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Original Articles

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

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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CONTENTS

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EDITORIAL

2019 Issue 3 at a Glance:

This issue of our journal includes six original articles, one review, and four case reports representing national and international research on the cornea, glaucoma, and retinal disease. We hope you will find these articles both interesting and beneficial.

Keratoconus is a bilateral, progressive corneal disease characterized by central corneal thinning, high myopia, and irregular astigmatism. Even if one eye is unaffected initially, it eventually becomes involved in the majority of cases. With the development of the Scheimpflug camera system (Pentacam), which can also evaluate the posterior corneal surface, it was shown that there are early changes in the posterior surface of the cornea in eyes considered clinically normal. Değirmenci et al. compared the keratoconus eyes (Group 1) and fellow eyes (Group 2) of 31 patients initially diagnosed as unilateral keratoconus and the right eyes of 30 healthy individuals (Group 3) based on detailed anterior segment parameters obtained with Pentacam at time of presentation. The results of their comparisons showed that eyes not initially diagnosed as keratoconus were not completely normal, and the authors emphasized the importance of monitoring for disease progression and advising avoidance of mechanical trauma in these patients (see pages 117-122).

Özalp et al. investigated the phosphate and osmolarity levels of 53 eye drops commercially available in Turkey and used on a chronic basis. They found that approximately 40% of antiglaucoma drops and about 60% of corticosteroid and antihistamine drops contained phosphate at levels exceeding the physiological concentration in tears (1.45 mmol/L), while most products in the artificial tear group were hypoosmolar (71%) or isoosmolar (21%). The authors concluded based on their results that being familiar with the chemical composition of topical formulations and selecting drops that have suitable tonicity and pH based on the disease profile and contain a buffer that will not promote corneal deposition will help prevent ocular surface complications associated with the use of eye drops (see pages 123-129).

Mayalı et al. conducted a study comparing intraocular pressure measurements taken with the Icare One tonometer and the Icare Pro tonometer for clinical use. Measurements were first obtained with the Icare Pro and then with the Icare One in 52 right-handed glaucoma patients and 52 right-handed healthy subjects, and the comparison showed that Icare One measurements were lower than those taken with the Icare Pro (see pages 130-133).

A prospective study by Abdullayev et al. evaluated the incidence of glaucoma in patients with obstructive sleep apnea syndrome (OSAS) who did and did not use continuous positive airway pressure therapy. The study included a total of 59 polysomnography-confirmed OSAS patients with mild (19 patients), moderate (16 patients), or severe (24 patients) disease based on apnea-hypopnea index (AHI) values, as well as 19 healthy controls. Average ganglion cell complex (GCC) thickness in the left eyes of the mild OSAS group, GCC thickness in the inferior and inferonasal sectors of both eyes in the mild OSAS group, and minimum GCC thickness in the left eyes of all OSAS groups were significantly lower when compared to the control group. This result highlights the importance of periodic evaluation of retinal nerve fiber layer (RNFL) and GCC thickness in OSAS patients (see pages 134-141).

Vayısoğlu et al. conducted a survey of 254 lecturers using the Ocular Surface Disease Index (OSDI) and a questionnaire prepared based on a literature review. The OSDI scores indicated that dry eye was mild in 20.5% of the participants, moderate in 15%, and severe in 36.5%. Significant differences were observed between OSDI score categories in terms of sex, smoking status, use of glasses, previous diagnosis of dry eye, and presence of dry eye symptoms. The authors concluded that only daily duration of computer use was significantly associated with OSDI score (see pages 142-148).

Uğurlu et al. evaluated the effectiveness of diagnostic methods such as color fundus photography, 10-2 central visual field, microperimetry (MP), optical coherence tomography (OCT), and fundus autofluorescence (FAF) in the follow-up of 300 eyes of 150 patients who had been using hydroxychloroquine for at least 2 years. MP, FAF, OCT, fundus photography, and central 10-2 visual field examinations performed 3 times at 6-month intervals revealed significant differences in FAF with duration of use and cumulative dose of hydroxychloroquine, demonstrating that subjective methods should be used together with objective methods such as FAF for patient follow-up and early detection of toxic maculopathy (see pages 149-153).

Low vision rehabilitation is gaining importance due to the longer life expectancy at birth and rising incidence of age-

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EDITORIAL

related macular degeneration. In low vision rehabilitation, vision loss may be central, peripheral, or associated with media opacity. The type of rehabilitation required by a low vision patient varies depending on their visual acuity, age, sociocultural status, and especially their diagnosis. The aim of low vision rehabilitation is to enable patients to use their residual vision as effectively as possible to make their lives easier, allow them to lead independent, productive lives, and enhance their quality of life. In this issue's review, Altınbay and İdil share with readers a comprehensive overview of current low vision rehabilitation and treatment methods (see pages 154-163).

Tularemia is a zoonotic infection caused by *Francisella tularensis*, a highly virulent gram-negative coccobacillus. Köse and Hoşal discuss a 33-year-old man who reported having systemic complaints while traveling abroad 1 year earlier, followed by enlargement of the right cervical lymph nodes. In Turkey he was recommended various antibiotic therapies in different hospitals for presumed pharyngitis, but his symptoms did not resolve. Based on a positive *F. tularensis* agglutination test in a university hospital, he was diagnosed with oropharyngeal tularemia and treated with streptomycin and doxycycline. The lymphadenopathy regressed, but a few weeks later he presented with complaints of epiphora and recurrent swelling, hyperemia, and pain in the lacrimal sac area of the right eye. He was started on oral amoxicillin-clavulanic acid 1 g twice daily and topical ciprofloxacin drops every 6 hours. Dacryocystorhinostomy was recommended after evaluation in the otorhinolaryngology department. This report draws attention to the fact that nasolacrimal duct occlusion and subsequent dacryocystitis may occur as a rare complication of oropharyngeal tularemia (see pages 164-167).

Kızıloğlu et al. describes a 63-year-old woman with a history of metastatic breast cancer who presented with complaints of diplopia and right abduction deficit. Abduction was completely restricted in the right eye and globe retraction and narrowing of the palpebral fissure were observed on abduction. Magnetic resonance imaging (MRI) showed isolated enlargement of the right medial rectus muscle. Biopsy confirmed the diagnosis of breast carcinoma metastasis in the right medial rectus muscle. Radiotherapy and chemotherapy for the orbital mass resulted in partial recovery of right abduction at 15 months. This case report emphasizes that ocular motility deficits in patients with a history of breast cancer should raise suspicion of a possible orbital metastatic lesion involving the extraocular muscles (see pages 168-170).

Metastasis to the optic nerve is very rare. A 39-year-old female patient who had undergone surgery and chemotherapy 6 years earlier due to breast cancer presented with complaints of progressive reduction in visual acuity in the right eye for the last 2 months. Fundus examination revealed peripapillary flame-shaped hemorrhages and an enlarged optic disc infiltrated by a yellowish mass. Humphrey visual field test of the right eye revealed an enlarged blind spot and altitudinal defect. OCT showed significant RNFL thickening in all four quadrants in the right eye. Fluorescence angiography (FA) of the right eye revealed a hyperfluorescent mass on the optic disc with no signs of infiltrating optic neuropathy. No pathological findings were detected on MRI. Aghdam et al. first considered a diagnosis of infiltrative optic neuropathy based on the patient's history, symptoms, and findings. The patient was referred to the oncology department for further systemic evaluation and necessary interventions. With this case, the authors point out that in cancer patients who develop optic neuropathy, metastasis and infiltration should be the primary suspicion unless there evidence to the contrary (see pages 171-174).

Ekinci et al. describe the case of a 54-year-old man who presented with reduced vision in the left eye that he had noticed for about a week. Based on indirect ophthalmoscopy, OCT, and FA, they diagnosed the patient with macular edema associated with branch retinal vein occlusion and decided to administer an intravitreal dexamethasone implant. During injection, transient hypotony was noted just before pulling the trigger. At 1-month follow-up, sporadic hemorrhages and a full-thickness retinal hole about 1 disc diameter in size were noted in the temporal region of the macula, and laser photocoagulation was applied around the retinal hole. The authors suspected that this rare complication may have resulted from the transient hypotony during implantation shortening the distance between the entry site and retina, enabling the implant to cause direct damage to the retina. They emphasized that for this reason, patients who show globe softening during injection require extra caution, and that the clinician should at least carefully aim away from the macula (see pages 175-177).

Respectfully on behalf of the Editorial Board,
Özlem Yıldırım, MD

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Turk J Ophthalmol 2019;49:117-122

Original Article

Topographic Evaluation of Unilateral Keratoconus Patients

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Abstract

Objectives: To compare data obtained by Scheimpflug camera (Pentacam) from both eyes of unilateral keratoconus patients and normal controls.

Materials and Methods: This study was performed by retrospective chart review of 919 keratoconus patients. From these patients, 31 keratoconus eyes of 31 patients with unilateral keratoconus (Group 1), 31 normal fellow eyes of these patients (Group 2), and 30 right eyes of 30 normal controls (Group 3) were included in the study. Detailed ophthalmologic examination and Pentacam parameters at initial examination were analyzed and relationships between Groups 1, 2, and 3 were statistically evaluated. ROC curve analysis was also performed to determine the sensitivity and specificity of parameters that could be used to differentiate Group 2 from Groups 1 and 3.

Results: The mean age was 30.07±11.00 (15-60) in Group 1-2 patients and 32.33±9.30 (18-45) in Group 3 patients (p=0.392). In comparison of Pentacam data, there were statistically significant differences between Groups 1 and 2 in all parameters except corneal volume (p<0.05). Group 1 and Group 3 were significantly different in all evaluated parameters (p<0.05). Steep keratometry, flat keratometry, mean keratometry, and posterior elevation (PE) were statistically similar between Groups 2 and 3 (p>0.05), while the other evaluated parameters differed significantly (p<0.05). ROC curve analysis showed that the difference in corneal thickness between the apex and thinnest point, PI, index of surface variance, index of height asymmetry and inferior-superior had the highest sensitivity and specificity in differentiating Group 2 from Group 3, while CCTapex, CCTmin, PE, and Rmin had the highest sensitivity and specificity in differentiating Group 2 from Group 1.

Conclusion: In patients with unilateral keratoconus, fellow eyes appear to not be completely normal. Thus, it is recommended that fellow eyes also be evaluated in every examination of unilateral keratoconus patients.

Keywords: Amsler-Krumeich, Scheimpflug camera, unilateral keratoconus

Introduction

Keratoconus is a progressive corneal disease characterized by central corneal thinning, high myopia, and irregular astigmatism. The incidence of keratoconus is approximately 1/2000 and its prevalence is 54.5/100,000. The disease is caused by both genetic and environmental factors.[1,2,3,4]

In addition to clinical examination, various auxiliary instruments are used in the diagnosis of keratoconus. In the past, keratoconus was diagnosed using Placido-disc based topographers, which are only able to evaluate the anterior surface of the cornea. The development of the Scheimpflug camera system (Pentacam, Oculus Optikgerate GmbH, Wetzlar, Germany) also enabled evaluation of the posterior cornea surface. This device allowed the detection of early changes originating in the posterior cornea in clinically normal patients, which was a major breakthrough in the diagnosis and monitoring of the disease.[5,6,7]

Keratoconus is usually progressive and bilateral. Even if one eye is not affected initially, the fellow eye is eventually affected as well in the majority of patients. Holland et al.[8] determined that 50% of patients initially diagnosed with unilateral keratoconus also developed keratoconus in the apparently normal fellow eye. However, Imbornoni et al.[9] emphasized that keratoconus was not

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observed during long-term follow-up in any of the fellow eyes in a series of 5 cases. Therefore, different terms such as preclinical keratoconus, forme fruste keratoconus, and keratoconus suspect are used instead of unilateral keratoconus.[5,10,11] Although different rates have been reported for unilateral keratoconus, the proportion generally ranges between 0.5% and 4.5%.[8,12,13,14,15,16] Various keratoconus studies have demonstrated abnormalities in the Pentacam data of fellow eyes considered unaffected.[2,11,17,18,19]

The aim of this study was to compare anterior segment parameters of the apparently normal fellow eyes of patients who presented to our center with unilateral keratoconus with those of keratoconus eyes and the eyes of healthy control subjects.

Materials and Methods

This study was carried out with the approval of the Ege University Faculty of Medicine Ethics Committee (129362). The medical data of patients with keratoconus who presented to the Cornea Unit of the Ege University Faculty of Medicine Department of Ophthalmology were retrospectively analyzed. Patients who had a history of trauma or corneal surgery for keratoconus and those from whom reliable measurements could not be obtained were not included in the study. In addition, patients who used contact lenses at time of presentation and those with a history of allergic conjunctivitis were excluded from the study. Of the remaining 919 patients, 31 patients (3.3%) who had been evaluated as having unilateral keratoconus at initial presentation were included in the study. The patients' best corrected visual acuity, intraocular pressure measurements, and anterior and posterior segment examination findings were evaluated. In addition, the patients' keratometric parameters, topometric parameters, posterior elevation, corneal pachymetry, and pachymetric index values obtained with Pentacam were analyzed.

The eyes were divided into 3 groups: keratoconus eyes (Group 1, 31 eyes of 31 patients), fellow eyes considered clinically and topographically normal (Group 2, 31 eyes of 31 patients), and the healthy right eyes of control subjects (Group 3, 30 eyes of 30 patients). The Amsler-Krumeich classification was used when diagnosing keratoconus.[20] According to this classification, stage 1 is defined as eccentric steepening, myopia and/or astigmatism <5 D, and/or central keratometry value <48 diopter (D); stage 2 involves myopia and/or astigmatism of 5-8 D, central keratometry value <53 D, and minimum corneal thickness >400 µm; stage 3 is defined as myopia and/or astigmatism of 8-10 D, central keratometry value >53 D, and minimum corneal thickness 300-400 µm; and in stage 4, refraction is not measurable, central keratometry value is >55 D, there is central corneal scarring and minimum corneal thickness is <200 microns. The groups were compared in terms of demographic and Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany) data. Measurements were repeated until a reliable measurement was obtained according to the Pentacam device's software. Our analysis included the following Pentacam data: the anterior corneal surface keratometric parameters steep keratometry (Ks), flat keratometry (Kf), mean keratometry (Km), and the inferior-superior (I-S) difference at 4 mm; the topometric parameters index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), and minimum radius (Rmin); and posterior elevation (PE), corneal thickness at the apex and the thinnest point (CCTapex, CCTmin), corneal volume (CV), and mean pachymetric progression index (PPI).

Statistical Analysis

Statistical analyses were done using the SPSS software package version 20 (IBM Corp., 2011). The Shapiro–Wilk test was used to test all parameters for normal distribution. Comparisons between groups were done with one-way ANOVA with post-hoc Bonferroni test. Chi-square test was used to compare demographic data. ROC curve analysis was done to determine the sensitivity and specificity of the parameters. A p value below 0.05 was considered statistically significant.

Results

Mean age was 30.07±11.00 (15-60) years in Groups 1/2 and 32.33±9.30 (18-45) years in Group 3 (p=0.392) (Figure 1). The female to male ratio was 11/19 in Groups 1/2 and 16/14 in Group 3 (p=0.194).

Comparison of Pentacam data between Groups 1 and 2 showed that Ks, Kf, Km, PE, I-S difference, ISV, IVA, KI, CKI, IHA, IHD, and PPI values were significantly higher in Group 1 (p<0.05) (Table 1). In contrast, Rmin, CCTapex, and CCTmin were significantly lower in Group 1 (p<0.05), while CV was similar between the groups (p=0.383).

In comparisons of Groups 1 and 3, Group 1 had significantly higher Ks, Kf, Km, PE, I-S difference, ISV, IVA, KI, CKI, IHA, IHD, and PPI (p<0.001) and significantly slower Rmin, CCTapex, and CCTmin (p<0.001). CV was also significantly lower in Group 1 than in Group 3 (p=0.009).

Comparisons of Groups 2 and 3 revealed similar Ks, Kf, Km, and PE (p=0.139, 0.473, and 0.239, respectively). The other analyzed parameters (I-S difference, ISV, IVA, KI, CKI, IHA, IHD, PPI, Rmin, CCTapex, CCTmin, and CV) all differed significantly between the two groups (p<0.05).

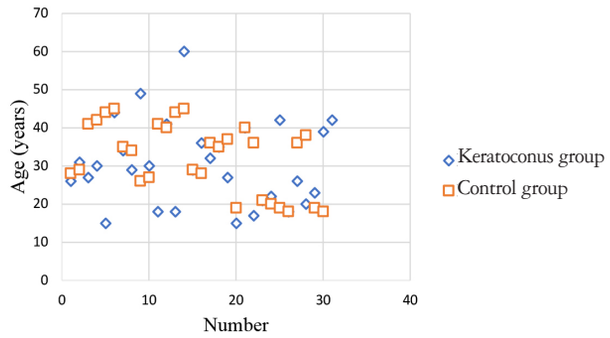

Figure 1. Age distribution curves of the groups

Table 1. Mean values of anterior segment parameters and comparisons between groups						
	Group 1	**Group 2**	**Group 3**	**Group 1 vs. Group 2**	**Group 1 vs. Group 3**	**Group 2 vs. Group 3**
	Mean ± Standard deviation (minimum-maximum)			p value		
Anterior corneal surface keratometry indexes						
Ks	50.89±6.07 (42.3-67.1)	44.54±1.59 (41.3-47.2)	43.97±1.50 (41.5-46.3)	<0.001	<0.001	0.139
Kf	47.13±4.92 (39.6-61)	43.32±1.64 (40.2-45.8)	43.03±1.47 (40.4-45.3)	<0.001	<0.001	0.473
Km	48.92±5.41 (42.1-64.1)	43.91±1.53 (41-46.1)	43.49±1.46 (41.1-45.7)	<0.001	<0.001	0.239
I-S	6.85±6.40 (-11.8-20.40)	1.53±1.05 -1.33-3.67	0.30±0.80 -1.13-2.23	<0.001	<0.001	<0.001
Topometric indexes						
ISV	80.90±43.87 (23-175)	24.6±11.0 (15-76)	16.00±5.00 (9-36)	<0.001	<0.001	<0.001
IVA	0.78±0.47 (0.09-1.97)	0.23±0.08 (0.09-0.51)	0.13±0.06 (0.04-0.33)	<0.001	<0.001	<0.001
KI	1.21±0.17 (0.87-1.66)	1.05±0.02 (1-1.10)	1.02±0.02 (0.98-1.06)	<0.001	<0.001	<0.001
CKI	1.06±0.05 (1-1.19)	1.00±0.01 (0.99-1.09)	0.99±0.006 (0.98-1.01)	<0.001	<0.001	0.021
IHA	31.26±30.71 (2.60-130.9)	8.51±5.82 (0.5-21.10)	3.58±3.59 (0.10-14.9)	<0.001	<0.001	<0.001
IHD	0.09±0.08 (0.004-0.323)	0.02±0.01 (0.006-0.07)	0.008±0.005 (0.001-0.03)	<0.001	<0.001	<0.001
Rmin	6.20±0.86 (4.45-7.59)	7.35±0.39 (5.94-7.94)	7.57±0.28 (7.16-8.09)	<0.001	<0.001	0.021
Posterior elevation (PE)						
PE	29.35±17.64 (-12.00-66.00)	6.57±4.45 (-2.00-15.00)	6.39±0.25 (5.91-6.88)	<0.001	<0.001	0.439
Corneal thickness parameters						
Apex	491.63±38.95 (401-580)	520.5±22.58 (461-560)	558.37±31.98 (514-624)	<0.001	<0.001	<0.001
Minimum	465.77±45.66 (356-545)	514.1±23.65 (445-557)	556.33±31.50 (510-619)	<0.001	<0.001	<0.001
Corneal volume	58.67±3.30 (52.4-66.3)	59.29±3.15 (54.9-64.10)	61.62±4.35 (55.30-71.70)	0.383	0.009	0.031
Mean pachymetric progression index						
PPI	2.23±1.21 (0.90-5.40)	1.17±0.20 (0.80-1.80)	0.93±0.15 (0.50-1.20)	<0.001	<0.001	<0.001

Ks: Steep keratometry, Kf: Flat keratometry, Km: Mean keratometry, I-S: Inferior-superior difference at 4 mm, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Minimum radius, PE: Posterior elevation, PPI: Pachymetric progression index

In ROC curve analysis to identify parameters that could be used to differentiate Groups 2 and 3, the parameters with the largest areas under the curve (AUC) were ISV (threshold 18.50, AUC=0.88) and I-S (threshold 1.25, AUC=0.84). In addition, PPI, IHA, and CCTdiff, which is the difference between CCTapex and CCTmin, also had significantly high AUC values (Table 2, Figure 2). ROC curve analysis between the eyes in Groups 1 and 2 aimed to differentiate the apparently normal fellow eyes in Group 2 from keratoconus eyes and showed that CCTapex, CCTmin, PE, and Rmin had high sensitivity and specificity in the differentiation of Group 2 from Group 1 (Table 3 and Figure 3).

Table 2. ROC curve analysis for discriminating normal fellow eyes of unilateral keratoconus patients from eyes of the control group

Parameter	AUC	SD	p value	Threshold value	Sensitivity	Specificity
CCTdiff	0.79	0.05	<0.001	2.50	0.70	0.70
Mean Pi	0.79	0.06	<0.001	1.05	0.60	0.83
ISV	0.88	0.04	<0.001	18.50	0.80	0.80
IHA	0.77	0.06	<0.001	4	0.80	0.63
I-S	0.84	0.06	<0.001	1.25	0.60	0.90

AUC: Area under the curve, SD: Standard deviation, CCTdiff: Central corneal thickness difference, PI: Progression index, ISV: Index of surface variance, IHA: Index of height asymmetry, I-S: Inferior-superior difference at 4 mm

Table 3. ROC curve analysis for discrimination of the keratoconus eyes and normal fellow eyes of patients with unilateral keratoconus

Parameter	AUC	SD	p value	Threshold value	Sensitivity	Specificity
CCTapex	0.77	0.06	<0.001	502.5	0.83	0.70
CTmin	0.85	0.05	<0.001	491.5	0.87	0.73
PE	0.63	0.07	0.04	6.01	0.50	0.77
Rmin	0.84	0.05	<0.001	6.93	0.96	0.63

AUC: Area under the curve, SD: Standard deviation, CCTapex: Central corneal thickness at the apex, CTmin: Minimum corneal thickness, PE: Posterior elevation, Rmin: Minimum radius

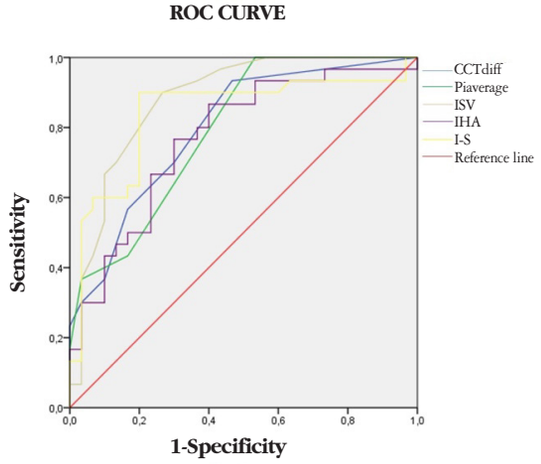

Figure 2. ROC curve between normal fellow eyes of keratoconus patients and healthy controls

I-S: Inferior-superior, IHA: Index of height asymmetry, ISV: Index of surface variance, CCT: Central corneal thickness

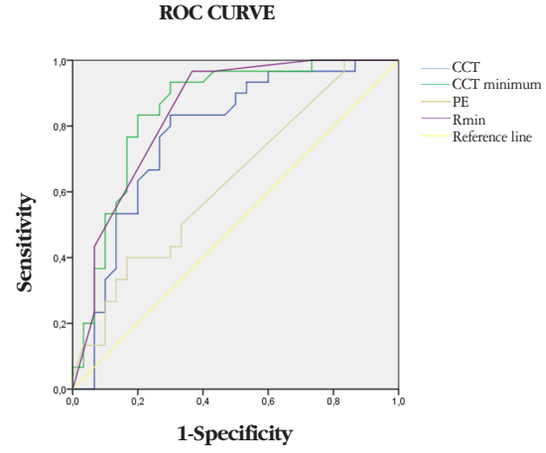

Figure 3. ROC curve between the keratoconus eyes and normal fellow eyes of keratoconus patients

CCT: Central corneal thickness, PE: Posterior elevation, Rmin: Minimum radius

Discussion

Keratoconus is a chronic, usually bilateral, non-inflammatory corneal ectasia.[1] The corneal thinning seen in keratoconus is not central, but usually occurs in the inferonasal region. The Pentacam has a key role in the early diagnosis and monitoring of keratoconus due to its ability to evaluate the anterior and posterior corneal surfaces together. Abnormalities emerge in the posterior surface of the cornea in early keratoconus. Therefore, development of the Pentacam led to a significant increase in diagnostic sensitivity in keratoconus.[1,2,4]

In this study, we attempted to identify differences between the apparently normal fellow eyes of patients with unilateral keratoconus and the patients' keratoconus eyes and the healthy eyes of controls. Comparison of Pentacam data revealed significant differences between Groups 1 and 2 in all parameters except CV. Çağıl et al.[21] compared CV in keratoconus patients, subclinical keratoconus patients, and normal control subjects and showed that this parameter is helpful in distinguishing keratoconus eyes from normal eyes but not in differentiating between keratoconus and subclinical keratoconus. In their study of patients with keratoconus, Emre et al.[22] found that CV decreased with disease

progression. The results of our study also support these data. We found that the keratoconus eyes in Group 1 differed significantly from the eyes in Groups 2 and 3. We also determined that the Pentacam data of the eyes in Group 2 were statistically closer to the results in Group 3, especially in terms of keratometry readings. In another study on this subject, Bae et al.[17] compared the affected and unaffected eyes of patients with keratoconus and reported a significant difference, with normal fellow eyes being more similar to the eyes of healthy volunteers. Hashemi et al.[23] found that the normal fellow eyes of patients with keratoconus were not significantly different in terms of average keratometry values, but did show significant differences in topometric indexes. These findings are consistent with the data obtained in the current study. These results may be due to evaluating the patients' fellow eyes before emergence of the disease or to the patients having true unilateral keratoconus. However, in contrast to these studies, Muftuoglu et al.[11] found that the fellow eyes of patients with keratoconus were significantly different from healthy controls. Further studies are needed to be able to clearly differentiate these eyes.

In this study, we also performed ROC curve analysis to enable the discrimination of clinically unaffected fellow eyes of keratoconus patients from keratoconus eyes and eyes of healthy subjects. According to our results, CCTdiff, PPI, ISV, IHA, and I-S showed high sensitivity and specificity for distinguishing Group 2 from Group 3, while CCTapex, CCTmin, PE, and Rmin values showed high sensitivity and specificity for differentiating between Group 2 and Group 1. In their study, Muftuoglu et al.[11] found that I-S and PPI had high sensitivity and specificity for discriminating keratoconus patients from healthy controls. Bae et al.[17] mentioned the importance of I-S and PE in evaluating the fellow eyes of patients with keratoconus in their study, while Mihaltz et al.[24] emphasized that PE was the most sensitive parameter for diagnosing keratoconus. Hashemi et al.[23] reported that in addition to pachymetric indices, IVA and ISV showed high accuracy rates in identifying cases of subclinical keratoconus. The results obtained in the present study are also consistent with the aforementioned studies. However, none of these values alone is sufficient for the diagnosis or discrimination of keratoconus. Combining them with other clinical data may increase their diagnostic value.

Study Limitations

Limitations of this study include its retrospective nature, the limited number of subjects, and the fact that conclusions were based solely on measurements made at the time of presentation.

Conclusion

To summarize, the results of this study indicate that although the fellow eyes of patients diagnosed with unilateral keratoconus did not exhibit measurement anomalies great enough to be considered keratoconic at the time of diagnosis, they were also not completely normal. However, based on the data obtained, it does not seem possible to diagnose these eyes with keratoconus using available diagnostic tests. In patients with unilateral keratoconus, it is particularly important to monitor fellow eyes evaluated as normal at presentation for development of keratoconus in the long term and to advise patients to avoid mechanical trauma.

Ethics

Ethics Committee Approval: Ege University, 129362.
Informed Consent: Obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Melis Palamar, Sait Eğrilmez, Ayşe Yağcı, Concept: Melis Palamar, Design: Melis Palamar, Cumali Değirmenci, Data Collection or Processing: Nergis İsmayilova, Cumali Değirmenci, Analysis or Interpretation: Melis Palamar, Cumali Değirmenci, Sait Eğrilmez, Ayşe Yağcı, Literature Search: Melis Palamar, Cumali Değirmenci, Writing: Melis Palamar, Cumali Değirmenci, Sait Eğrilmez, Ayşe Yağcı, Nergis İsmayilova.

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Original Article

Assessment of Phosphate and Osmolarity Levels in Chronically Administered Eye Drops

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Abstract

Objectives: To assess phosphate and osmolarity levels of chronically administered eye drops commercially available in Turkey.

Materials and Methods: A total of 53 topical eye drops including 18 antiglaucoma drugs, 4 nonsteroidal anti-inflammatory drugs (NSAIDs), 10 corticosteroids, 7 antihistaminics, and 14 artificial tears identified using the Vademecum Modern Medications Guideline (2018) were included in the study. Phosphate levels were assessed using Roche Cobas C501 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) and the respective kits. Osmolarity was assessed using Vescor Vapro 5600 vapor pressure osmometer (Sanova Medical Systems, Vienna, Austria). Mean phosphate and osmolarity levels were obtained after averaging three measurements. Eye drops were categorized as isoosmolar, hypoosmolar and hyperosmolar based on physiologic tear osmolarity range (296.5±9.8 mOsm/L).

Results: The highest phosphate concentration was found in the antiglaucoma group (20.3±35.4 mmol/L), followed by antihistaminics (17.3±17.9 mmol/L), corticosteroids (15.2±19.1 mmol/L), artificial tears (0.8±1.0), and NSAIDs (0.04±0.08). Percentage of medications in the hyperosmolar category was highest in the NSAI group (75%), followed by antihistaminics (43%), corticosteroids (20%), and antiglaucoma drugs (19%). Nearly all of the artificial tear formulations were in the hypoosmolar (71%) or isoosmolar (21%) categories.

Conclusion: Approximately 40% of glaucoma medications and approximately 60% of corticosteroid and antihistaminic medications had a phosphate concentration higher than the physiologic tear phosphate level (1.45 mmol/L).

Keywords: Phosphate, eye drops, osmolarity, corneal calcification

Introduction

While topical eye drops have an important place in the treatment of eye diseases, long-term and inappropriate use may cause serious complications and side effects affecting the ocular surface. These side effects may be caused by an active pharmaceutical ingredient, preservative, or vehicle in the topical formulation.[1] The side effect profiles of active ingredients are thoroughly investigated during the stages of drug development, and the process of monitoring for adverse effects also continues after the molecule enters the market. After recent studies revealed that preservatives can also cause severe toxicity, efforts have been made to develop less toxic preservative molecules or preservative-free eye drops. However, the potential toxicity of molecules comprising eye drop vehicles has been a relatively neglected topic that has not been given due importance.

Vehicles are involved in buffering eye drops and ensure that the formulation has the appropriate tonicity and viscosity.[2] Buffering agents include molecules like acetic, boric, and hydrochloric acid, potassium or sodium bicarbonate, phosphate, and citrate.[1] Phosphate, a commonly used buffer, is a vehicle with high buffering capacity that stabilizes the pH level at 7.4, and can also be found in some formulations as part of the active ingredient.[1,3,4] In addition, it has the added advantage of making corticosteroid-containing solutions more transparent.[3]

Although phosphate is an effective buffer, it interacts with calcium cations on the ocular surface to disrupt the structure of the precorneal tear film and form insoluble hydroxyapatite

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[$Ca_5(PO_4)_3OH$] or calcium phosphate crystals in the cornea.[2,5,6,7] The resulting crystals cause irreversible stromal opacification and reduced vision, and can also have a serious impact on patient comfort.[5,6,8] An example of this crystallization was previously demonstrated in a patient with chemical burn of the ocular surface that was irrigated with a phosphate-buffered saline solution.[9] The development of irreversible corneal calcification after the use of phosphate-buffered artificial tears for ocular surface disorders occurs for a similar reason.[5] The extent of accumulation depends on factors such as the size of the epithelial defect, the presence of dry eye, the pH and tonicity of the formulation, and the frequency and duration of use.[2,9,10]

The aim of our study was to examine the phosphate concentrations and osmolarity levels of chronically administered eye drops commercially available in Turkey. We hereby intend to highlight the distinct importance of phosphate levels in eye drops in addition to the known hazards imposed by the active ingredients and preservatives.

Materials and Methods

The Vademecum Modern Drug Directory (2018) was screened for antiglaucoma drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antihistamines, and artificial tears for chronic topical use that are commercially available in Turkey. A total of 53 topical drugs, including 18 antiglaucoma drugs, 4 NSAIDs, 10 corticosteroids, 7 antihistamines, and 14 artificial tears, were included in the study in order to examine their phosphate and osmolarity levels (Table 1). Because this study did not involve humans or the use of human biological material, it was considered exempt from ethics board approval by the Ethics Committee of Eskişehir Osmangazi University. Topical formulations with high viscosity were excluded from the research due to technical reasons. Phosphate levels were determined at the Medical Biochemistry Department Laboratory of the Medical Faculty at Eskişehir Osmangazi University using a Roche Cobas C501 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with an inorganic phosphate kit based on the molybdate UV method.[11] The kit has a measurement range of 0.1-6.46 mmol/L and a lower limit of detection of 0.1 mmol/L. Samples above the measurable range were diluted and analyzed again. The kit has good reproducibility (CV<1.5%). Osmolarity of the topical drops was evaluated with a Vescor Vapro 5600 model steam pressure osmometer (Sanova Medical Systems, Vienna, Austria) found in the same laboratory. Three levels of control were used to calibrate the device: low (100±2 mOsm/L), normal (290±3 mOsm/L), and high (1000±5 mOsm/L). The phosphate and osmolarity levels of each eye drop were determined three times and the average values were included in the analysis.

Information about the preservatives found in the drops was obtained from the Vademecum Modern Drug Directory.

Drops within the physiological osmolarity range of tears (296.5±9.8 mOsm/L)[12] were classified as isoosmolar, and those below and above this range were classified as hypoosmolar and hyperosmolar, respectively.

Based on their phosphate concentrations, the topical drops were classified as being within physiological range (≤1.45 mmol/L), slightly high (1.45-25 mmol/L), moderately high (25-50 mmol/L), and very high (≥50 mmol/L).[2]

Statistical Analyses

All statistical analyses were made with SPSS version 21.0 (SPSS, Inc. IBM, Chicago, IL). The average phosphate values of drugs with different preservative ingredients and in the different osmolarity categories were evaluated with Kruskal-Wallis test. Statistical significance was set at $p<0.05$.

Results

The phosphate concentrations and osmolarity categories of the eye drops included in the study are summarized in Table 1. The highest measured average phosphate level was in the antiglaucoma group (20.3±35.4 mmol/L), followed by antihistamines (17.3±17.9 mmol/L), corticosteroids (15.2±19.1 mmol/L), artificial tears (0.8±1.0 mmol/L), and NSAIDs (0.04±0.08 mmol/L) (Figure 1). Thirty-one (58.5%) of the 53 topical drops contained phosphate levels within the physiological range. Preparations containing moderately and very high levels of phosphate accounted for 22.2% of the antiglaucoma drops and 42.9% of the antihistamines (Figure 2).

In the antiglaucoma group, it was noted that drops containing latanoprost contained especially high phosphate levels (Table 1). In the antihistamine group, drops containing olopatadine were found to contain high levels of phosphate, while other drops contained trace amounts of phosphate (Table 1). In the artificial tear group, most preparations had trace amounts of phosphate, while those containing sodium hyaluronate had slightly high levels of phosphate (Table 1).

When different drug groups were evaluated based on their osmolarity levels, it was found that preparations in the NSAID group were of hyperosmolar character, while preparations in the artificial tear group were mostly hypoosmolar or isoosmolar (Figure 3).

Evaluation of the phosphate levels of drugs in different osmolarity categories showed that hypoosmolar and hyperosmolar drugs contained similar levels of phosphate (9.0±24.6 mmol/L and 10.2±19.6 mmol/L, respectively); isoosmolar drugs had a relatively higher mean phosphate level (22.1±25.6 mmol/L), but the difference was not statistically significant ($p>0.05$) (Figure 4).

It was noted that of the 53 drugs, 34 contained benzalkonium chloride (BAK) as a preservative, 9 contained a non-BAK preservative, and the remaining 10 drugs contained no preservatives. When phosphate levels were evaluated based on preservative, the highest phosphate level was in those containing BAK (16.9±27.4 mmol/L), followed by preservative-free drops (5.2±14.4 mmol/L) and drops containing non-BAK preservatives (0.14±0.42 mmol/L) (Figure 5).

Table 1. Phosphate and osmolarity levels in the different categories of eye drops

		Main ingredient	Dose	Preservative	Laboratory	Phosphate (mmol/L)	Osmolarity
Antiglaucoma agents	**Beta-blockers**						
	Betoptic S	Betaxolol	Multidose	BAK	Alcon	<0.1	Hyperosmolar
	Carteol LP 2%	Carteolol	Multidose	BAK	Bausch & Lomb	5.5	Hypoosmolar
	Timoptic XE	Timolol	Multidose	Benzododecinium bromide	Ashfield	<0.1	
	Alpha-2 agonists						
	Alphagan P	Brimonidine	Multidose	Purite	Allergan	<0.1	Hyperosmolar
	Brimogut	Brimonidine	Multidose	BAK	Bilim	<0.1	Hypoosmolar
	Prostaglandin analogues						
	Latapol	Latanoprost	Multidose	BAK	Abdi İbrahim	67.7	Isoosmolar
	Lumigan RC	Bimatoprost	Multidose	BAK	Allergan	10.3	Hypoosmolar
	Travatan	Travoprost	Multidose	Polyquad	Alcon	<0.1	Hypoosmolar
	Xalatan	Latanoprost	Multidose	BAK	Pfizer	68.7	Hypoosmolar
	Carbonic anhydrase inhibitors						
	Azopt	Brinzolamide	Multidose	BAK	Alcon	<0.1	Hyperosmolar
	Parasympathomimetics						
	Pilosed	Pilocarpine	Multidose	BAK	Bilim	<0.1	
	Prostaglandin analogue + beta-blocker						
	Duotrav	Travoprost + timolol	Multidose	Polyquad	Alcon	<0.1	Hypoosmolar
	Ganfort	Bimatoprost + timolol	Multidose	BAK	Allergan	10.1	Isoosmolar
	Xalacom	Latanoprost + timolol	Multidose	BAK	Pfizer	71.3	Isoosmolar
	Carbonic anhydrase inhibitors + beta-blocker						
	Azarga	Brinzolamide + timolol	Multidose	BAK	Alcon	<0.1	Isoosmolar
	Oftomix	Dorzolamide + timolol	Multidose	BAK	Bilim	<0.1	Hypoosmolar
	Tomec	Dorzolamide + timolol	Multidose	BAK	Abdi İbrahim	<0.1	Hypoosmolar
	Alpha agonist beta-blocker						
	Combigan	Brimonidine + timolol	Multidose	BAK	Allergan	111.2	Hypoosmolar
NSAIDs	Acular LS	Ketorolac	Multidose	BAK	Allergan	0.16	Hypoosmolar
	Inflased	Diclofenac	Multidose	Thimerosal	Bilim	<0.1	Hyperosmolar
	Nevanac	Nepafenac	Multidose	BAK	Alcon	<0.1	Hyperosmolar
	Rediclon	Diclofenac	Single dose	(-)	Deva	<0.1	Hyperosmolar
Corticosteroids	Blephamide	Prednisolone + sulfacetamide	Multidose	BAK	Allergan	51.2	Hyperosmolar
	Dexa-sine SE	Dexamethasone	Single dose	(-)	Liba	46.2	Hyperosmolar
	Efemoline	Fluorometholone + tetrahydrozoline	Multidose	BAK	Novartis	<0.1	Hypoosmolar
	Flarex	Fluorometholone	Multidose	BAK	Alcon	7.6	Isoosmolar
	FML	Fluorometholone	Multidose	BAK	Allergan	20.7	Isoosmolar
	Lotemax	Loteprednol	Multidose	BAK	Abdi İbrahim	<0.1	Hypoosmolar
	Maxidex	Dexamethasone	Multidose	BAK	Alcon	14.5	Isoosmolar
	Onadron	Dexamethasone	Multidose	BAK	I.E. Ulagay	12.1	Hypoosmolar
	Pred forte	Prednisolone	Multidose	BAK	Allergan	0.14	Hypoosmolar
	Zylet	Loteprednol + tobramycin	Multidose	BAK	Bausch & Lomb	<0.1	Hypoosmolar

Table 1. Continued

Antihistaminics	Emadine	Emedastine	Multidose	BAK	Liba	<0.1	Hyperosmolar
	Detofen	Ketotifen	Multidose	BAK	Deva	<0.1	Hypoosmolar
	Dupatin	Olopatadine	Multidose	BAK	Deva	14.4	Hyperosmolar
	Ofnol S	Olopatadine	Multidose	BAK	Abdi İbrahim	35.9	Isoosmolar
	Oladin	Olopatadine	Multidose	BAK	Bilim	35.5	Isoosmolar
	Patanol	Olopatadine	Multidose	BAK	Alcon	35.5	Hypoosmolar
	Zaditen	Ketotifen	Multidose	BAK	Thea	<0.1	Hypoosmolar
Artificial tears	Artelac advanced	Sodium hyaluronate	Single dose	(-)	Bausch & Lomb	2.1	Hypoosmolar
	Artelac complete	Sodium hyaluronate	Single dose	(-)	Bausch & Lomb	<0.1	Hypoosmolar
	Artelac splash	Sodium hyaluronate	Multidose	(-)	Bausch & Lomb	2.04	Isoosmolar
	Dryex	Sodium hyaluronate	Multidose	BAK	Abdi İbrahim	1.9	Hypoosmolar
	Eyestil	Sodium hyaluronate	Multidose	BAK	Teka	1.9	Hypoosmolar
	Eyestil single dose	Sodium hyaluronate	Single dose	(-)	Teka	1.9	Hypoosmolar
	Novaqua	Polyvinyl alcohol + povidone	Single dose	(-)	Deva	<0.1	Hyperosmolar
	Refresh liquigel	Sodium carboxymethylcellulose	Multidose	Purite	Allergan	<0.1	Hypoosmolar
	Refresh tears	Sodium carboxymethylcellulose	Multidose	Purite	Allergan	1.3	Hypoosmolar
	Refresh single dose	Polyvinyl alcohol + povidone	Single dose	(-)	Allergan	<0.1	Hypoosmolar
	Systane	Polyethylene glycol + propylene glycol	Multidose	Polyquad	Alcon	<0.1	Isoosmolar
	Tears naturale free	Dextran 70 + hypromellose	Single dose	(-)	Alcon	<0.1	Hypoosmolar
	Tears naturale II	Dextran 70 + hypromellose	Multidose	Polyquad	Alcon	<0.1	Isoosmolar
	Thealoz duo	Trehalose + sodium hyaluronate	Multidose	(-)	Thea	<0.1	Hypoosmolar

BAK: Benzalkonium chloride, NSAIDs: Nonsteroidal anti-inflammatory drugs

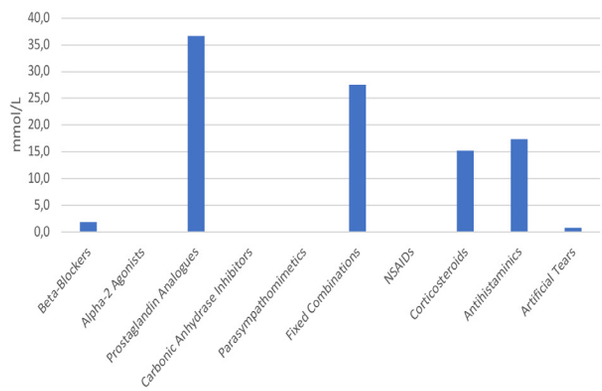

Figure 1. Mean phosphate levels of different drug groups
NSAIDs: Nonsteroidal anti-inflammatory drugs

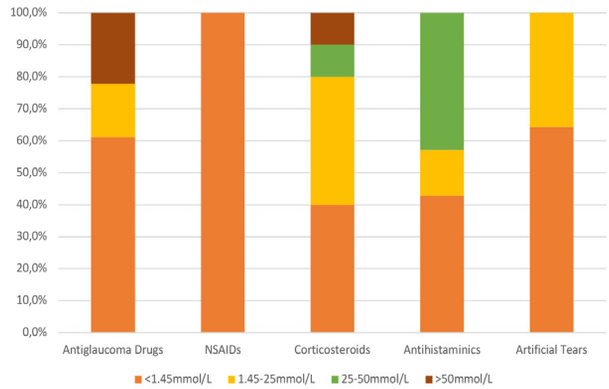

Figure 2. Percent distribution of phosphate levels in the different drug groups
NSAIDs: Nonsteroidal anti-inflammatory drugs

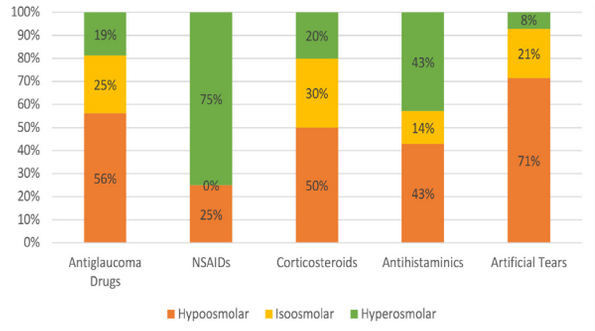

Figure 3. Percent distribution of osmolarity levels in the different drug groups
NSAIDs: Nonsteroidal anti-inflammatory drugs

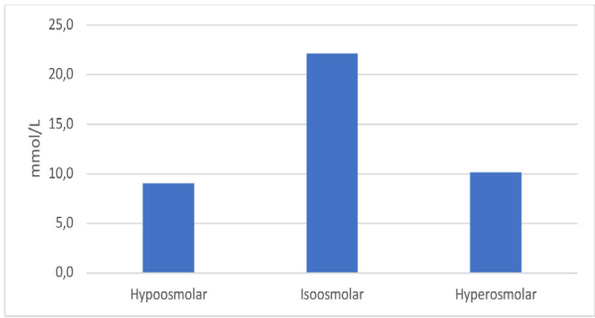

Figure 4. Average phosphate levels of drugs by osmolarity category

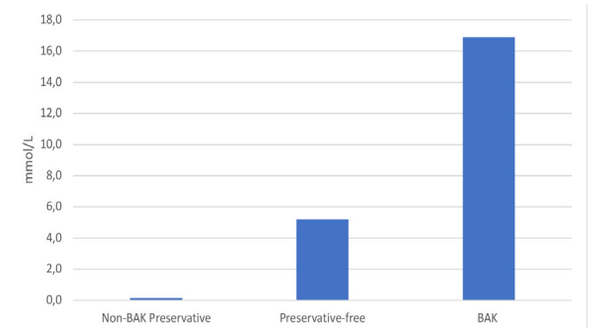

Figure 5. Average phosphate levels according to preservative
BAK: Benzalkonium chloride

There was a significant difference between the group containing BAK and the group containing non-BAK preservatives (p=0.04), but the other comparisons did not yield statistically significant results.

Discussion

Corneal calcification can result in severely reduced vision and in most cases irreversible corneal opacification, and may be associated with long-term use of eye drops with high phosphate content.[5,6,13] The formation of crystals without visible calcification due to the use of high-viscosity artificial tears can also lead to irritation and thereby disrupt patient comfort.[8] Rapid corneal calcification has also been reported in patients with large epithelial defects that were irrigated with phosphate-buffered solutions after chemical burns.[9,14,15] In this study, we found that 22 (41.5%) of the 53 drops analyzed contained levels of phosphate exceeding physiological concentration (0-1.34 mmol/L) and that the majority of these were in the antiglaucoma and antihistamine drug groups.

The deposition of hydroxyapatite [$Ca_5(PO_4)_3OH$] crystals in Bowman's layer and the superficial stroma of the cornea is called band keratopathy.[16] In cases with both epithelial damage and disruption of Bowman's membrane, accumulation occurs in the deeper corneal stroma and Descemet's membrane in the form of calcareous degeneration.[17] The solubility of these crystals decreases with alkaline pH and high temperature.[18] The pH value (physiological range 7.6-7.8)[19] and tonicity of the ocular surface, extent of epithelial damage, and presence of inflammation and barrier dysfunction are among the factors responsible for the development of corneal calcification.[2,9] Especially in dry eye patients, the tear film becomes more alkaline and hyperosmolar.[20,21,22] An alkaline shift in the tear film has also been reported in association with age, independent of dry eye disease.[23,24] The hyperosmolar state that occurs in dry eye disease is known to trigger the release of inflammatory mediators and proteases, which cause epithelial destruction.[25] Similarly, topical drops with a hyperosmolar character have also been shown to alter tear osmolarity and increase inflammation.[26] As ocular inflammation is a known risk factor for corneal calcification, hyperosmolar drops are not recommended for patients with a predisposition to corneal calcification.[27,28]

Although the phosphate content of the artificial tears analyzed in our study were within physiological limits, factors such as high-frequency use, inadequate lacrimal drainage, extended tear turnover time, and the high viscosity of artificial tears can increase the duration of contact between the ocular surface and the phosphate found in the formulation and thus lead to a tendency for calcification.[2,10] Because dry eye also involves an inflammatory component, treatment may involve the intermittent use of steroids. Full-thickness calcification in the corneal stroma following the long-term use of dexamethasone phosphate was reported in a patient with Stevens-Johnson syndrome (SJS).[6] Therefore, in the presence of an epithelial defect, it may be beneficial to prefer topical steroids that have low phosphate content or contain a non-phosphate buffer and are preferably acidic. Notably, the only BAK-free formulation in the topical steroid group contains phosphate at a concentration above the physiological limit.

In our study, the highest phosphate concentrations were detected in the antiglaucoma drops. Drops containing latanoprost in particular contained approximately 50 times more phosphate than the upper limit of the physiological range. Although the more acidic pH values (≈6.4)[10] of these drops may seem like an advantage, the high phosphate concentrations increase their risks. In contrast, although bimatoprost drops and bimatoprost

fixed combination drops contain less phosphate, they are more alkaline.[10] The disclaimers in the package inserts of both of these prostaglandin analogues stating that "in rare cases, patients with severe damage to the cornea may develop cloudy patches due to the calcium build-up during treatment" should be evaluated in this context.[29,30] Considering that predisposition to phosphate deposition in the cornea is a pH-dependent process, it will be valuable to demonstrate the effect of both preparations *in vivo*. In addition to drug pH values, the presence of ocular surface inflammation in glaucoma patients may be a factor that increases the risk of corneal deposits. Although trace amounts of phosphate were detected in the drops containing timolol in our study, accumulation in the superficial corneal stroma associated with timolol has been reported in the literature.[31,32]

Combining the reduced tear film breakup time, ocular pH changes, and ocular surface temperature and chronic inflammation that occur in allergic conjunctivitis with the chronic use of drugs containing high phosphate levels may promote the formation of corneal deposits.[33,34,35] It is important to evaluate the topical antihistamines, steroids, and artificial tears used in treatment with this in mind. Shield ulcers that may occur in vernal conjunctivitis are another condition in which the risk of corneal disposition should be assessed.

Conclusion

In summary, cases of acute or chronic corneal calcification associated with the use of topical drops or irrigation solutions with high phosphate levels have been reported in patients with chemical burns, dry eye, and chronic keratoconjunctivitis secondary to SJS.[5,6,9] Considering evidence that phosphate-buffered tears but not citrate-buffered tears caused corneal calcification in some rabbits with mechanical abrasion-induced epithelial defect, drops containing a non-phosphate buffer can be considered for at-risk patients.[18] A European Medicines Agency report evaluating 117 cases related to this topic emphasized that there is a possible association between corneal calcification and the use of topical drops in patients with corneal surface disorders.[36] The reported concluded by stating that due to the very low risk, there is no need to refrain from using phosphate buffered drops, but that the risk-benefit balance should be considered when prescribing these drugs to patients with corneal damage.[36] Knowing the chemical structure of topical formulations and selecting drops that have suitable tonicity and pH according to the disease profile and contain a buffer that will not promote accumulation will help prevent ocular surface complications associated with the use of eye drops.

Ethics

Ethics Committee Approval: Because this study did not involve humans or the use of human biological material, it was considered exempt from ethics board approval by the Ethics Committee of Eskişehir Osmangazi University.

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Nilgün Yıldırım, İbrahim Özkan Alataş, Eray Atalay, Design: Nilgün Yıldırım, İbrahim Özkan Alataş, Data Collection or Processing: Onur Özalp, Eray Atalay, Zeynep Küskü Kiraz, İbrahim Özkan Alataş, Nilgün Yıldırım, Analysis or Interpretation: Eray Atalay, Zeynep Küskü Kiraz, İbrahim Özkan Alataş, Nilgün Yıldırım, Literature Search: Onur Özalp, Eray Atalay, Nilgün Yıldırım, Writing: Onur Özalp, Eray Atalay, Nilgün Yıldırım.

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Original Article

Comparison of Icare Pro Tonometry and Icare One Tonometry Measurements in Healthy Eyes

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Abstract

Objectives: To compare intraocular pressure (IOP) measurements obtained with the Icare Pro tonometer used in clinical practice and the Icare One self-tonometer.

Materials and Methods: Fifty-two eyes of 52 healthy, right-handed individuals with no prior intraocular surgery or ocular trauma, structural ocular pathology, or systemic disease were evaluated. IOP was first measured using the Icare Pro tonometer. The participants were then told how to use the Icare One tonometer and asked to measure their own IOP. The results were analyzed statistically using SPSS v.24.

Results: Of the 52 healthy participants, 16 (30.7%) were male and 36 (69.3%) were female. Their mean age was 31.6±6.3 (23-47) years. Mean IOP measured with the Icare Pro was 17.10±6.2 (11.5-25.2) mmHg, and the mean self-measured IOP with Icare One was 14.01±3.4 (7-24) mmHg. When the two methods were compared using Levene's t-test, there was a significant mean difference of -3.08±0.6 (95% confidence interval: -4.39 -1.78; p<0.001).

Conclusion: In this study, there was a significant difference between the IOP measurements we made using the Icare Pro and the participants' self-measured IOP using the Icare One, with the latter being relatively lower. This may be related to the fact that the participants were unfamiliar with using the Icare One. Although the Icare One is a promising tool for glaucoma patients to self-monitor their IOP, further studies are needed.

Keywords: Glaucoma, intraocular pressure, Icare, tonometry

Introduction

The accurate measurement and regular monitoring of intraocular pressure (IOP) are critical in the diagnosis, follow-up, and treatment of glaucoma. Various devices are currently used to measure IOP, but the Goldmann applanation tonometer (GAT) is still the gold standard.[1,2]

The Icare Pro is a small, portable, easy-to-use tonometer that operates on the principle of rebound measurement and does not require topical anesthesia. Measurements are obtained by striking the central cornea with a single-use probe on the device's tip. The average of six measurements obtained by the device is displayed as the IOP value.[2] The Icare One tonometer was designed to allow individuals to measure their own IOP.[3]

The development of home tonometers patients can use to assess their IOP is important for evaluating the effectiveness of antiglaucoma therapy in reducing IOP.[4]

This study was conducted to compare measurements obtained with the Icare Pro tonometer and Icare One tonometers in healthy eyes.

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Materials and Methods

The study was carried out in accordance with the principles of clinical research set forth in the Declaration of Helsinki and was approved by the ethics committee of Manisa Celal Bayar University Faculty of Medicine. The study included 52 right eyes of 52 healthy, right-handed individuals with no history of intraocular surgery or trauma and no structural ocular pathology or systemic disease. All participants underwent best corrected visual acuity assessment, slit-lamp anterior segment examination, and fundus examination.

IOP measurements were obtained with the Icare Pro tonometer, changing probes between each measurement.

Measurements were performed an average of 6 times from the central cornea with the device held approximately 4-8 mm from the right eye without topical anesthesia, and the average IOP value was determined.

Statistical Analyses

Ten minutes after measuring with the Icare Pro tonometer, the participants were told how to use the Icare One tonometer and were instructed to measure the IOP of their right eye using their right hand. The results were statistically analyzed using SPSS 24. The two methods were compared using Levene's test with level of significance accepted as $p<0.05$.

Results

Of the 52 healthy individuals included in the study, 16 (30.7%) were male and 36 (69.3%) were female. Their mean age was 31.6±6.3 (23-47) years. Mean IOP values were 17.10±6.2 (11.5-25.2) mmHg with the Icare Pro and 14.01±3.4 (7-24) mmHg with the Icare One tonometer. Comparison of the two methods with Levene's t-test revealed that the mean difference between the values was -3.08±0.6 with a 95% confidence interval of (-4.39 -1.78), which was a statistically significant difference ($p<0.001$). Mean IOP measured with the Icare One tonometer was found to be about 3 mmHg lower than the mean IOP measured with the Icare Pro tonometer.

Discussion

Accurate measurement and regular monitoring of IOP are important in the diagnosis, follow-up, and treatment of glaucoma. The GAT, developed by Goldmann and Schmidt, is widely accepted and is still used as the gold standard method for the measurement of IOP.[1,2] The Icare tonometer is a small, portable, easy-to-use device that enables measurement without the use of biomicroscope or anesthetic, provides rapid results in uncooperative patients, and is useful in daily routine clinical practice. It is especially convenient for children, individuals with deep-set eyes, and patients who have poor mobility or cannot be examined at the slit-lamp due to physical problems.[5,6]

Studies in the literature comparing the Icare Pro tonometer and GAT reported that IOP measurements obtained with the Icare Pro tonometer were 0.1-3.36 mmHg higher.[7,8] Vandewalle et al.[9] and Munkwitz et al.[10] reported a high correlation and no statistically significant difference between mean IOPs with the Icare tonometer and GAT in glaucoma patients. Pakrou et al.[11] also reported that mean IOP was measured as 18.2 mmHg by GAT and 17.6 mmHg with the Icare tonometer, with high correlation ($r=0.95$). Brusini et al.[2] compared Icare Pro and GAT measurements in a study of 178 primary open-angle glaucoma patients and reported that there was a statistically significant correlation between the measured values, but noted that measurements were affected by central corneal thickness.

The Icare One tonometer is a home tonometer designed for patients to measure their own IOP. Self-tonometry is important for enabling the evaluation of the IOP-lowering effect of treatment and demonstrating diurnal IOP fluctuations. Moreno-Montañés et al.[4] compared GAT, Icare Pro, and Icare One tonometer measurements in 60 healthy individuals and 90 glaucoma patients and reported no significant difference between GAT and the Icare Pro tonometer, while IOP measurements obtained with the Icare One were an average of 0.3 mmHg higher compared to the other two methods.

Witte et al.[12] compared Icare One and GAT measurements in 40 glaucoma patients and found that they were significantly correlated in the <60 age group, but not in the >60 age group. They reported that adults over the age of 60 may have difficulty using the device properly, and that tremors and other systemic conditions seen in older adults may reduce the utility and reliability of the device in these patients. In another study comparing Icare One tonometer and GAT measurements, Rosentreter et al.[3] evaluated 74 glaucomatous and 52 nonglaucomatous right eyes of 126 patients. Among the 95 patients (75.3%) that were able to use the Icare One tonometer and were included in the study, the mean IOP difference between the Icare One and GAT was 0.6 mmHg. In addition, a survey about the use of the Icare One tonometer conducted among the study participants revealed patients aged 70 years and older considered the device difficult to use. Halkiadakis et al.[13] reported that the mean IOP measured by Icare One tonometer was 2.3 mmHg higher than those obtained with GAT in 60 healthy individuals. Gandhi et al.[14] compared IOP measurements made with Icare One tonometer and GAT in 60 children with diagnosed or suspected glaucoma. Icare One tonometer measurements were taken twice, once by a clinician and once by a family member. Clinician-measured Icare One IOP values were 3.3 mmHg higher on average than GAT measurements. Measurements obtained by the clinician with the Icare One tonometer were an average of 1.9 mmHg higher than those obtained by the patient's family. In addition, families were surveyed in the study about the use of the Icare One tonometer and 98% of the participants stated that the device was easy to use.

In the present study, mean IOP was 17.10±6.2 mmHg with the Icare Pro tonometer and 14.01±3.4 mmHg with the Icare One tonometer, with a statistically significant mean difference of -3.08±0.6 mmHg (95% confidence interval: -4.39 – -1.78; p<0.001). The discrepant IOP values obtained with the Icare One tonometer likely stem from inability to use the device properly or obtain measurements from the correct location, or may be related to using the device for the first time. In order to accurately measure IOP with the Icare One tonometer, it must be held horizontally during measurement, but the device does not have any indicator of its position. To avoid the effect of device orientation on IOP values, an updated version of the Icare One, called the Icare Home, equipped with an eye recognition system and position sensors, has recently been introduced to the market. Due to its position sensors, the Icare Home will not obtain measurements if it is not in a horizontal position. In addition, the Icare Home gives an error signal and does not take measurements if the probe is too close to the eye or if the patient's hand or hair comes between their eye and the probe. In addition, while the Icare One shows IOP measurements as being in a certain range by classifying the values into 11 categories, the Icare Home does not have a display that shows the measured value. Icare Home measurements can be viewed by connecting the device to a computer with the appropriate software.[15] In our study, we cannot be sure that the participants using the Icare One were holding the device in the proper horizontal position, due to its lack of position sensors. In addition, reduced IOP due to the accommodative reflex may have also contributed to this difference.[16,17]

Conclusion

IOP measurements obtained at home using the Icare One tonometer can provide guidance in the follow-up of glaucoma patients. However, the reliability of the Icare One is reduced by older adults' difficulties using the device and the inability to prevent position errors by the user. Because the sample population in this study was small and included younger adults, our findings should be supported by larger and more inclusive patient series.

Ethics

Ethics Committee Approval: Manisa Celal Bayar University Faculty of Medicine Ethics Committee of Health Sciences (28/03/2018 20.478.486).

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Hüseyin Mayalı, Çağlar Sarıgül, Concept: Süleyman Sami İlker, Özcan Rasim Kayıkcıoğlu, Emin Kurt, Design: Hüseyin Mayalı, Çağlar Sarıgül, Data Collection or Processing: Hüseyin Mayalı, Çağlar Sarıgül, Analysis or Interpretation: Hüseyin Mayalı, Çağlar Sarıgül, Süleyman Sami İlker, Özcan Rasim Kayıkcıoğlu, Emin Kurt, Literature Search: Hüseyin Mayalı, Çağlar Sarıgül, Writing: Hüseyin Mayalı, Çağlar Sarıgül.

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Original Article

Investigation of the Presence of Glaucoma in Patients with Obstructive Sleep Apnea Syndrome Using and Not Using Continuous Positive Airway Pressure Treatment

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Abstract

Objectives: To evaluate the frequency of glaucoma in patients with obstructive sleep apnea syndrome (OSAS) using and not using continuous positive airway pressure treatment.

Materials and Methods: This prospective study included 59 patients diagnosed with OSAS based on the Apnea-Hypopnea Index (AHI). OSAS patients were divided into 3 groups according to their AHI scores: 5-15 was considered mild (19 patients), 16-30 was considered moderate (16 patients), and >30 (24 patients) was considered severe. Twenty-eight (47.5%) of the OSAS patients had been using continuous positive airway pressure treatment. The control group included 19 healthy subjects. Retinal nerve fiber layer and ganglion cell complex (GCC) thickness analyses were performed.

Results: Average GCC thickness in left eyes was significantly lower in the mild OSAS group than in the control group (p=0.013). The GCC was significantly thinner in the inferior and inferonasal sectors of both eyes in the mild OSAS group compared to the control group (p=0.029, p=0.022, p=0.037, and p=0.019 respectively). Minimum GCC thickness in the left eyes of all OSAS groups was significantly lower than in the control group (p<0.05).

Conclusion: In OSAS patients, there may be changes in retinal nerve fiber layer and ganglion cell complex thickness before alterations in the visual field emerge.

Keywords: Glaucoma, ganglion cell complex, obstructive sleep apnea syndrome, ocular hypertension, optic disc

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by reduction of air flow or interrupted respiration due to repeated upper respiratory tract blockages during sleep, and is often associated with decreased oxygen saturation.[1] In the adult population, it is estimated to affect 1.2-2.5% of women and 1-5% of men.[2,3] Studies have reported higher prevalence of primary open-angle glaucoma (POAG) in OSAS patients as well as higher prevalence of sleep disorders in POAG patients.[4,5] Several mechanisms have been proposed to explain the development of glaucomatous optic neuropathy in OSAS patients, including dysregulation of optic nerve head blood flow as a result of repeated prolonged apneas, disruption of optic nerve blood flow secondary to arteriosclerosis and arterial blood flow changes, and optic nerve damage induced directly by repeated prolonged hypoxia.

Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells.[6] It has been shown that 40% of retinal ganglion cell axons may be lost before visual field

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defects develop in glaucoma patients. In this study, we aimed to evaluate retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness in OSAS patients.

Materials and Methods

This prospective study included 59 patients diagnosed with OSAS. The OSAS patients were contacted by phone and invited for ophthalmological examination. The control group consisted of 19 healthy individuals who were fully evaluated to rule out OSAS signs and symptoms. After the study procedures were explained to the participants in full, informed consent forms were obtained. The study was conducted in line with the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Ankara University prior to the initiation of the study (date: 13 October 2014, 16-686-14). The OSAS patients were divided into three groups based on the apnea-hypopnea index (AHI). AHI of 5-15 events/hour was considered mild, 16-30 was considered moderate, and >30 was considered severe OSAS. According to this classification, there were 19 patients (37 eyes) in the mild group, 16 patients (31 eyes) in the moderate group, and 24 patients (47 eyes) in the severe group. The methods used for OSAS treatment in patients were also questioned. Twenty-eight OSAS patients (47.5%) (2 in the mild group, 8 in the moderate group, and 18 in the severe group) were under continuous positive airway pressure (CPAP) treatment.

Exclusion criteria were:

a) History of intraocular surgery,

b) History of ocular trauma,

c) History of uveitis,

d) Family history of glaucoma,

e) Hypermetropia greater than +4 diopters (D) and/or myopia greater than -5 D; astigmatism exceeding ± 1.00,

f) Presence of retinal disease,

g) History of antiglaucoma medication use at any time in the past,

h) Presence of corneal opacity interfering with optical coherence tomography (OCT) imaging,

i) Previous retinal laser treatment for any reason,

j) Presence of central apnea,

k) Presence of optic neuropathies.

A complete ophthalmological examination was performed on all participants. Iridocorneal angle was analyzed in four quadrants using a gonio lens (Ocular Instruments, Washington, USA). Intraocular pressure (IOP) was measured using Goldmann applanation tonometry. Central corneal thickness (CCT) measurements were determined ultrasonically using a pachymetry device (Ocuscan RXP Alcon, USA). SITA standard 24-2 visual field test (Humphrey Field Analyzer Model 750i, Zeiss, USA) was performed. Tests complying with reliability criteria (less than 20% loss of fixation, 33% false negatives) were included in the study. Automated visual field analyses were performed at least twice on all subjects. After dilatation of the pupil with 1% tropicamide, the fundus was examined.

Optical coherence tomography (Cirrus HD-OCT, Carl Zeiss Meditec, Inc, software version 4.0) was used to evaluate the optic disc and RNFL. The GCC was analyzed using ganglion cell analysis (GCA) software. Cirrus HD-OCT is a spectral domain OCT device with a scanning speed of 27.000 A-scans per second. Measurements were performed using the optic disc cube 200x200 scanning protocol. Optic disc cube is a glaucoma scanning protocol that monitors the optic disc and parapapillary retinal region in a 6x6-mm^2 area (200x200 data points). Rim area, disc area, and vertical cup/disc ratios were recorded in the disc analysis. RNFL thickness was determined as the average of the whole image and within quadrants. Ganglion cell-inner plexiform layer (GCIPL) was examined using the macular cube 512x128 protocol on the GCA software. Average, minimum, and sectoral (superior, inferior, superonasal, superotemporal, inferonasal, inferotemporal) GCIPL thicknesses were measured in the oval ring around the fovea. Measurements with signal power of 6 and above were used to prevent segmentation errors. Images with movement artifact or signal power lower than 6 were repeated. All measurements were performed prospectively by the same physician (A.A.). Three measurements were taken for each eye and the average values were calculated.

Statistical Analysis

The data were analyzed using the SPSS for Windows 15 package software. Descriptive statistics were given as mean ± standard deviation for normally distributed variables, median (minimum-maximum) for nonparametric variables, and number of eyes and percentage (%) for nominal variables.

Depending on the distribution of the data, comparisons of means or medians of independent variables were performed using t-test or Mann-Whitney U test. Nominal variables were analyzed using Pearson chi-squared test or Fisher's Exact test. Regarding the relationships among continuous variables, Spearman correlation test was used for non-normally distributed data and Pearson correlation test was used for normally distributed data. $P<0.05$ was accepted as the criterion for statistical significance.

In the statistical analyses, right and left eyes were compared between the mild, moderate, and severe OSAS groups and the control group. Left and right eyes were also compared within the groups.

Results

Fifty-nine patients with OSAS confirmed by polysomnography and a control group consisting of 19 healthy individuals were included in the study. OSAS patients were divided into 3 groups based on AHI values: 19 patients (32.2%, 37 eyes) had mild OSAS (AHI 5-15); 16 patients (27.1%, 31 eyes) had moderate OSAS (AHI 16-30); and 24 patients (40.67%, 47 eyes) had severe OSAS (AHI >30). The OSAS patient group included 34 men (57.6%) and 25 women (42.3%). The control group included 6 men (31.57%) and 13 women (68.42%). There was a statistically significant difference in sex distribution between the groups ($p=0.018$). Table 1 shows the demographic characteristics in detail.

Three eyes of 2 patients with severe OSAS had ocular hypertension (OHT). However, the automated visual field test and optic nerve analyses were normal in both cases and they were included in statistical analyses. The frequency of OHT was found to be 3.44% in patients with OSAS.

There was no significant difference between the right and left eyes in the mild, moderate, and severe OSAS groups or the control group in terms of IOP, best-corrected visual acuity (BCVA), mean RNFL and optic nerve head parameters, or mean deviation in visual field testing (p>0.05). Compared to the control group, pattern standard deviation (PSD) values were significantly higher in the right eye in the mild OSAS group and in the left eye in the moderate OSAS group (p=0.051 and p=0.033, respectively). The details are given in Table 2.

Average RNFL thickness values in right and left eyes were 91.0±10.3 µm and 89.7±10.3 µm in the mild OSAS group, 93.2±7.01 µm and 89.6±8.5 µm in the moderate OSAS group, 95.5±10.4 and 93.1±8.7 in the severe OSAS group, and 95.2±9.8 and 95±8.6 in the control group. There were no statistically significant differences among the groups (p>0.05) (Table 3). AHI was positively correlated with average RNFL thickness in left eyes in the moderate OSAS group (p=0.010, r=0.620).

Table 1. Demographic characteristics of obstructive sleep apnea syndrome patients and the control group

	Mild OSAS	Moderate OSAS	Severe OSAS	Control	p value
Number of patients	19	16	24	19	-
Number of eyes	37	31	47	38	-
Female/Male	12/7	7/9	6/18	13/6	**0.018**
Age (years)	56.63±7.93	55.63±6.03	55.67±9.50	52.58±6.17	0.405
AHI (events/hour)	8.63±2.69	22.31±6.30	66.21±28.96	-	**0.000**

OSAS: Obstructive sleep apnea syndrome, AHI: Apnea-hypopnea index

Table 2. Comparison of visual acuity, intraocular pressure, central corneal thickness, visual field and optic nerve head parameters among groups

	Mild OSAS (n=19)	Moderate OSAS (n=16)	Severe OSAS (n=24)	Control (n=19)	p value
Visual acuity (LogMAR)					
Right eye	0.01±0.03	0.01±0.04	0.01±0.03	0.0	0.358
Left eye	0.00±0.03	0.00	0.01±0.03	0.0	0.095
IOP (mmHg)					
Right eye	14.42±2.63	15.07±2.43	15.74±3.55	14.47±1.77	0.243
Left eye	14.58±2.50	14.69±2.33	15.58±3.45	14.63±1.34	0.553
CCT (µm)					
Right eye	532.32±27.47	528.93±31.70	536.0±31.64	547.21±30.98	0.339
Left eye	537.53±28.72	531.87±30.94	516.46±113.92	553.63±34.48	0.216
MD					
Right eye	-1.86±1.61	-3.07±6.04	-2.05±1.92	-1.33±1.37	0.705
Left eye	-2.40±2.53	-3.54±6.56	-2.39±2.00	-1.12±1.36	0.072
PSD					
Right eye	**2.87±1.72**	2.94±2.49	2.48±0.98	**1.80±0.45**	**0.051**
Left eye	2.93±1.97	**3.31±2.83**	2.06±0.65	**1.86±0.73**	**0.033**
Rim area (mm^2)					
Right eye	1.42±0.18	1.46±0.44	1.45±0.39	1.57±0.23	0.252
Left eye	1.45±0.19	1.52±0.19	1.45±0.19	1.55±0.19	0.277
Vertical C/D					
Right eye	0.48±0.12	0.40±0.14	0.41±0.18	0.38±0.15	0.219
Left eye	0.45±0.14	0.38±0.15	0.36±0.19	0.37±0.14	0.403
Disc area (mm^2)					
Right eye	1.97±0.31	1.94±0.30	2.02±0.31	1.97±0.44	0.931
Left eye	2.06±0.50	1.93±0.33	1.93±0.34	1.94±0.35	

OSAS: Obstructive sleep apnea syndrome, IOP: Intraocular pressure, CCT: Central corneal thickness, MD: Mean deviation, PSD: Pattern standard deviation, C/D: Cup-to-disc ratio, n: Number of patients

Table 3. Comparison of retinal nerve fiber layer and ganglion cell complex thickness (µm) among obstructive sleep apnea syndrome groups

	Mild OSAS (n=19)	Moderate OSAS (n=16)	Severe OSAS (n=24)	Control (n=19)	p value
Right eye	n=18	n=15	n=23	n=19	
Average RNFL	91.0±10.30	93.20±7.01	95.52±10.44	95.21±9.80	>0.05
RNFL S	110.79±16.62	117.93±14.37	116.13±12.35	115.74±14.38	0.784
RNFL T	60.26±8.89	64.20±9.45	69.43±10.67	64.53±9.08	0.066
RNFL I	122.79±15.07	123.07±8.79	126.91±19.77	125.63±17.10	0.826
RNFL N	70.21±8.82	67.33±12.06	69.70±11.76	72.63±12.64	0.909
Average GCC	79.26±9.85	75.27±19.70	81.61±6.19	85.63±5.42	0.052
Minimum GCC	67.68±23.30	69.47±25.55	76.48±10.71	82.26±6.36	0.063
GCC S	77.47±16.40	76.53±19.29	81.35±11.00	86.47±6.55	0.142
GCC ST	79.21±22.31	74.33±21.13	80.65±7.09	82.63±6.8	0.593
GCC IT	82.00±15.86	74.47±21.51	82.87±5.94	85.32±5.68	0.063
GCC I	**79.06±8.17**	75.80±17.92	**80.30±7.51**	**85.95±5.61**	**0.029, 0.049**
GCC IN	**77.94±11.69**	74.33±19.60	78.52±16.99	**86.47±5.31**	**0.037**
GCC SN	79.58±9.88	76.80±20.65	82.43±8.65	86.74±5.84	0.163
Left eye	n=19	n=16	n=24	n=19	
Average RNFL	89.79±10.34	89.60±8.5	93.13±8.71	95.0±8.61	>0.05
RNFL S	115.53±16.67	109.69±20.04	119.71±14.66	120.74±11.52	0.124
RNFL T	60.95±8.73	62.62±8.08	66.50±11.12	62.16±7.93	0.401
RNFL I	119.11±14.77	120.13±12.28	121.35±17.52	125.68±18.28	0.578
RNFL N	63.79±11.07	66.56±11.34	66.29±13.27	71.0±10.87	0.199
Average GCC	**72.32±17.40**	77.88±10.72	77.12±13.48	**84.79±5.89**	**0.013**
Minimum GCC	**65.05±22.12**	**67.63±23.43**	**65.92±23.65**	**82.16±6.33**	**0.010, 0.019, 0.004**
GCC S	71.11±20.16	76.94±15.57	77.92±17.63	85.58±7.26	0.058
GCC ST	70.74±20.64	74.81±16.9	75.04±20.86	83.26±6.1	0.113
GCC IT	72.79±18.92	80.06±7.38	80.08±17.12	84.26±6.25	0.076
GCC I	**73.37±16.22**	79.69±7.01	76.75±12.98	**84.21±6.00**	**0.022**
GCC IN	**72.42±17.07**	79.31±9.06	76.41±13.11	**84.68±5.26**	**0.019**
GCC SN	**72.89±17.42**	76.13±16.60	77.92±15.61	**86.63±5.72**	**0.011**

OSAS: Obstructive sleep apnea syndrome, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, S: Superior, T: Temporal, I: Inferior, N: Nasal, ST: Superotemporal, IT: Inferotemporal, IN: Inferonasal, SN: Superonasal, n: Number of patients; n: Number of eyes

Table 4. Comparison of patients using CPAP, those not using CPAP, and the control group

	CPAP (n=28)	Non-CPAP (n=31)	Control (n=19)	p value
Visual acuity (LogMAR)				
Right eye	0.01±0.04	0.00±0.02	0.0	0.500
Left eye	0.00±0.02	0.00±0.03	0.0	0.615
IOP (mmHg)				
Right eye	15.62±3.16	14.60±2.82	14.47±1.77	0.222
Left eye	15.71±2.74	14.39±2.89	14.63±1.34	0.117
CCT (µm)				
Right eye	530.35±27.61	535.67±32.39	547.21±30.98	0.185
Left eye	513.29±103.95	540.19±31.84	553.63±34.48	0.080
MD				
Right eye	-1.78±1.49	-2.59±3.92	-1.33±1.37	0.594
Left eye	-2.34±1.79	**-3.04±5.08**	**-1.12±1.36**	**0.054**
PSD				**0.016**
Right eye	**2.42±0.82**	**3.0±2.19**	**1.80±0.45**	**0.014**
Left eye	2.29±0.82	3.03±2.51	1.86±0.73	0.057
Rim area (mm^2)				
Right eye	1.45±.038	1.44±0.33	1.57±0.23	0.327
Left eye	1.46±0.21	1.47±0.17	1.55±0.19	0.262
Vertical C/D				
Right eye	0.41±0.17	0.44±0.14	0.38±0.15	0.478
Left eye	0.38±0.17	0.41±0.16	0.37±0.14	0.688
Disc area (mm^2)				
Right eye	2.01±0.30	1.96±0.31	1.97±0.44	0.740
Left eye	1.91±0.34	2.01±0.45	1.94±0.35	0.736

CPAP: Continuous positive airway pressure, IOP: Intraocular pressure, CCT: Central corneal thickness, MD: Mean deviation, PSD: Pattern standard deviation, C/D: Cup-to-disc ratio, n: Number of patients

Comparison of average GCC thickness values between right and left eyes of the groups showed significantly lower values in the left eyes of the mild OSAS group compared to the control group (p=0.013). Minimum GCC thickness in left eyes was significantly lower in the mild, moderate, and severe OSAS groups compared to the control group (p=0.010, p=0.019 and p=0.004, respectively). The details are given in Table 4. In comparisons of GCC thickness by sector, significantly lower values were observed in the inferior and inferonasal sectors of right and left eyes in the mild OSAS group when compared with the control group (p=0.029, p=0.022, p=0.037 and p=0.019, respectively). Inferonasal GCC thickness was positively correlated with AHI in right eyes in the mild OSAS group (r=0.594, p=0.007). Superonasal GCC thickness was significantly lower in left eyes in the mild OSAS group in comparison with the control group (p=0.011). In addition, superonasal GCC thickness was correlated with AHI in right eyes in the mild OSAS group (r=0.612, p=0.005). Inferior GCC thickness was significantly lower in the right eyes of the severe OSAS group compared to the control group (p=0.049). Details are shown in Table 3.

Twenty-eight OSAS patients (47.5%) (2 in the mild group, 8 in the moderate group, and 18 in the severe group) were under CPAP treatment. There was no statistically significant difference in age, BCVA, CCT, average RNFL, and ONH values between OSAS patients with and without CPAP and the control group. The mean deviation value in left eyes in the non-CPAP group was significantly higher than that of the control group (p=0.054). Mean PSD values in the right eyes of the CPAP and non-CPAP groups were significantly higher than those of the control group (p=0.016 and p=0.014, respectively). The details are provided in Table 4.

In RNFL analysis by quadrant, RNFL in the nasal quadrant of left eyes was significantly thinner in the non-CPAP group than in the control group (p=0.047). Details are provided in Table 5.

Average GCC thickness was significantly lower in right eyes in the CPAP group than in the control group (p=0.021) and in the left eyes of both the CPAP and non-CPAP groups compared to the control group (p=0.008 and p=0.042, respectively). Similarly, minimum GCC thickness was significantly lower in the right eyes in the CPAP group than in the control group (p=0.039) and in the left eyes of both the CPAP and non-CPAP groups than in the control group (p=0.000 and p=0.005, respectively). Table 5 shows the GCC analysis by sector.

Table 5. Comparison of RNFL and GCC thickness (µm) in the group using CPAP, the group not using CPAP, and the control group

	CPAP (n=28)	Non-CPAP (n=31)	Control (n=19)	p value
Right eye				
Average RNFL	93.38±8.54	94.10±10.09	95.21±9.80	0.817
RNFL S	113.73±11.61	117.43±13.93	115.74±14.38	0.533
RNFL T	66.92±9.09	64.03±10.88	64.53±9.08	0.421
RNFL I	123.81±16.43	125.27±15.75	125.63±17.10	0.919
RNFL N	69.08±12.05	69.60±9.98	72.63±12.64	0.853
Average GCC	**79.0±11.67**	80.23±11.97	**85.63±5.42**	**0.021**
Minimum GCC	**73.50±15.07**	72.50±19.97	**82.26±6.36**	**0.039**
GCC S	79.08±14.35	80.47±12.31	86.47±6.55	0.094
GCC ST	78.27±12.19	80.97±16.85	82.63±6.8	0.323
GCC IT	79.88±12.26	81.70±16.54	85.32±5.68	0.059
GCC I	**78.15±11.89**	**79.17±11.01**	**85.95±5.61**	**0.005, 0.022**
GCC IN	**75.5±18.66**	**78.70±13.62**	**86.47±5.31**	**0.006, 0.041**
GCC SN	80.31±12.63	80.30±13.63	86.74±5.84	0.136
Left eye				
Average RNFL	91.71±8.81	90.84±9.62	95.0±8.61	0.283
RNFL S	112.82±19.76	118.19±14.10	120.74±11.52	0.186
RNFL T	64.11±10.27	63.26±9.46	62.16±7.93	0.804
RNFL I	122.04±14.51	118.81±15.65	125.68±18.28	0.335
RNFL N	68.29±12.26	**63.10±11.29**	**71.0±10.87**	**0.047**
Average GCC	**75.11±13.79**	**76.39±14.76**	**84.79±5.89**	**0.008, 0.042**
Minimum GCC	**63.36±24.68**	**68.58±20.91**	**82.16±6.33**	**0.000, 0.005**
GCC S	**74.21±19.41**	76.58±16.72	**85.58±7.26**	**0.033**
GCC ST	71.43±22.69	75.55±16.38	83.26±6.1	0.061
GCC IT	**79.54±15.80**	76.10±16.09	**84.26±6.25**	**0.047**
GCC I	**76.00±12.30**	76.87±13.66	**84.21±6.00**	**0.005**
GCC IN	**75.37± 17.02**	76.42±14.87	**84.68±5.26**	**0.010**
GCC SN	**75.29±17.14**	**76.29±15.84**	**86.63±5.72**	**0.010, 0.013**

CPAP: Continuous positive airway pressure, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, S: Superior, T: Temporal, I: Inferior, N: Nasal, ST: Superotemporal, IT: Inferotemporal, IN: Inferonasal, SN: Superonasal, n: Number of patients

Discussion

A recent cohort study indicated that sleep apnea was not associated with higher risk of glaucoma.[7] However, previous studies have reported a wide range of glaucoma prevalence, between 2% and 27%.[8] In our study, 2 of the 59 OSAS patients (3.44%) were diagnosed with OHT.

In OSAS patients, glaucomatous optic neuropathy may develop as a result of severe hypoxia and the subsequent increase in vascular resistance and decreases in perfusion and oxygen saturation.[9] Although apnea episodes are temporary, the chronic nature of the disease may lead to structural changes in the RNFL. Some studies have reported decreases in mean RNFL thickness in patients with OSAS.[9,10,11,12] Moreover, a correlation was reported between OSAS severity and RNFL thickness.[9,10]

An RNFL study by Kargi et al.[10] including 34 OSAS patients and a control group of 20 individuals showed that RNFL thickness was significantly reduced in OSAS patients. Lin et al.[9] evaluated 105 OSAS patients and 20 control individuals and reported significantly lower mean RNFL thickness in moderate and severe OSAS groups compared to the mild OSAS and control groups. Gutierrez-Diaz et al.[13] examined 10 OSAS patients diagnosed with normal-tension glaucoma (NTG), 10 OSAS patients without glaucoma, and 10 participants in a control group and found that RNFL values were significantly lower in the NTG and non-NTG OSAS groups than in the control group. Xin et al.[14] reported significant thinning of the nasal RNFL in the mild, moderate, and severe OSAS groups and of the inferior RNFL in the mild and moderate OSAS groups compared with the control group. Shiba et al.[15] reported lower nasal RNFL thickness in both the right and left eyes of 124 OSAS patients compared with other quadrants. They also observed a negative correlation between nasal RNFL and AHI in both eyes.[15] Similarly, Casas et al.[16] compared 50 OSAS patients and 33 healthy individuals and found that nasal RNFL thickness was significantly lower in the OSAS patients. Topcon 3D and Stratus-OCT devices were used in these studies. However, in our study we used a Cirrus HD-OCT device to compare mild, moderate, and severe OSAS patients with a control group and observed no statistically significant difference in mean RNFL thickness ($p>0.05$). In the moderate OSAS group, a positive correlation was found between AHI and average RNFL thickness in the left eye ($r=0.620$, $p=0.010$). However, this correlation was not clinically significant. In terms of quadrants, there was no difference among groups in the superior, temporal, inferior, or nasal quadrants. In regards to the use of CPAP, we found that nasal RNFL was significantly thinner in the left eyes of patients not using CPAP when compared with the control group ($p=0.047$).

Kergoat et al.[17] reported that retinal ganglion cells are especially sensitive to abnormal perfusion and reduced oxygen saturation. When we reviewed the relevant literature, we did not find any study investigating the GCC in OSAS patients. Thus, we analyzed changes in the GCC in OSAS patients. Minimum GCC thickness in left eyes was lower than that of the control group in all three OSAS groups. When patients using CPAP (n=28) and those not using CPAP (n=31) were compared with the control group, the average GCC thickness in the right eyes of the CPAP group was found to be significantly thinner than that of the control group ($p=0.021$). In left eyes, average GCC thickness was lower in the CPAP and non-CPAP groups in comparison with the control group ($p=0.008$, $p=0.042$). Minimum GCC thickness in right eyes of the CPAP group and left eyes of the CPAP and non-CPAP groups was thinner compared with the control group ($p=0.039$, $p=0.000$, and $p=0.005$, respectively). In sector analysis, inferior and inferonasal GCC was thinner in the right eyes of the CPAP and non-CPAP groups compared to the control group ($p=0.005$, 0.022, 0.006, 0.041, respectively). In left eyes, GCC was thinner in the superior, inferotemporal, inferior, and inferonasal sectors in the CPAP group compared to the control group ($p=0.033$, 0.047, 0.005, 0.010, respectively) and in the superonasal sector in both the CPAP and non-CPAP groups in comparison with the control group ($p=0.010$ and 0.013, respectively).

Recently, Shinmei et al.[18] studied IOP changes during nocturnal sleep using a contact lens sensor and reported immediate decrease in IOP during apnea phases. This finding showed that IOP-independent etiology such as the vascular hypothesis may be the mechanism underlying the association between OSAS and glaucoma. Vasodilatation caused by hypoxia and hypercapnia in OSAS patients indirectly disrupts cerebral perfusion and blood flow to the optic nerve by increasing intracranial pressure. This mechanism may explain the RNFL and GCC thinning in OSAS patients. As symptoms are more noticeable in severe and moderate groups, such patients usually visit otorhinolaryngology and pulmonology clinics. Patients in the mild group visit doctors less frequently due to fewer symptoms, which prolongs the duration of untreated illness. The longer untreated duration in mild cases may make retinal ganglion cells more sensitive. This may explain why the results of our study were mostly significant in the mild group.

Conclusion

Patients with OSAS may be more likely to have OHT or glaucoma. Hence, patients should be monitored thoroughly for glaucoma development and both otolaryngologists and pulmonologists should be informed about this issue. As RNFL and GCC changes may precede visible optic disc and visual field abnormalities in glaucoma, periodic evaluation of RNFL and GCC thickness may have diagnostic value in the early detection of glaucoma in OSAS cases.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Ankara University prior to the initiation of the study (date: 13 October 2014, 16-686-14).

Informed Consent: Received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Oya Tekeli, Turan Acıcan, Banu Gülbay, Concept: Oya Tekeli, Turan Acıcan, Banu Gülbay,

Design: Ahmet Abdullayev, Oya Tekeli, Özge Yanık, Turan Acıcan, Banu Gülbay, Data Collection or Processing: Ahmet Abdullayev, Özge Yanık, Analysis or Interpretation: Oya Tekeli, Literature Search: Ahmet Abdullayev, Özge Yanık, Writing: Ahmet Abdullayev, Özge Yanık.

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Original Article

Investigation of Dry Eye Symptoms in Lecturers by Ocular Surface Disease Index

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Abstract

Objectives: The aim of this study was to evaluate the prevalence of dry eye symptoms among lecturers.

Materials and Methods: The study included 254 lecturers employed at Mersin University. The lecturers were selected by simple random sampling from lists obtained from the personnel department. Data were obtained between November 15 and December 15, 2017 using a questionnaire developed by the researchers and the Ocular Surface Disease Index (OSDI). The data were evaluated using descriptive statistics, Student's t-test, ANOVA, and correlation tests with the SPSS package program.

Results: Of the lecturers who participated in the study, 52.8% were male and 47.2% were female, and the mean age was 39.29±9.41 years. According to OSDI scores, 20.5% of the participants had mild, 15% had moderate, and 36.5% had severe disease. There were significant differences in mean OSDI score based on sex ($p<0.001$), alcohol use ($p=0.01$), continuous drug use ($p=0.03$), wearing glasses ($p=0.04$), history of dry eye ($p<0.001$), and presence of dry eye symptoms ($p<0.001$). There were also significant differences between the OSDI score categories in terms of sex ($p<0.001$), smoking status ($p=0.04$), wearing glasses ($p=0.03$), history of dry eye ($p<0.001$), and presence of dry eye symptoms. The only factor significantly correlated with OSDI score was daily duration of computer usage ($p=0.009$).

Conclusion: Our study showed that a substantial proportion of lecturers experience dry eye symptoms, and OSDI scores were associated with daily duration of computer use. Determining the factors associated with dry eye is important for the planning of preventive interventions.

Keywords: Dry eye, ocular surface disease index, OSDI, lecturers

Introduction

Dry eye is a multifactorial disease of the ocular surface characterized by loss of tear film homeostasis, in which neurosensory abnormalities play an etiological role.[1] Accompanied by ocular surface inflammation and damage, dry eye is an important disease that can impair quality of life. According to the DEWS II report, the reported prevalence of dry eye varies between 5% and 50%, with the frequency of signs being higher and more variable compared to symptoms.[2]

The development of dry eye involves two basic mechanisms, excessive tear evaporation and aqueous deficiency. Approximately 10% of patients have aqueous deficiency alone, while more than 80% have both aqueous deficiency and excessive evaporation due to meibomian gland dysfunction (MGD).[3] There are modifiable and nonmodifiable risk factors associated with these mechanisms of dry eye development. The main nonmodifiable risk factors are age, female sex, Asian race, Sjögren's syndrome, soft tissue diseases, MGD, androgen deficiency, and the use of certain drugs (e.g., isotretinoin), while modifiable risk factors include intensive computer use, contact lens use, and environmental factors (pollution, low humidity, sick building syndrome, etc.).[2,3,4] Prolonged use of computers and smartphones, which have become a part of daily life, are major factors contributing to

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the increased prevalence of dry eye.[5] Reduced blinking rate when looking at the screen, the type of screen used, and the angle and distance between the eyes and screen can pose a risk for dry eye. Eye fatigue and dry eye syndrome are especially common among individuals who are also exposed to these factors in the workplace.[5,6] The dry eye diagnosis flowchart begins with history-taking, risk factors are questioned in suspicious cases, and a screening test such as the Ocular Surface Disease Index (OSDI) or Dry Eye Questionnaire is applied. In light of these data, confirming the diagnosis by clinical examination is recommended in necessary cases.[1]

The literature includes previous studies conducted to determine the prevalence of dry eye in different occupational groups that use computers, but we found no study evaluating the prevalence of dry eye among academicians. The aim of the present study was to use the OSDI to determine the incidence of dry eye symptoms among university lecturers. This study is important because it demonstrates that academicians are also at risk of dry eye due to prolonged computer use, and it may facilitate the planning of preventive interventions.

Materials and Methods

This cross-sectional study was performed between November 15 and December 15, 2017. There were a total of 1615 lecturers working at Mersin University during the study period. Sample size was calculated as 244 people using Epi Info software for a 95% confidence interval and 5% sampling error with an estimated dry eye prevalence of 25%.[1] The numbers of lecturers were stratified according to school, and the schools to be included in the sample were determined by lottery method. Lecturers were selected using simple random sampling from lists obtained from the personnel department. Those with a history of contact lens use or ocular surgery and those using topical eye drops were excluded. The study data were collected after obtaining ethics committee approval (78017789/050.01.04/478270) and institutional permission. The study was carried out in accordance with the Declaration of Helsinki. Prior to data collection, participants were informed about the study and their consent was obtained. Data collection forms were given in person to those who agreed to participate in the study and collected the next day. Questionnaires were provided to a total of 284 lecturers. After eliminating those with missing data, the questionnaires of a total of 254 lecturers were included in the analysis. The participation rate was 89.4%.

Using a questionnaire developed based on a review of the literature, the lecturers were asked about their socio-demographic characteristics, cigarette/alcohol use, dry eye symptoms, chronic diseases, and medications used, as well as average time per day spent at work, using a computer, smartphone, or tablet, in air-conditioned environments, and sleeping (Figure 1).[5,6,7,8] Cigarette use was categorized based on the number of cigarettes smoked per day, and alcohol use was categorized by the number of glasses consumed per month. As there were no standards in the literature, daily computer and smartphone use was categorized by 8-hour and 4-hour intervals, respectively. Moreover, systemic drug use was questioned and categorized by drug class.

OSDI scores of 0-12 were classified as normal, 13-22 as mild, 23-32 as moderate, and 33-100 as severe ocular surface disease.[1] Participants with a score of 13 or higher and those with symptoms of dry eye were considered at risk and referred for eye examination.

Statistical Analysis

The data were analyzed using SPSS package software. Mean, standard deviation, minimum, and maximum were used for descriptive statistics. Chi-square test was used to analyze categorical variables, correlation analysis was used to evaluate relationships between scores, and mean scores were compared using Student's t-test and ANOVA. A p value <0.05 was considered significant.

Lecturer Dry Eye Questionnaire

1. **Your age:** ……..
2. **Your sex:** ( ) Male ( ) Female
3. **Do you smoke?** ( ) No ( ) Yes, …….. cigarettes/day for …….. years
4. **Do you drink alcohol?** ( ) No ( ) Yes, …….. glasses per day/week/month/year
5. **Do you have any chronic diseases?** ( ) No ( ) Yes, ……..……..
   Pregnancy: …….. / Menopause: ……..
6. **Do you use any medications regularly?** ( ) No ( ) Yes (please write all)
   ……..……..……..…..……...
   ……..……..……..…..…….....
7. **Do you wear glasses?** ( ) No ( ) Yes
8. **Have you ever seen a doctor for dry eye?** ( ) No ( ) Yes
9. **How often do you experience the following eye-related symptoms?**

	Never	Occasionally	Frequently	Constantly
Pain, ache				
Itching				
Dryness				
Stinging				
Burning				

10. **What are your working hours?** I work an average of …….. hours per day
11. **How many hours per day do you use a smartphone on average?** …….. hours
12. **How many hours per day do you use a computer on average?** …….. hours/day
13. **How many hours of sleep do you get a night on average?** …….. hours/day
14. **In an average day, how many hours do you spend in an air-conditioned environment?** …… hours/day

Figure 1. Dry eye questionnaire given to the lecturers

Results

Of the lecturers included in the study, 52.8% were male, 47.2% were female and the mean age was 39.29±9.41 years (Table 1). Mean time spent at work per day was 8.98±2.15 hours, while the durations of computer and smartphone use were 5.52±2.29 and 2.36±2.50 hours, respectively. The lecturers spent a mean of 7.15±0.99 hours per day in an air-conditioned environment, and their mean sleep duration was 6.85±0.96 hours (Table 2). Categorization of the lecturers based on OSDI score showed that 20.5% had mild, 15% had moderate, and 36.5% had severe ocular surface disease, 52.8% had symptoms of dry eye, and 72.4% experienced symptoms occasionally (Table 2).

Mean OSDI score varied depending on sex (p<0.001), alcohol use (p=0.01), long-term medication use (p=0.03), wearing glasses (p=0.04), previous diagnosis of dry eye (p<0.001), and presence of dry eye symptoms (p<0.001). However, mean OSDI score was not associated with daily activity durations (Table 3).

There were significant differences between OSDI score categories in terms of sex (p<0.001), cigarette use (p=0.04), wearing glasses (p=0.03), previous diagnosis of dry eye (p<0.001), and presence of dry eye symptoms (Table 4). The sex difference was between the normal and severe disease groups, and there was a significant correlation between duration of daily computer use and OSDI score (r=0.164, p=0.009).

Discussion

A review of the literature shows that some studies evaluating the prevalence of dry eye were based on either symptoms or clinical diagnostic tests, while other studies used both symptoms and clinical signs. Therefore, the outcomes of epidemiological studies vary.[2] The clinical diagnostic tests used for the diagnosis of dry eye do not always correlate with patients' symptoms, and the presence of symptoms is important for a preliminary diagnosis of dry eye. In light of this, the main objective of population studies is to identify high-risk individuals and evaluate them using advanced diagnostic methods. The DEWS II report recommended using the OSDI for screening purposes, as this index is considered valid and reliable.[2] Thus, participants in the present study were assessed with OSDI, and at-risk

Table 1. Socio-demographic, clinical, and lifestyle characteristics of the lecturers

n=254	**n**	**%**		**n**	**%**
Department			**Chronic disease**		
Faculty	202	79.5	No	212	83.5
Graduate School	31	12.2	Yes	42	16.5
Vocational School	21	8.3	**Regular medication use**		
Age			No	198	78.0
24-33	86	33.9	Yes	56	22
34-43	79	31.1	**Type of medication used**		
44-53	71	28.0	Antihypertensive	17	29.8
54-67	18	7.0	Hormone	11	19.3
Sex			Antidiabetics	9	15.8
Male	134	52.8	Antihistaminics	5	8.8
Female	120	47.2	Antidepressants	4	7.0
			Other	11	19.3
Pregnant (n=120)			**Menopause (n=120)**		
No	116	96.7	No	106	88.3
Yes	4	3.3	Yes	14	11.7
Smoker			**Alcohol use**		
No	197	77.6	No	131	51.6
Yes	57	22.4	Yes	123	48.4
Cigarette consumption (number/day)			**Alcohol consumption (glasses/month)**		
10 or fewer	26	10.2	1 or fewer	27	10.6
11-20	20	7.9	2-5	45	17.7
21 or more	2	0.8	6-10	25	9.8
No response	9	3.5	11 or more	11	5.9
			No response	11	4.3

*Some respondents used multiple drugs

Table 2. The dry eye symptoms, Ocular Surface Disease Index scores, and daily activity durations of lecturers

	n	%
Wears glasses		
No	117	46.1
Yes	137	53.9
History of dry eye		
No	204	80.3
Yes	50	19.7
Symptoms of dry eye		
Yes	134	52.8
No	120	47.2
Frequency of dry eye symptoms (n=134)		
Occasional	97	72.4
Frequent	35	26.1
Constant	2	1.5
Ocular Surface Disease Index		
Normal (0-12)	71	28.0
Mild (13-22)	52	20.5
Moderate (23-32)	38	15.0
Severe (33-100)	93	36.5
Duration of daily activities (hours/day)	**Minimum-maximum**	**Mean ± SD**
Working	4.00-18.00	8.98±2.15
Using mobile phone	0.00-17.00	2.36±2.50
Using computer	0.00-12.00	5.52±2.29
Sleeping	4.00-10.00	6.85±0.96
Being in an air-conditioned environment	0.00-24.00	7.15±0.99

SD: Standard deviation

Table 3. Distribution of mean Ocular Surface Disease Index scores according to demographic characteristics and daily activity durations

Variable		n	OSDI Mean ± SD	p
Sex	Female	120	20.76±17.13	**t=-5.45 <0.001**
	Male	134	33.80±20.96	
Smoker	No	197	26.63±20.42	t=-0.435 0.66
	Yes	57	27.95±19.03	
Alcohol use	No	131	30.24±20.80	**t=2.76 0.01**
	Yes	123	23.38±18.73	
Chronic disease	No	212	26.38±19.64	t=0.97 0.33
	Yes	42	29.66±22.26	
Regular medication use	No	198	25.46±19.41	**t=-2.19 0.03**
	Yes	56	32.09±21.71	
Wears glasses	No	117	24.13±20.26	**t=-2: 06 0.04**
	Yes	137	29.30±19.69	
History of dry eye	No	204	23.76±17.93	**t=-5.34 <0.001**
	Yes	50	39.83±23.23	
Dry eye symptoms	Yes	134	34.61±19.93	**t=-7.03 <0.001**
	No	120	18.34±16.52	
Pregnancy	No	116	33.81±20.63	t=0.05 0.96
	Yes	4	33.33±33.29	
Menopause	No	106	34.07±20.61	t=0.39 0.69
	Yes	14	31.72±24.19	
Computer use	0-8.0 hours	230	26.40±19.94	t=-1.25 0.21
	8.1-12.0 hours	24	31.81±21:22	
Mobile phone use	0-4.0 hours	227	25.79±19.67	F=2.38 0.07
	4.1-8.0 hours	15	34.74±21.81	
	8.1-12.0 hours	9	37.65±24.69	
	12.1 hours or more	3	40.97±10.70	
Time in air-conditioned environment	0-6.0 hours	117	23.91±19.79	F=1.87 0.135
	6.1-12.0 hours	110	29.42±19.88	
	12.1-18.0 hours	17	32.22±21.84	
	18.1-24.0 hours	10	25.61±20.25	
Sleep duration	3.0-6.0 hours	83	24.42±18.79	t=-1.39 0.167
	6.1-10 hours	171	28.14±20.63	
Work duration	4.0-7.0 hours	31	22.36±16.05	F=0.94 0.39
	7.1-11.0 hours	194	27.43±20.97	
	11.1-18.0 hours	29	28.36±17.60	

SD: Standard deviation, OSDI: Ocular Surface Disease Index

individuals with OSDI scores over 13 and dry eye symptoms were referred for clinical examination. However, the inability to follow up on the examination findings of the participants is a significant limitation of this study.

Dry eye reduces labor productivity due to its physical effects and time allocated to treatment, can cause psychiatric problems such as depression and anxiety, and can seriously impair sleep quality in some patients.[9,10,11,12] Therefore, it is important to not overlook the diagnosis, to closely follow patients and control modifiable risk factors, and arrange the necessary treatments.

Globally, the reported incidence of symptomatic or asymptomatic dry eye ranges between 5% and 50%.[2] Moreover, the frequency of dry eye varies among studies conducted in different geographical regions. In a study conducted in the USA, Farrand et al.[13] reported the frequency of dry eye among adults over 18 years of age as 6.8%. Unlike these studies, approximately half of the lecturers who participated in our survey reported having at least one symptom of dry eye and three-fourths of the respondents scored 13 or higher on the OSDI, indicating severe disease. These findings are important as an overall indicator that this group is at high risk. The primary factor associated with high risk among the lecturers was prolonged screen time.

Table 4. Distribution of demographic characteristics according to Ocular Surface Disease Index score categories					
Variable	**Normal 0-12 points**	**Mild 13-22 points**	**Moderate 23-32 points**	**Severe 33-100 points**	
Age (years)	n (%)	n (%)	n (%)	n (%)	p
24-33	16 (22.5)	21 (40.4)	9 (23.7)	40 (40.3)	0.06
34-43	30 (42.3)	15 (28.8)	13 (34.2)	21 (22.6)	
44-53	21 (29.6)	11 (21.2)	11 (28.9)	28 (30.1)	
54-67	4 (5.6)	5 (9.6)	5 (13.2)	4 (4.3)	
Sex					
Male	52 (73.2)**	25 (48.1)	24 (63.2)	33 (35.5)**	<0.001
Female	19 (26.8)**	27 (51.9)	14 (36.8)	60 (64.5)**	
Smoker					
No	58 (81.7)	44 (84.6)	23 (60.5)	72 (77.4)	0.04
Yes	13 (18.3)	8 (15.4)	15 (39.5)	21 (22.6)	
Alcohol use					
No	31 (43.7)	25 (48.1)	17 (44.7)	58 (62.4)	0.07
Yes	40 (56.3)	27 (51.9)	21 (55.3)	35 (37.6)	
Chronic disease					
No	58 (81.7)	46 (88.5)	34 (89.5)	74 (79.6)	0.37
Yes	13 (18.3)	6 (11.5)	4 (10.5)	19 (20.4)	
Regular medication use					
No	58 (81.7)	44 (84.6)	31 (81.6)	65 (69.9)	0.13
Yes	13 (18.3)	8 (15.4)	7 (18.4)	28 (30.1)	
Wears glasses					
No	39 (54.9)	29 (55.8)	12 (31.6)	37 (39.6)	0.03
Yes	32 (45.1)	23 (44.2)	26 (68.4)	56 (60.2)	
History of dry eye					
No	65 (91.5)	44 (84.6)	33 (86.8)	62 (66.7)	<0.001
Yes	6 (8.5)	8 (15.4)	5 (13.2)	31 (33.3)	
Dry eye symptoms					
No	52 (73.2)	28 (53.8)	19 (50.0)	21 (22.6)	<0.001
Yes	19 (26.8)	24 (46.2)	19 (50.0)	72 (77.4)	
Pregnancy (n=120)					
No	17 (89.5)	27 (100.0)	14 (100.0)	58 (96.7)	0.21
Yes	2 (10.5)	0 (0.0)	0 (0.0)	2 (3.3)	
Menopause (n=120)					
No	14 (73.7)	26 (96.3)	12 (85.7)	54 (90.0)	0.12
Yes	5 (26.3)	1 (3.7)	2 (14.3)	6 (10.0)	
**p<0.05					

A meta-analysis by Courtin et al.[14] showed that the prevalence of dry eye among individuals who used video display terminals (VDTs) for long periods was between 9.5% and 87.5%, with a mean prevalence of 49.5%. In another study by Kawashima et al.[15], the prevalence of dry eye among workers using VDTs for an average of six hours a day was 60%. Yazici et al.[16] reported that the incidence of dry eye among individuals who used VDTs for an average of 6.9 hours/day was 27.4%, while this rate was 15.4% among those used VDTs less than an hour per day. Similar to the studies by Kawashima et al.[15] and Yazici et al.[16], the average duration of VDT use in our study was nearly 6 hours and 52.8% of participants had symptoms of dry eye. This result seems compatible with the studies in the literature.

The relationship between daily duration of computer use and OSDI scores is known. Gümüş et al.[17] reported higher OSDI scores among those who used VDTs for an average of 8 hours

per day. Simavlı et al.[5] reported that OSDI scores indicated moderate to severe ocular surface disease in 64% of participants who used a computer for at least 5 hours per day and duration of computer use was positively correlated with OSDI score. Similar results were obtained in another study performed by Büyükbaş et al.[8], Yazici et al.[16] and Bayhan et al.[18] reported significantly higher OSDI scores in those with 7-8 hours of computer use daily compared to those with less than 1 hour per day. Although Akkaya et al.[19] observed similar OSDI scores in individuals with average daily computer use of 7 hours and less than 1 hour, they noted a difference in their tear breakup times and reported that dry eye developed in the heavier computer users due to excessive tear evaporation. In the current study, half of the participants had OSDI scores indicating moderate/severe ocular surface disease and a significant positive correlation was detected between OSDI score and daily duration of computer use.

In addition to an individual's daily habits, the physical environment in which they spend their time is important in terms of dry eye development. The DEWS II report stated that the risk of dry eye may increase with the length of time spent in an air-conditioned environment.[2] Iyer et al.[20] reported that blurred vision increased with the duration of exposure to air-conditioned environments and could be treated with the use of lubricants, and suggested that this was associated with dry eye. Büyükbaş et al.[8] found no correlation between air-conditioning and tear volume and function, but emphasized that their findings could not be generalized because the environments in which the measurements were taken were not standardized. In the present study, we observed no significant correlation between OSDI score and length of time spent in an air-conditioned environment. However, similar to the study by Büyükbaş et al.[8], the accuracy of this finding is uncertain because temperature and humidity of the environment were not measured. In spite of these results, considering the DEWS II report, modifying the physical environments where dry eye patients spend time is recommended. For studies conducted in this context, it is advised to assess the average daily temperature and humidity in workplaces.

Studies have reported that the incidence of dry eye is higher among women and increases with age.[2,14,15] In the study by Farrand et al.[13], the prevalence of dry eye was 2.7% in the 18-34 year age group and increased to 18.6% for those 75 or older, and the prevalence was twice as high in women than in men. In another study conducted among Japanese office workers, the prevalence of definite and probable dry eye among women was 76.5% and 60.2% among men. In the same study, it was found that the prevalence of dry eye among those aged 30 or over was 2.22 times higher than in those aged 30 or under.[10] Consistent with the literature, the prevalence of dry eye symptoms and OSDI scores were significantly higher among the women in our study than the men. However, there was no significant correlation between age and the prevalence of dry eye symptoms. This may be due to the relatively lower mean age of the participants enrolled to our study compared to other studies in the literature.

There is insufficient evidence on the correlation between dry eye and cigarette and alcohol use. Findings of the present study that cigarette use differed between OSDI score categories but OSDI symptom scores did not differ significantly according to cigarette use may be interpreted as evidence that cigarette use exacerbates dry eye symptoms but is not associated with the development of dry eye. However, further studies on this subject are required.

In the current study, mean OSDI score was significantly lower in participants with a history of alcohol use compared to those without. Although data regarding the effect of alcohol use on dry eye development are insufficient, there is evidence suggesting that alcohol increases the symptoms of dry eye.[2] In the current study, high OSDI scores among participants not using alcohol may be due to them discontinuing alcohol use due to the discomfort it causes, or may be related to the amount of alcohol consumed. Although a meta-analysis suggested that the prevalence of dry eye is 1.15 times higher in alcohol users compared to those who do not use alcohol, it was noted that there may be a false reduction in dry eye prevalence due to the development of peripheral neuropathy in heavy drinkers.[21] Only present alcohol use was evaluated in our study, and not enough data on lifelong alcohol use were given. The correlation between alcohol and dry eye should be evaluated in different studies.

In the current study, participants with a previous history of dry eye and chronic drug use had higher OSDI scores. Simavlı et al.[5] reported that there was no correlation between OSDI score and the use of glasses. In the present study, it was found that participants who wore glasses had higher OSDI scores than those who did not. An association between dry eye and contact lenses use has been reported in the literature. Lecturers who were actively using contact lenses were excluded from our study, and previous history of contact lens use was not questioned. This finding may stem from the presence of other risk factors independent of wearing glasses. Higher OSDI scores are expected among participants who were previously diagnosed with dry eye and did not receive appropriate and adequate treatment. Certain medications (beta-blockers, diuretics, hormone treatments, anxiolytics) have been reported among the risk factors for dry eye.[2] In the present study, the medications the participants reported using were consistent with the drugs identified in the literature, which we believe contributed to their dry eye symptoms.

Conclusion

In conclusion, a significant proportion of lecturers in our sample had dry eye symptoms, and OSDI scores were correlated with daily duration of computer use. This indicates that lecturers are prone to developing dry eye. However, new studies involving more centers and participants should be planned.

Ethics

Ethics Committee Approval: The study data were collected after obtaining Ethics Committee approval (78017789/050.01.04/478270) and Mersin University Faculty of Medicine permission.

Informed Consent: Received.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Sümbüle Köksoy Vayısoğlu, Emine Öncü, Design: Sümbüle Köksoy Vayısoğlu, Emine Öncü, Data Collection or Processing: Sümbüle Köksoy Vayısoğlu, Emine Öncü, Analysis or Interpretation: Sümbüle Köksoy Vayısoğlu, Emine Öncü, Özer Dursun, Erdem Dinç, Literature Search: Sümbüle Köksoy Vayısoğlu, Emine Öncü, Özer Dursun, Erdem Dinç, Writing: Sümbüle Köksoy Vayısoğlu, Erdem Dinç, Final Cheks: Emine Öncü, Özer Dursun.

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Original Article

Evaluation of Maculopathy in Patients Using Hydroxychloroquine

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Abstract

Objectives: To determine length of hydroxychloroquine use and cumulative dose and evaluate the ocular effects by 10-2 central visual field test, microperimetry (MP), color fundus photography, optical coherence tomography (OCT), and fundus autofluorescence (FAF) in hydroxychloroquine users.

Materials and Methods: Patients who used hydroxychloroquine continuously for at least 2 years for various connective tissue diseases were included in the study. A total of 300 eyes of 150 patients aged 19-78 years who were followed due to risk of developing hydroxychloroquine maculopathy in the İstanbul University İstanbul Faculty of Medicine Ophthalmology Department between the years 1995-2017 were evaluated. Best corrected visual acuity (BCVA), biomicroscopic, and fundoscopic examination were performed at all visits. MP, FAF, OCT, fundus photography, and central 10-2 visual field examinations were performed 3 times at 6-month intervals.

Results: The mean age of patients was 48.9±10.8 years; 141 (94%) patients were female and 9 (6%) were male. The mean duration of hydroxychloroquine use was 10.5±6.4 (2-30) years. Fifty-six patients had been using the drug for 5 years or less. The mean cumulative drug dose was 754.7±447.2 (146-1825) g. Mean BCVA was 0.02±0.08 LogMAR at all follow-up visits (p=0.999). Mean MP values at the first, second, and third examinations were 14.07±3.24 dB, 14.18±3.35 dB, and 14.54±2.79 dB, respectively (p>0.05). Mean central macular thickness was 221.9±19.8 µm at initial examination, 221.8±19.9 µm at the second visit, and 221.8±19.8 µm at the final visit (p=0.113). There was a weak negative correlation between age and MP values at all three visits (visit 1: p=0.003, r=-0.170; visit 2: p=0.001, r=-0.185, visit 3: p=0.011, r=-0.146). There was statistically significant relationship between MP values and hydroxychloroquine length of use and cumulative dose (p=0.027 and p=0.049, respectively). Duration of use was not associated with changes in 10/2 visual field (p=0.124). There were significant relationships between alterations in FAF and hydroxychloroquine length of use and cumulative dose (p=0.027 and p=0.049, respectively).

Conclusion: FAF alterations were significantly associated with duration of hydroxychloroquine use and cumulative dose. As objective methods are more reliable, examinations such as FAF can be recommended as auxiliary methods in the follow-up and early detection of toxic maculopathy.

Keywords: Hydroxychloroquine, maculopathy, cumulative, dose, fundus autofluorescence

Introduction

Chloroquine is an antimalarial drug with weak anti-inflammatory and immunomodulatory effects. Because it has fewer side effects and is better tolerated than other immunomodulatory drugs, it has been widely used for about 50 years for the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome, and other autoimmune diseases.[1]

Toxic retinopathy first appeared in the late 1950s with the introduction of chloroquine.[2,3] Today, hydroxychloroquine

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has replaced chloroquine in the treatment of connective tissue diseases due to its lower toxicity.[1] Although the therapeutic and toxic dose ranges of these two drugs differ, the toxic retinopathy they cause is similar.

Chloroquine and hydroxychloroquine are melanotropic and tend to accumulate in melanin-rich tissues such as the retinal pigment epithelium (RPE) and iris/ciliary body.[4] Bilateral, irreversible retinal damage in the advanced stages leads to permanent reduction in vision. In some patients, there is no visible lesion in the fundus despite visual field loss. While early changes can resolve upon drug discontinuation, changes in later stages may persist even if the drug is discontinued.[2] Therefore, early detection of the adverse effects of antimalarial drugs on the retina and immediate drug cessation are important.[2,4]

Many assessment methods are used to aid in the detection of retinal toxicity associated with the use of hydroxychloroquine. The Amsler chart, color vision examination, and central visual field testing are used in routine screening. In recent years, fundus autofluorescence (FAF), optical coherence tomography (OCT), microperimetry (MP), and electrophysiological tests have also been increasingly used in the follow-up of these patients.[3,5,6]

The aim of this study was to determine risk factors and evaluate the effectiveness of diagnostic methods such as color fundus photography, 10-2 central visual field testing, MP, OCT, and FAF in monitoring for the development of maculopathy in patients who have used hydroxychloroquine for at least 2 years.

Materials and Methods

The eyes of patients who had used hydroxychloroquine continuously for at least 2 years due to RA, SLE, Sjogren's syndrome, or other connective tissue diseases were included in the study. Those with a previously diagnosed anterior segment or retinal disease, glaucoma, or nystagmus, history of vitreoretinal surgery, media opacity preventing posterior segment imaging, and those who did not attend regular follow-up visits were excluded. All patients were informed in detail about the study and their written informed consent was obtained. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Age, sex, systemic comorbidities, history of other ocular pathology, and hydroxychloroquine length of use, daily dose, and cumulative dose were recorded for all patients included in the study. All patients included in the study underwent central 10-2 visual field testing, MP examination, and best corrected visual acuity (BCVA) measurement based on a Snellen chart at each of 3 follow-up examinations conducted at 6-month intervals. BCVA values were converted into LogMAR equivalents. After inducing pupil dilation, fundoscopic examination, fundus photography, OCT, and FAF were performed.

For fundus photography, a Zeiss FF 450 plus (Carl Zeiss Meditec AG, Jena) fundus camera was used to capture 50-degree macular images after pupil dilation. Visual field was assessed by automated static visual field testing using a Humphrey computerized visual field device (Carl Zeiss Meditec Inc., Dublin, CA) after applying refractive correction appropriate for the test distance determined before pupil dilation. Central visual field testing was done using a 10-2 threshold central test program, which scans a 10-degree area at intervals of 2 degrees. If the visual field results showed ≥33% false positive or false negative responses or loss of fixation, they were considered unreliable and the patient was invited back to repeat the test. Loss of more than 5 dB at three or more adjacent points or loss exceeding 10 dB at a single point was accepted as visual field deterioration. OCT was conducted using a Spectralis (Heidelberg Engineering, Heidelberg) device to acquire a horizontal scan with 49 sections passing through the macula. Central macular thickness was measured and the foveal, parafoveal, and perifoveal regions were evaluated for losses in the outer retinal layers, losses in the photoreceptor inner segment/outer segment (IS/OS) band, and RPE irregularity/loss. FAF images were also obtained with the Spectralis (Heidelberg Engineering, Heidelberg) device and were evaluated for anomalies in terms of hypo- and/or hyperautofluorescent points in the parafoveal and perifoveal areas. An OCT/SLO (scanning laser ophthalmoscope) (OTI, Toronto, Canada) device was used for microperimetric examination. During testing, stimulus intensity was changed between 0 dB and 20 dB by increments of 1 dB. A 4-2 strategy was implemented during the test, consisting of a total of 74 Goldmann III stimuli within a circular 20-degree area centered on the fovea. Scans with more than 20% false negative or false positive responses were considered unreliable. Average foveal sensitivity was evaluated in dB. The patients' data were analyzed to identify any changes that occurred during follow-up. The patients were also compared based on their total duration of use and cumulative dose of hydroxychloroquine.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) version 22.0 statistical software package was used for statistical analyses. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Between-group comparisons were made using Student's t-test and analysis of variation (ANOVA) for continuous variables, Friedman test was used to compare variables in repeated measures, Wilcoxon's signed rank test was used for pairwise comparisons of these variables, and Pearson and Spearman correlation tests were used to assess correlations between variables. A ROC curve analysis was performed to enable prediction of the toxic dose of hydroxychloroquine. The results were evaluated within a confidence interval of 95% based on a significance level of $p<0.05$.

Results

The study included 300 eyes of 150 patients, 141 (94%) female and 9 (6%) male, with a mean age of 48.9±10.79 (19-78) years. Forty-six (30.7%) of the patients were over the age of 60. Duration of hydroxychloroquine use ranged from 2 to

30 years, with a mean of 10.51±6.44 years. Only 56 (37.3%) patients had used the drug for was less than 5 years. The daily hydroxychloroquine dose used by the patients was 200 mg/day and the mean cumulative dose was 754.69±447.19 (146-1825) g.

Diagnosis was SLE in 73 patients (48.7%), RA in 41 (27.3%), Sjögren's syndrome in 23 (15.3%), SLE + Sjögren's syndrome in 4 (2.7%), scleroderma in 3 (2%), RA + Sjögren's syndrome in 3 (2%), sarcoidosis in 1 (0.7%), SLE + RA in 1 (0.7%), and Antiphospholipid syndrome in 1 (0.7%). No additional ocular pathology was detected in 83 (55.3%) of the patients, while 58 (38.7%) had dry eye, 7 (4.7%) had cataract, and 2 (1.3%) had amblyopia (Table 1).

Mean BCVA was 0.02±0.08 LogMAR at the start of the study and was unchanged at the second and final follow-up visits (p=0.999). Mean central macular thickness (CMT) was 221.9±19.8 µm at the first visit, 221.8±19.9 µm at the second visit, and 221.8±19.8 µm at the final visit (p=0.113).

Fundus photographs were normal in 85% (n=255) of the patients, while nonspecific (location and character inconsistent with antimalarial drug toxicity) RPE changes in the posterior pole were detected in 26 (8.7%) eyes.

Findings in FAF imaging at the start of the study were normal in 284 (94.7%) eyes, whereas parafoveal and/or perifoveal hyperautofluorescent + hypoautofluorescent spots in the macula were detected in 14 (4.7%) eyes and a bull's-eye appearance was observed in 2 (0.7%) eyes. The patient exhibiting the bull's-eye lesion had a history of chronic renal failure + chronic hepatitis B and had rapidly developed bull's-eye maculopathy within a period of 4 years. There was no significant difference between FAF values at the initial, 6-month, and 12-month examinations (p>0.05). New lesions or the enlargement of existing lesions were not observed. However, there was a significant relationship between FAF anomalies and total length of use and cumulative dose of hyrdoxychloroquine (p=0.027 and p=0.049, respectively).

Table 1. The patients' sex, additional ocular pathology, and systemic comorbidities

	n (eyes)	%
Sex		
Male	18	6.0
Female	282	94.0
Disease		
SLE	146	48.7
RA	82	27.3
Sjögren's syndrome	46	15.3
SLE + Sjögren's syndrome	8	2.7
Scleroderma	6	2.0
RA + Sjögren's syndrome	6	2.0
Sarcoidosis	2	0.7
SLE + RA	2	0.7
Antiphospholipid syndrome	2	0.7
Additional ocular pathology		
None	166	55.3
Dry eye	116	38.7
Cataract	14	4.7
Amblyopia	4	1.3

SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis

OCT revealed irregularity of the IS/OS band in 19 eyes (6.3%) at initial examination and in 18 eyes (6%) in the 6- and 12-month examinations. RPE irregularity was detected in 18 eyes (6%) at initial examination and in 17 eyes (5.7%) at 6 and 12 months. Bilateral changes were observed in 2 patients, while unilateral minimal sporadic atypical RPE irregularity was detected in 7 patients and were not attributed to hydroxychloroquine toxicity.

MP values did not vary over the course of follow-up and there was no significant difference between measurements (p=0.533). However, there were statistically significant but weak negative correlations between age and initial, second, and final MP sensitivity values (r=-0.170, p=0.003; r=-0.185, p=0.001; and r=-0.146, p=0.011, respectively). A significant relationship was detected between MP values and duration of hydroxychloroquine use and cumulative dose (p=0.027 and p=0.049, respectively).

During the course of the study, central 10-2 visual field test revealed defects in 20 patients in both eyes or in a single eye, and the test was repeated in patients whose scans were evaluated as having low reliability; hydroxylchloriquine was discontinued in these patients after consulting with the rheumatology or dermatology department they were attending for follow-up. The average age of these patients was 49±10.45 (34-67) years, their mean length of drug use 10.25±7.4 (2-30) years, and their mean cumulative dose was 720.9±472.8 (146-1825) g. Six of these 20 patients also showed a decrease in MP values. After discontinuing the medication, 11 patients showed resolution of the scotoma in final visual field testing. No lesions were detected on OCT, FAF, or fundus photography in these patients, and they were evaluated as premaculopathic.

Taken alone, changes in 10-2 central visual field were not associated with length of hydroxychloroquine use (p=0.124) or cumulative dose (p=0.234).

Based on patients with defects on FAF and computerized visual field testing and their cumulative drug doses, a ROC curve analysis was done to determine whether a cut-off value for cumulative drug dose could be identified to predict toxicity. A cumulative hydroxychloroquine dose over 425 g indicated higher risk of retinal toxicity with 91% sensitivity and 70% specificity. In addition, the incidence of retinal toxicity increased with duration of hydroxychloroquine use, being approximately 5% in those who used the drug for up to 5 years and 10% in those using for up to 10 years, whereas the incidence increased to 31% among those with over 20 years of use (Figures 1 and 2).

The patients were separated into two groups, those above and below the age of 50 years. When patients with FAF abnormalities and visual field defects were evaluated based on age, there was no significant difference between the two age groups (p=0.313).

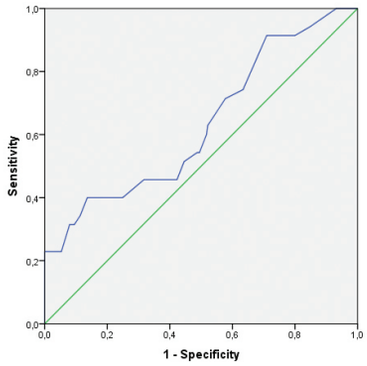

Figure 1. ROC curve analysis

Area under the curve: 0.632, SE: 0.053, p=0.11

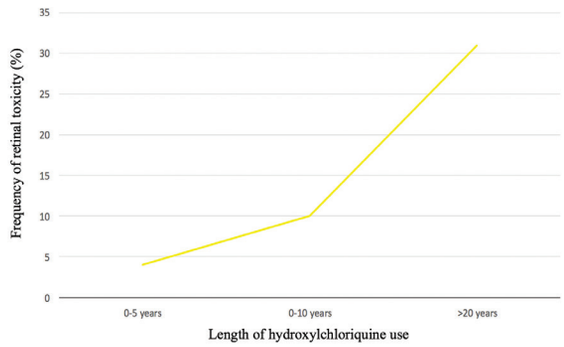

Figure 2. Relationship between length of hydroxychloroquine use and retinal toxicity

Discussion

FAF examination of the 300 eyes of the 150 patients included in our study showed that total duration of use and cumulative dose of hydroxychloroquine significantly altered the results of this test. According to ROC curve analysis of patients with defects in FAF and automated visual field testing based on amount and duration of drug use, a cumulative hydroxychloroquine dose over 425 grams increased the risk of retinal toxicity with 91% sensitivity and 70% specificity.

In 2002, the American Academy of Ophthalmology published a recommendation statement reporting that because the cumulative dose poses a more significant risk for hydroxychloroquine toxicity, it should not exceed 460 g.[7,8] This values is similar to the cumulative dose seen in our study.

Hydroxychloroquine is metabolized and eliminated by the liver and kidneys. Therefore, hydroxychloroquine clearance is reduced in those with liver and kidney disease, increasing the risk of toxicity.[6,9] This explains the rapid development (within 4 years) of bull's-eye maculopathy in our patient with history of chronic kidney disease and chronic hepatitis B. This case highlights the need for special attention to the close monitoring of patients at high risk for retinal toxicity caused by antimalarial drugs.

There are not many studies on the evaluation of hydroxychloroquine maculopathy with MP. Martínez-Costa et al.[10] evaluated 209 patients using hydroxychloroquine with MP and compared the results with those of a control group. They observed no significant difference between the two groups based on age or hydroxychloroquine use. In our study, there was a statistically significant relationship between MP values and the total duration of use and cumulative dose of hydroxychloroquine.

Kellner et al.[11] compared multifocal electroretinogram (mERG) and FAF imaging to detect early changes in patients who used hydroxychloroquine for over 1 year. Multifocal ERG revealed pericentral, central, and generalized amplitude reduction in all patients with FAF abnormalities and in 4 patients with normal FAF findings. The authors stated that early RPE changes due to antimalarial drug use could be detected accurately with FAF imaging. When mERG and FAF images were compared, it was shown that more retinal anomalies were detected by mERG. The authors recommended discontinuing the drug in patients with retinal anomalies on FAF and mERG.[11] In another study, Kellner et al.[12] performed mERG, FAF, and SD-OCT imaging in 8 patients using hydroxychloroquine. FAF revealed pericentral hyperautofluorescent areas and mERG showed pericentral amplitude reduction consistent with these areas.

Bergholz et al.[13] stated that normal FAF findings could not rule out toxic maculopathy and claimed that OCT and mERG were more sensitive in the early diagnosis of maculopathy.

Study Limitations

The limitations of our study are that baseline tests could not be performed on patients before they started using hydroxylchloroquine, that all patients were tested at the same time and at 6-month intervals regardless of when they started using the drug, and that more current testing methods like mERG could not be performed.

Conclusion

Our study demonstrates that care should be taken to ensure that patients at high risk for toxic maculopathy have detailed and regular ophthalmological follow-up. Normal findings in some parameters may be misleading. No matter how meticulously they are applied, methods based on predominantly psychophysical subjective phenomena should not be completely trusted. All kinds of visual field testing and methods based on self-reporting can yield widely varying results over time, even in the same individual. Our study shows that subjective methods should be used in combination with objective methods like FAF in patient follow-up and the early detection of toxic maculopathy. In addition, patients should be more carefully monitored for the development of retinopathy by tracking duration of drug use and approximate cumulative doses, and both patients and rheumatologists should be informed of the risk factors.

Ethics

Ethics Committee Approval: İstanbul University İstanbul Faculty of Medicine Ethics Commitee for Clinical Trials (number: 822 date: 30.06.2017).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nur Kır Mercül, Zafer Cebeci, Concept: Nur Kır Mercül, Zafer Cebeci, Design: Adem Uğurlu, Maise Aslanova, Zafer Cebeci, Nur Kır Mercül, Data Collection or Processing: Adem Uğurlu, Maise Aslanova, Analysis or Interpretation: Adem Uğurlu, Nur Kır Mercül, Literature Search: Maise Aslanova, Adem Uğurlu, Nur Kır Mercül, Zafer Cebeci, Writing: Adem Uğurlu, Zafer Cebeci, Maise Aslanova.

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Review

Current Approaches to Low Vision (Re)Habilitation

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Abstract

With increased life expectancy at birth and especially the rising incidence of age-related macular degeneration, low vision (re)habilitation is becoming more important today. Important factors to consider when presenting rehabilitation and treatment options to patients presenting to low vision centers include the diagnosis of the underlying disease, the patient's age, their existing visual functions (especially distance and near visual acuity), whether visual loss is central or peripheral, whether their disease is progressive or not, the patient's education level, and their expectations from us. Low vision patients must be guided to the right centers at the appropriate age, with appropriate indications, and with realistic expectations, and the rehabilitation process must be carried out as a multidisciplinary collaboration.

Keywords: Low vision, low vision (re)habilitation, Current approaches, LVA

Introduction

Visual impairment in low vision (re)habilitation may be central or peripheral vision loss or reduced vision due to media opacity. Among these groups, the most common diagnosis in patients presenting to low vision clinics is age-related macular degeneration (AMD), which causes central vision loss.[1,2,3,4,5,6,7]

The type of rehabilitation required by the low vision patient varies depending on their visual acuity, age, sociocultural status, and especially their diagnosis. The approach to a patient who has central scotoma due to AMD is quite different from the approach to a patient who has tunnel vision due to retinitis pigmentosa. Some cases can involve the coexistence of both central and peripheral vision loss, as in the patient with concurrent diabetic maculopathy and diabetic retinopathy who underwent argon laser treatment to the peripheral retina.

The aim of low vision rehabilitation is for patients to use their residual vision as effectively and efficiently as possible to enable them to live as self-sufficient, independent, and productive individuals, to make their lives easier, and enhance their quality of life. Low vision rehabilitation is not limited to simply recommending aids such as telescopic glasses or magnifying glasses. More important are training in the use these devices and the rehabilitation process. Rehabilitation is a collaborative effort involving many professional groups, such as vocational therapists, psychologists, and social workers, led by an ophthalmologist.

The Vision Research and Low Vision Rehabilitation Center of the Department of Ophthalmology of Ankara University Faculty of Medicine is the first vision rehabilitation center in Turkey to be established within the body of a university, and has facilitated the rehabilitation of 5500 individuals with low vision to date. The center also runs a thesis master's program on the subject for ophthalmologists.

What are the Current (Re)Habilitation/Treatment Methods for Low Vision?

- Field expansion prisms for peripheral visual field loss,
- Microperimetry,
- Telescopic intraocular lenses,

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- Telescopic contact lenses,
- Argus II epiretinal prosthesis (bionic eye),
- BrainPort,
- Stem cell therapy,
- Platelet-rich plasma (PRP) and electrical stimulation,
- Gene therapy.

Prisms for Field Expansion in Patients with Peripheral Vision Loss

Magnification is the main objective in the aid and rehabilitation of low vision patients. An object is enlarged and/or zoomed into. This method provides satisfactory results in the rehabilitation of patients with central visual field loss, especially for reading. However, in patients with peripheral vision loss (PVL), as in retinitis pigmentosa and glaucoma, magnification may further reduce existing vision instead of being helpful if the patient's visual field has become too narrow. In this case, telescopes that expand the visual field (reverse telescopes) can be used. However, this will decrease the patient's visual acuity. A 0.5X telescope increases a patient's visual field by 2 fold, but also decreases their visual acuity by half, and this method is therefore not highly preferred by patients.

The use of field expansion prisms is more appropriate than telescopes in patients with PVL. Peli's field expansion prisms can be used in patients who have homonymous hemianopsia due to neurological causes. In such cases, prisms are placed on the affected side with the base toward the side of the field defect (e.g., on the left eye with the base facing outward for left-sided homonymous hemianopsia). The prisms are monocular and are placed on the posterior surface of the spectacle lens in the upper and lower quadrant with a central opening between them, bases facing the defect. The central opening is 12 mm. There are horizontal and oblique varieties (Figure 1, oblique peli prism). These high-diopter (D) prisms expand the patient's visual field in the direction of the field defect. After the initial application of Fresnel prisms, the patient is given training exercises. If the patient is comfortable and adapted to the visual field expansion, the prisms are permanently attached to the lens.[8] These prisms are used at our center.

In a patient with left-sided hemianopsia, a 40Δ D horizontal prism placed base-out over the left eye provides a field expansion of 20 degrees, while a 40Δ D oblique prism with upper segment base out and down and lower segment base out and up provides a field expansion of 30 degrees.

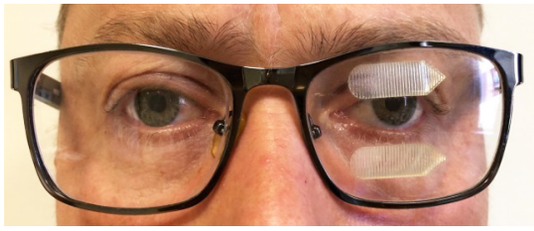

Figure 1. The ML Peli Prism/Multilens field expansion Peripheral Fresnel prism (from the archive of Prof. Şefay Aysun İdil, MD)

Patients with tunnel vision are also a challenging group in low vision rehabilitation. Especially in diseases like retinitis pigmentosa and choroideremia, patients can have PVL in all quadrants. In such cases, patients may be recommended a Trifield prism. Trifield prisms are monocular and placed base-out in the temporal quadrant and base-in in the nasal quadrant of the spectacle lens, and the other eye provides central vision. Three fields are available to the patient and field expansion is provided in all directions of view. Training is very important. The prisms are colored to reduce double vision and confusion.[9]

These field expansion prisms provide awareness of the absent field, but cannot treat visual field losses.[10]

Microperimetry

Since traditional visual field tests are based on the premise that the patient has central and stable fixation during the test, their reliability is reduced for patients with macular disease who have extrafoveal and/or unstable fixation and whose central vision is primarily affected. Standard visual field testing is also unable to detect small scotomas or provide reliable results in patients with very low vision. Therefore, traditional visual field tests remain inadequate for patients with macular disease. Obtaining reliable test results from macular sensitivity measurements is difficult in patients with advanced macular disease due to unstable fixation.[11,12] Microperimetric examination has been shown to enable assessment of retinal sensitivity as well as fixation characteristics, even in patients with severe visual impairment.[13]

Microperimetry is as valuable as standard visual field testing for demonstrating retinal sensitivity, and superior to standard visual field tests for demonstrating the early stages of vision loss.[14,15]

By superimposing visual field test results on fundus images, the microperimetry device allows morphological and functional examination to be performed together. It can also determine scotoma location and the location and stability of fixation in patients with macular disease. It can show retinal sensitivity in the target retinal area in decibels (dB) numerically, schematically, or on a color scale. A reference point is marked on an infrared image taken at the start of acquisition, and visual field results are superimposed on a color fundus image taken after the procedure to demonstrate the relationship between the scotoma and macular pathology. With the eye tracking system of the microperimetry device, even if the patient's fixation characteristics change over the course of follow-up, measurements in later scans can be made from the reference points marked in the initial reading, thus ensuring reliability of the results.

AMD is the leading cause of severe visual impairment and legal blindness in developed countries, especially in those aged 65 years and older. Central scotomas in the advanced stage cause central vision loss and limit capacity to perform daily activities, decreasing patients' quality of life. Impairment of visual function in AMD has been demonstrated in microperimetry as reduction in fixation stability, loss of central fixation, and loss of retinal sensitivity.[16] In these patients, the nonfunctional fovea is replaced

by eccentric locations in healthier retinal regions, called the preferred retinal locus (PRL). Fixation characteristics and the PRL are of great importance in patients with central scotomas in terms of ability to perform activities of daily living. This area can be detected by microperimetry. Determining scotoma size and location and knowing the location and stability of fixation are essential for low vision rehabilitation.

In some patients, the PRL is not in an appropriate place, and must be moved to a location that is more suitable for the patient and has higher retinal sensitivity. Using the biofeedback feature of the microperimetry device, this area can be relocated to healthier retinal regions with PRL shifting exercises (trained retinal locus, TRL).[17]

Approximately 60% of patients referred to low vision centers present due to difficulty reading. Fixation stability and location are among the factors that most affect a patient's vision quality and reading performance in particular. A study by Giacomelli et al.[18] including diabetic retinopathy and AMD patients with mild to moderate low vision (0.3-1.0 LogMAR) showed that fixation instability and loss of contrast sensitivity were the factors that most affected reading performance. In another study, a strong correlation was detected between fixation stability and reading speed.[19]

In this patient group, monitoring and rehabilitation carried out with the microperimetry device will improve reading performance and may thereby improve the patients' quality of life.

Microperimetry is used not only in patients with low vision due to AMD, but also for the rehabilitation of patients with low vision due to causes such as retinitis pigmentosa, Stargardt disease, diabetic retinopathy, and glaucoma. Microperimetry has also been reported to provide valuable information on macular function in cases of ABCA4-associated retinal degenerative diseases (Stargardt disease and cone-rod dystrophy) and night blindness.[20]

Parameters Evaluated by Microperimetry

PRL-high: The center of the points obtained while focusing on the fixation point in the first 10 seconds, before stimulus presentation.

PRL-low: The center of all fixation points calculated at the end of the testing period.

P1 and P2 are the proportions of fixation points within 1° and 2° areas, respectively.

Fixation stability: P1>75% indicates stable fixation, P1<75% and P2>75% indicate relatively stable fixation, and P2<75% indicates unstable fixation.

Fixation location: More than 50% of fixation points falling within the central standard fixation area is classified as predominantly central fixation, 25-50% within the central standard fixation area as weak central fixation, and less than 25% being within the central standard fixation area as predominantly eccentric fixation.

Macular integrity index (MII): Provides age-matched average data. Loss is considered normal if less than 40%, suspicious if 40-60%, and abnormal if above 60%.

Average retinal sensitivity: Results range from 0 dB to 36 dB. Values of 0-23 dB are considered normal, 23-25 dB suspicious, and 25-36 dB abnormal.

BCEA (bivariate contour ellipse area): Indicates the elliptical area of major and minor axes covered by fixational eye movements.

These parameters are shown in the device's output (Figure 2).

Interpretation of Microperimetry Results (Figure 2)

- Right eye, 91-year-old atrophic AMD patient,
- PRL is located in the superotemporal aspect of the atrophic site and retinal sensitivity is 11–17 dB in this region,
- Mode: Expert Test, Strategy: 4-2,
- Thirty-seven points, central 10°,
- Average sensitivity: 6.5 dB,
- MII: 100,
- Fixation Stability: Unstable (P1=20%, P2=62%),
- BCEA: 63% = 4.6°x3.7°, 13.1°^{2} BCEA: 95% = 7.9°x6.3°, 39.3°^{2},
- Fixation location (PRL): Superotemporal,
- Test duration: 6'13",
- Central scotoma, fixation is unstable and extrafoveal.

In macular diseases, microperimetry reveals reduced fixation stability, loss of central fixation, and loss of retinal sensitivity. In this example from a patient with AMD, it can be seen that there is a decrease in fixation stability (P1=20%, P2=62%), loss

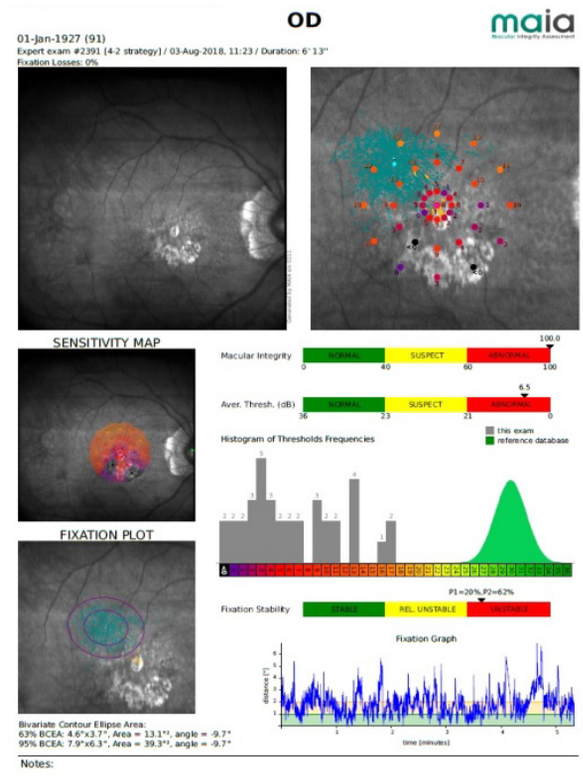

Figure 2. Sample microperimetry output (from the archive of Prof. Şefay Aysun İdil, MD)

OD: Right eye

of central fixation (superotemporal fixation), and severe loss of retinal sensitivity (average 6.5 dB).

Microperimetry TRL (trained retinal locus) mode: The microperimetry TRL mode improves the stability of the PRL formed by the patient if its location is favorable. The microperimetry readings of a macular disease patient with an unstable PRL (P1 8%, P2 35%) obtained before and after PRL training are shown in Figures 3 and 4. Comparison of the microperimetry readings demonstrate a remarkable increase in the stability of the patient's PRL (P1: 68%, P2: 99%, relatively stable PRL) (Figures 3 and 4).

If the location of the patient's PRL is unfavorable, it is shifted to an area more appropriate for the patient. The PRL Training mode helps patients with low vision, especially those with a central scotoma and unstable fixation, to better utilize their residual vision with auditory and visual biofeedback signals and eccentric viewing therapy. When choosing a new PRL, the area closest to the fovea and the patient's existing PRL and with the highest retinal sensitivity should be selected.

The purpose of using microperimetry in low vision rehabilitation is to help the low vision patient use their residual vision as efficiently as possible. In rehabilitation, the aim is to use the microperimetry device to enhance fixation stability if the patient's PRL is in a suitable location but is not stable enough or if the PRL is not in a suitable location, to identify and relocate the PRL to a locus with higher retinal sensitivity through TRL training sessions.

Telescopic Intraocular Lenses

With recent advances in technology and subsequently in intraocular lenses, attempts have been made to provide magnification in low vision patients with AMD via surgical methods.

To date, seven types of intraocular lenses have been used in patients with AMD. None of the current telescopic lenses are ideal, and only short-term results have been published. These include the implantable miniature telescope (IMT), IOL-VIP System, Lipshitz macular implant (LMI), sulcus-implanted Lipshitz macular implant (LMI-SI), Fresnel prism intraocular lens, iolAMD, and Scharioth Macula Lens. The magnification power of the lenses are as follows: 1.2X with the iolAMD lens, 2.5X with the IMT, 1.3X with the IOL-VIP system, 2.5X with the LMI, and 1X in the Fresnel prism intraocular lens.

The IMT is larger than the other implantable telescopic lenses and requires a large incision. There may be some difficulties in fundus imaging after implantation.[21]

The LMI and LMI-SI utilize lenses with two miniature mirrors in a Cassegrain telescope configuration and magnify the image reflected on the retina 2.5 times.[22] There may be difficulties in fundus imaging due to glare. While the LMI is implanted in the capsular bag, the LMI-SI can be implanted in the sulcus in pseudophakic patients.

The aim of Fresnel prism intraocular lenses is not magnification, but rather to shift the position of the scotoma.

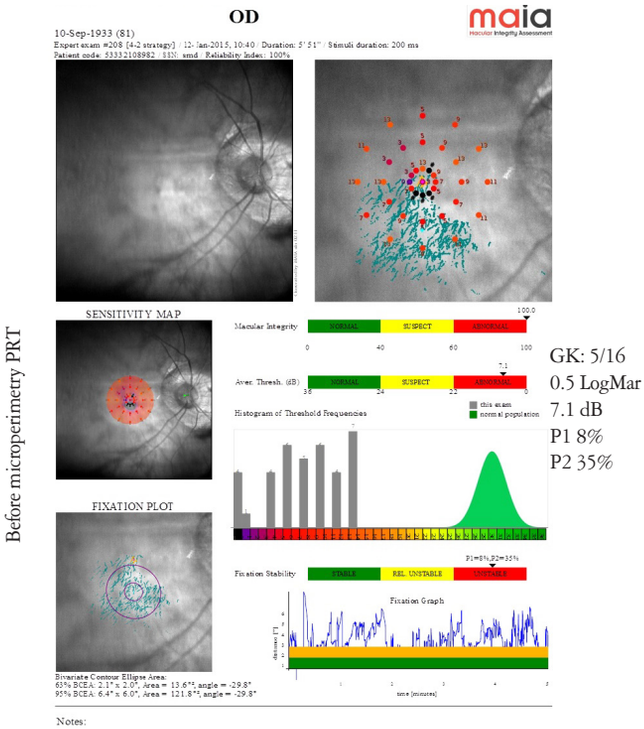

Figure 3. Microperimetry values of a patient with macular disease with unstable fixation before preferred retinal locus training (from the archive of Prof. Şefay Aysun İdil, MD)

OD: Right eye

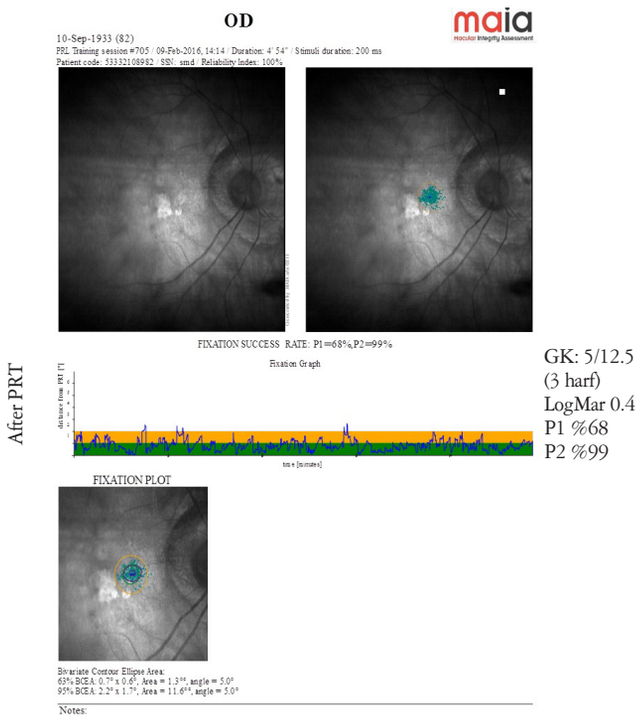

Figure 4. Microperimetry shows increased stability in the same patient after preferred retinal locus training (from the archive of Prof. Şefay Aysun İdil, MD)

OD: Right eye

A Fresnel prism is present on the rear surface of the optical part of the lens.[23]

The iolAMD is acrylic and aims to create a Galilean telescopic effect using -49 D and +63 D lenses. The disadvantage of this lens is that its power cannot be adjusted according to the axial length of the eye.[24]

IOL-VIP system telescopic intraocular lenses: The IOL-VIP system uses -66 D biconcave and +55 D biconvex lenses and provides 1.3X magnification. Simulation should be performed prior to surgery. With the IOL-VIP Revolution, two lenses are placed in the capsule with a tension ring to create a telescopic effect. At the same time, the intention is to shift the image from the diseased retina to the healthier retinal area via prismatic effect (about 10 prism D). The visual rehabilitation process is complex.[25]

Indications

- Atrophic AMD,
- Visual acuity lower than 0.3,
- Visual acuity is enhanced by a simulator,
- Patient willingness,
- After completion of a rehabilitation program (6 weeks).

Contraindications

- Exudative AMD,
- Progressive visual field loss, as in glaucoma, retinitis pigmentosa, and diabetic retinopathy,
- Presence of corneal guttata, endothelial cell count less than 1600,
- Microphthalmia,
- Vision is not enhanced by an external simulator,
- Young patients (power of accommodation is lost postoperatively).

Scharioth macula lens (SML) telescopic intraocular implant: These are used in pseudophakic patients. They are acrylic, and feature a +10.00 addition in the center of the lens (Figure 5).[26] The goal is to facilitate near reading. The SML enables near distance reading without distorting distance vision. The patient should be informed before the operation that they will have a short reading distance (10-15 cm) postoperatively. In a study presenting the 6-month results of 8 patients who received SML implants, it was reported that patients had difficulties with reading speed and reading distance that improved with reading exercises, and atrophic AMD progressed to wet AMD in 1 of the 8 patients at postoperative 3 months.[27]

Indications

- Pseudophakic patients over 55 years of age,
- Visual acuity ≤0.32,
- Visual acuity increases >3 rows when reading from a distance of 15 cm with a +6.00 addition preoperatively,
- Atrophic AMD (preferred) or stable exudative AMD,
- Monocular and should be implanted in the better seeing eye,
- Patient willingness,
- If the patient is a candidate for cataract surgery, implantation should be done 3 months after the surgery.

Contraindications

- Visual acuity <0.1,
- Exudative AMD, aphakia,
- Zonular weakness, pseudoexfoliation, or lens subluxation,
- Photopic pupil diameter <2.5 mm, narrow angle (< grade 2),
- Chronic uveitis, rubeosis iridis, retinal detachment, severe ocular trauma,
- Progressive glaucoma, extensive visual field defect,
- Conditions such as corneal diseases if the fundus cannot be clearly visualized.

Telescopic Contact Lenses

Research on telescopic contact lenses is also currently ongoing. A telescopic lens that allows shifting between normal and magnified vision with three-dimensional glasses and electrical polarization was first designed experimentally in 2013 by Tremblay et al.[28] based on an optomechanical eye model. It provided 2.8X magnification.

Designed as 1.6 mm-thick scleral contact lenses, corneal oxygenation was a problem with the long-term use of these telescopic contact lenses, and further research to solve this problem was recommended.[29] A later study mentions work on a scleral telescopic contact lens in which polarization is switched by blinking, thereby allowing a shift between normal and magnified vision (Figure 6).[30] This telescopic system is used in combination with battery-operated glasses that use LCD technology to complement the contact lens (Figure 7).[30]

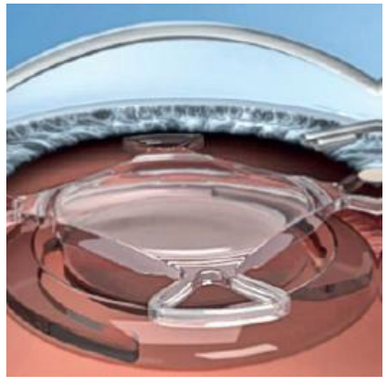

Figure 5. Scharioth macula lens (from the KMDT [Kesin Distribution and Foreign Trade Co. Ltd.] and Medicontur Turkey representative brochure)

Figure 6. Telescopic scleral contact lens

In addition to their psychosocial benefits, telescopic contact lenses have advantages such as lower weight and cost and wider visual field compared to conventional spectacle-mounted telescopes.[31]

Argus II Epiretinal Prosthesis (Bionic Eye)

This model is used in patients with severe photoreceptor cell loss. Although both retinitis pigmentosa and AMD patients experience photoreceptor cell loss, currently the primary indication for the Argus is advanced retinitis pigmentosa. It is the first and only retinal prosthesis approved by the Food and Drug Administration, and directly stimulates internal retinal cells. The Argus II delivers electrical stimulation to the retinal ganglion cells to produce spots of light called phosphenes. Patients learn to interpret these visual perceptions, thus providing some level of vision.[32,33] The vision provided is artificial vision. This surgery was performed with endoscopic assistance for the first time in Turkey and the world by Ozmert E and Demirel S[34] at Ankara University.

The Argus II epiretinal prosthesis has two parts, intraocular and extraocular. The extraocular part consists of a pair of glasses with a camera in the middle, a transmitter, and a video processing unit, and can be worn and removed independent of the intraocular part (Figure 8). The intraocular part consists of an array of 60 electrodes, receiver coil, electronics case, and scleral band (Figure 9). The electrode array is placed epiretinally on the macula through a vitrectomy and screwed to the retina (Figures 10 and 11).[35]

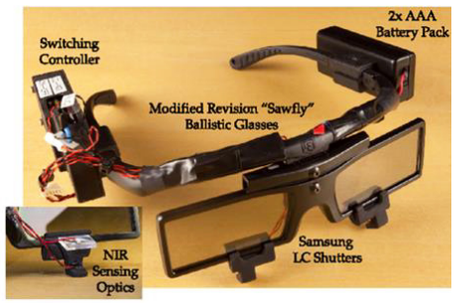

Figure 7. The glasses worn with telescopic scleral contact lenses

Figure 8. Argus II, extraocular part (http://secondsight.com/photos.html. Accessed on 08.18.2018)

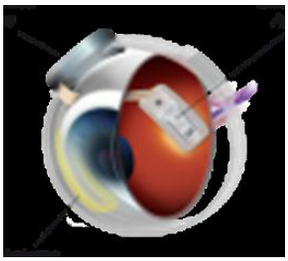

Figure 9. Argus II, intraocular part (http://secondsight.com/photos.html. Accessed on 08.18.2018)

How do Patients See with the Argus Epiretinal Prosthesis?

The camera in the glasses captures images and transmits the information to the VPU, which is worn at the waist. The VPU converts images into electronic signals which it sends to the transmitters on the glasses. Electronic signals are sent to the receiver in the eye. The data are transmitted to the electrode array implanted in the retina via a thin cable. The optic nerves then send these electrical signals to the brain. Currently the image is black and white and is artificial vision, but studies are being conducted on how to produce color vision.

Following implantation, patients require approximately 1 year of rehabilitative support to adapt to this new system of artificial vision. The Argus rehabilitation room in our center is specially designed for the adaptation exercises and training done during the rehabilitation period (Figures 12 and 13).

Indications for ARGUS II Epiretinal Prosthesis

- Age 25 years and older,
- Severe outer retinal cell destruction (late stage retinitis pigmentosa, geographic atrophy),
- Axial length 20-26 mm,
- Has light perception and pupillary light reflex in camera flash test,
- Has vision experience, has previously seen shapes,

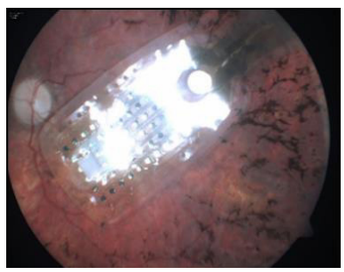

Figure 10. The electrode array of the Argus epiretinal prosthesis when implanted on the macula (from the archive of Prof. Emin Özmert, MD)

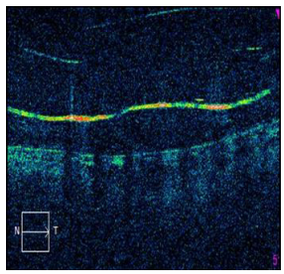

Figure 11. Appearance of shadows of the electrodes implanted on the macula in optical coherence tomography (from the archive of Prof. Emin Özmert, MD)

Figure 12. Argus rehabilitation room (from the Vision Research and Low Vision Rehabilitation Center)

Figure 13. Illuminated path designed for the walking exercises of patients undergoing Argus rehabilitation (from the Vision Research and Low Vision Rehabilitation Center)

- Has realistic expectations,
- Patient and relative compliance with rehabilitation.

Contraindications for ARGUS II Epiretinal Prosthesis

- Optic nerve disease,
- Thin conjunctiva (failed surgery),
- Severe ocular pruritus,
- Inability to receive general anesthesia,
- Severe macular edema, macular scar, severe retinal thinning, posterior staphyloma,
- Severe strabismus and nystagmus,
- Neurologic and psychiatric illnesses.

In the Functional Low-Vision Observer Rated Assessment Study, 26 patients that underwent Argus II Retinal Prosthesis implantation were monitored for 18-44 months (mean 36 months) and a significant increase was reported in the rate of their completion of vision-related tasks when the device was on compared to when it was off.[36]

The Argus II Epiretinal prosthesis has been found to provide the following benefits: seeing capital letters, reading short words (best recorded visual acuity: 20/1262), discerning the direction of movements, discerning orientation and being able to move, increased mobility, ability to act independently, and increased quality of life.[35]

BrainPort

This device also provides artificial vision, and the patient must have previously experienced vision. In the BrainPort, a 2.5-cm camera mounted on glasses sends the image it records to a handheld remote-control unit and the image is converted into a low-resolution black and white photo. This photo is then transmitted to the tongue through a thin tube containing hundreds of electrodes and the user can feel the shape and movement projected on their tongue. By visualizing the sensation on the tongue, the person learns to see the photograph (Figure 14).[37,38]

Figure 14. BrainPort usage (Courtesy of Wicab, Inc.)

Stem Cell Therapy in Low Vision Patients

Stem cells are progenitor cells, meaning they possess the abilities of self-renewal and differentiation into mature cells. Stem cell therapy aims to replace diseased retinal cells with new retinal cells that grow from stem cells. Stems cells have properties and functions such as high proliferative capacity, immune system regulation, secretion of neurotrophic factors, and an antiapoptotic effect on neurons. Stem cell therapy is promising for degenerative diseases of the retina such as retinitis pigmentosa, Stargardt macular dystrophy, and AMD. The outcomes of phase I and II trials have been quite successful, and no systemic side effects have been observed.[39]

Embryonic stem cells are pluripotent, but their use is unethical and prohibited by the health ministry in Turkey. Adult mesenchymal stem cells are most commonly used in patients with low vision. These cells are multipotent. Adipose tissue and bone marrow are the most preferred sources. In addition, induced pluripotent stem cells, umbilical cord blood stem cells, and amniotic fluid stem cells also have areas of application in various diseases.[40]

In patients with low vision, stem cell therapy can be used in patients over 18 years of age who have a degenerative retinal disease and is applied to the poorer seeing eye. Subretinal mesenchymal stem cell injection is performed with total vitrectomy. The procedure can be repeated when the stem cells lose functionality. The purpose is to preserve the visual field and prevent disease progression. It is not necessary to wait for a decrease in visual acuity; this treatment can be applied if visual field loss has begun. There are currently some uncertainties regarding this treatment. Controversial issues include which type of stem cell to use, at what dose, through what administration route, and at what stage of disease. In a study by Oner et al.[41] including 11 patients with retinitis pigmentosa, only 1 of which showed improvement in electroretinogram results and significant improvement in visual acuity and visual field, the authors reported that the procedure may cause ocular complications and must be performed very carefully.

The vitreoretinal complications seen after intravitreal and subretinal stem cell injections were reported to occur less frequently with suprachoroidal administration.[42]

Platelet-Rich Plasma Therapy and Electrical Stimulation in Patients with Low Vision

In PRP therapy, blood from the patient is centrifuged to obtain a platelet concentration 2-4 times that in the blood. PRP therapy is an autologous method. Injection enables growth factors produced by platelets (NGF, BDNF, BFGF, IL-6) to maintain the viability of the retinal photoreceptor cells. The goal is to maintain the viability of dormant cells. Treatment aims to slow disease progression, expand the visual field, and increase visual acuity. In a study of 71 eyes of 48 patients with retinitis pigmentosa, of which 49 eyes received autologous PRP via sub-Tenon's injection, statistically significant improvements in multifocal electroretinogram values and microperimetry readings were reported and positive visual outcomes were also observed. The patients were monitored for 1 year. Long-term outcomes are unknown.[43] Further studies with longer follow-up periods are needed to determine the duration of effect and optimal frequency of administration.

Transcorneal Electrical Stimulation - Okuvision

Low-dose electrical stimulation is delivered to retinal cells. It can be performed in conjunction with PRP injection. Treatment aims to protect retinal cells and prevent further vision loss with the release of neurotrophic growth factors. It is performed transcorneally. An electrode is placed in the cornea (Figure 15). The procedure lasts 30 minutes, with sessions performed once a week for 6-8 weeks. Some problems may be arise due to contact with the cornea. Bittner AK and Segeer K[44] reported significant improvements in visual acuity, rapid contrast sensitivity function, and/or Goldmann visual field test results in 4 of 7 patients in the retinitis pigmentosa patient group who underwent 6 weeks of transcorneal electrical stimulation (TES) therapy. Three of these 4 patients were monitored for 29-35 months and no regression in the achieved improvements was observed.

Transcranial Electromagnetic Stimulation - Magnovision

The aim is to stop the apoptosis cascade and reduce cell death. Magnovision uses magnetic stimulation; however, unlike the electrical stimulation in TES, the stimulus is not applied to the retina locally, but is delivered centrally. While TES involves contact with the cornea, Magnovision does not. It can be performed in conjunction with PRP injection. The goal of Magnovision combined with PRP therapy is revival of dormant photoreceptors and expansion of the visual field.

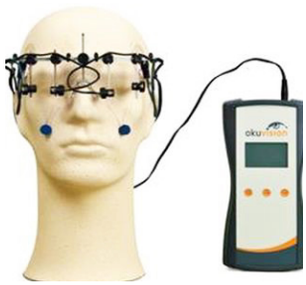

Figure 15. Implementation of transcorneal electrical stimulation - okuvision (https://www.retina-implant.de/en/. Accessed on 08.18.2018. Reproduced with permission from Retina Implant AG)

Gene Therapy in Low Vision Patients

This treatment modality involves a genome that encodes a functional product that exerts its effect in another cell, with or without being added to that cell's genome. The genes are carried by vectors. Adenoviruses and lentiviruses are most commonly used for this purpose. It is administered as a subretinal injection. It can be used for treating autosomal recessive and X-linked diseases. Currently, the biggest drawbacks to this method are the large number of genes that cause disease and the mutations that have occurred within the same gene.

More than 220 genes have been identified in retinal diseases. More than 160 genes and different mutations in the same gene have been identified in retinitis pigmentosa. The most studied diseases in terms of gene therapy are Leber's congenital amaurosis and retinitis pigmentosa. The *RPE65* gene is the most studied.[45] The roles of the *CNGA3* and *CNGB3* genes in achromatopsia and of the *ABCA4* gene in Stargardt disease are being investigated.[46]

LUXTURNA™-Spark (voretigene neparvovec-rzyl) is the only drug approved by the Food and Drug Administration for use in gene therapy. It was approved for use in the treatment of hereditary retinal diseases.[47] It can be administered as a subretinal injection. Its use is not permitted in those under the age of 1 year or over the age of 65 years.

Requirements for implementing gene therapy include a significant decrease in vision, compatibility of the target gene with the vector capacity, completed human trials involving the target gene, and the presence of intact retinal cells that can be repaired with gene therapy.

Conclusion

There are many exciting and promising developments regarding the rehabilitation and treatment of patients with low vision. However, a patient's age, diagnosis, education level, and sociocultural status should be considered when presenting rehabilitation and treatment options, and patients with low vision should be guided at the right age, to the right centers, and most importantly, with realistic expectations.

Ethic

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Deniz Altınbay, Şefay Aysun İdil, Concept: Deniz Altınbay, Design: Şefay Aysun İdil, Data Collection or Processing: Deniz Altınbay, Şefay Aysun İdil, Analysis or Interpretation: Deniz Altınbay, Şefay Aysun İdil, Literature Search: Deniz Altınbay, Şefay Aysun İdil, Writing: Deniz Altınbay, Şefay Aysun İdil.

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Case Report

A Rare Complication of Oropharyngeal Tularemia: Dacryocystitis

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Abstract

Tularemia is a zoonotic disease caused by *Francisella tularensis*, a highly virulent gram-negative coccobacillus. Oropharyngeal tularemia, one of the clinical subtypes, is the most common clinical form of the disease in Eastern Europe, including Turkey. This clinical form affects mostly the head and neck region and the most common complaints of patients are mass in the neck, sore throat, and fever. This form of tularemia may be confused with tonsillitis, pharyngitis, or cervical lymphadenitis caused by other microbial agents due to the nonspecific clinical and laboratory features. In this study, we present a patient with nasolacrimal duct obstruction and dacryocystitis caused by oropharyngeal tularemia.

Keywords: Tularemia, nasolacrimal duct obstruction, dacryocystitis

Introduction

Tularemia is a zoonotic infection caused by *Francisella tularensis*, a highly virulent gram-negative coccobacillus. *F. tularensis* is endemic in the northern hemisphere, especially in Russia, Kazakhstan, Turkmenistan, some states of the USA, Canada, and some European countries such as Finland and Sweden.[1] Due to its high virulence, it periodically causes epidemics in Turkey. Rodents such as rabbits, beavers, rats, and mice and mammals such as raccoons, cats, dogs, and cattle are the primary reservoirs of infection for humans.[2,3] Studies have shown that the most common sources of transmission to humans are rodents such as field mice and house mice.[4,5] Mosquitoes, horseflies, fleas, and lice act as vectors of *F. tularensis*. Farmers, hunters, and forest workers in endemic areas are groups at risk of infection. In humans, the infection usually occurs after contact with infected animals or through the bites of arthropod vectors. Other routes of transmission include contact with the body fluids of an infected person, consumption of contaminated food or drink, inhalation of contaminated aerosols, contact of these fluids or aerosols with the eye, or rubbing the eyes with contaminated fingers.[6]

Tularemia has six clinical subtypes: ulceroglandular, glandular, pneumonic, typhoidal, oculoglandular, and oropharyngeal. The oropharyngeal form is the most common clinical presentation in the Eastern European region, including Turkey.[7] In this form, the disease is localized to the head and neck area and manifests with signs such as sore throat, fever, and neck mass.[8,9]

In this study, we discuss a patient who developed nasolacrimal duct obstruction and dacryocystitis associated with oropharyngeal tularemia.

Case Report

A 33-year-old man presented to our clinic with complaints of watering, redness, and purulent discharge in the right eye. The patient reported seeing a physician a year earlier in Georgia due to fatigue, nausea, vomiting, and diarrhea. After his diarrhea and vomiting had resolved, he had swelling of the lymph nodes on the right side of the neck. After returning to Turkey for treatment, he had received cephalosporin and penicillin for suspected pharyngitis. When night sweating and weight loss were added to his complaints, he had presented to another hospital where

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his treatment was changed to amoxicillin-clavulanic acid 1 g 3 times a day and ciprofloxacin 750 mg twice a day, and incisional drainage was performed on the lymph nodes of his neck. When his symptoms failed to resolve completely, he had presented to the department of infectious diseases of a different university hospital. Serum agglutination test was positive for *F. tularensis* at a titer of 1/1280 and he was prescribed streptomycin 1 g per day for 9 days followed by 1 g twice a day for 5 days for a total of 14 days, followed by doxycycline 100 mg twice a day for 1 week. Ultrasound examination of the neck had revealed multiple abscesses in the right submandibular region and pathological lymph nodes including multiple calcifications in the right cervical chain, while magnetic resonance imaging of the neck showed retropharyngeal abscess narrowing right nasopharynx and oropharynx and submandibular lymphadenopathies (LAP) including cystic and necrotic areas (Figure 1). He reported that the LAPs had resolved after a few months with no recurrence, but complaints of watering, swelling in the lacrimal sac area, hyperemia, and pain in the right eye developed a few weeks later. The patient presented to our clinic with recurrent swelling around the lacrimal sac, hyperemia, and purulent discharge.

On examination his best corrected visual acuity was 20/20 in both eyes. Intraocular pressure measured by automatic tono-pneumometry was 15 mmHg in each eye. On slit-lamp examination, epiphora was noted in the right eye and the left eye was normal. There was swelling in the area of the right lacrimal sac (Figure 2). Fundus examination was normal in both eyes. In nasolacrimal lavage, the patient's right nasolacrimal duct was occluded and the common canaliculus was patent. Discharge of purulent material from the right lower punctum was noted after lavage. A sample of the purulent discharge was collected and sent to the microbiology laboratory for culturing and the patient was started on oral amoxicillin-clavulanic acid 1 g twice a day and topical ciprofloxacin drops 4 times a day. Antibiotherapy was discontinued because the culture was negative. Consultation from the otorhinolaryngology (ENT) department was requested to rule out any intranasal pathology. The patient underwent ENT examination, followed by nasal endoscopic examination. In addition, to rule out intranasal pathologies that may present an obstacle to surgery, the paranasal sinuses were examined using computed tomography. No intranasal pathologies were detected in ENT evaluation. Dacryocystorhinostomy surgery was recommended to the patient, but he refused the procedure.

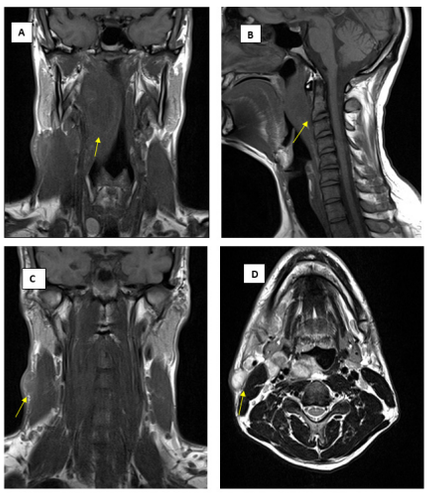

Figure 1. A,B) Magnetic resonance images of the retropharyngeal abscess occluding the right oropharynx (yellow arrows). C,D) Magnetic resonance images of lymphadenopathies including cystic and necrotic areas in the right submandibular region (yellow arrows)

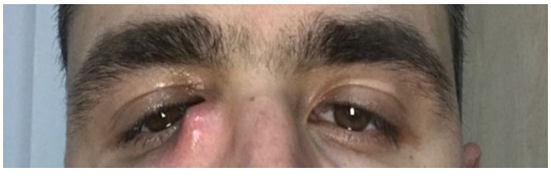

Figure 2. Clinical presentation of the patient with abscess in the nasolacrimal area

Discussion

F. tularensis causes infections in humans after entering the body via direct inoculation to the skin or mucous membrane, inhalation of the bacteria, or consumption of contaminated water or food. Its incubation period varies between 1 and 14 days, though it usually appears 3-6 days after exposure. Although the symptoms of tularemia vary depending on the area of involvement, onset is usually characterized by fever, flu-like symptoms, and cervical LAP.[10,11]

Because *F. tularensis* is very small and stains weakly in Gram staining, direct detection in patient samples has no diagnostic value. A rich medium is required for its growth, and its high virulence and ability to spread via inhalation pose a risk for laboratory personnel. Therefore, routine isolation of the bacteria is not recommended.[12] Microagglutination assay is a valuable serological diagnostic method, with a single titer ≥1/160 or rising titer being diagnostic. Antibodies against *F. tularensis* can be detected using tube agglutination, microagglutination, hemagglutination, and enzyme linked immunosorbent assay methods.[13] Due to the difficulty of growing *F. tularensis* in culture and the late reporting of serological test results, research is ongoing to develop rapid diagnostic methods. Detection of antigens in urine, direct fluorescent antibody staining, and polymerase chain reaction (PCR) are some of these methods. The most commonly used and most advantageous of these methods is PCR.[12,13]

Ulceroglandular disease, which is the most common subtype of tularemia, is usually transmitted by tick bite.[10] After an incubation period of 3-6 days, it manifests with signs such as flu-like symptoms, fever, headache, and fatigue. Local proliferation of the bacteria at the bite leads to the formation of papules and skin ulcers. The bacteria spread via the lymph system from the ulcer at the site of the tick bite to local lymph nodes.[11,14] Similarly, the glandular form is also transmitted via arthropod vector but is not characterized by skin ulcers. Pneumonic disease is the most severe clinical form, presenting with symptoms such as dry cough, chest pain, and difficulty breathing.[15] Typhoidal

disease, which is a very rare form, manifests with fever, vomiting, diarrhea, splenomegaly, and hepatomegaly.[11]

In oculoglandular disease, a relatively rare form, the infectious agent is usually transmitted via rubbing the eyes with contaminated fingers or by contact of contaminated aerosols and fluids with the eye.[16] Clinically, oculoglandular tularemia usually manifests as unilateral conjunctivitis and painful LAP. Oculoglandular disease accounts for approximately 3-5% of all cases. It can involve the eyes, eyelids, and more rarely, the lacrimal system.[16,17,18] Lacrimal system involvement in oculoglandular tularemia was previously reported as purulent conjunctivitis and dacryocystitis in a 27-year-old woman who was 18 weeks pregnant.[19] Considering the patient's pregnancy, the disease was treated with topical gentamicin and oral amoxicillin-clavulanic acid therapy for 2 weeks, and clinical cure was achieved. The dacryocystitis was treated with surgical drainage, which was repeated a few weeks later due to relapse. After resolution of acute dacryocystitis, no further relapse was observed.

Oropharyngeal disease is the most common clinical form of the disease in the Eastern European region, including Turkey.[8] This clinical form is localized to the head and neck area and manifests with signs such as sore throat, fever, and neck mass. The source of infection is usually contaminated water and food. Due to the nonspecific clinical and laboratory findings, it can be misdiagnosed as tonsillitis, pharyngitis, or cervical lymphadenitis associated with other microbial agents. In oropharyngeal tularemia, neutrophilic and granulomatous infiltration in the cervical lymph nodes leads to necrotizing lymphadenitis and abscess formation. The lymph nodes are filled with pus and may spontaneously rupture and drain to the skin. This suppuration may also continue after the initiation of antibiotic therapy. Bacteria can also be disseminated via the bloodstream to the spleen, liver, lungs, kidneys, colon, and skeletal muscles.[9,20]

The macrophage cell-mediated immune response plays a major role in the pathogenicity of *F. tularensis*, which is a facultative intracellular bacterium. When macrophages attempt to digest the bacterium, it escapes from the phagosome into the cytoplasm. Continuing to proliferate in the cytoplasm, it induces macrophage cell death, which enables the infection to spread.[21] Similar mechanisms also apply to neutrophils. After phagocytosis, *F. tularensis* suppresses oxidative pathways by inhibiting nicotinamide adenine dinucleotide phosphate oxidase. The natural immune response that occurs as an early response to infection causes the release of proinflammatory cytokines such as interleukin 1, interleukin beta, and interleukin 18 from macrophages in the cytoplasm, which in turn induce caspase-1-dependent cell death. In this way, type-1 interferon is secreted. With CD4+ and CD8+ T-cell activation in response to protein antigens, macrophages can kill the bacteria via phagocytosis with the help of tumor necrosis factor-α, γ-interferon, and reactive oxygen species.[22,23] Phenotypic characteristics of the bacteria such as lipopolysaccharides, type-4 pili, capsule, acid phosphatase enzyme, and siderophores are among its virulence factors.[24]

Paulsen et al.[25] reported that inflammation in the nasolacrimal duct can lead to the development of dacriostenosis. Inflammation triggers edema in the mucous membranes, remodeling of the helical structure of connective tissue fibrils, and disruption of subepithelial cavernous body function due to reactive hyperemia, resulting in temporary occlusion of the lacrimal system. Recurrent dacryocystitis episodes associated with this occlusion can affect the epithelial and subepithelial tissues, and a fibrous occlusion may develop in the lumen of the nasolacrimal duct.[25]

Lingberg and McCormick[26] showed that inflammatory infiltrates and edema in the nasolacrimal duct lead to the development of chronic dacryocystitis. They reported that with prolonged inflammation in the nasolacrimal duct, the inflammatory process is replaced by fibrosis in the mid-term, and fibrous occlusion forms in the nasolacrimal duct in the long term.

Another recent finding about acquired nasolacrimal duct occlusion is the mucosa-associated lymphoid tissue surrounding the lacrimal sac and duct. It is believed that these local lymphoid structures, called lacrimal drainage-associated lymphoid tissue, are involved in immune modulation and that damage to these structures may lead to the development of nasolacrimal duct occlusion.[27,28]

We believe that in our patient, oropharyngeal tularemia infection spread to the mucosa-associated lymphoid tissue around the nasolacrimal duct via the lymphatic system through the cervical lymph nodes or via local adjacency caused by inflammation in the area, and this inflammation led to the development of edema in the mucous membranes and later to fibrosis development in the nasolacrimal duct. Occlusion of the lacrimal system due to fibrosis manifested with recurrent episodes of dacryocystitis.

In conclusion, any infectious or inflammatory event within the nasal cavity may lead to the development of nasolacrimal duct occlusion, especially in individuals with predisposition due to anatomic factors. Nasolacrimal duct occlusion and associated dacryocystitis may develop as a rare complication of oropharyngeal tularemia.

Ethics

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Melek Banu Hoşal, Helin Ceren Köse, Concept: Melek Banu Hoşal, Helin Ceren Köse, Design: Melek Banu Hoşal, Helin Ceren Köse, Data Collection or Processing: Helin Ceren Köse, Analysis or Interpretation: Helin Ceren Köse, Literature Search: Helin Ceren Köse, Writing: Helin Ceren Köse.

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

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Case Report

Breast Carcinoma Metastasis to the Medial Rectus Muscle: Case Report

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Abstract

A 63-year-old woman with metastatic breast carcinoma presented to the ophthalmology clinic with diplopia and right abduction deficit. Magnetic resonance imaging showed isolated enlargement of the right medial rectus muscle. Biopsy of the enlarged muscle revealed metastasis of breast carcinoma. Ocular motility deficit in a patient with breast carcinoma should raise suspicion of metastasis to the orbit involving the extraocular muscles. Orbital imaging and biopsy are necessary for diagnosis and appropriate treatment.

Keywords: Breast carcinoma, extraocular muscle, medial rectus muscle, orbital metastasis

Introduction

The orbit is an unusual site for metastasis, being involved in 2 to 3% of cancer patients.[1] The most prevalent primary tumor metastasizing to the orbit is breast carcinoma, which accounts for 28.5-58.8% of all orbital metastases.[2,3,4]

Orbital metastasis can present as the initial manifestation of breast carcinoma; however, in most cases, there is a previous history of breast cancer that has been treated, or an orbital mass occurs in a patient with active malignancy affecting multiple organs.[1] Orbital breast carcinoma metastases may localize within orbital fat, bone, or extraocular muscles. Scirrhous infiltration of the orbit can also occur; resulting in enophthalmos.[5] Definite diagnosis of orbital metastasis can be made by biopsy of the affected tissue.

Orbital metastasis of breast carcinoma involving single or multiple extraocular muscles is infrequently diagnosed and has been reported in a small number of studies.[6,7,8,9,10,11] The purpose of this report is to describe a patient with metastatic involvement of the medial rectus muscle by breast carcinoma and to discuss related literature on orbital metastasis of breast carcinoma.

Case Report

A 63-year-old woman with metastatic breast carcinoma presented to the ophthalmology clinic with diplopia in right gaze and head turn to the right. Medical history revealed that she was diagnosed with estrogen receptor (ER)-positive and progesterone receptor (PR)-positive invasive ductal carcinoma 1 year earlier with mediastinal lymph node and bone metastasis at the time of diagnosis. She was treated with zoledronic acid 4 mg monthly and paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by endocrine therapy with letrozole.

On ophthalmological examination, best corrected visual acuity was 20/25 in both eyes. Slit-lamp examination of the anterior segment and fundus was unremarkable other than bilateral posterior chamber intraocular lenses. On motility exam, abduction was totally limited in the right eye with globe retraction and narrowing of the palpebral fissure on attempted

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abduction (Figure 1). Abnormal head position towards the right side was noted. Magnetic resonance imaging (MRI) revealed isolated enlargement of the right medial rectus muscle (Figure 2). Clinical evaluation and laboratory studies were carried out for differential diagnosis. There were no clinical findings suggestive of thyroid eye disease and thyroid function tests were normal. Rheumatologic assessment for inflammatory and vasculitic diseases was not contributory. Biopsy of the right medial rectus muscle was performed to establish a definite diagnosis and initiate appropriate treatment.

Hematoxylin and eosin staining of the biopsy specimen revealed large, round to polygonal epithelioid tumor cells arranged in loosely cohesive clusters and sheets infiltrating fibrocollagenous tissue and muscle fibers (Figure 3A). Immunohistochemical analyses using streptavidin-biotin peroxidase complex method revealed panCytokeratin and cytokeratin 7 positivity (Figure 3B). ER, PR and human epidermal growth factor receptor 2 (HER2/neu) were negative (triple-negative). Based on the patient's clinical history and the morphological and immunohistochemical features of the tumor, she was diagnosed with breast carcinoma metastasis to the right medial rectus muscle. Pathological examination demonstrating a triple-negative breast carcinoma indicated discordance with the primary tumor, which was ER- and PR-positive at the time of diagnosis.

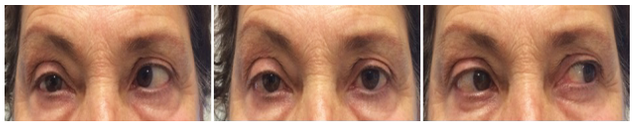

Figure 1. Images of the patient at presentation. Abduction of the right eye is limited with retraction of the globe and narrowing of the palpebral fissure

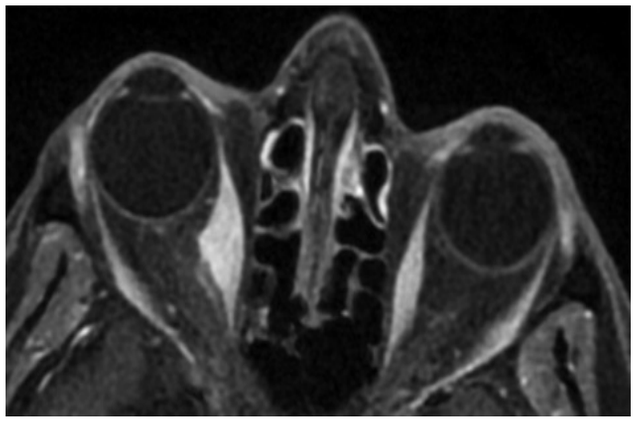

Figure 2. Magnetic resonance imaging of the orbit. Axial postcontrast T1-weighted image showing thickening of the right medial rectus muscle with sparing of the tendon

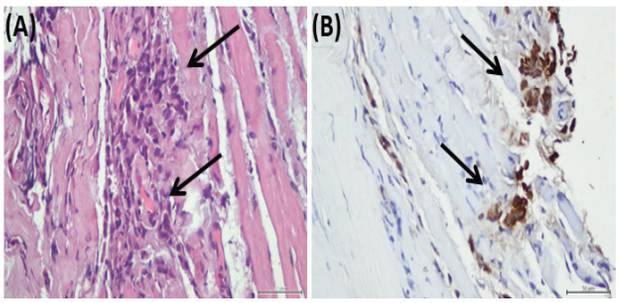

Figure 3. (A) Hematoxylin-eosin stain. The biopsy specimen of the right medial rectus muscle showing tumor cells (arrows) infiltrating muscle fibers; 400x. (B) Cytokeratin 7 immunohistochemistry of the specimen showing tumor cells (arrows); 400x

The patient was referred to the radiation oncology department for external beam radiation therapy. The orbital mass was irradiated with 45 Gy in 15 fractions. Following radiotherapy, chemotherapy with docetaxel 100 mg/m^2 once every 21 days was initiated. After 15 months of follow-up, abduction of the right eye has partially recovered; the patient is stable and continuing to receive palliative chemotherapy.

Discussion

Among all orbital tumors, metastatic cancer has a prevalence of 1-13%.[1] The majority of ocular and orbital metastases are caused by breast cancer.[12] The reported incidence of breast cancer metastasis to the ocular structures in clinical series varies between 8 and 10%. However, its incidence may be underestimated because of the concurrent involvement of major organs like lungs, liver, or bone, which may have more serious consequences dominating the patient's clinical situation.

Extraocular muscles are rarely infiltrated by metastatic tumors from distant sites. The rarity of extraocular muscle involvement by metastases has been attributed to the constant movement of these muscles, which prevents lodging of neoplastic cells, and to their unfavorable chemical environment for neoplastic growth.[13] On the other hand, orbital metastases of breast carcinoma have a tendency to spread to the extraocular muscles and surrounding orbital fat.[5] With the advancement of treatment options and prolonged survival of breast carcinoma patients, the possibility of extraocular muscle metastases of breast carcinoma may increase.[14]

Diplopia and ocular motility disorder in a patient with neoplastic disease should initially raise suspicion of tumor involvement of extraocular muscles; however, broad differential diagnosis is required to determine the cause and to institute appropriate treatment. Imaging with computed tomography or MRI is helpful in demonstrating extraocular muscle enlargement and determining extent of orbital involvement. Laboratory studies should be carried out to exclude other conditions that may cause extraocular muscle enlargement like granulomatous, vasculitic, endocrine, and immunologic diseases. Biopsy of the involved tissue is necessary for definite diagnosis.

In breast carcinoma cases, discordance of ER, PR and HER2/neu status between the primary tumor and subsequent metastases is well recognized.[15] Several studies have shown substantial discordance rates between primary breast carcinoma and metastatic disease, reporting hormone receptor discordance rates between 30% and 40%.[16,17,18] The primary tumor in our patient was ER-/PR-positive. However, biopsy and immunohistochemical staining of the metastatic lesion in

the medial rectus muscle demonstrated triple-negative breast carcinoma, indicating discordance with the primary tumor. The result of the metastatic biopsy led to the modification of our treatment from endocrine therapy to chemotherapy.

The time interval between diagnosis of primary breast carcinoma and detection of orbital metastasis is usually long; the mean interval has been reported to range from 4.5 to 6.5 years.[14] In the current case, the orbital metastasis was diagnosed 1 year after the primary tumor, a relatively short interval in comparison to previous reports.

Treatment of orbital metastatic lesions may help to control the growth of the tumor, to preserve visual function, and to improve patient comfort. External-beam radiotherapy to the orbital metastatic lesion is the mainstay treatment.[5] Chemotherapy and hormone therapy are other options, depending on the status of the systemic disease. The prognosis of breast carcinoma with orbital metastases is poor; survival ranges from 1 to 116 months with a mean of 31 months.[4]

In conclusion, ocular motility deficit in a patient with breast carcinoma should raise suspicion of a possible orbital metastatic lesion involving the extraocular muscles. Biopsy is required for definite diagnosis. The metastatic lesion may show discordance from the primary tumor, which may alter treatment decisions and follow-up of the disease.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özge Yabaş Kızıloğlu, Fatma Paksoy Türköz, Özgün Melike Totuk Gedar, Mert Mestanoğlu, Özlem Yapıcıer, Concept: Özge Yabaş Kızıloğlu, Mert Mestanoğlu, Fatma Paksoy Türköz, Özgün Melike Totuk Gedar, Design: Özge Yabaş Kızıloğlu, Özgün Melike Totuk Gedar, Mert Mestanoğlu, Data Collection or Processing: Özge Yabaş Kızıloğlu, Mert Mestanoğlu, Fatma Paksoy Türköz, Özlem Yapıcıer, Analysis or Interpretation: Özge Yabaş Kızıloğlu, Özgün Melike Totuk Gedar, Özlem Yapıcıer, Fatma Paksoy Türköz, Literature Search: Özge Yabaş Kızıloğlu, Mert Mestanoğlu, Writing: Özge Yabaş Kızıloğlu, Mert Mestanoğlu, Fatma Paksoy Türköz, Özlem Yapıcıer.

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

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Case Report

Isolated Unilateral Infiltrative Optic Neuropathy in a Patient with Breast Cancer

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Abstract

Metastasis to the optic nerve is very rare. We report a case of metastatic breast cancer to the optic nerve head without the involvement of other ocular or orbital structures. The patient, a 39-year-old female who had been previously treated for breast cancer, reported a gradually progressive decrement in visual acuity of the right eye during the past two months. Fundus examination of the affected eye revealed swelling of the optic disc which was infiltrated by a yellowish mass. Further evaluation using optical coherence tomography and fluorescein angiography showed optic disc swelling. Magnetic resonance imaging revealed no pathologic findings. With a diagnosis of unilateral infiltrative optic neuropathy, we referred the patient to an oncologist for further evaluation.

Keywords: Optic nerve head infiltration, breast cancer, ocular metastasis

Introduction

Ocular metastasis is rare and metastasis to the optic nerve is even rarer. In a case series study, Shields et al.[1] reported metastases to the optic disc in 4.5% of patients with ocular metastases. In another study on patients with ocular metastasis, orbital metastasis, or both, Ferry and Font[2] reported that 1.3% involved metastases limited to the optic nerve, and metastatic breast cancer was seen in only 0.4%. We report a case of metastatic breast cancer to the optic nerve head which was unilateral. The diagnosis was based upon the previous history of breast cancer, optic disc examination in the affected eye, and imaging results.

Case Report

The patient was a 39-year-old female who had experienced a gradually progressive decrement in visual acuity of the right eye during the past 2 months. Her medical history indicated that she had been treated for breast carcinoma, which had been originally diagnosed in her right breast 6 years ago, with no signs of metastases. Histopathological evaluation confirmed invasive ductal adenocarcinoma of the breast. She had been since treated by mastectomy and adjuvant chemotherapy with docetaxel until 3 years ago when her treatment with oral tamoxifen was begun. The treatment limited the neoplastic process and there were no clinical or radiological signs of progressive disease during these years.

The patient had no significant medical history. She was taking tamoxifen. She had no history of alcohol or tobacco use and there was no environmental toxic exposure. Her family history was negative for breast cancer and other diseases.

Office examination revealed a best-corrected visual acuity of counting fingers at 2 meters in the right eye and 10/10 in the left eye (by Snellen E chart from six meters). There was a 3^+ relative afferent papillary defect in the right eye. Extraocular motility was intact in both eyes. Intraocular pressures were within normal limits in both eyes in applanation tonometry. Color plate testing results (by Ishihara's color plate test) was 1/14 for the right eye and 14/14 for the left eye. Anterior segment examination was unremarkable. Dilated fundus examination of the right eye demonstrated 1^+ cells in the vitreous, optic disc swelling, obscuration of vessels and infiltration by a large yellowish mass that disrupted the normal structure of the optic disc, and flame-

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shaped hemorrhages in the peripapillary (PP) region (Figure 1). Fundus examination of the left eye was normal. Humphrey visual field testing in the right eye showed an altitudinal defect with enlarged blind spot (Figure 2). PP optical coherence tomography (OCT) demonstrated significant retinal nerve fiber layer thickening in all four quadrants in the right eye (Figure 3). Fluorescein angiography (FA) of the right eye detected a hyperfluorescent mass on the right optic disc with no sign of leakage, which suggested infiltrative optic neuropathy (Figure 4). Humphrey visual field testing in the left eye revealed a non-specific arcuate scotoma (Figure 2). OCT and FA in the left eye were normal (Figures 3 and 4). B-Scan ultrasonography of right eye revealed slight abnormal increase in right optic nerve sheath diameter (Figure 5). Magnetic resonance imaging (MRI) was unremarkable and intraorbital and intracranial portions of both optic nerves had normal appearance.

According to the patient's present condition, her past history of breast cancer, optic disc features on fundus examination, and imaging findings, the first diagnosis was infiltrative optic neuropathy of the right eye. The patient was referred to an oncologist for further systemic examination and necessary interventions.

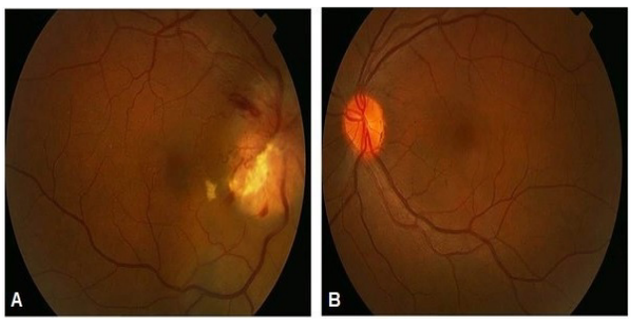

Figure 1. Fundus photography of both eyes. (A) Optic disc swelling with obscuration of blood vessels and peripapillary flame-shaped hemorrhages. A large yellowish infiltrative mass, with disruption of the architecture of the optic disc is noticeable. (B) The left eye seems normal

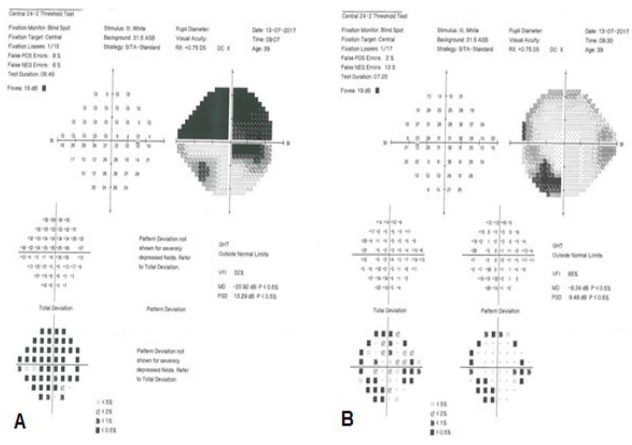

Figure 2. Humphrey visual field testing in both eyes. (A) The right eye shows an altitudinal defect with enlargement of the blind spot. (B) The left eye shows a non-specific arcuate scotoma

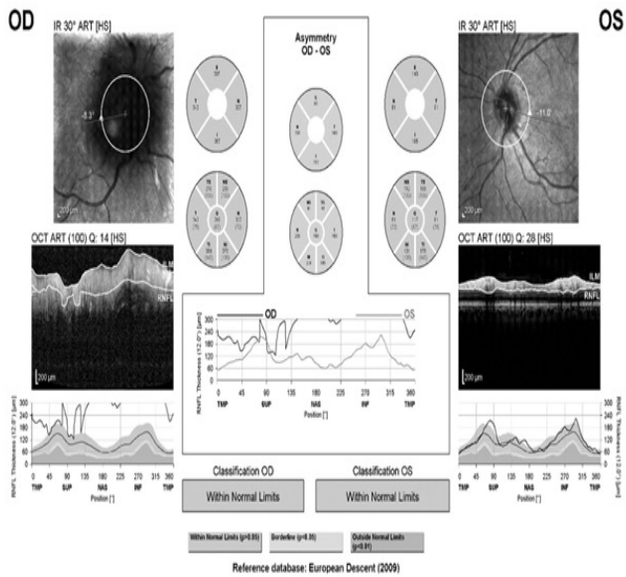

Figure 3. Peripapillary optical coherence tomography (PP-OCT) of both eyes. The right eye shows significant thickening of the retinal nerve fiber layer in all four quadrants due to optic disc swelling and an infiltrative mass. PP-OCT of the left eye is normal

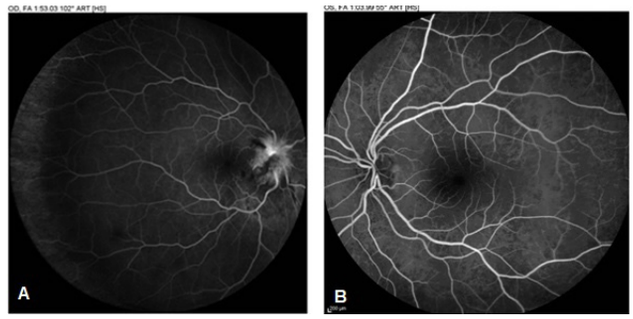

Figure 4. Fluorescein angiography of both eyes, mid phase. (A) Hyperfluorescent mass on the right optic disc with no evidence of leakage along with peripapillary hypofluorescent areas compatible with blocking effect from flamed-shape hemorrhages. (B) Fluorescein angiography of the left eye seems normal

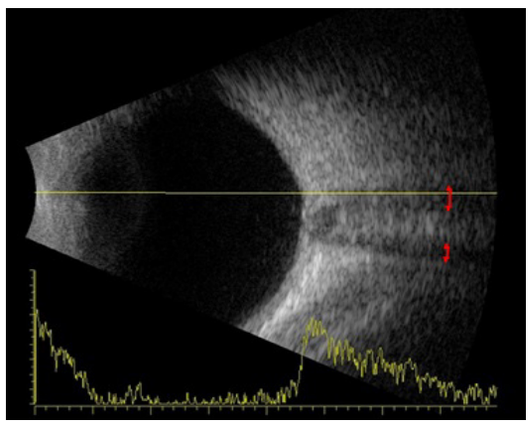

Figure 5. B-scan ultrasonography of the right eye shows abnormally increased optic nerve sheath diameter (red double-headed arrows)

Discussion

The optic nerve can be infiltrated by primary or secondary tumors and inflammatory processes. The most common secondary tumors that involve the optic nerve are metastatic and locally invasive carcinomas and hematologic malignancies, especially lymphoma and leukemia.[3] Metastases can reach the optic nerve via the choroid, by vascular dissemination, by invasion from the orbit, and through the central nervous system.[4,5,6] In patients with infiltrative lesions of the optic nerve, optic disc elevation can be due to swelling and/or infiltrative masses. Consequently, the patient may have impairments in visual acuity, color vision, and visual field in the affected eye(s). When the involvement is unilateral or asymmetric, the patient may have a relative afferent pupillary defect.[3] In a literature review of 13 patients with breast carcinoma metastasis to the optic nerve, Cherekaev et al.[7] reported that in the majority of cases (10 of 13), loss of vision was the main symptom. The visual acuity of our patient had diminished progressively, with impaired color vision and a visual field defect in the right eye due to an infiltrative optic neuropathy. She had also a relative afferent pupillary defect due to unilateral involvement of the right eye.

When the metastasis is located in the orbital portion of the optic nerve, the optic disc is usually swollen and a yellow-white infiltrative mass that protrudes from the surface of the nerve can be seen on the optic disc. Tumor cells can sometimes be seen in the vitreous body.[4,8,9,10] In metastases involving the posterior aspect of the orbital portion of the optic nerve, the optic disc appears normal in the early stages.[3] In our patient, the right optic disc was swollen with peripapillary flame-shaped hemorrhages and a yellowish infiltrative mass on the disc. Some cells were detected in the vitreous body of the affected eye. PP-OCT also revealed swelling of the affected optic disc. FA findings did not show any evidence of leakage, suggesting infiltrative optic neuropathy.

The most common metastatic tumors to the optic nerve are adenocarcinomas. In females, breast and lung cancers and in males, carcinomas of the lung and intestinal tract are the most common causes.[1,4,11,12,13] Likewise, carcinomas of the pancreas, stomach, uterus, ovary, kidney, prostate, and larynx can metastasize to the optic nerve.[14,15] Our patient had a previous history of treatment for breast cancer, which was considered the most probable cause of infiltrative optic neuropathy of the affected eye.

Neuroimaging is crucial in patients suspected of infiltrative optic neuropathy due to cancer. MRI findings include optic nerve enlargement that is diffuse (more common) or in a circumscribed area, associated exudates or hemorrhage, and optic canal involvement in osteophilic metastatic tumors such as prostate carcinoma.[10,11,16,17,18,19] Our patient had normal orbital and brain MRI.

Most metastatic optic nerve tumors show a variable response to radiotherapy.[17,20] The prognosis for patients with isolated breast cancer who suffer metastasis to the optic nerve is relatively poor.[21] We referred our patient to an oncologist for further evaluation and treatment.

In conclusion, most patients with optic nerve metastatic tumors exhibit a known diagnosis of a primary malignancy along with other evidence of metastases. Thus, when a known cancer patient develops optic neuropathy, metastases and infiltration should be suspected as the cause unless proven otherwise.

Ethics

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mostafa Soltan Sanjari, Kaveh Abri Aghdam, Concept: Kaveh Abri Aghdam, Design: Amin Zand, Data Collection or Processing: Kaveh Abri Aghdam, Amin Zand, Analysis or Interpretation: Mostafa Soltan Sanjari, Kaveh Abri Aghdam, Amin Zand, Literature Search: Kaveh Abri Aghdam, Amin Zand, Writing: Amin Zand.

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

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Case Report

Extramacular Retinal Hole Following Intravitreal Dexamethasone Implant: Case Report

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Abstract

The intravitreal dexamethasone implant Ozurdex is indicated for the treatment of macular edema due to diabetes and branch retinal vein occlusion. While the most common ocular side effects are elevated intraocular pressure and cataract formation, rare complications related to the injection have been reported. We present a case with extramacular retinal hole after Ozurdex injection.

Keywords: Intravitreal dexamethasone implant, Ozurdex, retinal hole

Introduction

The intravitreal dexamethasone implant (Ozurdex®, Allergan Inc., Irvine, CA, USA), which provides sustained drug release when injected into the vitreous cavity, is used in the treatment of macular edema due to branch retinal vein occlusion (BRVO) as well as many other retinal diseases.[1] Although intraocular pressure elevation and cataract are the most common complications after Ozurdex injection, there have also been reports of retinal tears, retinal hemorrhage, intralenticular implantation, subretinal injection, implant migration to the anterior chamber, endophthalmitis, and macular hole.[2] In this case report, we present a patient with extramacular retinal hole, a rarely reported complication after Ozurdex injection.

Case Report

A 54-year-old man presented with complaints of decreased visual acuity in his left eye for approximately 1 week. His medical history included no systemic disease other than hypertension that had been present for 5 years and was controlled with medical treatment. In ophthalmologic examination, his corrected visual acuity was 1.0 in the right eye and 0.2 in the left eye. He had no history of previous ocular surgery, and anterior segment examination was normal. Fundus examination revealed no pathology in the right eye but BRVO was detected in the superotemporal region of the left eye (Figure 1a). Intraocular pressure was 15 mmHg in the right and 14 mmHg in the left eye. Fundus fluorescein angiography of the left eye showed late filling, dilation, and increased tortuosity of the superotemporal retina vein and areas of capillary nonperfusion consistent with BRVO (Figure 1b). Spectral domain optical coherence tomography (OCT) demonstrated retinal thickening (710 µm) and cystoid macular edema (Figure 1c). The patient was diagnosed with macular edema associated with BRVO and Ozurdex was injected. The injection was done in aseptic conditions from the superotemporal quadrant 4 mm from the limbus using the recommended standard procedure. During implantation, slight deflation of the globe and momentary hypotony were observed immediately after inserting the sharp tip of the implant through the sclera and before pulling the trigger, despite the absence of vitreous leakage. Vitreous leakage or hypotony were not observed after injection and no complications were noted in routine follow-up examination the next day.

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At 1-month follow-up, the patient's visual acuity had increased to 0.5. Hemorrhage was observed in the superotemporal region on fundus examination (Figure 2a). Macular OCT examination revealed that the cystoid macular edema had resolved, foveal thickness was 266 µm, and foveal contour had normalized (Figure 2b). A full-thickness retinal hole about 1 disc diameter in size surrounded by sporadic hemorrhages was noted in the temporal region of the macula (Figure 3). The patient was informed of their condition and laser photocoagulation was performed on the ischemic areas and around the retinal hole. At follow-up 4 months after injection, visual acuity in the left eye was 0.3 and intraocular pressure measured by Goldmann applanation tonometry was 15 mmHg in both eyes. Central macular thickness had increased to 613 µm. The patient was given a second Ozurdex implant. He was last seen 1 month after the second injection. At that time, his visual acuity increased to 0.4 in the left eye. The retina was attached and the laser spots showed pigmentation. Central macular thickness had decreased to 284 µm.

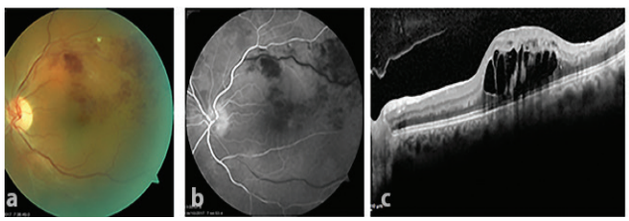

Figure 1. At presentation, a) color fundus image showed superotemporal branch retinal vein occlusion; b) fundus fluorescein angiography showed late filling and dilation of the superotemporal vein and areas of capillary nonperfusion; and c) optical coherence tomography showed macular thickening and cystoid edema

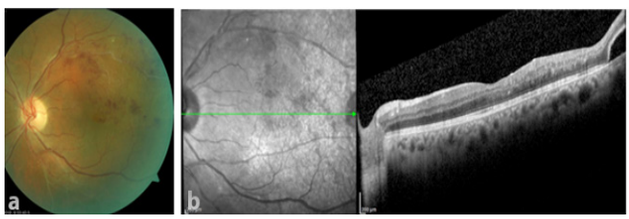

Figure 2. At follow-up 1 month after Ozurdex injection, a) color fundus image showed regression of superotemporal hemorrhages and b) optical coherence tomography showed resolution of cystoid macular edema and normalization of the foveal contour

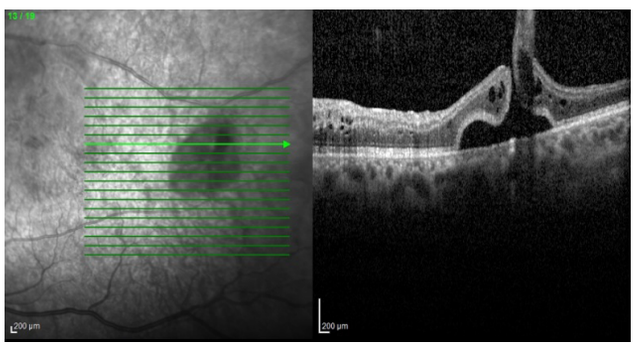

Figure 3. Optical coherence tomography section passing through the hole temporal of the macula at 1 month after injection

Discussion

Ozurdex is an intravitreal sustained-release dexamethasone implant known to be effective in the treatment of macular edema due to BRVO. The most commonly observed side effects are increased intraocular pressure and cataract formation, though other complications have been associated with the implant, such as migration into the anterior chamber, intralenticular implantation, confinement to Berger's space, and conditions like endophthalmitis, vitreomacular traction, and macular hole.[2]

Extramacular retinal hole following Ozurdex injection, as seen in our case, has only been reported previously by Christensen et al.[3] Their case report was based on the patient's anamnesis, which suggested that the eccentric macular hole that developed after receiving an Ozurdex injection abroad was likely due to direct contact of the Ozurdex implant with the retina. The patient did not have records from before the Ozurdex injection. In an experimental apparatus created for this case report, the authors determined that the force created by the implant at a distance of 16 mm with Ozurdex applicator was 0.77 Newton (N) in air and 0.024 N in BSS. They reported that these values were lower than the 0.1-0.2 N necessary for a foreign body to damage the retina according to previous studies. In this case, which they referred to as the "magic bullet", the authors believed that no mechanism other than direct contact by the implant could have created the retinal hole and suggested that this complication may be attributable to the retina becoming more susceptible to trauma in chronic retinal disease.

One point to consider here is the relationship between the speed at which the trigger is pushed and the velocity with which the implant is released. Meyer et al.[4] reported in an experimental study that the Ozurdex implant exited the applicator at a speed of 0.8 m/s and decelerated progressively, and that its deceleration was more rapid in the vitreous compared to water. They concluded that the retinal impact energy calculated in their analyses did not reach the previously reported levels necessary to reach the retina. In addition, the authors followed the patient without treatment and reported that the hole was stable. For our patient, however, we preferred to treat with laser photocoagulation because the hole appeared to be large and causing traction.

In our case, the momentary hypotony observed immediately before pushing the trigger during injection may have shortened the distance between the entry site and retina, thus allowing the implant to cause direct damage to the retina. Therefore, we believe that patients who exhibit globe softening during implantation require special care, and that at the very least, the clinician should attempt to aim the implant toward the extramacular area.

Ethics

Informed Consent: Received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Hakan Özdemir, Concept: Alp Kayıran, Design: Alp Kayıran, Hakan

Özdemir, Cansu Ekinci, Data Collection or Processing: Cansu Ekinci, Hakan Özdemir, Analysis or Interpretation: Cansu Ekinci, Alp Kayıran, Literature Search: Alp Kayıran, Cansu Ekinci, Writing: Cansu Ekinci, Alp Kayıran, Hakan Özdemir.

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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2019 INTERNATIONAL CONGRESSES

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TOA 3rd Live Surgery Symposium
June 20 – 23, 2019
İstanbul, Turkey

21st Esat Işık Course
September 7 – 8, 2019
Sivas, Turkey

32nd Summer Symposium: Systemic Diseases with the Eye of Ophthalmologist: From Review to Diagnosis
September 27 – 29, 2019
İzmir, Turkey

TOA 53rd National Congress
November 6 – 10, 2019
Antalya, Turkey