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EVALUATION OF DRY EYE PARAMETERS IN PATIENTS WITH UNILATERAL HERPETIC KERATITIS

UNİLATERAL HERPETİK KERATİTLİ HASTALARDA KURU GÖZ PARAMETRELERİNİN DEĞERLENDİRİLMESİ

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Abstract

Objective: Our aim in this study was to examine the tear parameters between affected and unaffected eyes of unilateral herpes simplex virus (HSV) keratitis patients, especially the meibomian glands status.
Methods: The examinations and tear parameters including; tear film meniscus height (TMH) and area (TMA), non-invazive break up time (NIBUT), schirmer test, meibomian gland's ekspressibility grade, drop out grade and microstructure of patients who were treated in our clinic with the diagnosis of unilateral herpetic endothelitis or herpetic stromal keratitis, and who had a quiescent period of about 3 months, were evaluated retrospectively.
Results: The median age of our patients was 58.0 (55.25-72.25) years. The median NIBUT was 6.85 (4.62-17.0) sec. in affected eye and 15.85 (10.47-17.15) sec. in unaffected eye. NIBUT values were observed to be remarkable lower in the affected eye, although the change between groups was not statistically significant. Schirmer test values, TMH and TMA were similar between affected and unaffected eyes. Meibomian gland evaluations of affected and unaffected eyes were shown similar distribution across meibomian expressibility and drop out grades.
Conclusion: We observed similar effects in both morphological and microstructural features of meibomian glands in both eyes. This condition makes us think that the developing dry eye disease in both eyes may be caused not only by neurosensorial anomalies but also by changes in the meibomian glands.

Keywords: *Herpetic keratitis, meibomian gland, tear film meniscus, in vivo confocal microscopy.*

Öz

Amaç: Çalışmamızın amacı tek taraflı herpes simpleks virüs (HSV) keratiti olan hastalarda etkilenen ve etkilenmeyen gözler arasındaki gözyaşı parametrelerinin özellikle meibomian bezlerinin durumunun değerlendirilmesidir.
Yöntem: Kliniğimizde tek taraflı HSV endoteliti ve HSV stromal keratiti tanılarıyla tedavi uygulanmış ve 3 aydan uzun süredir sakin dönemde seyreden hastaların muayeneleri ve gözyaşı filmi menisküsü yüksekliği (GFMY), alanı (GFMA), non-invazif gözyaşı kırılma zamanı (NIGKZ), schirmer testi, meibomian bezleri ekspressibilite gradeleri, drop-out dereceleri ve mikroyapısının değerlendirilmesini içeren gözyaşı parametreleri retrospektif olarak değerlendirildi.
Bulgular: Hastalarımızın yaş ortalaması 58,0 (55,25-72,25) yıldı. Medyan NIGKZ etkilenen gözde 6,85 (4,62-17,0) sn. ve etkilenmemiş gözde 15,85 (10,47-17,15) sn. idi. Gruplar arasındaki değişim istatistiksel olarak anlamlı olmasa da, etkilenen gözde NIGKZ değerlerinin belirgin şekilde daha düşük olduğu gözlendi. Schirmer test değerleri, GFMY ve GFMA, etkilenen ve etkilenmeyen gözler arasında benzerdi. Etkilenen ve etkilenmeyen gözlerin meibomian bezi değerlendirmeleri, meibomian ekspresyonu ve bırakma dereceleri benzer dağılım gösterdi.
Sonuç: Her iki gözde meibom bezlerinin hem morfolojik hem de mikroyapısal özelliklerinde benzer etkiler gözlemledik. Bu durum bize her iki gözde gelişen kuru göz hastalığının sadece nörosensoriyel anomalilerden değil meibomian bezlerdeki değişikliklerden de kaynaklanabileceğini düşündürmektedir.

Anahtar Kelimeler: *Herpetik keratit, meibomian bezi, gözyaşı film menisküsü, in vivo konfokal mikroskopi.*

Introduction

Herpes simplex virus (HSV) is a common cause of recurrent ocular surface disease with a rate of 90% seen unilaterally.[1] HSV lesions are immunoinflammatory lesions that may recur throughout life and often cause visual impairment with progressive corneal scarring. In treatment, topical steroids are used together with antiviral agents to suppress immunity.

One of the outcomes of HSV keratitis is neurotrophic ulcers. In the quiescent period of the disease, both severe dry eye and non-healing corneal ulcers can be seen with impaired corneal sensitivity.[2] It has been reported that unilateral HSV keratitis may cause contralateral effects on fellow eye such as decrease in sub-basal nerve plexus and tear dysfunction.[3-6] Decreased sensitivity of the cornea is a general finding of eyes infected with HSV. Disease duration, severity and frequency of active period determine the amount of corneal sensitivity loss that will develop.[6] Ma et al. reported a significant increase in tear osmolarity and a decrease in the Schirmer test and tear break-up time (TBUT) in both eyes of unilateral HSV keratitis patients compared to the control group. They explained this result as dry eye in both eyes due to loss of corneal sensitivity in the affected eye in patients with unilateral silent HSV keratitis.[7] According to Jabbarvand et al. reported impaired ocular surface parameters in both affected and unaffected eyes of patients with unilateral neurotrophic ulcer and unilateral HSV keratitis compared to healthy corneas. They speculated this result like that the fellow eye may had asymptomatic herpes virus involvement which provoke the ocular surface findings with inflammation.

Another hypothesis emphasized in this regard is as follows. In unilateral HSV keratitis, the decrease in corneal sensitivity in the affected eye may disrupt the afferent pathway of the tear reflex bilaterally. Permanent influence of this pathway may cause to decrease of blinking frequency, high level of evaporation, became hiperosmolar and unstable of tear film in the fellow eye.[8,9] Dry eye findings in the fellow eye of unilateral HSV patients have generally been attributed to decreased corneal sensitivity. Our aim was to examine the tear parameters between affected and unaffected eyes of HSV patients, especially the condition of the meibomian glands.

Methods

The examinations and tear parameters of the patients who were treated in our clinic with the diagnosis of unilateral herpetic endothelitis or herpetic stromal keratitis, and who had a quiescent period of about 3 months, were evaluated retrospectively. Twenty eyes of 10 patients were compared. The diagnosis of HSV keratitis was made by clinical findings and response to treatment. Local Ethics Committee approved the study and also the study adhered to the tenets of the Declaration of Helsinki (GOKAEK-2022/11.17).

Complete ophthalmic examination including; visual acuity, intraocular pressure (IOP) measurement by the Goldmann Applanation Tonometry, anterior and posterior segment evaluation, assesment of ocular surface disease index (OSDI), evaluation of meibomian gland ekspressibility grade. Schirmer test with topical anesthesia was performed. Meibomian gland morphologic drop out scoring and non invaziv tear break up time (NITBUT) values evaluated with Sirius corneal topography (CSO, Italy), tear film meniscus height (TMH) and area (TMA) with anterior segment optical coherence tomography (OCT, Heidelberg, Germany) using Image J software[10] and meibomian gland microstructure with in vivo confocal microscopy (Heidelberg Retina Tomography, Rostock Cornea modüle, Germany).

Meibomian gland drop-out was graded for inferior eyelids as follows: Grade 0 = no partial glands; grade 1 = 25% partial glands; grade 2 = 26–50% partial glands; grade 3 = 51–75% partial glands; and grade 4 = > 75% partial glands.[11] Meibomian gland expressibility was graded according to Shimazaki et al. (Grade 0 = clear secretion, grade 1 = cloudy meibum expressed with mild pressure, grade 2 = cloudy meibum expressed with more than moderate pressure, grade 3 = toothpaste secretion or no expressible secretion).[12] Meibomian gland microstructures were investigated with in vivo confocal microscopy. Meibomian gland acinar density (MAD) was manually marked inside each 400*400-µm frame and the density was automatically calculated using device cell counting system. The meibomian asiner irregularity (MAI) was assessed, with virtually round or elliptical shape as grade 0, minimal presence of lobulated shaped acinar units as grade 1, moderate presence as grade 2 and heavy presence as grade 3.[13,14] The meibum secretion reflectivity (MSR) was evaluated on a 4-point scale: black secretion color was scored as grade 0, dark gray color as grade 1, light gray color as grade 2, and white color as grade 3. The asiner wall inhomogenity (AWI) were rated on a 4-point scale: absence of punctate reflecting elements was scored as grade 0, minimal presence of punctuate reflecting elements as grade 1, moderate presence as grade 2, and heavy presence as grade 3.[13,14]

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were performed using Mann-Whitney U test. A *p*-value <0.05 was considered as statistically significance.

Results

The median age of our patients was 58.0 (55.25-72.25) years. Four of them (40%) were female and 6 of them (60%) were male. None of our patients had any systemic disease and another ocular disease. The mean duration of disease was 4.50±5.50 years. In all of them, at least 3 months had passed since the last disease activation.

The mean OSDI score of patients was 40.0±14.92. The median best corrected visual acuity (BCVA) of affected eye was 0.7 (0.35-1.0) decimal. The median NIBUT was 6.85 (4.62-17.0) in affected eye and 15.85 (10.47-17.15) in unaffected eye. NIBUT values were observed to be remarkable lower in the affected eye, although the change between groups was not statistically significant. Schirmer test values and TMH and TMA were similar between affected and unaffected eyes (Table 1).

Meibomian gland evaluations of affected and unaffected eyes were shown similar distribution across meibomian expressibility and drop out grades. Microstructural evaluation grades of meibomian glands with in vivo confocal microscopy were shown similar distribution between groups (Table 2) (Figure 1).

Table 1. Clinical parameters of patients with unilateral herpetic keratitis

	Affected eye	Unaffected eye	*p* value
BCVA*	0.70 (0.35-1.00)	1.00 (0.97-1.00)	**0.023**
NIBUT**	6.85 (4.62-17.0)	15.85 (10.47-17.15)	0.105
Schirmer test	10.0 (7.5-12.0)	11.0 (5.75-16.25)	0.529
Tear meniscus height (µm)	246.10 (209.69-256.77)	248.45 (224.22-298.77)	0.393
Tear meniscus area (µm^2)	25625 (19218-30156)	28437 (19687-36250)	0.353

*BCVA: Best corrected visual acuity; **NIBUT: Non-invasive tear break up time

Table 2. Clinical, topographical and in vivo confocal microscopical evaluation of meibomian glands

	Affected eye	Unaffected eye	*p* value
Meibum expressibility Grade 1/2/3	1(10%)/3(30%)/6(60%)	1(10%)/5(50%)/4(40%)	
Meibomian drop out inferior (%)	11.15(6.47-15.22)	12.80(9.75-18.50)	0.218
Meiboscor inferior Grade 0/1/2	3(30%)/6(60%)/1(10%)	3(30%)/6(60%)/1(10%)	
Meibomian drop out superior (%)	15.75(7.52-23.10)	14.20(9.12-21.20)	0.912
Meiboscor superior Grade 0/1/2	4(40%)/5(50%)/1(10%)	4(40%)/5(50%)/1(10%)	
Meibomian gland asiner density (MAD)	217.50(172.0-253.75)	201.50(167.75-211.25)	0.089
Meibomian asiner irregularity (MAI) Grade 0/1/2/3	0/3/7/0	0/5/4/1	
Meibum secretion reflectivity (MSR) Grade 0/1/2/3	0/4/6/0	1/1/7/1	
Asiner wall inhomogenity (AWI) Grade 0/1/2/3	0/4/6/0	1/3/4/2	

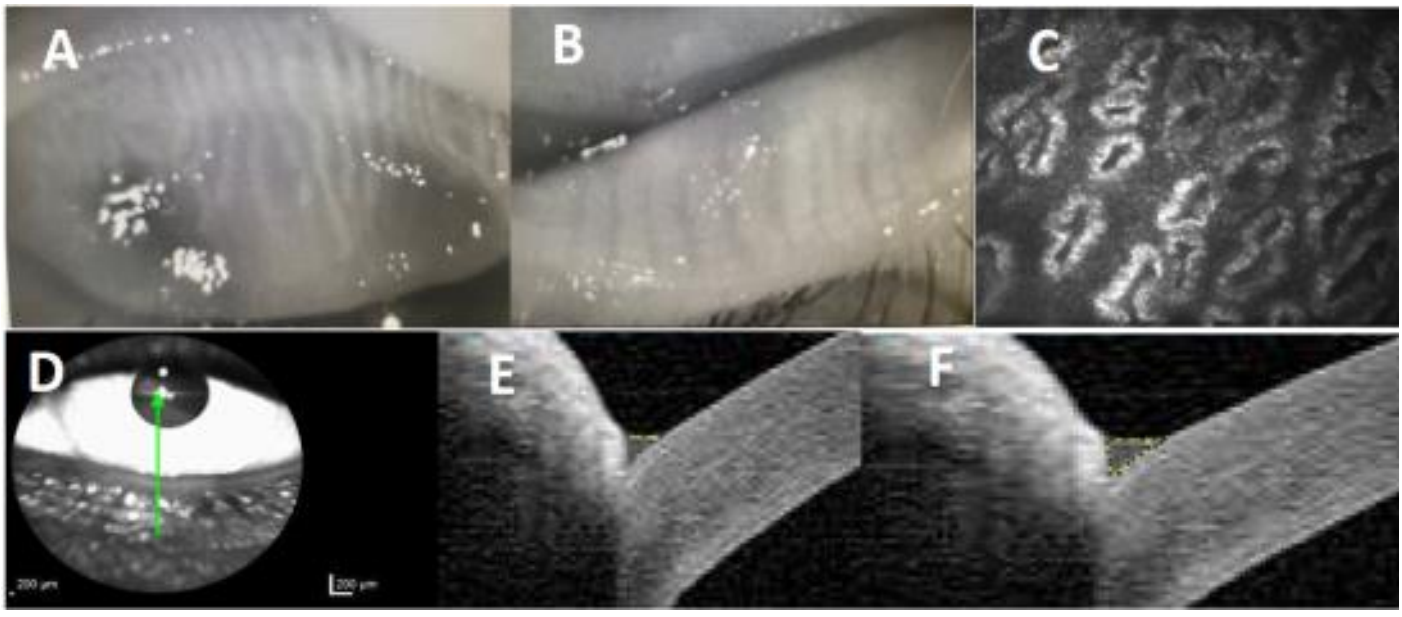

Figure 1. Representative images of meibomian gland drop out evaluation of superior eyelid (A) and inferior eyelid (B) with noncontact meibography, meibomian microstructure with in vivo confocal microscopy (C), tear film (D) height (E) and area (F) with optical coherence tomography

Discussion

In this study we investigated tear film parameters and meibomian gland status of unilateral HSV keratitis patients' both affected and unaffected eyes. We demonstrated that the effect on tear film parameters and meibomian glands was bilateral. Although it has been reported in the literature that bilateral dry eye findings are seen in unilateral HSV keratitis and this is due to neurosensory involvement,[7,15] there is no study about the relationship of HSV keratitis with the meibomian glands and its effect on the meibomian glands. Our study includes interesting results showing the effect on the meibomian glands.

One of the most important causes of corneal blindness is due to HSV infection. Liedtke et al., in their study in 1993, showed that almost 100% of people over 60 years old have latent HSV virus in the trigeminal ganglion by polymerase chain reaction.[16] There is a hypothesis that the contralateral unaffected eyes may have an asymptomatic herpetic involvement which may cause ocular inflammation and eventually lead to dry eye. Another alternative hypothesis is that the patient with unilateral HSV has pre-existing bilateral dry eyes, which predisposes them to HSV infection. In the study of Yamaguchi et al. in 2013, it was shown that the experimental unilateral neurotrophic keratopathy model causes bilateral nerve abnormalities.[17] In our study, we evaluated the tear parameters as well as the meibomian glands, and we found similar effects in both morphological and microstructural features in both eyes. This condition makes us think that the developing dry eye disease may be caused not only by neurosensorial anomalies but also by changes in the meibomian glands. This symmetrical change in the meibomian glands may be due to both neurosensorial and viral involvement, that are thought to be present in the asymptomatic eye.

The limitations of our study are the small number of patients and the inability to make comparisons with a healthy control group. There is a need for studies with large patient series comparing both patient and healthy eyes with healthy control group data.

In conclusion, during the treatment of the patients with unilateral HSV keratitis, the eye that is not involved should also be carefully examined and treated for dry eye and meibomian gland dysfunction when necessary.

Conflict of Interest

Author declares that there is no conflict of interest.

Ethical approval

Kocaeli University Non-Invasive Clinical Research Ethics Committee approved the study (Date: 26.06.2022, No: 2022/187) and also the study adhered to the tenets of the Declaration of Helsinki (GOKAEK-2022/11.17).

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