the correlations were significant correlations but very weak (r=0.150, p=0.017 and r=0.157, p=0.013, respectively). Figures 1 and 2 are scatter plots illustrating the correlations between average and inferior RNFL thickness and ONH area, respectively.

Discussion

To assess RNFL thickness, a circular scan concentric to the ONH is performed. In 1996 Schuman et al.[11] found a circle diameter of 3.4 mm to be the most accurate in terms of reproducibility and all studies since then have used circular scans with this diameter, independently of ONH size. However, it is generally recognized

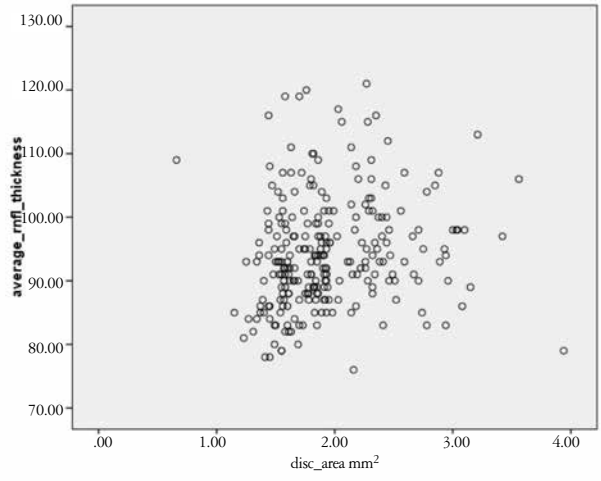

Figure 1. Scatter plot showing the correlation between average retinal nerve fiber layer thickness and optic nerve head area. RNFL: Retinal nerve fiber layer

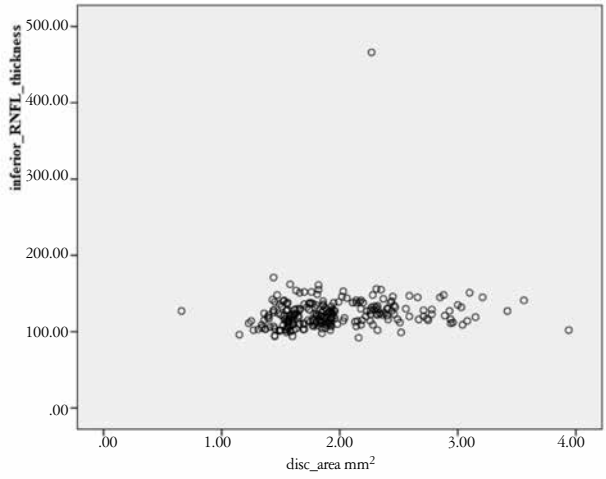

Figure 2. Scatter plot showing the correlation between inferior retinal nerve fiber layer thickness and optic nerve head area. RNFL: Retinal nerve fiber layer

that optic disc size shows a high inter-individual variability in normal eyes and its area may range between 0.8 and 6.0 mm2.[12] Therefore, using a fixed-diameter circular scan in all eyes may result in RNFL thickness measurements performed at different distances from ONH margin.[8]

In our study, we obtained significant differences for superior, inferior and average RNFL thickness between ONH size groups.

Table 1. Comparison of mean retinal nerve fiber layer thickness values in optic disc size groups

RNFL thickness	ONH sizes	n	Mean (µm)	SD	p values
Superior	Small	77	114.32	14.11	0.008
	Medium	89	117.72	14.04	
	Large	85	121.33	14.51	
	Total	251	117.90	14.44	
Temporal	Small	77	67.35	11.47	0.364
	Medium	89	69.65	9.58	
	Large	85	68.80	10.32	
	Total	251	68.66	10.44	
Inferior	Small	77	117.47	15.67	0.004
	Medium	89	122.36	13.09	
	Large	85	130.93	39.28	
	Total	251	123.76	26.15	
Nasal	Small	77	66.44	12.70	0.233
	Medium	89	67.52	9.17	
	Large	85	69.31	10.50	
	Total	251	67.79	10.82	
Average thickness	Small	77	91.65	8.66	0.001
	Medium	89	94.43	7.72	
	Large	85	96.72	9.04	
	Total	251	94.35	8.68	

RNFL: Retinal nerve fiber layer, SD: Standard deviation, ONH: Optic nerve head

Table 2. Correlation between retinal nerve fiber layer thickness and optic nerve head area

RNFL thickness	ONH area
Superior	r=0.125
	p value=0.048
Temporal	r=0.025
	p value=0.692
Inferior	r=0.150
	p value=0.017
Nasal	r=0.063
	p value=0.321
Average thickness	r=0.157
	p value=0.013

RNFL: Retinal nerve fiber layer, ONH: Optic nerve head, r: Correlation coefficient,

There were weak but significant positive correlations between ONH size and inferior and average RNFL thickness. In addition, we observed that the RNFL thicknesses in all quadrants increased with ONH size.

Savini et al.[8] showed that RNFL thickness measured by Stratus OCT is positively correlated with ONH size, as determined by measurements of its area and diameter. The authors detected this correlation in the superior, inferior and nasal quadrants; in the temporal quadrant they detected a similar trend, but it did not reach statistical significance. They suggested such a correlation may be the result of either an increased number of nerve fibers in the eyes with larger discs or an artifact produced by the use of a fixed-diameter scan. The latter hypothesis was derived from the notion that if a fixed-diameter circular scan is used, the distance between the scan and the ONH margin will be reduced in the presence of a large ONH, which would lead to overestimation of RNFL thickness in patients with large ONH as the measurement would be made closer to the optic disc edge. In a subsequent study by Savini et al.,[9] RNFL thickness was measured with a fixed 3.4 mm diameter circular scan and 2 customized-diameter scans (at 0.5 mm and 1 mm from the ONH edge) in 81 healthy subjects by Stratus OCT. It was found that when a fixed-diameter circular scan is used, larger discs show higher values; conversely, when the diameter is adjusted on the basis of ONH size, larger discs show lower values.

In a study by Kaushik et al.,[10] the peripapillary RNFL of 32 normal eyes was scanned with the fast-scanning protocol at a diameter of 3.4 mm using Stratus OCT and disc area did not affect RNFL thickness measurement. They suggested that RNFL thickness is dependent on the distance from the center of the optic disc rather than the point of exit from the scleral canal and that RNFL thickness should be measured at similar distances from center of the optic disc, regardless of the size of scleral canal.

There are a few studies on this subject using spectral OCT. Mansoori et al.[13] examined 65 healthy eyes using spectral OCT/SLO (scanning laser ophthalmoscope) and were unable to demonstrate significant correlation between optic disc size and average or quadrant peripapillary RNFL thickness. It was hypothesized that large inter-individual variability in RNFL thickness and disc area within the population probably minimizes the effect of various ONH size on RNFL thickness measurement. Huang et al.[14] found a similar result; in their study including 196 normal eyes, there was no significant association between RNFL thickness and optic disc area. In another study by Mansoori et al.,[15] RNFL thickness and optic disc measurements were performed using spectral OCT/SLO in 102 normal subjects in the upper, average, and lower ranges of ONH size. In eyes with disc area <4 mm2, disc area did not affect RNFL thickness measurement. Average, superior and temporal quadrant RNFL thickness measurements were inversely proportional to disc area in eyes with disc area >4 mm2. The authors explained this by stating that RNFL fibers emerging from a large ONH must be distributed over a wider circumference and, as a consequence, the larger spatial distribution will result in a thinner RNFL when large ONHs are analyzed. In our study, the large ONH group

comprised patients with ONH larger than 1.97 mm^2. Mansoori et al.'s[15] study included much larger ONHs compared to our study. We found a correlation between ONH size and RNFL thickness in the large ONH group in our study. However, contrary to our results, Mansoori et al.[15] found far thinner RNFL in patients with an ONH larger than 4 mm^2.

It is likely that the positive correlation between ONH size and RNFL thickness depends on the distance between the OCT circular scan and the ONH margin. If a fixed-diameter circular scan is employed, the distance between the scan and the ONH margin will be reduced in the presence of a large ONH. We are proposing this as an another theory to explain the varying nerve fiber thicknesses according to the ONH size at the fixed diameter of 3.4 mm via a resemblance to bicycle wheel spokes. The thickness of the RNFL measured at a fixed diameter of 3.4 mm may depend on the distances between the fibers on the circumference. In an eye with a small disc these distances between the fibers may be larger than those in an eye with a larger disc at that fixed circumference so that the thickness of RNFL in an eye with a large disc is measured thicker than the thickness of RNFL in an eye with a small disc.

Conclusion

In conclusion, we showed that RNFL thickness as measured by Cirrus HD Spectral OCT is positively correlated with ONH size, and the differences in RNFL thickness between ONH size groups were statistically significant. This correlation and difference may arise due to a varying distance between the circular scan and the ONH margin. We believe that there is a need for studies that measure the RNFL thickness at a specific distance from the margin of the ONH regardless of varying ONH size.

Ethics

Ethics Committee Approval: Başkent University Faculty of Medicine, Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ahmet Akman, Design: Ahmet Akman, Data Collection or Processing: Sirel Güngör, Ali Küçüködük, Analysis or Interpretation: Meriç Çolak, Literature Search: Sirel Güngör, Writing: Sirel Güngör.

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Original Article

Ophthalmologic Findings in Children with Leukemia: A Single-Center Study

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Summary

Objectives: Ophthalmologic disease in patients with acute leukemia occurs due to primary leukemic infiltration (involvement), or secondary to the disease and its treatment. In recent years the life expectancy of acute leukemia patients has increased with the advent of modern therapies. The present study aimed to determine the incidence of ocular manifestations in children with acute leukemia.

Materials and Methods: The study included 120 patients diagnosed with acute leukemia at Başkent University Hospital, Pediatric Hematology Department between 1995 and 2010. All the patients were examined by an ophthalmologist via direct and indirect ophthalmoscopy.

Results: Among the patients, 83 (69.2%) were diagnosed with acute lymphoblastic leukemia, 35 (29.1%) with acute myeloblastic leukemia, and 2 (1.7%) with mixed-lineage leukemia. In all, 58 ophthalmic manifestations were noted in 41 patients (34.2%). In our patients, 12 ophthalmologic involvements were present at admission and 46 ocular findings occurred during follow-up. The incidence of these manifestations increased with age.

Conclusion: Ophthalmologic manifestations were not correlated with gender, hematological parameters at disease onset, type of leukemia, or the frequency of relapse and survival. To more clearly determine the effect of ophthalmologic manifestations on the prognosis of leukemia, larger scale and multi-center studies are needed.

Keywords: Children, leukemia, ophthalmologic findings

Introduction

Though less commonly observed compared to the other organs, ocular findings may occur in patients with leukemia.[1] Since the initial description of leukemic retinopathy in the 1860s, it has been shown that nearly all eye structures may be affected in leukemia patients.[2] Since the mean life expectancy of leukemic patients is increasing due to the advances in diagnosis and treatment, the incidence of ocular findings is increasing. Ophthalmic signs in leukemia can be observed at the onset of disease or during follow-up. According to the literature, ocular involvement occurs in 9% to 90% of leukemia patients and most frequently affects the retina;[3,4] however, the relationship between the prognosis of leukemia and ocular manifestations remains unclear. In the present study, we aimed to investigate ophthalmic manifestations in patients with acute leukemia and to determine whether there is a relationship between these manifestations and morbidity or prognosis.

Materials and Methods

The study included 120 children with acute leukemia who were treated in our department between 1995 and 2010. Patient age, gender, hematologic parameters at diagnosis, organomegaly, and extramedullary involvement was recorded.

Acute leukemias were classified according to the French-American-British (FAB) classification as follows: acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), and acute mixed leukemia. For morphological classification, a bone marrow aspirate was stained with Wright stain, then examined with an optical microscope. Immunophenotyping was performed via flow-cytometry (Becton Dickons Canto II, Sysmex XT-2000i®). Conventional cytogenetic analysis was performed in all patients. Since 2003, fluorescence in situ hybridization analysis for specific areas of chromosomes was performed, as well as chromosomal analysis.

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Patients diagnosed with ALL between 1995 and 2005 were given the St. Jude Total XIII protocol, those diagnosed with ALL between 2005 and 2006 were given the ALL-Berlin-Frankfurt-Munster-1990 (ALL-BFM 90) protocol, and those diagnosed with ALL between 2006 and 2010 received the ALL-BFM 95 protocol. Patients diagnosed with AML received the AML-Berlin-Frankfurt-Munster-1993 (AML-BFM 93) protocol between 1995 and 2007, and after 2007 they received the AML-BFM 2004 protocol.

Findings at admission (FAA) were defined as the ocular manifestation(s) observed at the time of leukemia diagnosis, whereas findings during follow-up (FDF) were defined as ocular manifestations observed during or after the treatment of leukemia. At first admission with the diagnosis of acute leukemia, the patients underwent a detailed ophthalmologic examination by an ophthalmologist. All the patients who were followed in our department were also examined at remission and at the end of treatment. Ophthalmologic examinations were repeated in cases of relapse or any complaints concerning the eyes. Ocular manifestations at the time of leukemia diagnosis and during the course of follow-up were recorded. Visual acuity measurement and biomicroscopic examination including direct and indirect ophthalmoscopy were performed in all patients at diagnosis and during follow-up. Fundus photographs were obtained from selected patients as needed.

Statistical Methods

Statistical evaluation of the data was performed using Statistical Package for the Social Sciences v.19.0 for Windows. Benchmark analysis of categorical data was performed using chi-square and Fisher's exact tests, Kruskal-Wallis ANOVA analysis of quantitative data and Mann-Whitney U test were used. Arithmetic mean ± standard deviation and median values were used for quantitative data and frequency and percentage were used for qualitative data as descriptive statistics. The level of statistical significance was set at α=0.05.

The present study was performed in accordance with the ethical standards set forth in the 1964 version of the Declaration of Helsinki, and the Başkent University Ethics Committee approved the study protocol.

Results

In total, 83 (69.2%) patients had ALL, 35 (29.1%) had AML, and 2 (1.7%) had acute mixed leukemia. Table 1 shows the patients' demographic data. The distribution of gender, leukemic cell morphology, and immune-phenotype did not differ between the patients with ALL and AML. Considering complete blood count data at diagnosis, only the platelet counts were different, being lower in AML patients compared to those in patients with ALL (p=0.002). In all, 30% of the AML patients and 33% of ALL patients admitted with a leukocyte count >20x10^9/L. However, there was no correlation between

Table 1. Demographic and organ involvement data of patients with leukemia

		ALL	AML	Total
Number of patients (%)		83 (69.2)	35 (29.1)	120
Male/Female		55/28	22/13	79/41
Age at the diagnosis		5.5±3.5	9.0±5.5	6.6±4.5
Extramedullary involvement at diagnosis	Kidney	10	2	12 (31%)
	Central neurvous system	7	2	9 (23%)
	Gastrointestinal system	1	5	6 (15%)
	Eye	2	3	5 (13%)
	Bone	2	0	2 (5%)
	Others*	3	2	5 (13%)
	Total	25	14	39 (13%)
Sites of ophthalmologic manifestations**	Retina	1/9	1/5	16
	Conjunctiva	1/9	-/5	15
	Optic disk	1/6	-/2	9
	Cranial nerve	1/5	1/-	7
	Orbita	1/1	3/1	6
	Choroid	1/-	1/-	2
	Cornea	-/2	-/-	2
	Lens	-/1	-/-	1
	Total	6/33	6/13	58

*Pleura, pericardium, and thymus

**Numbers in the first two columns represent number of "primary/secondary" manifestations

ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia

the high leukocyte counts and ophthalmologic manifestations in our patients.

Extramedullary Involvement

In total, 39 (32.5%) of the patients had extramedullary involvement at the time of diagnosis; 64% (n=25) of cases were observed in ALL patients, versus 36% (n=14) in AML patients (Table 1). The most frequently involved extramedullary organ was the kidney [n=12 (31%)], followed by the central nervous system (CNS) [n=9 (23%)], gastrointestinal system [n=6 (15.4%)], eye [n=5 (13%)], bone [n=2 (5.1%)], pleura [n=2 (5%)], pericardium [n=2 (5%)] and thymus [n=1 (2.5%)]. Eye and gastrointestinal involvement were more common in the AML patients than in the ALL patients, but the difference was not significant (p=0.053) (Table 1). Relapse occurred in 20 of the patients with acute leukemia. Only one of the patients with acute mixed-lineage leukemia had orbital relapse together with CNS involvement 10 months after diagnosis. He was given a protocol for the treatment of children with relapsed ALL (ALL REZ-BFM relapse protocol) and cranio-spinal radiotherapy was administered. The last eye examination was normal. The patient later died due to sepsis.

Ophthalmologic Manifestations and Anatomic Distribution

Ophthalmologic manifestations occurred in 41 (34.2%) of the patients (17 male and 24 female) with acute leukemia. Among these, 32 had manifestations at the time of diagnosis (FAA), whereas 9 of them developed secondary ophthalmic manifestations after the diagnosis (FDF) (mean 9 months). There were no significant differences in ophthalmic manifestations according to the patients' leukemia morphology or immune-phenotype. Since some patients had multiple ophthalmic manifestations, 58 ophthalmic manifestations in total were observed in 41 patients. In our study, survival and relapse rates were similar in children who had ophthalmological manifestations at admission compared to those without ophthalmological findings.

Mean age at diagnosis of leukemia was higher in the patients with ophthalmologic manifestations (for ALL 6.4, AML 10.9, total 7.9 years) than those without ophthalmologic involvement (for ALL 5.2, AML 7.6, total 5.9 years). This difference was significant in patients with AML (n=35, p=0,006) and it was consistent when we analyzed all the patients with leukemia (n=120, p=0.04). Although the mean age at diagnosis was also higher in ALL patients with ophthalmologic findings, the difference was not significant (n=83, p=0.375).

In all, ophthalmic manifestations observed in our patients were mostly FDF [46 FDF manifestations (79%) vs 12 FAA manifestations (21%)]. The retina was the most common site of involvement. In total, there were 16 retinal manifestations (2 FAA and 14 FDF). Retinal manifestations did not differ significantly according to the hematological parameters. Among patients with retinal involvement at admission, an 18-month-old male diagnosed with B-cell ALL and significant leukocytosis ($400x10^9$/L) at the time of diagnosis showed extended leukemic mass below the retina and retinal detachment (Figure 1). Following leukapheresis and systemic chemotherapy, the mass disappeared. Unfortunately, approximately 1 year after diagnosis, the patient had bone marrow relapse without ocular involvement. He underwent bone marrow transplantation, but had another relapse after transplantation and passed away. The other patient with retinal involvement at admission was a 14-year-old female diagnosed with secondary AML-M5 who had completed chemotherapy for osteosarcoma 2 years earlier. At the initial examination, the patient had blurred vision and serous retinal detachment. An orbital tumor was also observed via cranial magnetic resonance imaging. Cytogenetic analysis of the bone marrow was normal. Following treatment, her ocular symptoms improved; however, during the third month of treatment she died due to sepsis. Another patient with retinal detachment at diagnosis was a 15-year-old male with AML-M2 blast cell morphology and t(8;21) translocation. His hemoglobin level was 5.1 g/dl; leukocyte and thrombocyte counts were 6,100/mm^3 and 7,000/mm^3 respectively. In addition to the retinal detachment, intraretinal hemorrhage and orbital granulocytic sarcoma were observed at time of diagnosis. The patient was treated with AML BFM 93 protocol and short-term high dose methylprednisolone. His ocular findings completely resolved after the methylprednisolone treatment.[5]

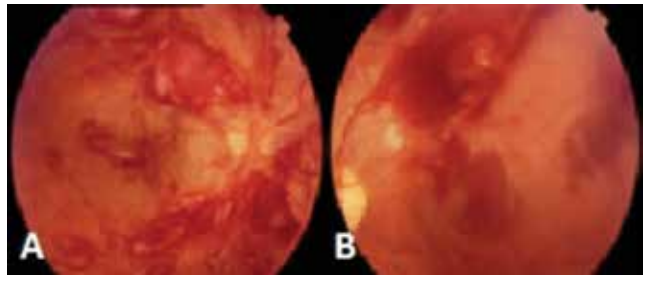

Figure 1. The retinal hemorrhages of patients with acute leukemia (A, right eye; B, left eye)

Figure 2. Retinal detachment in a patient with acute leukemia

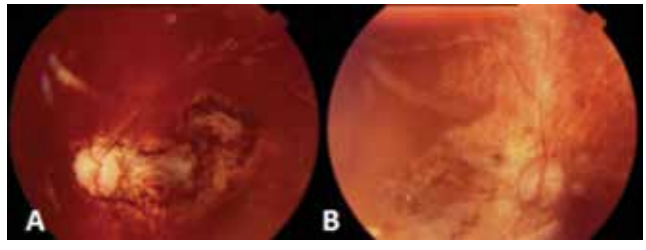

Figure 3. Retinal scar in a patient with acute myeloblastic leukemia (A, right eye; B, left eye)

Retinal pathologies during follow-up included retinal hemorrhage (n=10; 8 in ALL and 2 in AML patients), retinal detachment (n=2; 1 ALL and 1 AML), and retinitis (n=2; both AML) in our patients (Figure 2). Retinitis was noted in 2 patients with AML. One of them was diagnosed with FAB AML-M5 at the age of 7 months. During maintenance of AML-BFM treatment, he developed cytomegalovirus (CMV) retinitis treated with intravenous ganciclovir, then with oral valganciclovir for 1 year. This patient healed with a retinal scar and as of the time this manuscript was prepared had been in remission for 3 years (Figure 3).

Conjunctival manifestations were observed in 15 patients (10 ALL and 5 AML). Conjunctival involvement at admission was observed in only 1 patient, a 12-year-old female with pre-B-cell ALL. Leukemic infiltration was present in the right auricle along with both conjunctivas. Leukemic infiltration was noted in samples obtained from the ear, but conjunctival samples could not be obtained. The patient started chemotherapy; her ophthalmologic evaluation was normal after two weeks of treatment. She has been in remission for the last 7 years. In all, 14 patients had conjunctival manifestations during follow-up, of which 9 (6 ALL and 3 AML) had conjunctivitis. In 8 of these patients, conjunctivitis was infectious in origin and in the other it was allergic. In 2 of the 5 patients with conjunctival hemorrhage the platelet count was $<20x10^9$/L at the time of hemorrhage. Trauma was suspected in these cases.

Optic disc manifestations were observed in 9 patients (1 FAA and 8 FDF). The patient with involvement at admission had Philadelphia chromosome positive T-cell ALL. He had papilledema with optic nerve and CNS involvement at the time of diagnosis (Figure 4). The Non-Hodgkin Lymphoma-Berlin-Frankfurt-Munster-1990 (NHL-BFM 90) treatment protocol was initiated, along with cranial radiation therapy. Ophthalmic examination was normal 3 months after the initiation of ALL treatment. He has been in remission for the last 4 years.

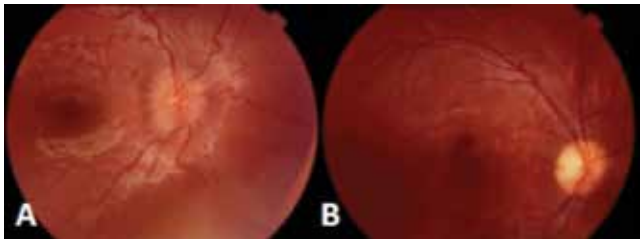

Figure 4. Optic disc signs in patients with acute leukemia. A. Papillary edema at optic disc. B. Atrophy at optic disc

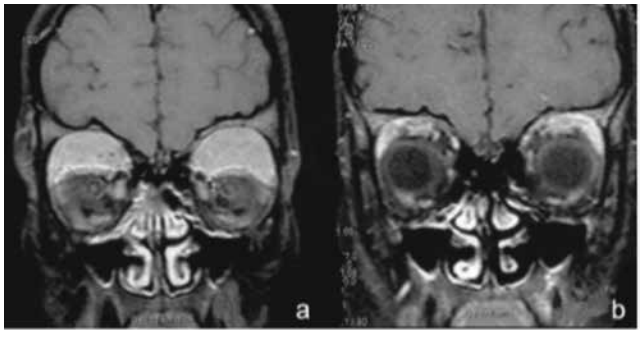

Figure 5. Orbital magnetic resonance images of patient with orbital granulocytic sarcoma before (a) and after (b) treatment

Cranial nerve manifestations were noted in 7 patients (2 FAA and 5 FDF). Both patients with primary involvement had Horner's syndrome at the time diagnosis; one of the patients was an 8-year-old male with AML-M4 with inversion of chromosome 16. After treatment, he has been well for the last 10 years without any ocular problems. The other patient was a 3-year-old male with B-cell ALL. This patient has been in remission for the last 5 years and his ophthalmic examination was normal at the last visit.

Orbital manifestations were recorded in 6 patients (4 FAA and 2 FDF). All orbital involvements at admission diagnosed with orbital granulocytic sarcoma were patients with AML (Figure 5). Three of them also had retinal involvement. All granulocytic sarcomas disappeared within 10 days of AML treatment.

In total, 2 patients, one with ALL-L1 and the other with AML-M5 had choroidal manifestations; both had involvement at admission and serous retinal detachment due to choroidal infiltration. They both returned to normal with leukemia treatment.

Two patients with ALL developed corneal pathology during follow-up that was related to toxicity of chemotherapeutics. One patient had evidence of subcapsular cataract as a secondary manifestation, which was also related to chemotherapy.

During bone marrow relapse, 5 patients had ocular manifestations; retinal manifestations during follow-up were observed in 3 of them (2 intraretinal hemorrhage and 1 retinitis) and cranial nerve findings were noted during follow-up in 2 patients.

Discussion

As the life expectancy of children with leukemia has increased due to advances in diagnosis and treatment methods, observation of the complications associated with leukemia has also increased. The limited studies on ophthalmologic signs in acute leukemia showed that the use of modern treatments has caused an increase in secondary ophthalmologic manifestations.[6] Ophthalmologic manifestations in pediatric leukemia patients may occur either directly due to leukemia or as a result of problems that occur during the course of disease. Although our study was retrospective in design, the ophthalmologic manifestations of all patients, both at the time of diagnosis and as needed during the course of illness, were observed and followed by experienced ophthalmologists at the same center; therefore, we think this study is comparable in nature to a prospective study. Although age and gender distribution in the study population was normal, the percentage of patients with AML (approximately 30%) was higher than in previously reported (15-20%) studies,[7] which might have been because patients referred to our hospital were mostly children with AML.

Russo et al.[8] studied ophthalmologic manifestations in 180 children with acute leukemia and observed that ocular manifestations occurred with a higher frequency in AML patients than in those with ALL. In addition, bone marrow relapse developed more frequently in the patients with specific ocular manifestations than in the patients with non-specific eye lesions or non-ophthalmologic manifestations. Furthermore, CNS and bone marrow relapse occurred more frequently in the patients with specific ocular lesions, resulting in a decrease in mean duration of survival. In the present study ocular involvement occurred more frequently in patients with AML compared to those with ALL, but the difference was not significant (p=0.053). There was no correlation between ophthalmologic manifestations and the frequency of relapse, morphologic or immunophenotype, or gender distribution in the present study. Our study includes a considerable number of patients with acute leukemia; however, inconsistent results compared to the study mentioned above indicates the need for larger/multi-centric studies.

Many studies have examined the effect of age on prognosis in acute leukemia.[9] In the present study, the occurrence of ophthalmologic manifestations increased with age in children with leukemia. Age is a strong prognostic factor in ALL, therefore our finding that the ALL patients with ophthalmologic findings were older than those without ophthalmologic findings supports this notion. However, in AML the age is not a strong prognostic factor.[7] Our study suggests that children with AML, especially those in the older age group, should be considered for ophthalmologic findings. Nevertheless, this finding should also be confirmed with further studies.

With the advent of modern treatment regimens, some prognostic factors that were once important are becoming less significant. As such, identification of novel risk factors that can be used to inform patient treatment and follow-up are needed. In 1976 Ridgway et al.[10] reported that among 657 children admitted with acute leukemia, 9% had ocular signs, the most common of which was retinal hemorrhage. In addition, 29 patients with leukemic involvement in the eyes mostly had bone marrow relapse, of which 27 patients had meningeal involvement based on evaluation of cerebrospinal fluid. None of these patients were treated with CNS prophylaxis, because the chemotherapy protocols did not include CNS prophylaxis at that time. In the present study 7 (17%) patients had CNS involvement with ocular manifestations (3 optic disc, 2 orbital, and 2 cranial nerve involvement) at the time of diagnosis. Only 1 patient who had CNS relapse also had orbital relapse. These findings suggest that including CNS prophylaxis in leukemia protocols prevents ocular involvement; however, larger scale studies are needed to confirm this conclusion.

In a recent report, Curto et al.[11] revealed that 32 of 38 patients with leukemic ocular involvement remitted, but that 6 of those patients had ocular relapse; therefore, more aggressive treatment was suggested in patients with ocular involvement, which could improve not only survival, but visual function as well. According to the literature, CNS and bone marrow relapse are more common in ALL patients with ocular signs, and result in a decrease in the duration of survival.[6,12] Therefore, the presence of ophthalmologic manifestations was thought to be a marker of poor prognosis. However, the present study's findings do not support this notion. In the present study there was no difference in survival between the ALL patients with and without ocular signs, and survival and relapse rates were similar overall in children who had ophthalmological manifestations at admission compared to those without ophthalmological findings.

Several reports indicated that the most common ocular signs were retinal findings, of which the most common was retinal hemorrhage.[12,13,14,15] Lower platelet counts and higher leukocyte counts were found in the acute leukemia patients with intraretinal hemorrhage. The researchers suggested that ocular signs in acute leukemia might be associated with the leukocyte and platelet counts. In the present study retinal involvement was the most common ophthalmic manifestation, consistent with these reports. However, we found no correlation between either retinal manifestations at admission or during follow-up and hematologic parameters, especially the leukocyte and platelet counts. Similarly, Ergur et al.[16] studied 42 children with acute leukemia and reported that 24 had ocular manifestations, but that ophthalmic manifestations and hematological parameters were not correlated.

Conclusion

In the present study, ophthalmic manifestations at admission or during follow-up differed according to gender and type of leukemia, and increased in frequency with age at admission. Ophthalmic manifestations were observed more frequently in the patients with AML than in those with ALL, but the difference was not significant. Despite various recommendations regarding the treatment of patients with primary ocular involvement, definitive information is still lacking. As this study did not directly demonstrate that ophthalmic manifestations negatively affect prognosis, alterations to current treatment protocols are not recommended. Multi-centric studies with larger patient groups are needed to further elucidate this issue.

Ethics

Ethics Committee Approval: The present study was performed in accordance with the ethical standards set forth in the 1964 version of the Declaration of Helsinki, and the Başkent University Ethics Committee approved the study protocol, Informed Consent: "Informed Consent Forms" were approved by all patients' parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Betül Orhan, Barış Malbora, Sezin Akça Bayar, Zekai Avcı, Bülent Alioğlu, Namık Özbek, Concept: Betül Orhan, Namık Özbek, Design: Betül Orhan, Namık Özbek, Data Collection or Processing: Betül Orhan, Barış Malbora, Analysis or Interpretation: Betül Orhan, Barış Malbora, Sezin Akça Bayar, Zekai Avcı, Bülent Alioğlu, Namık Özbek, Literature Search: Betül Orhan, Barış Malbora, Namık Özbek, Writing: Betül Orhan, Barış Malbora, Namık Özbek.

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Original Article

Clinical Characteristics and Low Vision Rehabilitation Methods for Partially Sighted School-Age Children

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Summary

Objectives: To determine the clinical features and the distribution of diagnosis in partially sighted school-age children, to report the chosen low vision rehabilitation methods and to emphasize the importance of low vision rehabilitation.

Materials and Methods: The study included 150 partially sighted children between the ages of 6 and 18 years. The distribution of diagnosis, accompanying ocular findings, visual acuity of the children both for near and distance with and without low vision devices, and the methods of low vision rehabilitation (for distance and for near) were determined. The demographic characteristics of the children and the parental consanguinity were recorded.

Results: The mean age of children was 10.6 years and the median age was 10 years; 88 (58.7%) of them were male and 62 (41.3%) of them were female. According to distribution of diagnoses among the children, the most frequent diagnosis was hereditary fundus dystrophies (36%) followed by cortical visual impairment (18%). The most frequently used rehabilitation methods were: telescopic lenses (91.3%) for distance vision; magnifiers (38.7%) and telemicroscopic systems (26.0%) for near vision. A significant improvement in visual acuity both for distance and near vision were determined with low vision aids.

Conclusion: A significant improvement in visual acuity can be achieved both for distance and near vision with low vision rehabilitation in partially sighted school-age children. It is important for ophthalmologists and pediatricians to guide parents and children to low vision rehabilitation.

Keywords: Low vision, low vision rehabilitation, school-age children

Introduction

The main goals of visual habilitation and rehabilitation for children with low vision are developing visual perception, increasing quality of life by maximizing their existing sight using appropriate methods and helping them use this level of vision optimally, and providing these children equal opportunities in both education and social contexts.[1,2]

In a 2002 congress held in Australia by the International Council of Ophthalmology, use of the following terminology regarding low vision was recommended:[3,4]

Blindness: Conditions involving complete loss of visual function, where the individual can only be rehabilitated with vision substitution methods.

Low Vision: Conditions with lesser degrees of vision loss, where the individual benefits from vision enhancement devices.

The World Health Organization (WHO) bases its legal definitions of low vision and blindness on visual acuity and visual field. Low vision is thus defined as visual acuity in the better eye after refractive correction between 20/70 (0.3) and 20/400 (0.05, 3 mps) or a visual field less than 20 degrees. Blindness is defined as visual acuity less than 20/400 (0.05, 3 mps) in the better eye after refractive correction or a visual field less than 10 degrees.[3,4]

These boundaries are especially important in terms of determining the legal rights given to individuals with visual impairment. However, these arbitrary limits are not as important as an individual's life goals when determining the need for visual rehabilitation. The decision to pursue low vision rehabilitation is not made according to legal limits, but is made individually based on that individual's vision requirements and life goals.[5,6]

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Based on WHO data from 2010, there are an estimated 1.5 million blind children and 5 million children with low vision worldwide. Visual impairment significantly affects the development and education of an estimated 1.5 to 2 million children. In Turkey, the disability rate is 12.58%, with the visually impaired accounting for 8.4% of the total disabled population. Approximately 32% of the Turkish population is under the age of 18, and 44% is under the age of 25. Using these data, the estimated number of visually impaired individuals in the child and adolescent age group in Turkey is about 350,000.[7]

The purpose of this study was to determine the diagnosis distribution and clinical characteristics of school-age children presenting for low vision rehabilitation services, to share methods chosen for low vision rehabilitation, and to emphasize the importance of rehabilitation in children with low vision.

Materials and Methods

The study included a total of 150 children with low vision attending the Ankara University Department of Public Health, Vision Rehabilitation and Research Center between 1 April 2012 and 28 February 2013.

The study was conducted in accordance with the Declaration of Helsinki. Approval to conduct the study was granted by the Ankara University Ethics Committee. Written informed consent was obtained from all children included in the study and their legal guardians.

Each child's diagnosis, accompanying ocular findings, distance and near visual acuity with and without a low vision aid (LVA), and the type(s) of LVA used for distance and near vision were determined. Demographic characteristics of the children in the study and the consanguinity of their parents were recorded.

Refractive error was assessed with autorefractometer and retinoscope prior to visual acuity examination. Values for corrective lenses for optimal distance vision were determined taking into account the smallest increase in visual acuity value noticeable by each child. First, distance vision was determined using LogMAR scales in normal lighting conditions from a distance of 4 meters. For children with low visual acuity, the examination was repeated from 2 meters and 1 meter. Children's near vision was then assessed using MNREAD cards at a distance of 25 cm.

Each child's required magnification power was calculated based on Kestenbaum's formula (1/visual acuity=dioptric power [1/VA=D]), then adjusted according to the individual and his/her desired visual function to obtain the final magnification power. Near and distance visual acuity with the resulting LVA was recorded. For low vision children with photophobia, lenses filtering the appropriate wavelengths based on the diagnosis were used.

The presence of strabismus was evaluated using a cover test, cover-uncover test and alternating cover test. In patients with deviations, an alternate prism cover test was used to measure the degree of deviation. Binocular vision was evaluated using the Worth 4 dot test. Anterior and posterior segment examinations were performed using a biomicroscope and binocular indirect ophthalmoscope.

The data were analyzed using Statistical Package for the Social Sciences version 11.0 for Windows (SPSS Inc., Chicago, USA) statistical software. Data are expressed as minimum (min), maximum (max), mean, standard deviation (SD), number or percent (%). Visual acuity with and without the use of an LVA was compared using a paired samples t test. P values less than 0.05 were accepted as statistically significant.

Results

The mean age of the children included in the study was 10.6±3.0 years and the median age was 10 years (range, 6-18 years). There were 88 (58.7%) males and 62 (41.3%) females; 45 (30.0%) of the children had been born in Ankara and 52 (34.7%) were living in Ankara at the time. The families of 7 of the children who had previously lived elsewhere stated that they had moved to Ankara to accommodate their child's need for special education and rehabilitation.

The children living outside of Ankara came primarily from the Central Anatolia (14.6%) and Black Sea (14%) regions, while the fewest came from the Aegean (4.7%) and Eastern Anatolia (5.3%) regions (Table 1).

Analysis of the distribution of the children's diagnoses revealed that the most common were hereditary vision impairment with 36% and cortical vision impairment with 18%. The distribution of the subjects' diagnoses is shown in Table 2. The most frequent accompanying ocular findings were nystagmus (35.3%) and strabismus (30.0%).

Investigation of parental consanguinity revealed a 66% rate of consanguineous marriage, with 29.3% of the parents being first degree relatives, 24.0% second degree relatives, and 12.7% more distant relatives.

The most commonly employed vision enhancement aids were telescopic lenses (91.3%) for distance and magnifiers (38.7%) for near vision. The second most common near vision rehabilitation method was telemicroscopic systems, with 26.0% (39 subjects). Electro-optical devices were used by 5 (3.3%) children for distance and 6 (4.0%) for near vision. Filters were used by 14% of the

Table 1. Distribution of the children with low vision included in the study based on the locations of their birth and residence

Characteristic	Number	Percent
Place of birth		
Ankara	45	30.0
Outside Ankara	105	70.0
Current location of residence		
Ankara	52	34.7
Outside Ankara		
Central Anatolia Region	22	14.6
Black Sea Region	21	14.0
Mediterranean Region	16	10.7
Marmara Region	14	9.3
Southeastern Anatolia Region	10	6.7
Eastern Anatolia Region	8	5.3
Aegean Region	7	4.7
Total	**150**	**100.0**

children, 66.7% of whom were being followed with a diagnosis of albinism (Table 3).

The subjects' near and distance visual acuities with and without vision enhancement aids and devices are shown in Table 4. LVA usage increased the mean distance visual acuity from 1.02 logMAR to 0.26 logMAR and provided an improvement in mean near visual acuity from 4.2 M to 1.38 M. The differences were statistically significant for both near and distance vision (paired samples t test, p=0.001).

Table 2. Distribution of the diagnoses of the children with low vision included in the study

Diagnosis	Number	Percent
Hereditary macular dystrophy	54	36.0
Cortical visual impairment	27	18.0
Albinism	16	10.7
Optic atrophy	15	10.0
Structural anomalies	14	9.3
Retinitis pigmentosa	7	4.7
Premature retinopathy	6	4.0
Amblyopia	4	2.7
Congenital cataract	3	2.0
Congenital glaucoma	2	1.3
Infantile nystagmus	2	1.3
Total	150	100.0

Table 3. Distribution of low vision children included in the study by low vision rehabilitation device usage

	Number	Percent
Aid used for distance vision		
Telescopic glasses	137	91.3
Glasses only	7	4.7
Electro-optical device	5	3.3
Other (e.g. iPad, Labo-clip)	1	0.7
Aid used for near vision		
Magnifier	58	38.7
Telemicroscope	39	26.0
Glasses only	31	20.7
Microscopic glasses	10	6.7
Electro-optical device	6	4.0
Other (e.g. iPad, Labo-clip spectacles)	6	4.0
Filter use		
Yes	21	14.0
No	119	86.0
Total	**150**	**100.0**

Table 4. Comparison of visual acuity levels of the study subjects before and while using low vision aids

Visual acuity	Before LVA Mean ± SD (min-max)	With LVA Mean ± SD (min-max)	p*
Distance (logMAR)	1.02±0.31 (0.2-2.1)	0.26±0.29 (0.0-1.2)	0.001
Near (25 cm) (M)	4.20±3.19 (1.0-16.0)	1.38±1.18 (1.0-10.0)	0.001

p*: Paired-samples t test
LVA: Low vision aid, SD: Standard deviation, min: Minimum, max: Maximum

Discussion

This study investigated clinical characteristics and low vision rehabilitation methods in school-age children with low vision. This type of study conducted with individuals presenting to clinics is advantageous over studies that are population-based or conducted in schools for the blind because they include more detailed ophthalmologic data.[8] However, a major disadvantage is that the data cannot be generalized to the entire population. The Ankara University Low Vision Rehabilitation and Research Center is a university-based center that serves patients from every region of Turkey. Therefore, although data in this context may not reflect the general population, we believe they will contribute both in terms of referring children with low vision to rehabilitation services and to the planning and implementation of low vision rehabilitation services.

It has been reported in the literature that male patients in both the pediatric and adult age groups present more frequently for low vision rehabilitation.[3,9,10,11] Consistent with the literature, the gender distribution in our study group was 58.7% male and 41.3% female. In a study conducted by Cardiff University in the United Kingdom, 67% of the children were male.[12] In another study by Gothwall and Herse[10] including children between the ages of 8 and 18 years with low vision living in India, 55% of the patients presenting for rehabilitation were male.

Forty-five (30%) of the children in the current study were born in Ankara, and 52 (34.7%) were living in Ankara at the time of the study, indicating that approximately 2 out of 3 children in our study were coming from outside Ankara. There were patients from each of the seven geographical regions of Turkey, with the highest proportion coming from the Central Anatolia and Black Sea regions, and the lowest proportion from the Aegean region. According to data from the Turkish Statistical Institute (TSI), the Aegean and Marmara regions have the lowest rates of consanguineous marriage.[7] The smaller number of low-vision children from the Aegean region compared to the other regions may be attributable to this. However, the Southeastern and Eastern Anatolia regions of Turkey, which have the highest rates of consanguineous marriage (43%), were not most represented in our study group. This demonstrates the need to consider various other factors including differences in economic development, transportation difficulties and distance from Ankara. Furthermore, individuals with low vision living in the Aegean and Marmara regions have access to local low vision rehabilitation services, which we believe may also contribute to the lower number of patients presenting from these regions.

The families of seven children stated that they had relocated to Ankara in order to accommodate their child's special educational and rehabilitation needs. This indicates a need for low vision rehabilitation centers in the other regions and provinces of Turkey. According to the WHO, a low vision rehabilitation center is required for every 10 million of population,[1,3] meaning there is a need for 6 additional centers in Turkey.

Analysis of the distribution of the diagnoses of the visually impaired children in our study revealed that the most common

diagnosis was hereditary macular dystrophy (36%), followed by cortical visual impairment (18%). Other common diagnoses, in order of frequency, were albinism, optic atrophy, structural anomalies, retinitis pigmentosa and retinopathy of prematurity. Olusanya et al.[8] published a study last year evaluating the patient profile in Nigeria's only low vision rehabilitation clinic over a period of 3 years and reported that 45 children between the ages of 0 and 15 years presented to the clinic, with the most common causes being optic atrophy (24.4%) and albinism (24.4%). Indian researchers Gothwall and Herse[10] reported that the most common diagnoses they found were retinal conditions, primarily heredomacular degeneration (21.5%) and retinitis pigmentosa (19.6%), followed by structural causes (12.0%) and albinism (5.0%). In a Turkish study by İdil[1,11] evaluating visually impaired children between 2004 and 2009, the leading diagnoses among those aged 7-18 were heredomacular degeneration (42%), albinism (21%) and optic atrophy (13%). In European, American and Australian studies, the most common diagnoses are retinopathy of prematurity (12-28%) and cortical causes of blindness (25-30%), while visual impairment due to hereditary causes is rarely encountered.[3,13,14,15]

Parental consanguinity is believed to be the leading cause of the prominence of hereditary conditions in children in Turkey. According to 2010 TSI data, the rate of consanguineous marriage in Turkey is 21%. This rate increases to 35% in Southeastern Anatolian provinces, and is lowest in Western Anatolia at 12-14%. Compared to the rate of 0.2-2% found in European countries, the proportion of consanguineous marriages in Turkey is extremely high.[16,17] Parental consanguinity increases the incidence of some hereditary diseases such as congenital cataract, retinitis pigmentosa, and congenital glaucoma up to 50 fold.[11,18]

Following hereditary causes, the most common diagnoses in this study were cortical visual impairment (18%), optic atrophy (10%) and retinopathy of prematurity (4.7%). A comparison with previous studies conducted by Turan et al.[19] and İdil[11] in 2002 and 2011, respectively, indicates that the frequency of vision loss due to these diagnoses has increased. This may be attributable to the development and wider availability of neonatal intensive care, which has allowed the survival of more premature newborns overall and of those with lower birth weight. Morbidities associated with prematurity include hydrocephaly and periventricular leukomalacia, as well as conditions resulting from these pathologies such as optic atrophy, cortical atrophy and retinopathy of prematurity due to incomplete retinal development.[20]

The most common vision enhancement aids utilized by the visually impaired children included in this study were telescopic glasses (91.3%) for distance and magnifiers (38.7%) for near vision. The second most common method for near vision rehabilitation was telemicroscopic systems (21.6%). Electro-optical devices were utilized by 5 children (3.3%) for distance and 6 children (4.0%) for near vision. Telescopic systems are chosen more often because they are more economical and portable than electro-optical systems. Similarly, magnifiers are most popular for near vision because they are economical and effective systems to which low vision patients, especially those newly starting rehabilitation, can adapt easily. However, for individuals with very low visual acuity (severe low vision), better results in both distance and near vision can be achieved with electro-optical systems. Mosuro et al.[21] screened low vision children attending schools for the blind in Nigeria and reported that telescopic systems were most commonly utilized for distance (94%), while magnifiers were used most often for near vision (69%). Similar results were reported in studies by Margrain[22] in the United Kingdom and DeCarlo et al.[23] in the United State of America in 2000 and 2012, respectively.

Filters were used by 14% of the low vision children included in this study, 66.7% of whom were being followed for albinism. In a 2013 study, Palomo-Álvarez and Puell[24] reported that special filters were effective in alleviating photophobia in hereditary fundus dystrophy and albinism but did not significantly improve reading performance. For the children in their study, filters were utilized to lessen photophobia and improve distance vision.

Comparing the subjects' near and distance vision levels to those achieved with vision enhancement aids, mean distance vision level increased from 1.02 logMAR to 0.26 logMAR and near vision improved from 4.20 M to 1.38 M with LVA use. The differences were significant for both near and distance ($p=0.001$). Low vision rehabilitation resulted in marked improvements in the vision levels of the visually impaired children included in this study.

Conclusion

In conclusion, low vision rehabilitation can facilitate significant improvement in both near and distance vision in visually impaired school-age children. Therefore, it is crucial that both pediatricians and ophthalmologists refer children with visual impairment to vision rehabilitation.

Ethics
Ethics Committee Approval: Ankara University Ethics Committee,
Informed Consent: Patient informed consent present.
Peer-review: Externally peer-reviewed.
Authorship Contributions
Surgical and Medical Practices: Low Vision Devices were applied by Zuhal Özen Tunay and Aysun İdil, Concept: Zuhal Özen Tunay, Design: Zuhal Özen Tunay, Deniz Çalışkan, Aysun İdil, Data Collection or Processing: Zuhal Özen Tunay, Aysun İdil, Analysis or Interpretation: Zuhal Özen Tunay, Deniz Çalışkan, Aysun İdil, Derya Öztuna, Literature Search: Zuhal Özen Tunay, Deniz Çalışkan, Writing: Zuhal Özen Tunay.
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Original Article

Necessity of Periodic Ophthalmological Examinations in Binocular B Class Driving Licence Holders Over 50 Years of Age

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Summary

Objective: To determine whether binocular B class driving licence (BBCDL) holders over 50 years old are in compliance with the BBCDL criteria for visual acuity, to determine the age-based prevalence of ophthalmological disorders reducing visual acuity in this group, and to investigate whether periodic ophthalmological examinations are needed in licence holders over 50 years of age.

Materials and Methods: This prospective study enrolled 451 adults over 50 years old having a BBCDL. The study subjects were categorized into 3 age groups as group 1 (51-60 years), group 2 (61-70 years), and group 3 (over 71 years).

Results: The mean age of the subjects was 60.02±7.27 years; 338 (74.9%) were male and 113 (25.1%) were female. The BBCDL criteria were met by 353 (78.3%) subjects whereas 98 (21.7%) subjects did not meet them. Eighty-four (85.7%) of 98 patients not meeting BBCDL criteria still drove. The mean age of the subjects meeting BBCDL criteria (58.82±6.77 years) was significantly lower than the subjects not meeting them (64.34±7.40 years) ($p<0.001$). The most common pathologies in the individuals still driving despite not meeting BBCDL criteria were senile cataract (38.5%) and diabetic retinopathy (23.1%) in group 1, senile cataract (55.3%) and diabetic retinopathy (14.9%) in group 2, and senile cataract (63.6%) and senile macular degeneration+senile cataract (18.2%) in group 3.

Conclusion: More than a fifth of individuals over 50 years old did not meet the BBCDL criteria, due predominantly to senile cataract, and the majority of these individuals continue to drive. Therefore, we believe that individuals over 50 years old who have a BBCDL should undergo periodic ophthalmological examinations.

Keywords: Binocular B class driving license, individuals over the age of 50, periodic ophthalmological examination

Introduction

Good vision is crucial for safe driving performance. The proportion of older individuals in the population is increasing, and visual acuity decreases with age. It has been reported that visual screening in older drivers is important for preventing traffic accidents.[1,2] Aging is accompanied by a higher incidence of sight-reducing conditions such as senile cataract, age-related macular degeneration (AMD) and diabetic retinopathy.[3,4,5] Diabetic retinopathy in particular progresses with disease duration and requires close follow-up.[6] The purpose of the current study was to determine whether the visual acuity of individuals over 50 years old with a binocular B class driving licence (BBCDL) is in compliance with the BBCDL criteria, to determine the prevalence of sight-limiting ocular diseases according to age group, and to assess whether periodic ophthalmologic examinations are necessary in this population.

Materials and Methods

For this prospective study, 451 BBCDL holders over 50 years old who presented to the ophthalmology clinic for various ocular complaints between 1 April 2014 and 15 August 2014 were enrolled consecutively. The study adhered to the Declaration of Helsinki and received approval from the local ethics committee. The subjects' age, gender, and vehicle use were recorded. Visual acuity was measured using the Snellen chart. BBCDL visual acuity requirements are regulated by the bylaw on health status and medical examination of prospective drivers and drivers entered into force through publication in the Official Gazette of the Republic of Turkey (date 26.09.2006, publication number 26301). The bylaw states that drivers receiving a B class licence must have a corrected or uncorrected visual acuity of at least 12/10 total in both eyes, with neither eye less than 2/10. A

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routine ophthalmologic examination was performed including intraocular pressure measurement and anterior and posterior segment examinations. Subjects were categorized into three groups based on age: group 1, 51-60 years old; group 2, 61-70 years old; group 3, over 71 years old.

Statistical Analysis

Statistical Package for the Social Sciences version 20 (SPSS, IBM, USA) software was used for statistical analyses. Descriptive statistics were expressed as mean ± standard deviation. Qualitative data were analyzed using the chi-square test. The Mann-Whitney U test was used to compare parameters with non-normal distribution between groups. P<0.05 was considered significant.

Results

The mean age of the subjects was 60.02±7.27 years (range, 51-82 years); there were 338 (74.9%) males and 113 (25.1%) females. Most of the subjects (78.3%, n=353) were in compliance with the BBCDL criteria for visual acuity, while 21.7% (n=98) did not meet the criteria (Table 1). Although 14 (14.3%) of the 98 noncompliant subjects did not drive, the remaining 84 (85.7%) continued to drive. It was noted that 47 of the 84 subjects who did not meet the BBCDL criteria but continued driving were in group 2 (61-70 years old) (Table 2). The mean age of the compliant subjects (58.82±6.77 years) was significantly lower than that of the subjects who were not in compliance with the BBCDL vision criteria (64.34±7.40 years, p<0.001).

The most common pathologies in subjects not compliant with the BBCDL vision criteria were senile cataract (35.5%), diabetic retinopathy (22.6%), amblyopia and choroidal rupture (9.7%) in group 1; senile cataract (56.0%), diabetic retinopathy (14.0%) and AMD+senile cataract (6.0%) in group 2; and senile cataract (58.8%), AMD (11.8%) and AMD+senile cataract (11.8%) (Table 3).

The most common pathologies in subjects still driving despite noncompliance with the BBCDL vision criteria were senile cataract (38.5%), diabetic retinopathy (23.1%), choroid rupture (11.5%) in group 1; senile cataract (55.3%), diabetic retinopathy (14.9%), and AMD+senile cataract (6.4%) in group 2; and senile cataract (63.6%), AMD+senile cataract (18.2%), posterior capsule opacity (9.1%) and branch retinal vein occlusion (9.1%) in group 3 (Table 4).

Discussion

The incidence of sight-reducing diseases rises with increasing age,[7,8] particularly senile cataract, glaucoma, AMD.[3,4,5,9] Even in the absence of ocular disease, visual function deteriorates with age.[8,10] A Turkish study comparing ophthalmologic examinations at the age of driving licence acquisition with those later in life showed that the frequency of refraction errors increased approximately 5 fold over a mean period of 20 years.[2] Therefore, the debate about vision and driving privileges should focus on elderly drivers. This topic will gain importance in the coming years due to the increasing elderly population and the subsequent rise in the number of elderly drivers on the road.

The United States of America and European countries require examinations and certain tests at regular intervals for drivers of advancing age in order to maintain the validity of their driving licence. However, there is no such legal obligation in Turkey.

Senile cataract develops in approximately 60% of adults 60 years of age.[11] Difficulty reading, driving and perceiving detail are among the resulting functional deficiencies.[12] Owsley et al.[13] conducted a visual and ophthalmologic assessment of 2,000 drivers over 70 years old and found that senile cataract had the greatest impact on visual acuity in that age group. Isawumi et al.[14] evaluated the ocular status of 99 commercial vehicle drivers with a mean age of 45.9 years and found cataract as the second most common (24.3%) cause of vision impairment, while Laudańska-Olszewska et al.[15] found cataract to be the third most common (6%) cause of vision impairment in a study of drivers aged 60 years and older. Consistent with the literature, in the current study the most common cause of low vision and noncompliance with the BBCDL criteria among all age groups was senile cataract.

The best predictor of diabetic retinopathy is the duration of the disease.[6] Patients having type 1 diabetes for 5 years or less rarely show any signs of diabetic retinopathy. In contrast, diabetic retinopathy develops in 27% of patients with diabetes for 5-10 years and 71-90% of patients with diabetes for more than 10 years. After 20-30 years the incidence increases to 95%, and 30-50% of these patients develop proliferative diabetic retinopathy.[16] Yanko et al.[17] reported the prevalence of diabetic retinopathy in type 2 diabetic patients as 23% at 11-13 years after the onset of type 2

Table 1. Distribution of binocular B class driving licence vision compliance in subjects overall and within age groups

	Compliant with BBCDL criteria, n (%)	Noncompliant with BBCDL criteria, n (%)	Total, n (%)
Overall	353 (78.27%)	98 (21.73%)	451 (100%)
Group 1 (51-60 years)	231 (88.17%)	31 (11.83%)	262 (100%)
Group 2 (61-70 years)	95 (65.52%)	50 (34.48%)	145 (100%)
Group 3 (over 71 years)	27 (61.36%)	17 (38.64%)	44 (100%)

BBCDL: Binocular B class driving licence, n: Number

diabetes and 60% at 16 or more years after onset. At 11 or more years after the development of type 2 diabetes, 3% of patients exhibited proliferative diabetic retinopathy. In the current study, the second most common cause of noncompliance with the BBCDL vision criteria in groups 1 and 2 was diabetic retinopathy.

In developed nations, AMD is the most common cause of central vision loss in individuals 65 and older. With a reported frequency of 10% in the 65-74 age range and 25% among those 75 and older, AMD is an important public health issue.[18] Vinding[19] found that AMD resulted in social blindness (6/60 or lower in both eyes) in 4.3 of every 1,000 people, and monocular blindness in 16.2 of every 1,000 people 60-80 years of age; they also reported that in Denmark, AMD led to visual acuity of 6/9 or lower in one or both eyes of individuals between 60 and 80 years of age. Laudańska-Olszewska et al.[15] found AMD to be the third most common (7%) cause of vision impairment among drivers 60 years and older. Furthermore, Szlyk et al.[20] evaluated the driving proficiency of 10 AMD patients with binocular vision of 20/70, and 11 age-matched individuals with normal vision. In the driving simulator test, AMD patients exhibited delayed braking response to stop signals, crossed more into the oncoming lane, and had more simulator accidents. In the current study, the third most common cause of noncompliance with the BBCDL vision criteria in group 2 was AMD+senile cataract, while the second most common cause in group 3 was AMD and AMD+senile cataract.

Visual acuity is easily assessed and is therefore the most commonly measured visual parameter. Although it varies from country to country, binocular vision of 0.5 is accepted as a standard for safe driving in most countries such as European nations and the United States of America (International Council of Ophthalmology at the 30th World Ophthalmology Congress Sao Paulo, Brazil, February 2006). However, in these countries a driving licence is not valid for life. In the United States of America, for example, driving licences have validity periods of several years depending on the state. In most states, driving licences are valid for 4, 5, 6 or 8 years, and in several states, older drivers receive licences with shorter validity periods and/or are subjected to a stricter renewal process. Driving licences are valid for 3 years for individuals over 75 years old in Indiana and for 2 years for drivers over the age of 70 in Iowa. Visual acuity testing is required when renewing a driving licence in Maryland after the age of 40 and in

Table 2. Vehicle usage among subjects not compliant with binocular B class driving licence criteria

	Noncompliant with BBCDL criteria	
	Driving n (%)	**Not Driving n (%)**
Group 1	26 (83.87%)	5 (16.13%)
Group 2	47 (94.00%)	3 (6.00%)
Group 3	11 (64.71%)	6 (35.29%)
Total	84	14

BBCDL: Binocular B class driving licence, n: Number

Table 3. Causes of noncompliance with the binocular B class driving licence vision criteria and their distribution by age group

Causes of reduced vision	Group 1	Group 2	Group 3
	n (%)	n (%)	n (%)
SC	11 (35.49%)	28 (56%)	10 (58.82%)
DRP	7 (22.58%)	7 (14%)	-
Optic Atrophy	2 (6.45%)	2 (4%)	-
Amblyopia	3 (9.67%)	2 (4%)	-
DRP+SC	-	2 (4%)	1 (5.88%)
AMD	1 (3.23%)	1 (2%)	2 (11.77%)
AMD+SC	1 (3.23%)	3 (6%)	2 (11.77%)
DRP+AMD	-	1 (2%)	-
Posterior capsule opacity	-	1 (2%)	1 (5.88%)
Branch retinal vein occlusion	-	1 (2%)	1 (5.88%)
Central retinal vein occlusion	-	1 (2%)	-
Glaucoma	1 (3.23%)	-	-
Choroidal rupture	3 (9.67%)	-	-
Evisceration, enucleation, phthisis	2 (6.45%)	-	-
Retinal detachment	-	1 (2%)	-
Total	31 (100%)	50 (100%)	17 (100%)

BBCDL: Binocular B class driving licence, SC: Senile cataract, DRP: Diabetic retinopathy, AMD: Age-related macular degeneration, n: Number

Table 4. Causes of reduced vision and their distribution by age group in subjects not compliant with the binocular B class driving licence vision criteria who continued to drive

Causes of reduced vision	Group 1	Group 2	Group 3
	n (%)	n (%)	n (%)
SC	10 (38.46%)	26 (55.32%)	7 (63.64%)
DRP	6 (23.07%)	7 (14.89%)	-
Optic Atrophy	1 (3.85%)	1 (2.13%)	-
Amblyopia	2 (7.69%)	2 (4.25%)	-
DRP+SC	-	2 (4.25%)	-
AMD	-	1 (2.13%)	-
AMD+SC	1 (3.85%)	3 (6.38%)	2 (18.18%)
DRP+AMD	-	1 (2.13%)	-
Posterior capsule opacity	-	1 (2.13%)	1 (9.09%)
Branch retinal vein occlusion	-	1 (2.13%)	1 (9.09%)
Central retinal vein occlusion	-	1 (2.13%)	-
Glaucoma	1 (3.85%)	-	-
Choroidal rupture	3 (11.54%)	-	-
Evisceration, enucleation, phthisis	2 (7.69%)	-	-
Retinal detachment	-	1 (2.13%)	-
Total	26 (100%)	47 (100%)	11 (100%)

BBCDL: Binocular B class driving licence, SC: Senile cataract, DRP: Diabetic retinopathy, AMD: Age-related macular degeneration, n: Number

Utah after the age of 65. In Illinois, driving licences are valid for 4 years, and individuals over 75 years old must take a driving test at each renewal. In addition, licences are renewed every 2 years for drivers aged 81-86 and each year after the age of 87 (http://www.ghsa.org/html/stateinfo/laws/olderdriver_laws.html).

According to data compiled by the Turkish Statistical Institute in 2013 including all licence classes, a total of 50,376 drivers (46,309 male, 4,067 female) aged 25-65 were reported injured and 355 (350 male, 5 female) were killed. A total of 2,732 drivers (2,678 male, 54 female) over 65 years old were injured and 60 (59 male, 1 female) lost their lives (Turkish Statistical Institute, Traffic Accident Statistics [Highway] 2013).

Individuals over 50 years old who hold a BBCDL may not have sufficient visual acuity according to the BBCDL specifications, especially due to certain ocular conditions that may occur between 61-70 years of age such as senile cataract, diabetic retinopathy and AMD. In this study, the mean age of patients who were not compliant with the BBCDL vision criteria was statistically higher. Therefore, BBCDL holders over 50 years old should undergo periodic ophthalmologic examinations. Furthermore, we believe that a scientific discussion and revision of the visual function criteria is necessary to improve driver safety in Turkey.

Ethics

Ethics Committee Approval: Recep Tayyip Erdoğan University Medical School Clinical Research Ethics Board-Date: 05/09/2014 Decision no: 127, Informed Consent: Available.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ali Kurt, Çağlar Öktem, Ayşe Karabıçak Acer, Özkan Kocamış, Sedat Taşdemir, Concept: Ali Kurt, Design: Ali Kurt, Data Collection or Processing: Ali Kurt, Çağlar Öktem, Ayşe Karabıçak Acer, Özkan Kocamış, Sedat Taşdemir, Analysis or Interpretation: Ali Kurt, Literature Search: Ali Kurt, Writing: Ali Kurt.

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Review

Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis

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Summary

Pediatric uveitis may be a serious health problem because of the lifetime burden of vision loss due to severe complications if the problem is not adequately treated. Juvenile idiopathic arthritis (JIA)-associated uveitis is characterized by insidious onset and potentially blinding chronic anterior uveitis. Periodic ophthalmologic screening is of utmost importance for early diagnosis of uveitis. Early diagnosis and proper immunomodulatory treatment are essential for good visual prognosis. The goal of treatment is to achieve enduring drug-free remission. The choice of therapeutic regimen needs to be tailored to each individual case. One must keep in mind that patients under immunomodulatory treatment should be monitored closely due to possible side effects. Local and systemic corticosteroids have long been the mainstay of therapy; however, long-term corticosteroid therapy should be avoided due to serious side effects. Steroid-sparing agents in the treatment of JIA-associated uveitis include antimetabolites and biologic agents in refractory cases. Among the various immunomodulatory agents, methotrexate is generally the first choice, as it has a well-established safety and efficacy profile in pediatric cases and does not appear to increase the risk of cancer. Other classic immunomodulators that may also be used in combination with methotrexate include azathioprine, mycophenolate mofetil, and cyclosporin A. Biologic agents, primarily tumor necrosis factor alpha inhibitors including infliximab or adalimumab, should be considered in cases of treatment failure with classic immunomodulatory agents.
Keywords: Uveitis, juvenile idiopathic arthritis, antimetabolites, biologic agents

Introduction

Despite advances in diagnosis and treatment, uveitis, especially in the pediatric age group, continues to be a serious health problem due to complications that may lead to blindness. Ocular involvement has particular importance in extra-articular manifestations of pediatric rheumatic diseases because of its high incidence and morbidity. Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease with both articular and ocular involvement.[1,2,3,4,5]

In the United States of America, 6% of all reported uveitis cases are pediatric, and approximately 80% of these are related to JIA.[6,7] In Turkey, JIA and Behçet's disease are the most common systemic diseases among pediatric uveitis cases, and the reported incidence of JIA varies between 3.3% and 30.4%.[8,9,10,11]

JIA is characterized by chronic arthritis beginning before the age of 16 and is the leading cause of arthritis in pediatric patients. It occurs more frequently in female children, with a reported female to male ratio of 3:2. The International League of Associations of Rheumatology (ILAR) classification system defines 7 subtypes of JIA which feature varying rates and types of uveitis. Approximately 78-90% of patients with JIA-associated uveitis have oligoarticular (≤4 joints) manifestation and 90% of these patients are antinuclear antibody (ANA) positive. Between 7-14% of the patients have polyarticular (≥5 joints) and 2-6% have systemic (systemic symptoms as well as articular involvement) manifestations. The average age of uveitis onset in JIA patients is 6-8 years old. In the majority of patients uveitis appears within 4-7 years of arthritis onset. However, uveitis occurs prior to arthritis in about 6% of cases and is only noticed if an eye exam is performed when the arthritis is diagnosed.[12,13,14,15,16] Therefore, it is imperative that all patients diagnosed with JIA undergo ophthalmologic examination and regular screening depending on the disease type. Oligoarticular and polyarticular JIA patients with arthritis onset at or before age 6, with arthritis for 4 years or less or positive for ANA should undergo an ophthalmologic examination every 3 months. Screening intervals for patients at lower risk of uveitis should be 6 to 12 months.[17] The diagnosis may be overlooked due to a lack of obvious ocular symptoms like redness, pain or light sensitivity, because some

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pediatric patients are unable to sufficiently communicate, or due to the chronic course of the disease. As a result, serious sight-threatening complications such as band keratopathy, cataract, glaucoma or hypotony may be observed at presentation.[1,18,19,20]

Patients with a consistently high degree of flare in the aqueous humour, which indicates the protein level, are at greater risk of complications. Risk factors for a poor prognosis are early age of uveitis onset, male gender, ANA positivity, short interval between arthritis and uveitis onset, oligoarticular manifestation and presence of ocular complications at time of presentation. Furthermore, patients with onset of arthritic involvement in early childhood are at high risk of chronic severe uveitis. In contrast, patients with arthritis onset at a later age exhibit recurrent acute anterior uveitis attacks and have a better prognosis.[18,21] The early diagnosis and correct treatment of these pediatric patients is critical for a good visual prognosis.

Cases of JIA-associated uveitis typically exhibit anterior uveitis characterized by iris and ciliary body involvement and is often bilateral. As a patient's arthritis and uveitis may follow different courses, the activity in each area of involvement should be evaluated independently, and treatment should be planned for each individual in cooperation with a pediatric rheumatologist. The results of numerous studies in the literature related to this topic can be used as the basis for a specific treatment algorithm for pediatric uveitis patients.[6,7,22]

Corticosteroids

Corticosteroids are essential in the treatment of uveitis, but their prolonged use is discouraged in order to avoid serious side effects, particularly in pediatric patients. Besides corticosteroids, long-term treatment options for the treatment of JIA-associated uveitis include antimetabolites, alkylating agents and biologic agents. These agents may also lead to serious side effects, and their risks to pediatric patients must be thoroughly evaluated; patients should be followed closely together with pediatric rheumatologists using a multidisciplinary approach.[6,7,23,24]

Topical corticosteroids and mydriatic agents can be administered as first-line treatment for patients with mild anterior uveitis diagnosed prior to the development of ocular complications (early band keratopathy, posterior synechia, cataract, macular edema). Prednisolone acetate (Predforte®), dexamethasone (Maxidex®, Dexasine®), fluorometholone (Flarex®, FML®) and loteprednol etabonate (Lotemax®) are the ophthalmic corticosteroids used in Turkey. Among these, prednisolone acetate and dexamethasone are the most potent and are the first choice in our clinical practice for the treatment of uveitis. Frequency of topical corticosteroid use should be evaluated for each patient based on inflammation severity. It is important to monitor intraocular pressure during the use of topical corticosteroids, especially in pediatric patients. Patients should be followed closely; if satisfactory treatment response is observed, the number of topical corticosteroid drops applied can be gradually decreased. However, in cases of insufficient treatment response or recurrence when the topical dose is reduced, local corticosteroid injections can be administered or short-term systemic corticosteroids can be added to the treatment regimen. Elevated intraocular pressure commonly occurs following intravitreal, peribulbar or sub-Tenon's corticosteroid (triamcinolone acetonide) injections, especially in pediatric patients. The recently introduced intravitreal dexamethasone implant (Ozurdex®, Allergan Inc, Irvine, CA, USA) has not caused significant intraocular pressure elevation in the majority of pediatric patients, and therefore may be preferable for cases requiring local corticosteroid injections.[25,26] However, it should be kept in mind that these implants may also lead to serious intraocular pressure elevation in some patients. Therefore, careful patient selection is important.[27]

As systemic therapy, 1-2 mg/kg oral prednisolone (Deltacortril® tablet) or methylprednisolone (Prednol® tablet) can be initiated as a loading dose, whereas 30 mg/kg intravenous pulse methylprednisolone (Prednol® ampoule) can be administered if a more rapid and potent effect is desired. Just as long-term topical corticosteroid use or local steroid injection can lead to ocular side effects like cataract and glaucoma, long-term systemic corticosteroid use can cause serious side effects such as growth and developmental delays due to adrenal suppression and premature epiphyseal closure, weight loss, hyperglycemia, infection and osteoporosis.[28] If a patient without ocular complications at the time of presentation exhibits recurrence when corticosteroid therapy is reduced, or elevated intraocular pressure is observed as a result of corticosteroid administration, immunomodulatory therapy should be started as soon as possible. However, patients presenting with at least one ocular complication in at least one eye require both systemic corticosteroid treatment and immunomodulatory therapy. Another point to be aware of is that although oral nonsteroid anti-inflammatory agents are effective for articular involvement in JIA patients, they have no effect in the treatment of uveitis.[29]

Antimetabolites, T-Cell Inhibitors and Alkylating Agents

Methotrexate is the first choice in immunomodulatory therapy because its efficacy and safety in pediatric patients is well established, and its long-term use does not increase cancer risk.[1,6,7,12,13,30,31] Approximately 60-82% of JIA-associated uveitis patients show improvement with methotrexate therapy.[1,6,31,32] Treatment with methotrexate is initiated early and continues for at least 3 years; a period of inactivity 2 years or longer before discontinuation lowers the risk for recurrence.[32] Methotrexate therapy begins at 10-15 mg/m^2 orally once per week and can be increased weekly for 6-8 weeks depending on response; a dose of up to 30 mg/m^2/week can be tolerated safely.[7,33] In JIA patients, the dose required for uveitis remission is generally higher than the dose administered for arthritis. In addition, as the dosage is set according to the patient's mass, children's weight should be followed regularly during growth periods. In cases where oral treatment is not tolerated by the patient or is not controlling the uveitis, treatment can be changed

to a parenteral route, which provides better bioavailability. The potential side effects of methotrexate therapy include bone marrow suppression, hepatotoxicity and interstitial pneumonia. Because methotrexate is a folic acid analogue, folic acid should be added to treatment in order to prevent side effects.[31] Aversion is another undesired side effect that can arise during methotrexate therapy. Prior to receiving an oral or injected dose, children frequently experience stomachache, nausea and may even vomit, symptoms which significantly impact the child's quality of life. In such cases it is important not to insist on treatment and instead employ alternative agents.

JIA-associated uveitis can cause intractable inflammation.[6] Samson et al.[34] found that uveitis symptoms were controlled with methotrexate in 59% of 21 patients with recurrent or chronic JIA-associated uveitis, while 41% had persistent inflammation. Other immunomodulatory agents or combined therapy can be started in cases where methotrexate is ineffective. Azathioprine, mycophenolate mofetil and cyclosporin are classic immunomodulatory agents alternative to methotrexate. Azathioprine is an effective agent for both adults and children, but is not preferred for pediatric patients due to its gastrointestinal side effects.[35,36] Mycophenolate mofetil, a better tolerated antimetabolite agent, inhibits purine synthesis and can be administered as an alternative treatment in patients who are resistant to methotrexate.[37] Cyclosporin A, a calcineurin inhibitor which interferes with T-cell activation, has limited efficacy in JIA-associated uveitis when used in isolation.[6] It is often administered in combination with methotrexate.[38] Cyclosporine can be used at 3-5 mg/kg/day.[39] Other less frequently employed T-cell inhibitors are tacrolimus and sirolimus. However, there is insufficient data regarding the use of these agents in pediatric patients. These agents may also cause hypertension and nephrotoxicity; therefore patients should be followed closely.[7]

Alkylating agents are utilized in cases showing insufficient treatment response to antimetabolites or combination therapy.[6,30] Although cyclophosphamide and chlorambucil are effective at suppressing inflammation, they have serious potential side effects such as pancytopenia, malignancy development in the long term, gonadal dysfunction and infertility.[40,41] With the introduction of biologic agents in the treatment of ocular inflammation, the use of alkylating agents in pediatric patients is becoming less common.

Biologic Agents

Among the monoclonal antibody biologic agents that suppress inflammation by binding proinflammatory cytokines, the most effective for ocular inflammation are the tumor necrosis factor (TNF)-alpha inhibitors infliximab and adalimumab. They can be used alone or in combination with classic immunomodulatory therapy.[7]

Infliximab is a chimeric mouse/human monoclonal antibody administered as an intravenous infusion at 5-20 mg/kg for 2 weeks as a loading dose and once every 4 weeks thereafter.[42] Low-dose antimetabolite therapy is often administered concomitantly to prevent antichimeric antibody production.[43] In our clinic we achieved successful outcomes in the short term with infliximab treatment in 20 pediatric patients with uveitis refractory to conventional treatment. Furthermore, successful surgical outcomes in cases with serious complications such as glaucoma and cataract have been achieved as a result of the anti-inflammatory effect of preoperative infliximab therapy. However, in long-term follow-up, 4 patients treated for 10-36 months reportedly developed resistance to treatment.[44]

Adalimumab, a fully human monoclonal antibody, is administered as a 20-40 mg subcutaneous injection every 7-14 days. In two separate clinical studies, Vazquez-Cobian et al.[45] and Biester et al.[46] demonstrated that adalimumab treatment was effective in 80.8% and 88% of pediatric uveitis cases, respectively. Although infliximab has a faster initial effect, evidence indicates that adalimumab is not associated with risk of inducing severe allergic reactions like anaphylaxis. Some studies comparing the efficacy of adalimumab and infliximab have shown that adalimumab is slightly more effective at inducing remission, while others have reported no significant differences between the two treatments.[47,48] A clinical study comparing methotrexate/adalimumab combined treatment and adalimumab monotherapy is still in progress.[49]

Etanercept, another anti-TNF agent, has been determined effective in the treatment of other rheumatologic manifestations of JIA but has not shown sufficient efficacy in JIA-associated uveitis and is even reported to lead to relapses causing the emergence of uveitis.[50,51,52,53] Our knowledge concerning the efficacy of golimumab and certolizumab pegol, also in this group of biologics, is limited to case studies; randomized clinical studies investigating the efficacy of these agents have yet to be conducted.[54,55]

Other biologic agents targeting immune cells can be utilized with pediatric uveitis patients who do not respond to anti-TNF therapy. These include tocilizumab, an inhibitor of pro-inflammatory cytokine interleukin (IL)-6; rituximab, an anti-CD-20 monoclonal antibody; anakinra, an IL-1 antagonist; daclizumab, an IL-2 antagonist; and abatacept, a cytotoxic T lymphocyte-associated antigen 4 fusion protein that inhibits T cell co-stimulation. Some studies with small case numbers have demonstrated the efficacy of these agents in suppressing inflammation in refractory JIA-associated uveitis.[22,56,57,58,59,60]

Surgical Treatment

Surgical intervention may be necessary in addition to medical treatment in cases of JIA-associated pediatric uveitis that develop complications like band keratopathy, cataract and glaucoma during follow-up. An important note to be aware of in these cases is that surgical success is highly dependent on the complete suppression of the ocular inflammation with medical treatment.[23]

Band Keratopathy

Band keratopathy is characterized by the deposition of calcium between the corneal epithelium and Bowman's layer. It frequently originates in the limbus near the 3 and 9 o'clock positions. It is one of the sight-threatening complications of JIA-associated uveitis. In a study with a large case series of 327 patients, 34.1% were shown to have band keratopathy at diagnosis.[21] When the condition threatens sight, chelation therapy with ethylenediaminetetraacetic acid (EDTA) can be performed. In a study by Najjar et al.[61] reporting the long-term outcomes of EDTA chelation in the treatment of calcific band keratopathy, they demonstrated that the method is effective, but that uveitic eyes exhibit a high recurrence rate. Therefore, its application is recommended in eyes with severely threatened sight or amblyopia risk.

Cataract Surgery

Cataract surgery in pediatric patients may be a challenge due to low scleral rigidity and existing ocular complications such as band keratopathy and posterior synechiae. In recent years, excellent visual outcomes have been achieved with good management of perioperative inflammation as well as modern surgical techniques and instruments. Intraocular lens (IOL) implantation during cataract surgery has been a controversy for many years. Until recently, the consensus was that IOL implantation was contraindicated in JIA-associated uveitis patients due to the severe postoperative inflammatory membrane formation around the IOL.[62,63] However, data from more recent studies contradict this stance.[64,65] Sijssens et al.[64] detected no significant difference in the postoperative complication rates of 19 aphakic eyes and 29 pseudophakic eyes, and demonstrated that pseudophakic eyes maintained better visual acuity up to 7 years postoperatively.

Glaucoma Surgery

Glaucoma may occur in uveitic eyes as a result of various mechanisms including aqueous outflow blockage due to peripheral anterior synechiae, reduced aqueous outflow due to increased aqueous protein concentration, trabecular inflammation and secondary damage.[66,67] Surgical intervention may be necessary in cases of failed medical treatment. The effectiveness of trabeculectomy is particularly limited in pediatric uveitis patients due to severe postoperative inflammation and fibrosis.[67,68,69] Glaucoma drainage implant surgery and goniotomy are other surgical methods that may be employed in pediatric uveitis patients.[70,71,72,73,74] An important point to keep in mind is that preoperative inflammation control is a crucial factor in the success of glaucoma surgery.

Conclusions and Recommendations

JIA-associated uveitis comprises a difficult disease group in terms of diagnosis and treatment. Diagnosing the condition before complications arise and starting immunomodulatory therapy immediately are critical for a good visual prognosis. Although the arthritis findings of patients with oligoarticular JIA may be inactive when uveitis is detected, treatment in that period should be planned according to uveitis activity. Appropriate treatment approaches can be planned on a case-by-case basis in order to achieve the ultimate aim of treatment, enduring remission after discontinuation of medication. The ocular complications which may occur as a result of disease-related inflammation and applied treatment methods as well as possible systemic complications resulting from immunomodulatory therapy should be monitored closely and treated immediately when necessary.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Merih Oray, İlknur Tuğal Tutkun, Design: Merih Oray, İlknur Tuğal Tutkun, Data Collection or Processing: Merih Oray, İlknur Tuğal Tutkun, Analysis or Interpretation: Merih Oray, İlknur Tuğal Tutkun, Literature Search: Merih Oray, İlknur Tuğal Tutkun, Writing: Merih Oray.

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Case Report

Polymicrobial Infection of the Cornea Due to Contact Lens Wear

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Summary
A 38-year-old male presented with pain and redness in his left eye. He had a history of wearing contact lenses. His ophthalmic examination revealed a large corneal ulcer with surrounding infiltrate. Cultures were isolated from the contact lenses, lens solutions, storage cases, and conjunctivae of both eyes and also corneal scrapings of the left eye. Fortified vancomycin and amikacin drops were started hourly. Culture results of conjunctivae of each eye and left cornea were positive for *Pseudomonas aeruginosa*; cultures from the contact lenses, lens solution and storage case of both eyes revealed *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*. Polymerase chain reaction of the corneal scraping was positive for *Acanthameoba*. The topical antibiotics were changed with ones that both bacteria were sensitive to and anti-amoebic therapy was added. The patient had two recurrences following initial presentation despite intensive therapy. Keratitis occurred due to multiple pathogens; the relapsing course despite adequate therapy is potentially associated with this polymicrobial etiology.
Keywords: Acanthamoeba, Alcaligenes, keratitis, Pseudomonas

Introduction

Infectious keratitis is a sight-threatening complication of contact lens (CL) wear. Most types of lenses have been reported to be associated with infectious keratitis. For a favorable outcome, it is essential to identify the causative agent. To date, several microbiological agents including bacteria, fungi and protozoa have been reported. It is known that microorganisms can reside on lenses and lens storage cases, and CL solutions also act as reservoirs for microbial growth. The latter is more strongly correlated with keratitis.[1,2]

The aim of this case report is to describe a case of polymicrobial keratitis due to CL wear. The causative agents identified were *Pseudomonas aeruginosa*, *Alcaligenes xylosoxidans*, and *Acanthameoba*. Ali and Reddy[3] reported a case of bilateral polymicrobial keratitis in which *Pseudomonas aeruginosa*, *Alcaligenes* spp., and *Flavobacterium meningosepticum* were involved. To the best of our knowledge, this is the first published case of CL-related polymicrobial keratitis with the aforementioned organisms.

Case Report

A 38-year-old otherwise healthy male presented to our outpatient cornea and CL clinic with complaints of pain, redness, photophobia and blurred vision in his left eye since the previous day. He had been using soft CLs for a period of time and had not had a follow-up ophthalmologic examination during this period. He could not give clear information about the commercially available brands of CL and CL solution he used. He was wearing daily CLs and replacing them monthly. He had slept with his lenses for two consecutive nights prior to these complaints, as he had frequently done. He placed the lenses in a cleaning solution when he removed them. He reported that he routinely showered while wearing his lenses, indicating a history of exposure to possibly contaminated water. He had used dexamethasone/netilmicin combination and ketorolac drops, which were not prescribed by a physician.

In his ophthalmologic examination, the right eye had 20/20 best-corrected visual acuity and both anterior and posterior segment findings were normal. His visual acuity in the left eye

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was counting fingers. Slit-lamp biomicroscopy revealed ciliary injection, large corneal ulcer (4x4 mm in size), and surrounding infiltrates involving the center and the upper half of the cornea, stromal thinning, and hypopyon (Figure 1). The fundus could not be visualized.

The patient was diagnosed with a CL-related corneal ulcer in the left eye and was hospitalized. Corneal scraping, cultures and Gram staining of the cornea and the conjunctiva were obtained. Right and left CLs, both lens storage cases, and two separate CL solutions were also sent for culture and Gram staining. Corneal scrapings were also examined by both polymerase chain reaction (PCR) and real time-PCR for the parasite *Acanthameoba*. Fortified vancomycin (50 mg/ml) and fortified amikacin (50 mg/ml) drops were started hourly. Additionally, cyclopentolate and artificial tears were prescribed.

Right and left conjunctival and left corneal cultures were positive for *Pseudomonas aeruginosa*. The remaining cultures revealed the following: left CL, *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*; right CL, *Pseudomonas aeruginosa*; both CL storage cases, *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*. The two microorganisms were sensitive to amikacin, piperacillin, and tazobactam. Hence, fortified vancomycin was replaced with fortified piperacillin (7 mg/ml). As corneal, left CL and left storage case cultures revealed positive PCR test for *Acanthamoeba*, hourly chlorhexidine (0.2 mg/ml) and propamidine isethionate (1 mg/ml) drops were added to the aforementioned regimen. On the 10th day of hospitalization, the hypopyon disappeared, the ulcer healed and corneal haze diminished. The patient's visual acuity improved to 20/400 and he was discharged; the hourly drops were diminished to every three hours.

In the third week of follow-up, the patient presented with diminished vision (counting fingers) and pain, although he was under close follow-up and receiving the drops every three hours. The ulcer was enlarged (7x6 mm) and there was a crescent-shaped stromal thinning at the nasal edge of the ulcer (Figure 2). Because these recent findings were thought to have occurred secondary to extensive use of the fortified antibiotics including chlorhexidine and propamidine, they were decreased to QID. Stromal thinning and the epithelial defect healed. After discharge the patient was lost to follow-up. In the 3rd month after initial presentation, he was admitted with total corneal opacity and a persistent epithelial defect in which a majority of the cornea was involved with stromal scarring resembling a persistent ulcer (Figure 3).

Microbiology Tests

All the samples were inoculated onto Columbia agar with 5% sheep blood, MacConkey agar, and chocolate agar with polyvitex for the aerobic bacterial culture and incubated at 37 °C for 24-48 hours. Specimens were inoculated onto Schaedler agar with 5% sheep blood and chocolate agar with polyvitex for the anaerobic bacteria culture and incubated in a jar including an AnaeroGen kit (BD GasPak anaerobe container system, Maryland, USA) at 37 °C for a week.

Achromobacter xylosoxidans and *Pseudomonas aeruginosa* were identified using Vitek-2 GN (gram-negative) identification

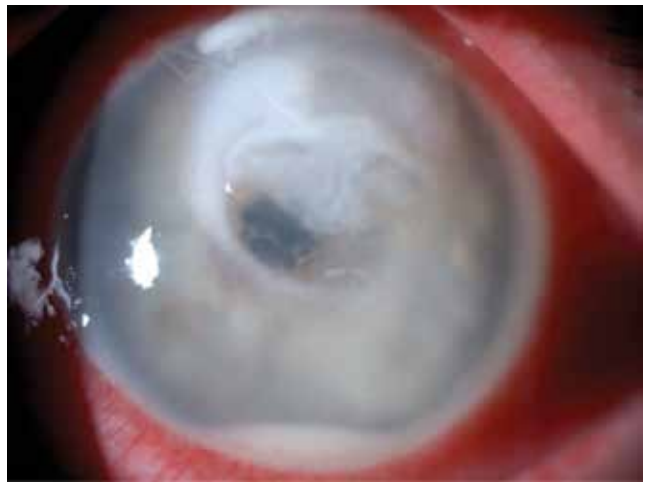

Figure 1. The initial presentation of the patient with large corneal ulcer and surrounding infiltrate involving the center and the upper half of the cornea, stromal thinning, and hypopyon in the left eye

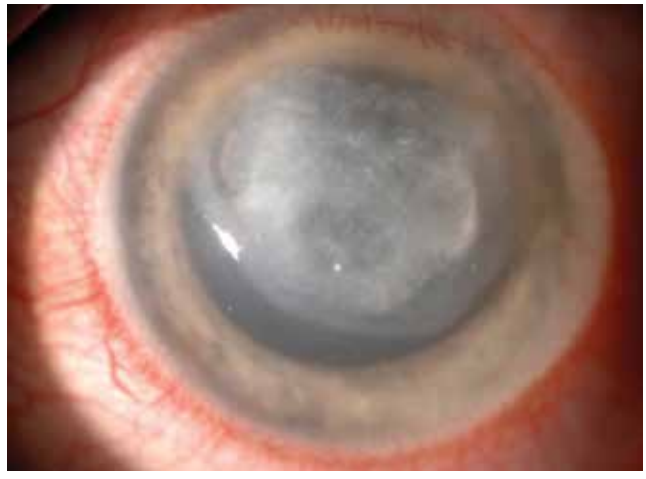

Figure 2. The left eye 3 weeks after initial presentation. Note, there is a crescent-shaped stromal thinning at the nasal edge of the ulcer

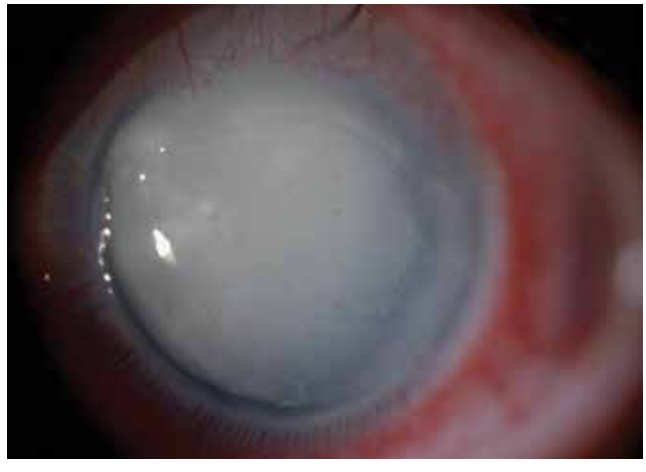

Figure 3. The large persistent epithelial defect involving the majority of the left cornea at final presentation

cards (Vitek 2 System, Biomerieux, USA). Antimicrobial susceptibility testing of these isolates was done using the Vitek-2 system. The criteria of the Clinical and Laboratory Standards Institute were used to interpret the antimicrobial resistance patterns of the isolates.

Discussion

All three causative organisms that were obtained from the current case are very well-known pathogens for CL-related keratitis, of which *Pseudomonas aeruginosa* is the most common.[1,2,3,4,5,6] *Acanthamoeba* spp. are free-living protozoan parasites and are particularly reported to be associated with poor hygienic conditions.[7] On the other hand, despite its relatively low prevalence *Alcaligenes* (formerly *Achromobacter*) xylosoxidans is an important cause of infection in CL wearers. *Alcaligenes* spp. are gram-negative, aerobic bacilli; although rare, they may cause keratitis, particularly in compromised corneas.[5,6]

Poor hygiene conditions enhance susceptibility to keratitis in CL wearers.[7] Overnight CL wear is a common compromising factor for corneal infections.[8] It was clear that our patient did not take good care of his hygiene and did not have any follow-up visits with an ophthalmologist. He was also unable to provide information regarding the brands CL and cleaning solution he was using. He had a prior history of two nights sleeping with CLs, which he reported to be actually longer. Moreover, he had a history of regular and uncontrolled topical corticosteroid use. As a result of these factors the patient became susceptible to a polymicrobial keratitis with destructive organisms. Also, the relapsing nature of the infection can be attributed to the polymicrobial etiology due to poor hygiene.

Pseudomonas and *Alcaligenes* were involved in both eyes of our patient, whereas *Acanthamoeba* was isolated from the left eye. As the patient had no sign of keratitis in his right eye, *Acanthamoeba*, which was isolated only from the left eye, is strongly considered to be the causative agent. On the other hand, we believe that the role of the other two organisms must be discussed in terms of their contribution to the clinical outcome. It might be considered that the polymicrobial nature of the infection could affect its course, resulting in high recurrence rates and poor visual acuity. We also considered possible toxic effects of intensive topical therapy including fortified antibiotics; hence, the drops were tapered in the second hospitalization, which was three weeks after the first one. Our patient had no problem with compliance to therapy during follow-up; however, *Alcaligenes* is reported to be particularly associated with frequently recurrent keratitis.[9]

One must always consider accompanying topical anesthetic abuse in cases with severe pain. Topical anesthetic abuse itself is known to cause superinfections with poor outcome.[10,11]

Silicone-hydrogel CLs are known to be associated with significantly lower *Pseudomonas aeruginosa* binding than conventional extended-wear soft CLs.[4] However, as we had no knowledge about the type of the CL our patient was wearing, we are not able to establish a relationship between the CL type and enhanced microbial binding.

Sharma et al.[12] stressed the risk of co-infection in their report, in which the patient did well following administration of propamidine isethionate 0.1%, chlorhexidine 0.02%, and polymyxine B eye drops in addition to previous anti-pseudomonal therapy. Immediately following presentation, we started fortified vancomycin and fortified amikacin. Both *Pseudomonas* and *Alcaligenes* were found to be sensitive to amikacin, piperacillin, and tazobactam. Hence, vancomycin was changed with piperacillin. As *Acanthamoeba* was identified by PCR, we started anti-amoebic therapy as well. Besides the polymicrobial nature, we believe that the intense topical therapy which would be expected to alter epithelial healing might also have played a role in the persistent course of the infection. As we tapered the topical regimen, the ulcer started to heal. Our plan was to administer topical therapy for an appropriate period of time, but the patient was lost to follow-up and later presented with recurrence.

Conclusion

To the very best of our knowledge this is the first report concerning these three organisms. *Pseudomonas* and *Acanthamoeba* are well known causes of CL keratitis, whereas because of the relative difficulty in its identification, the role of *Alcaligenes* might be underestimated.[6] Moreover, *Alcaligenes* spp. should be kept in mind in such persistent keratitis cases.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Selçuk Sızmaz, Sibel Bingöllü, Elif Erdem, Meltem Yağmur, Reha Ersöz, Concept: Selçuk Sızmaz, Sibel Bingöllü, Meltem Yağmur, Design: Selçuk Sızmaz, Elif Erdem, Meltem Yağmur, Reha Ersöz, Data Collection or Processing: Selçuk Sızmaz, Sibel Bingöllü, Filiz Kibar, Soner Koltaş, Analysis or Interpretation: Selçuk Sızmaz, Meltem Yağmur, Reha Ersöz, Literature Search: Selçuk Sızmaz, Sibel Bingöllü, Writing: Selçuk Sızmaz.

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Case Report

Herpetic Keratouveitis and Trabeculectomy Failure during Infliximab Therapy in a Patient with Behçet's Disease

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Summary

A 51-year-old man was diagnosed with Behçet's disease in 2001. The patient was resistant to all immunosuppressive therapies. After 6 months of infliximab therapy, he presented to our clinic with pain and blurred vision in his right eye. The visual acuity was 20/200 and the intraocular pressure was 35 mmHg in the right eye. Biomicroscopic examination revealed corneal dendritic ulcers and 2+ cells in the anterior chamber in the right eye. The herpetic keratouveitis attack was controlled with antiviral therapy but the patient needed another glaucoma surgery. Trabeculectomy with mitomycin C was performed about halfway through an eight-week interval between two doses of infliximab.

Keywords: Behçet's disease, herpetic keratouveitis, infliximab, trabeculectomy

Introduction

Behçet's disease (BD) is a serious sight-threatening clinical entity that involves uveitis accompanied by recurrent oral aphthous ulcers, genital ulcers, skin lesions, and other systemic lesions. Although infliximab, a humanized antibody against tumor necrosis factor-alpha (TNF-α), reduces uveitis attacks in patients with BD, anti-TNF-α therapy increases the risk of infections due to the systemic blockade of TNF-α.[1,2,3]

Here, we report herpetic keratouveitis triggered by treatment with the anti-TNF-α antibody infliximab in a uveitis patient with BD and the failure of the previous trabeculectomy during the course of the infection. To our knowledge, this is the first reported case of new-onset herpetic keratouveitis triggered by anti-TNF-α therapy in a patient with BD.

Case Report

A 51-year-old man was diagnosed with BD in 2001. Despite treatment with 5 mg/kg cyclosporine, 3 mg/kg azathioprine and corticosteroids, the patient experienced frequent and severe panuveitis attacks in both eyes. The patient was resistant to all treatments including interferon alpha and mycophenolate mofetil. The patient underwent phacoemulsification surgery in the right eye in 2004 and trabeculectomy in the same eye in 2006. Almost all systemic side effects were a result of steroid usage.

The patient suffered a bilateral panuveitis attack in January 2012 (Figure 1). The visual acuity decreased to 20/400 in the right eye and 20/40 in the left eye. He was started on infliximab in February 2012. Infliximab therapy at 5 mg/kg was administered at 0, 2, and 6 weeks, and every 8 weeks thereafter. Because he experienced side effects related to azathioprine and cyclosporine, the patient reduced the dose of the drugs and subsequently self-terminated the therapy. The visual acuity was 20/40 in the right eye and 20/25 in the left eye in the third month of infliximab therapy. The intraocular pressure was 14 mmHg in both eyes. The anterior and posterior segments were quiet in both eyes.

After 6 months of infliximab therapy, he presented to our clinic with pain and blurred vision in his right eye. The visual acuity was 20/200 in the right eye and 20/25 in the left eye. The intraocular pressure was 35 mmHg in the right eye and 16 mmHg in the left eye. Slit-lamp examination revealed corneal dendritic ulcers and 2+ cells in the anterior chamber in the right eye (Figure 2). There was no vitritis or vitreal flare. The posterior segment was quiet. There was no inflammation in the left eye. This was the first herpetic keratitis or keratouveitis attack the patient had experienced. Treatment with 800 mg oral acyclovir twice daily, topical acyclovir pomade five times daily, and topical brimonidine combined with dorzolamide/timolol fixed combination was started. After 5 days, the corneal ulcers

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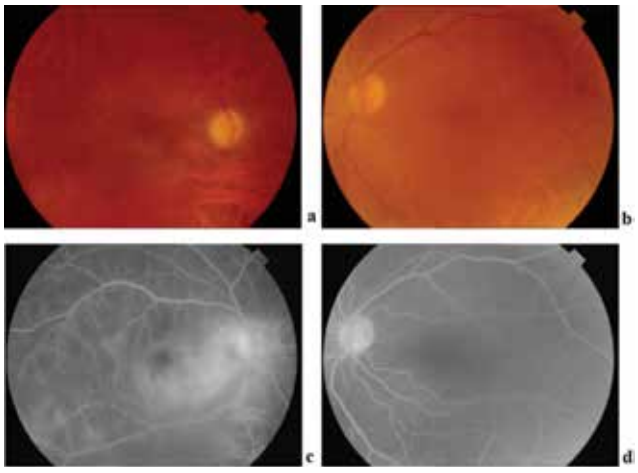

Figure 1. In the posterior segment examination, vitreous haze was observed in both eyes (a, b). Fundus fluorescein angiography revealed vascular leakage and cystoid macular edema in the right eye (c). There was no vascular leakage in the left eye (d)

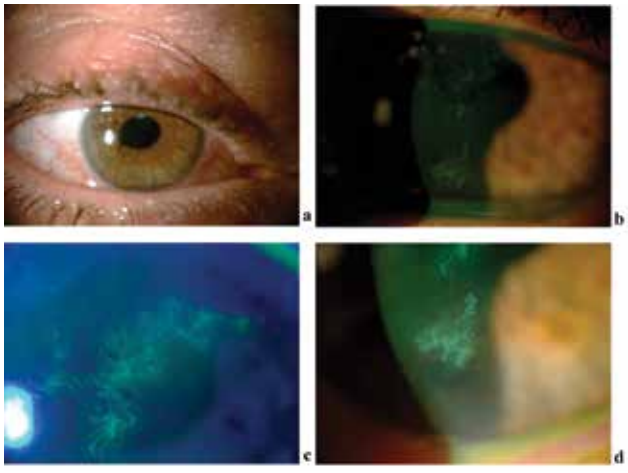

Figure 2. Biomicroscopic examination revealed mild ciliary injection (a) and corneal dendritic ulcers in the right eye (b, c, d)

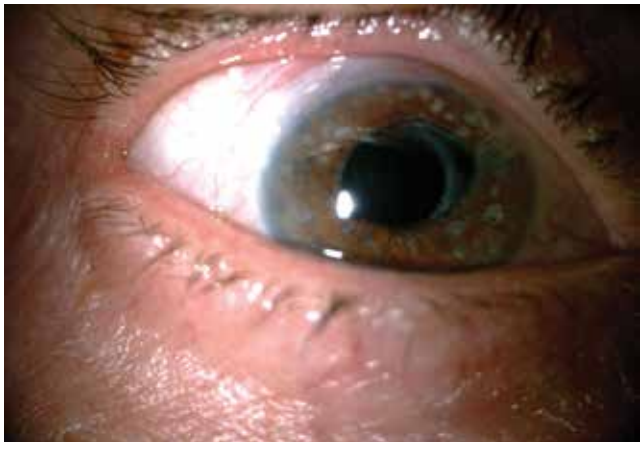

Figure 3. Six months after the keratouveitis attack, biomicroscopic examination revealed a clear cornea, patchy iris defects and two peripheral iridectomies

had regressed but the anterior chamber inflammation persisted. Therefore, topical prednisolone five times daily was added to the therapy. His intraocular pressure was still 31 mmHg. After 2 weeks the corneal ulcers healed, patchy iris atrophies were detected and the anterior chamber reaction was under 1+ (Figure 3), so the topical acyclovir therapy was discontinued. Topical prednisolone acetate was gradually tapered as the anterior chamber inflammation disappeared. His intraocular pressure was still over 30 mmHg and a repeat trabeculectomy with mitomycin C was planned. In the first month after the herpetic keratouveitis attack, trabeculectomy with mitomycin C was performed about halfway through an eight-week interval between two doses of infliximab. Neither ocular inflammatory attacks nor infectious complications were observed in the operated eye during postoperative follow-up with the use of acyclovir 800 mg/day. We attempted to gradually reduce the acyclovir dose but anterior chamber reaction was observed at doses lower than 800 mg.

Approximately 10 months after the operation, the patient discontinued the acyclovir therapy and he presented again to our clinic with ocular discomfort. A small corneal dendritic ulcer and 1+ cell reaction in the anterior chamber were observed on slit-lamp examination. Systemic acyclovir 800 mg/day and acyclovir pomade 5 times a day were reinitiated. The corneal ulcers and the anterior chamber inflammation were suppressed rapidly within a few days.

The patient has not experienced any further uveitis attacks due to herpes virus or BD during follow-up; the patient's right eye is currently in a good condition without inflammation in the anterior chamber for the last four months. His present right visual acuity is 20/30 and the intraocular pressure is around 12 mmHg. He is still receiving infliximab therapy and prophylactic oral acyclovir at 800 mg/day.

Discussion

Infliximab is a humanized antibody against TNF-α that can greatly reduce ocular inflammatory attacks in uveitic patients affected by BD. However, anti-TNF-α therapy is also associated with a risk of infectious complications due to the systemic blockade of TNF-α. In addition, patients with BD may frequently need ocular surgery. Therefore, intraocular surgery in BD patients under treatment with infliximab may be associated with a higher risk of ocular infections.[4] Moreover, it is unclear if trauma caused by surgery increases disease activity during anti-TNF-α treatment. Trabeculectomy with mitomycin C has provided long-term safety and was effective in reducing intraocular pressure in cases with secondary glaucoma associated with BD.[5,6] Trabeculectomy has also been successful in patients with BD receiving infliximab therapy.[7]

In addition to bacterial and fungal infections, biologic treatments may also increase the risk of viral infections; however, previous studies regarding this issue have not been conclusive enough.[8] There are some case reports and studies which reported that herpes zoster infections developed in patients

with rheumatologic disease during the biologic treatment course.[8,9,10,11,12,13] There are also some reported cases of cutaneous herpes simplex virus (HSV) infection following treatment with infliximab.[14,15] We are not aware of any published reports of ocular HSV infections associated with use of TNF inhibitors.

In vivo data indicate that TNF-α may have an antiviral effect in HSV-1 infections. In a model in which HSV-1 was reactivated in latently infected mouse cornea, TNF-α and interleukin-6 were the predominant cytokines within the trigeminal ganglion, suggesting a key role for these cytokines in viral clearance.[16] Absence of TNF in knockout mice increased susceptibility to primary corneal HSV-1 infections in one study[17] and lowered survival rates compared with wild-type mice in another.[18] While all three TNF inhibitors used in clinical practice inhibit the actions of TNF-α, their different mechanisms of action may result in a variable susceptibility to HSV-1 infections, although this has not specifically been studied.

In several small placebo-controlled trials, prophylactic use of oral acyclovir in immunocompromised patients was found to be successful in reducing the duration of viral shedding and preventing clinical HSV infections in 80% to 100% of patients.[19] The oral doses studied were 600 mg/day for 30 days and 800 mg/day for 180 days. In both studies, there were no additional adverse events compared with placebo. The most frequently reported adverse effects during acyclovir therapy are headache, nausea and abdominal cramping. Although oral acyclovir has a good safety profile, cases of rapidly progressive acute neurological and renal toxicity have been described.[20] Acyclovir-induced neurotoxicity can present with a variety of symptoms including agitation, delirium and hallucinations.[21] Dose reductions are recommended in patients with renal impairment and in the elderly. Our patient received acyclovir at 800 mg/day for 24 months and a dose reduction was attempted, inflammation in the anterior chamber developed. Although current evidence concerning the optimum duration and dose for long-term prophylaxis is lacking, a decision to continue at this level of therapy was made with the patient because of concerns about infection recurrence.

In our patient, herpetic keratouveitis occurred under infliximab therapy, and the previous trabeculectomy surgery failed due to this attack. The keratouveitis attack was controlled with antiviral therapy but the patient needed repeated glaucoma surgery. The trabeculectomy surgery was risky in this patient because the surgery might have induced both BD and herpetic uveitis; in addition to that, infection was another risk. After the glaucoma surgery under systemic antiviral and infliximab therapy, there were no occurrences of inflammatory or infectious complications.

Conclusion

In conclusion, systemic and ocular infections including HSV infections and reactivations can develop in patients receiving immunosuppressive or biologic agents; therefore, these patients should be monitored closely.

Ethics
Informed Consent: Received.
Peer-review: Externally peer-reviewed.
Authorship Contributions
Surgical and Medical Practices: Sirel Gür Güngör, Concept: Sirel Gür Güngör, Design: Sirel Gür Güngör, Data Collection or Processing: Sirel Gür Güngör, Analysis or Interpretation: Sirel Gür Güngör, Ahmet Akman, Literature Search: Sirel Gür Güngör, Onur Gökmen, Writing: Sirel Gür Güngör, Leyla Asena.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

Occult Macular Dystrophy

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Summary

Occult macular dystrophy is an inherited macular dystrophy characterized by a progressive decline of bilateral visual acuity with normal fundus appearance, fluorescein angiogram and full-field electroretinogram. This case report presents a 20-year-old female patient with bilateral progressive decline of visual acuity for six years. Her visual acuity was 3-4/10 in both eyes. Anterior segment and fundus examination, fluorescein angiogram and full-field electroretinogram were normal. She could read all Ishihara pseudoisochromatic plates. Fundus autofluorescence imaging was normal. There was a mild central hyporeflectance on fundus infrared reflectance imaging in both eyes. Reduced foveal thickness and alterations of the photoreceptor inner and outer segment junction were observed by optical coherence tomography in both eyes. Central scotoma was also found by microperimetry and reduced central response was revealed by multifocal electroretinogram in both eyes. These findings are consistent with the clinical characteristics of occult macular dystrophy.

Keywords: Occult macular dystrophy, optical coherence tomography, microperimetry, multifocal electroretinogram

Introduction

Occult macular dystrophy (OMD) is an inherited macular dystrophy characterized by progressive bilateral vision loss despite normal fundus appearance.[1] Fundus fluorescein angiogram (FFA) and full-field electroretinogram (ERG) are normal, whereas results of multifocal ERG (mfERG) of the central retina are markedly reduced.[1,2] Foveal thinning and disruptions of the photoreceptor inner and outer segment (IS/OS) junction are observed on spectral domain optical coherence tomography (SD-OCT). In many patients, disruptions of the photoreceptor layer detected by SD-OCT are correlated with visual acuity and disease progression.[3] Microperimetry (MP) is a visual field technique used in macular diseases to determine retinal sensitivity.[4] The method was developed to identify fixation alterations due to scotoma and vision loss in conditions involving the central retina, and can be utilized for this purpose in OMD patients.[5,6,7] On fundus infrared reflectance (IR) imaging, OMD patients exhibit central hyporeflectance which becomes more pronounced with disease progression.[8] Abnormalities are not apparent on fundus autofluorescence (FAF) imaging in most OMD patients, although mild central hyperautofluorescence can be observed in a minority of patients.[8,9]

In this case report, we aimed to present the clinical characteristics and diagnostic methods of a patient we diagnosed with OMD.

Case Report

A 20-year-old female patient with a 6-year history of progressive bilateral vision loss was referred to our clinic. The patient had no known systemic disease, previous trauma, family history, history of drug or cigarette use, or consanguineous marriage in her family. Her visual acuity was 3-4/10 in both eyes; intraocular pressure was 11 mmHg in the right eye and 13 mmHg in the left eye. No pathologies were detected during anterior segment examination. Fundus examination revealed no pathologies other than mild retinal vessel tortuosity (Figure 1A and 1B). Both eyes appeared normal on FAF imaging (Figure 2A and 2B). Mild central hyporeflectance was observed in both eyes on fundus IR imaging (Figure 3A and 3B). FFA was normal. Foveal thickness was determined by OCT thickness profile analysis as 155 µm and 188 µm in the right and left eyes, respectively. Disruption of the photoreceptor IS/OS junction was observed. The extension of the IS/OS band disruption on the horizontal axis was measured as 696 µm in the right and 348

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μm in the left eye (Figure 4A and 4B). On MP analysis both eyes exhibited relatively unstable fixation which was more pronounced in the right eye, and areas of absolute scotoma consistent with OCT were observed. Retinal sensitivity in the central 20° field of the macula was measured as 13.9 dB in the right and 13.5 dB in the left eye (Figure 5A and 5B). Full-field ERG was normal, but mfERG revealed a bilateral reduction in central response which was more pronounced in the right eye (Figure 6A and 6B).

Discussion

OMD is an inherited macular dystrophy, called occult because the fundus appears normal despite macular dysfunction. OMD was first described by Miyake et al.[1] and although it is autosomal dominantly inherited, sporadic cases have also been reported.

Many studies have reported that the age at onset for OMD ranges widely, from 6 to 81 years.[9] In our case, the patient's vision loss began at age 14 and she was diagnosed at age 20.

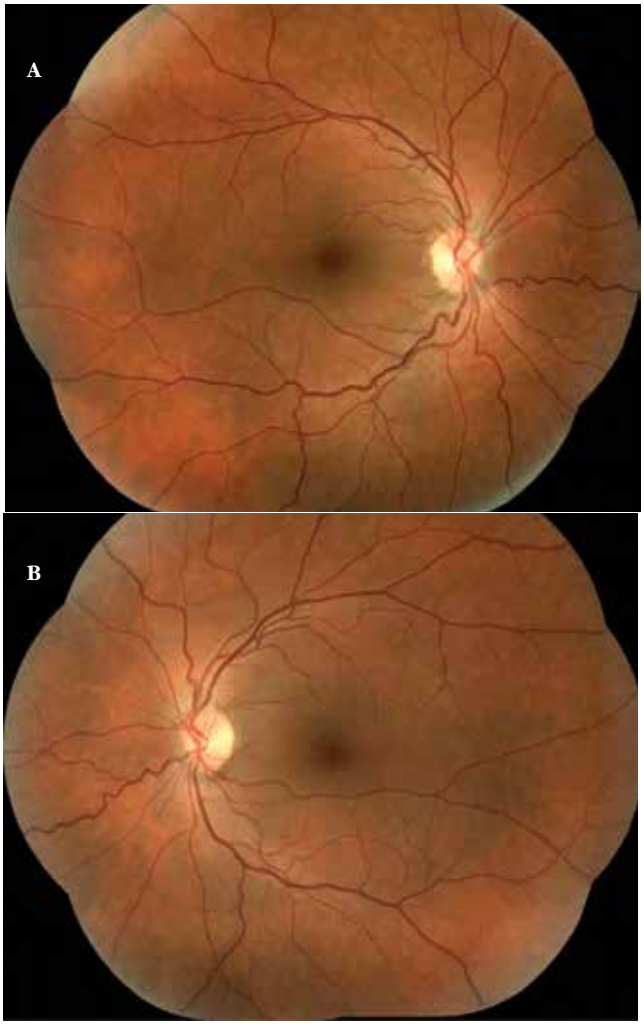

Figure 1. Fundus color image from right eye (A) and left eye (B)

As OMD is a central retinal disease, patients' full-field ERG results are normal, while responses in focal macular ERG and mfERG are markedly reduced.[1,2] In addition, measuring central retinal sensitivity by MP may reveal scotoma or fixation loss in OMD patients.[5] As described in the literature, our patient had normal full-field ERG results, but on mfERG she exhibited a bilateral reduction in central response that was more pronounced in the right eye. On MP we detected relatively unstable fixation in both eyes which was also more pronounced in the right eye. Reduced retinal sensitivity was observed in the central 8° field of the maculae of both eyes.

Structural changes in the photoreceptor layer in OMD patients are easily detected by SD-OCT. Many studies using

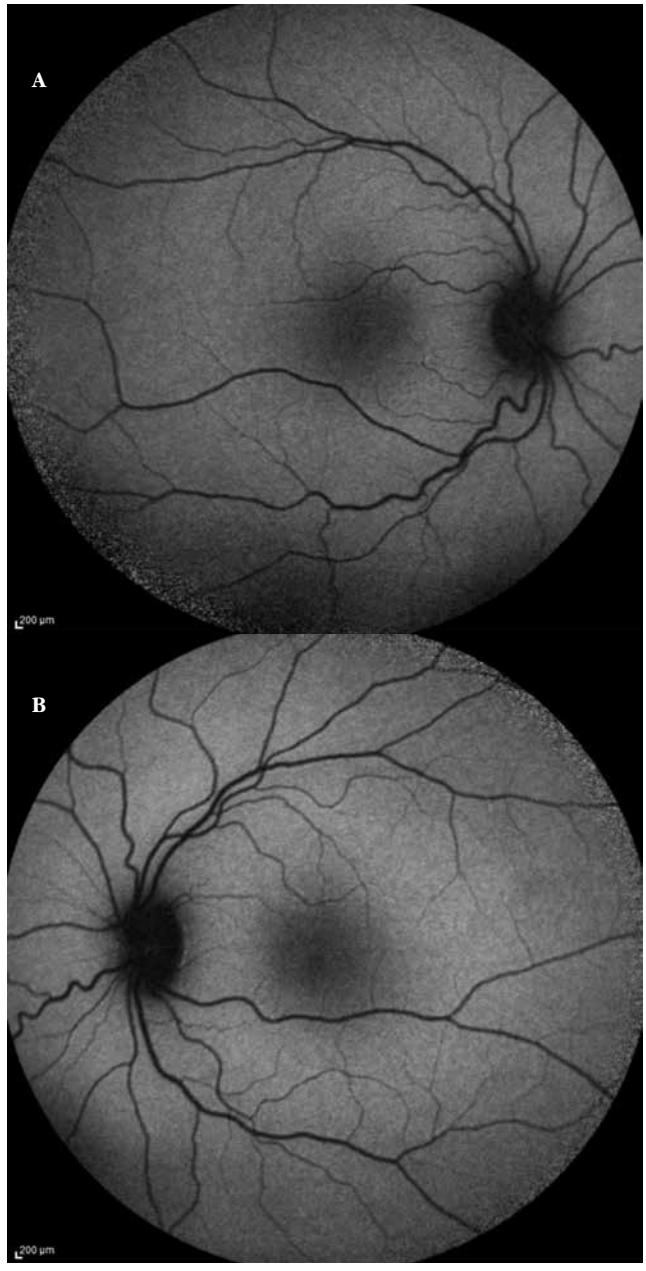

Figure 2. Fundus autofluorescence image from right eye (A) and left eye (B)

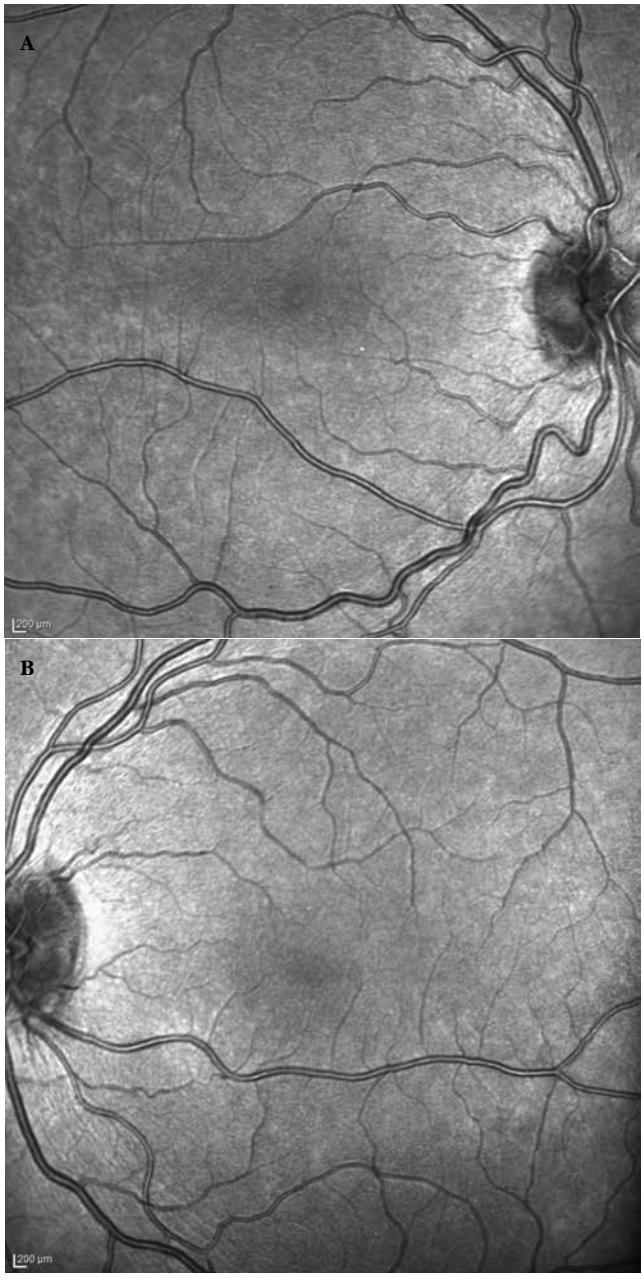

Figure 3. Infrared reflectance image from right eye (A) and left eye (B)

SD-OCT imaging have reported pronounced photoreceptor damage in the fovea, reduced foveal thickness and disruptions of the photoreceptor IS/OS junction in OMD patients.[3]

It has been demonstrated that the severity of photoreceptor layer disruption is correlated with visual acuity and disease progression.[3] Similarly, in our patient we observed bilateral foveal thinning and disruption of the photoreceptor IS/OS junction, both of which were more pronounced in the right eye.

Because fundus IR imaging is easily performed and reveals central hyporeflectance in OMD patients which becomes more apparent as the disease progresses, it can be utilized as an

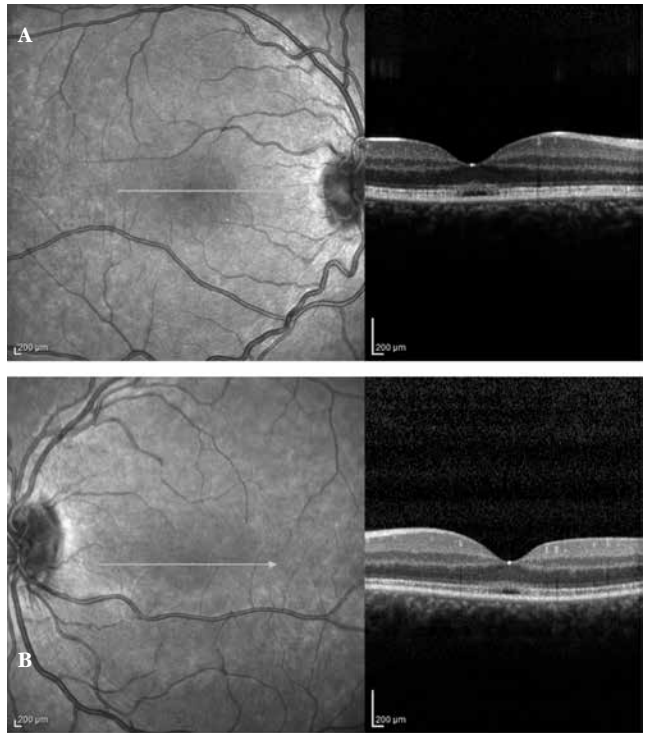

Figure 4. Optical coherence tomography image from right eye (A) and left eye (B)

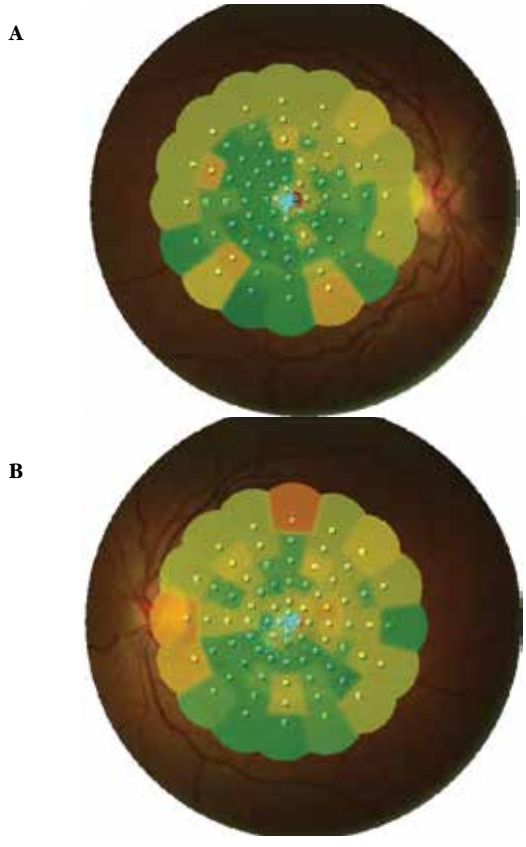

Figure 5. Microperimetry from right eye (A) and left eye (B)

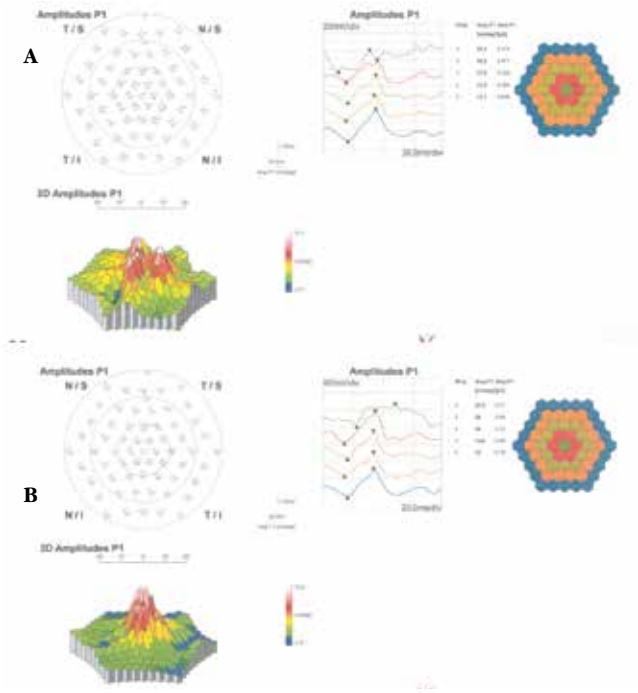

Figure 6. Multifocal electroretinogram from right eye (A) and left eye (B)

auxiliary diagnostic method.[8,9,10,11] In OMD, no discernible abnormality can be detected by FAF because the condition primarily affects the photoreceptors and there is no evident damage to the retinal pigment epithelium.[9] Our patient also appeared normal on FAF, while mild central hyporeflectance was observed on fundus IR imaging.

Conclusion

In summary, for patients with progressive vision loss and normal fundus appearance and FFA clinically consistent with OMD, SD-OCT is a primary tool which is non-invasive, easily performed, and clinically reliable. Fundus IR, mfERG and MP are other auxiliary diagnostic methods.

Ethics

Informed Consent: In accordance with the principles of the Declaration of Helsinki, patients were informed about their current status and natural course, consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serra Arf, Hakan Özdemir, Murat Karaçorlu, Concept: Işıl Sayman Muslubaş, Serra Arf, Hakan Özdemir, Murat Karaçorlu, Design: Işıl Sayman Muslubaş, Serra Arf, Murat Karaçorlu, Data Collection or Processing: Işıl Sayman Muslubaş, Mümin Hocaoğlu, Analysis or Interpretation: Işıl Sayman Muslubaş, Serra Arf, Murat Karaçorlu, Literature Search: Işıl Sayman Muslubaş, Mümin Hocaoğlu, Writing: Işıl Sayman Muslubaş, Mümin Hocaoğlu, Serra Arf, Hakan Özdemir, Murat Karaçorlu.

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2016 INTERNATIONAL CONGRESSES

American Association for Pediatric Ophthalmology and Strabismus (AAPOS) 42nd Annual Meeting
6-10 April 2016 - Vancouver, BC Canada
http://www.aapos.org/meeting/2016_annual_meeting/

Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
1-5 May 2016 - Seattle, USA
http://www.arvo.org/AM/

American Society of Cataract and Refractive Surgery (ASCRS) Annual Meeting
6-10 May 2016 - New Orleans, USA
http://www.ascrs.org/

16th European VitreoRetinal Society (EVRS) Meeting
5-7 June 2016 - Monaco
http://www.evrs.eu

12th European Glaucoma Society (EGS) Congress
19-22 June 2016 - Prague, Czech Republic
http://www.egs2016.org

American Society of Retina Specialists (ASRS) Meeting
10-14 August 2016 - San Francisco, USA
http://www.asrs.org/annual-meeting

54th International Society for Clinical Electrophysiology of Vision (ISCEV) Symposium and Courses
13-18 August 2016 - Singapore
http://www.iscev.org/symposia/2016/index.html

9th International Symposium on Uveitis
18-21 August 2016 - Dublin, Ireland
http://uveitis2016.ie/

16th European Society of Retina Specialists (EURETINA) Congress
8-11 September 2016 - Copenhagen, Denmark
http://www.euretina.org/copenhagen2016/default.asp

34th European Society of Cataract and Refractive Surgeons (ESCRS) Congress
10-14 September 2016 - Copenhagen, Denmark
http://www.escrs.org/

American Association for Pediatric Ophthalmology and Strabismus (AAPOS)/Strabismus and Pediatric Ophthalmological Society of India (SPOSI) Joint Conference: An Intercontinental Perspective of Pediatric Ophthalmology & Strabismus
2-4 December 2016 - Jaipur, India
http://www.aapos.org/meeting/2016_joint_meeting_jaipur_india_/

2016 NATIONAL CONGRESSES

Turkish Ophthalmological Society (TOS) Winter Symposium
22-24 January 2016 - Antalya, Turkey
http://todnet.org/KisSempozyumu2016/

TOS Cataract and Refractive Surgery Subsociety Live Surgery Symposium
20-21 February 2016 - İstanbul, Turkey
http://todnet.org/KRC-CanliCerrahi2016/

TOS March Symposium
11-13 March 2016 - Adana, Turkey

X Esat Işık Applied Course in Optical Refraction and Low Vision Rehabilitation
18-20 March 2016 - İzmir, Turkey

Education in Ophthalmology Meeting
31-31 March 2016 - Ankara, Turkey

TOS April Course
1-3 April 2016 - Ankara, Turkey

Medical Retina, Vitreoretinal Surgery and Uvea-Behcet's Subsocieties Active Members' Meeting
23-24 April 2016 - Mudanya, Turkey

Vitreoretinal Surgery Subsociety Live Surgery Meeting
14-15 May 2016 - İzmir, Turkey

Strabismus Subsociety Meeting
14-15 May 2016 - İstanbul, Turkey

Cornea and Ocular Surface Subsociety Active Members' Meeting
14-15 May 2016 - Cappadocia, Turkey

TOS Spring Symposium
27-29 May 2016 - İstanbul, Turkey

TOS Summer Symposium
2-4 September 2016 - Elazığ, Turkey

XI Esat Işık Applied Course in Optical Refraction and Low Vision Rehabilitation
7-9 October 2016 - İzmir, Turkey

TOS 50th National Congress
9-13 November 2016 - Antalya, Turkey

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Distance Visual Acuity Measurements Related Equivalency Table								
ETDRS Standard Line Number								***Spatial Frequency***
	Qualitative Measurements	Decimal	Snellen			LogMAR	Angle of Resolution	Cycle per Degree
-3		2.00	20	Ğ	10	-0.30	0.5	60.00
-2		1.60	20	Ğ	12.5	-0.20	0.625	48.00
-1		1.25	20	Ğ	16	-0.10	0.8	37.50
0		1.00	20	Ğ	20	0.00	1	30.00
		0.90				0.05		27.00
1		0.80	20	Ğ	25	0.10	1.25	24.00
		0.70				0.15		21.00
2		0.63	20	Ğ	32	0.20	1.6	18.75
		0.60				0.22		18.00
3		0.50	20	Ğ	40	0.30	2	15.00
4		0.40	20	Ğ	50	0.40	2.5	12.00
		0.30				0.52		9.00
5		0.32	20	Ğ	63	0.50	3.15	9.52
6		0.25	20	Ğ	80	0.60	4	7.50
7		0.20	20	Ğ	100	0.70	5	6.00
8		0.16	20	Ğ	125	0.80	6.25	4.80
9		0.13	20	Ğ	160	0.90	8	3.75
10	CF form 6 m	0.10	20	Ğ	200	1.00	10	3.00
11	CF from 5 m	0.08	20	Ğ	250	1.10	12.5	2.40
12	CF from 4 m	0.06	20	Ğ	320	1.20	16	1.88
13	CF from 3 m	0.05	20	Ğ	400	1.30	20	1.50
14		0.04	20	Ğ	500	1.40	25	1.20
15	CF from 2 m	0.03	20	Ğ	640	1.51	32	0.94
16		0.025	20	Ğ	800	1.60	40	0.75
17		0.020	20	Ğ	1000	1.70	50	0.60
18	CF from 1 m	0.016	20	Ğ	1250	1.80	62.5	0.48
21	CF from 50 cm	0.008	20	Ğ	2500	2.10	125	0.24
31	HM from 50 cm	0.0008	20	Ğ	25000	3.10	1250	0.02

Abbreviations:
CF: Counting fingers, HM: Perception of hand motions, m= meter, cm= centimeter

Equations of conversions for Microsoft Excel:
- Log10 (Decimal Acuity)= LogMAR Equivalent
Power (10; -Logmar Equivalent)= Decimal Acuity (for English version of Microsoft Excel)
Kuvvet (10; -Logmar Equivalent)= Decimal Acutiy (for Turkish version of Microsoft Excel)
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