Do Unilateral Herpetic Stromal Keratitis and Neurotrophic Ulcers Cause Bilateral Dry Eye?

Mahmoud Jabbarvand, MD, Hesam Hashemian, MD,* Mehdi Khodaparast, MD,* Amin Rafatnejad, MD,* Amirhooshang Beheshtnejad, MD,* and Amir Salami, MD†*

Purpose: To evaluate and compare the ocular surface condition in herpetic interstitial stromal keratitis and neurotrophic ulcer groups and their normal fellow eyes.

Methods: In this observational, cross-sectional case–control study, 85 consecutive patients were included, including 56 cases of treated herpetic interstitial keratitis and 29 patients with neurotrophic ulcers. Fifty-six age- and sex-matched participants were also recruited from a normal population as the control group. We evaluated and scored the subjective and objective measures of dry eye for both eyes of all patients. Then, we compared the score of the groups with one another and also with the control group. The main outcome measures were the discomfort level, visual symptoms of dry eye, conjunctival injection, conjunctival staining, corneal staining, corneal tear signs of dry eye, meibomian gland dysfunction, tear break-up time, Schirmer test score with anesthesia, and tear osmolarity.

Results: The normal fellow eye of the herpetic keratitis group had significantly higher discomfort levels (1.4 ± 0.9 vs. 1.3 ± 0.5, P = 0.003), visual symptoms (1.7 ± 0.8 vs. 1.3 ± 0.7, P = 0.002), tear break-up time (8.3 ± 3.2 vs. 12.1 ± 3.3 seconds, P = 0.003), Schirmer test scores (9.2 ± 3.9 vs. 12.9 ± 3 mm, P = 0.04), and tear osmolarity (9.2 ± 3.9 vs. 12.9 ± 3 mm, P = 0.003) in comparison with normal controls. The normal fellow eyes of the neurotrophic ulcer group had significantly worse values for discomfort level (1.9 ± 0.9 vs. 1.3 ± 0.5, $P < 0.001$), tear break-up time (7.9 ± 4 vs. 12.1 ± 3.3, P = 0.004), Schirmer test score (8.1 ± 3.9 vs. 12.9 ± 3, P = 0.005), and tear osmolarity (295 ± 9.2 vs. 292.7 ± 5.9, P = 0.02) compared with normal controls.

Conclusions: Both eyes of patients with neurotrophic ulcer and interstitial herpetic keratitis have a significantly poorer ocular surface condition compared with that of normal controls.

Key Words: herpes simplex, stromal keratitis, neurotrophic ulcer, dry eye

(*Cornea* 2015;34:768–772)

Herpes simplex keratitis is the most common infectious cause of blindness in developed countries.[1–3] Eighty percent of Europeans are positive for herpes simplex virus (HSV)-1 antibodies,[4,5] leading to the incidence of 20.7 cases of clinical HSV keratitis per 100,000 annually. Polymerase chain reaction of trigeminal ganglia of cadavers revealed HSV in approximately 100% of the above-60 population.[6]

A small group of the infected population has active infections, mainly classified into epithelial herpetic keratitis and herpetic stromal keratitis. However, decreased corneal sensation occurs in all types of herpetic infections.

One of the outcomes of HSV keratitis is neurotrophic ulcers, caused by devastated corneal nerve function. Neurotrophic ulcers are determined by a nonhealing corneal epithelial defect.[7] During the acute stages of the disease through which viral shedding happens, patients suffer from hyperlacrimation; however, in the chronic phase, the disease is usually associated with dry eye symptoms.[8,9] After the acute phase, the disease might go into remission for several years. Of the recurrent cases, 20% to 30% are in the form of herpetic stromal keratitis.[1,10] Stromal involvement of HSV usually occurs with significant morbidities[1,11] including corneal scarring, reduced sensitivity, and epithelial healing defects.[12]

Dry eye disease is a multifactorial condition associated with an unstable tear film and various symptoms of ocular surface deterioration. This condition is associated with an increase in tear film osmolarity and inflammatory tear markers.[13,14] It is a common complication, affecting 5 million Americans 50 years old and older. Tens of millions have mild complications of the disease because of factors such as low humidity and the use of contact lenses.[15] Although the condition is not life threatening, it can significantly reduce the quality of life.[16]

Although the prevalence of HSV keratitis is quite high and the sequelae of the resulted neurotrophic ulcer are serious and in many cases the symptoms are bilateral, no case–control study has so far evaluated the ocular surface condition of the fellow uninvolved eye.

A study by Simard-Lebrun et al[17] reported that most patients with HSV keratitis have tear film abnormalities. Another

Received for publication September 15, 2014; revision received February 6, 2015; accepted February 8, 2015. Published online ahead of print May 1, 2015.

From the *Ophthalmology Research Center, Department of Ophthalmology, Tehran University of Medical Sciences, Farabi Eye Hospital, Tehran, Iran; and †Iran University of Medical Sciences, Tehran, Iran.

The authors have no funding or conflicts of interest to disclose.

Presented at the ASCRS meeting (April 25–29, 2014, Boston, MA) as an oral presentation.

Reprints: Hesam Hashemian, MD, Department of Ophthalmology, Tehran University of Medical Sciences, Farabi Hospital, Qazvin Sq., Tehran, Iran 1336616351 (e-mail: shhlucky@yahoo.com).

study reported that not only the involved eye but also the fellow eye of unilateral herpetic interstitial keratitis patients suffer from dryness.[18] We believe that ocular surface involvement in herpetic keratitis and neurotrophic ulcers may be because of bilateral conditions. In this study, we compared the ocular surface condition and subjective symptoms between unilateral herpetic interstitial keratitis and unilateral neurotrophic ulcer groups and their normal fellow eyes with a normal control group.

METHOD

Eighty-five consecutive patients entered this cross-sectional study, including 56 cases of treated herpetic interstitial keratitis and 29 patients with neurotrophic ulcers. Fifty-six age- and sex-matched participants were also recruited from a normal population as the control group. One eye of normal controls was randomly considered in the study. Informed consent was obtained from all patients, after explanation of all possible treatment options. The Institutional Ethical Review Board of Farabi Eye Hospital approved this study, and the tenets of the Declaration of Helsinki were followed.

Patients with active herpetic keratitis during the previous 2 months were excluded from the herpetic group. Exclusion criteria for all groups were the following: (1) diabetes mellitus and any systemic diseases or systemic medication associated with dry eye; (2) history of contact lens usage; (3) history of trauma and ocular surgery; (4) history of any pathological ocular conditions except neurotrophic ulcers and herpetic keratitis; (5) bilateral involvement even in asymmetric cases. Patients in all groups did not receive any topical medication 1 week before evaluation.

Tear osmolarity was evaluated using a TearLab system (TearLab Corporation, San Diego, CA). No drops were instilled 5 minutes before the test. The system was calibrated once a day using monodose saline according to the manufacturer's guidelines. The discomfort level, visual symptoms of dry eye, conjunctival injection severity, conjunctival staining pattern, corneal staining, corneal tear signs (eg, tear debris, size of the tear meniscus, filamentary keratitis, mucus clumping, corneal ulceration), presence and severity of meibomian gland dysfunction (MGD), tear break-up time (TBUT), and Schirmer test results were scored according to the "dry eye severity grading scheme" adopted by Bahren et al.[14]

The Schirmer test was conducted after anesthetization with 0.5% tetracaine hydrochloride (Anestocaine; Sinadaru, Iran) drops. Schirmer strips were then inserted under the lower lid between the middle and outer thirds of the lid margin, and after 5 minutes, the paper was read.[19] Tear osmolarity measurement was performed using a TearLab osmometer according to the provided guidelines. The TBUT was measured 60 seconds after instillation of a drop of fluorescein 0.5% using a blue filter. The period from the last complete blink to the first appearance of a dry spot was defined as the TBUT. The Schirmer test, tear osmolarity, and TBUT were performed 3 times, and the average of the 3 values was recorded for the analysis.

Corneal fluorescein staining and conjunctival fluorescein staining were performed using a slit-lamp camera. One minute after fluorescein instillation, the upper eyelid was lifted slightly, and to grade the whole corneal surface, the patient was asked to look straight forward. To grade the temporal conjunctiva, the subject looked nasally and to grade the nasal conjunctiva, the subject looked temporally. Staining was presented by punctate dots on the cornea and conjunctiva and was scored from 1 to 4 based on its severity.[20] Data obtained from these tests on the involved and fellow eyes from each group, and also from the control group, were compared.

Using SPSS software, statistical analysis of the data was performed. The normality of all data samples was first checked by means of the Kolmogorov–Smirnov test. When parametric analysis was possible, the Student t test was performed for all parameter comparisons. Otherwise, variables were analyzed using the χ^2 test. The data were expressed as mean ± SD.

RESULTS

A total of 141 patients were included in the study: 56 patients in the herpetic group (mean age, 45.3 ± 9.1), 29 patients in the neurotrophic ulcer group (mean age, 49.4 ± 7.1), and 56 participants in the control group (mean age,

TABLE 1. *P* Values of Differences in Ocular Surface Measures Between Different Study Groups

	Herpetic vs. Control	Neurotrophic vs. Control	Fellow Herpetic vs. Control	Fellow Neurotrophic vs. Control	Herpetic vs. Neurotrophic
Discomfort	0.048	<0.001	0.003	<0.001	0.03
Visual symptoms	0.002	<0.001	0.002	0.04	0.04
Conjunctival injection	0.14	0.009	0.2	0.2	<0.001
Conjunctival staining	0.08	0.005	0.08	0.07	0.03
Corneal staining	0.02	0.006	0.7	0.09	<0.001
Corneal tear signs	0.03	0.008	0.5	0.2	<0.001
MGD	0.1	0.07	0.7	0.1	0.09
TBUT	0.04	0.006	0.003	0.004	0.8
Schirmer test	0.009	<0.001	0.04	0.005	0.1
Osmolarity	0.007	<0.001	0.003	0.02	0.6

MGD, meibomian gland dysfunction; TBUT, tear break-up time.

TABLE 2. Dry Eye Severity Grading Scoring[14] in Each Group of Patients

	Herpetic	Fellow Herpetic	Neurotrophic	Fellow Neurotrophic	Control
Discomfort	1.6 ± 0.7	1.4 ± 0.9	3 ± 0.6	1.9 ± 0.9	1.3 ± 0.5
Visual symptoms	1.7 ± 0.8	1.5 ± 0.9	3.4 ± 0.7	1.6 ± 0.8	1.3 ± 0.7
Conjunctival injection	1.7 ± 0.9	1.6 ± 0.9	2.8 ± 0.8	1.6 ± 0.6	1.5 ± 0.7
Conjunctival staining	1.8 ± 0.9	1.6 ± 0.9	3.2 ± 0.8	2.1 ± 1	1.3 ± 0.5
Corneal staining	2 ± 0.9	1.5 ± 0.8	3.2 ± 0.9	1.8 ± 0.9	1.4 ± 0.7
Corneal/tear signs	2.3 ± 0.9	1.7 ± 0.7	3.3 ± 0.8	1.8 ± 0.9	1.6 ± 0.7
Lid/meibomian glands	2.2 ± 1	1.6 ± 0.8	3.4 ± 0.7	1.9 ± 0.9	1.5 ± 0.7
TBUT, s	5.8 ± 3.6	8.3 ± 3.2	5.3 ± 3.9	7.9 ± 4	12.1 ± 3.3
Schirmer test, mm	6.3 ± 3.4	9.2 ± 3.9	4.5 ± 3	8.1 ± 3.9	12.9 ± 3
Osmolarity	304.8 ± 7.3	299.9 ± 8.1	305.9 ± 9	295 ± 9.2	292.7 ± 5.9

MGD, meibomian gland dysfunction; TBUT, tear break-up time.

47.9 ± 6.4). Comparative data and *P* values of each group are presented in Tables 1 and 2. The discomfort level (1.6 ± 0.7 vs. 1.3 ± 0.5, $P = 0.048$), visual symptoms of dry eye (1.7 ± 0.8 vs. 1.3 ± 0.7, $P = 0.002$), corneal staining (2 ± 0.9 vs. 1.4 ± 0.7, $P = 0.02$), corneal tear signs (2.3 ± 0.9 vs. 1.6 ± 0.7, $P = 0.03$), TBUT (5.8 ± 3.6 vs. 12.1 ± 3.3 seconds, $P = 0.04$), Schirmer test score (6.3 ± 3.4 vs. 12.9 ± 3 mm, $P = 0.009$), and tear osmolarity (304.8 ± 7.3 vs. 292.7 ± 5.9 mm, $P = 0.007$) were significantly higher in herpetic eyes compared with those of normal controls. There were no statistically significant differences between normal and herpetic groups in conjunctival injection (1.5 ± 0.7 vs. 1.7 ± 0.9, $P = 0.14$), conjunctival staining (1.3 ± 0.5 vs. 1.8 ± 0.9, $P = 0.08$), and MGD indices (1.5 ± 0.7 vs. 2.2 ± 1, $P = 0.1$). Neurotrophic ulcers have significantly inferior ocular surface values in all measured parameters compared with those of normal controls [discomfort level (3 ± 0.6 vs. 1.3 ± 0.5, $P < 0.001$), visual symptoms of dry eye (3.4 ± 0.7 vs. 1.3 ± 0.7, $P < 0.001$), conjunctival injection (2.8 ± 0.8 vs. 1.5 ± 0.7, $P = 0.009$), conjunctival staining (3.2 ± 0.8 vs. 1.3 ± 0.5, $P = 0.005$), corneal staining (3.2 ± 0.9 vs. 1.4 ± 0.7, $P = 0.006$), corneal tear signs (3.3 ± 0.8 vs. 1.6 ± 0.7, $P = 0.008$), TBUT (5.3 ± 3.9 vs. 12.1 ± 3.3, $P = 0.006$), Schirmer test score (4.5 ± 3 vs. 12.9 ± 3, $P < 0.001$), and tear osmolarity (305.9 ± 9 vs. 292.7 ± 5.9, $P < 0.001$)] except for the MGD index ($P = 0.07$).

The normal fellow eye of the herpetic keratitis group had significantly higher discomfort levels (1.4 ± 0.9 vs. 1.3 ± 0.5, $P = 0.003$), visual symptoms (1.5 ± 0.9 vs. 1.3 ± 0.7, $P = 0.002$), TBUT (8.3 ± 3.2 vs. 12.1 ± 3.3, $P = 0.003$), Schirmer test scores (9.2 ± 3.9, 12.9 ± 3, $P = 0.04$), and tear osmolarity (299.9 ± 8.1 vs. 292.7 ± 5.9, $P = 0.003$) in comparison with normal controls. The normal fellow eye of the neurotrophic ulcer group had significantly inferior values of discomfort level (1.9 ± 0.9 vs. 1.3 ± 0.5, $P < 0.001$), TBUT (7.9 ± 4 vs. 12.1 ± 3.3, $P = 0.004$), Schirmer test score (8.1 ± 3.9 vs. 12.9 ± 3, $P = 0.005$), and tear osmolarity (295 ± 9.2 vs. 292.7 ± 5.9, $P = 0.02$) compared with normal controls.

Although there were statistically significant differences between values in different groups, some mean scores in the affected groups were still in the normal range. The TBUT is considered normal if it is higher than 10 seconds and abnormal if it is lower than 5 seconds. The TBUT of 5 to 10 is within the borderline range.[21] The mean value is between 5 and 10 seconds in all groups (herpetic, neurotrophic, and their fellow uninvolved eyes) except for the normal control, which was higher than 10 seconds. The Schirmer I test result is considered normal if it is higher than 10 mm and abnormal if it is lower than 5 mm. The range of 5 to 10 is the borderline range.[21] The mean value is between 5 and 10 mm in 3 groups (herpetic, neurotrophic, and fellow neurotrophic groups) and above 10 mm in 2 groups (normal controls and fellow herpetic groups).

DISCUSSION

Although chronic inflammation of the ocular surface is not the etiologic cause of dry eye, it may influence tear secretion and increase tear evaporation by reduction in sensation and blinking.[21,22] The lack of clinical signs of viral replication is an important sign of disease improvement, but it does not imply complete resolution of the infection. Choudhary et al[23] reported that inflammation of the ocular surface can persist during the chronic phase of the disease and cause long-lasting dry eye. Another study reported that recurrent corneal herpes infection causes long-standing changes in the ocular surface, even when the patient is symptom free.[24]

In this study, 10 subjective and objective tests were applied to investigate tear dysfunction in quiescent herpetic eyes and fellow normal eyes and comparable results were observed.

Keijser et al[25] compared unilateral herpetic patients with normal control group participants with the aid of fluorometry and reported a decreased tear turnover in both eyes of unilateral herpetic patients. Fluorometry is not a routine clinical practice. Hence, we used tear osmolarity in addition to other objective and subjective measures to evaluate the ocular surface condition. Tear osmolarity is proposed as the gold standard diagnostic test for dry eye[26,27] and it is easily applicable in daily practice.[28] Keijser et al[25] reported the integrity of the ocular surface as an important factor in corneal health and vision quality. Similarly, in a similar study on unilateral quiescent herpetic keratitis,

M'Garrech et al[24] reported higher tear osmolarity and lower Schirmer scores and TBUT levels bilaterally. Simard-Lebrun et al[17] reported bilateral reduction in Schirmer test results in unilateral quiescent herpetic interstitial keratitis. They also found lower corneal sensitivity in the affected eye.

Another case–control study reported no significant difference between the herpetic eye and the fellow normal eye when the Schirmer test and TBUT are used as the measures of dry eye.[18] Hamrah et al[29] recently reported bilateral loss of the corneal nerve plexus in unilateral herpes zoster ophthalmicus.

In this report, both eyes of unilateral resolved herpetic stromal keratitis were compared with the normal population, and it was found that both the involved and uninvolved normal fellow eyes were drier than those of normal controls. The results are comparable with some studies mentioned in the discussion. Normal control group eyes and 4 study groups (resolved herpetic group, fellow eye of the herpetic group, neurotrophic group, and fellow eye of the neurotrophic group) were compared for 10 dry eye measures (Tables 1 and 2). Compared with normal controls, the group with neurotrophic ulcers had a significantly poorer condition in 9 of 10 dry eye values. The resolved stromal herpetic group had a significantly poorer condition in 7 of 10 values. Fellow eyes of herpetic and neurotrophic eyes had significantly poorer results compared with those of normal controls in 5 of 10 values. Therefore, it is proposed that the fellow eye of the herpetic or neurotrophic ulcer group has similar dry eye components, although not as severe as the involved eye. Involved eyes of herpetic and neurotrophic groups were also compared and poorer results in all subjective values (discomfort and visual symptoms) were obtained, in addition to conjunctival injection, conjunctival and corneal staining, and corneal tear signs in neurotrophic ulcers. This difference shows a poorer ocular surface condition in neurotrophic ulcers compared with quiescent herpetic eyes.

Some hypotheses have been presented to justify the fellow eye's ocular surface condition in unilateral corneal involvement. The fellow normal eye may suffer from asymptomatic herpetic involvement causing ocular surface inflammation and the ocular surface problem could be a result of this inflammation. Kumar et al[30] reported HSV-1 secretion in tears of symptom-free subjects. Another study reported 2% to 4% of HSV-1 genome incidence in corneas of eye banks,[31] whereas the prevalence of the disease in the normal population is approximately 0.1%.[32] This difference shows the large percentage of normal eyes with subclinical herpetic involvement, which may be presented as ocular surface abnormalities.

The reduction in corneal sensation in the involved eye of unilateral HSV keratitis or neurotrophic ulcers may cause defective afferent pathways of the tear reflex bilaterally.[33] Chronic involvement of this pathway may lead to reduced blinking rate, increased tear evaporation, increased tear osmolarity, instability of tear film, and ocular surface deterioration in the unaffected eye. This hypothesis agrees with many previous reports. Gilbard and Rossi[34] reported tear hyperosmolarity after surgical trigeminal denervation in rabbits. Gallar et al[35] reported bilateral reduction in corneal sensation in patients with quiescent herpetic keratitis. Topical anesthetic instillation in rabbit eyes reduced lacrimation up to 75% and blinking approximately 30% bilaterally.[36] Townsend reported secondary trigeminal nerve demyelination after HSV-1 keratitis[37] leading to the disruption of the neural reflex of tear secretion.

Bilateral neuronal involvement after unilateral neurologic injury has been reported previously.[38] Hamrah et al[39] using confocal microscopy documented bilateral changes in corneal nerves in HSK. Oaklander et al[40] reported contralateral skin nerve involvement in unilateral shingles. There are studies proving that peripheral trigeminal nerves project to contralateral brain stem nuclei and the caudal medulla.[41,42]

It can be concluded that the ocular surface condition is worse in neurotrophic ulcers in comparison with quiescent herpetic keratitis. However, normal fellow eyes of cases with unilateral herpetic keratitis and neurotrophic ulcers have inferior objective and subjective ocular surface scores compared with those of normal controls. Finally, we may conclude that dry eye disease by nature is a bilateral finding even if the initiating factors are unilateral. Further studies on other causes of dry eye may be helpful to confirm this finding.

REFERENCES

1. Liesegang TJ. Herpes simplex virus epidemiology and ocular importance. *Cornea*. 2001;20:1–13.
2. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *J Pain*. 2008;9(suppl 1):S3–S9.
3. Liesegang TJ. Varicella-zoster virus eye disease. *Cornea*. 1999;18: 511–531.
4. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology*. 2008;115(2 suppl): S3–S12.
5. Pavan-Langston D. Herpes zoster ophthalmicus. *Neurology*. 1995;45(12 suppl 8):S50–S51.
6. Liedtke W, Opalka B, Zimmermann CW, et al. Age distribution of latent herpes simplex virus 1 and varicella-zoster virus genome in human nervous tissue. *J Neurol Sci.* 1993;116:6–11.
7. Nishida T, Yanai R. Advances in treatment for neurotrophic keratopathy. *Curr Opin Ophthalmol.* 2009;20:276–281.
8. Moudgil SS, Singh M, Parmar IP, et al. Tear film flow and stability in herpes simplex keratitis and chronic blepharitis. *Acta Ophthalmol (Copenh).* 1986;64:509–511.
9. de Koning EW, van Bijsterveld OP. Schirmer test values and lysozyme content of tears in acute dendritic keratitis. *Invest Ophthalmol Vis Sci.* 1984;25:55–58.
10. Labetoulle M, Auquier P, Conrad H, et al. Incidence of herpes simplex virus keratitis in France. *Ophthalmology*. 2005;112:888–895.
11. Liesegang TJ. Epidemiology of ocular herpes simplex. Natural history in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol.* 1989;107:1160–1165.
12. Knickelbein JE, Hendricks RL, Charukamnoetkanok P. Management of herpes simplex virus stromal keratitis: an evidence-based review. *Surv Ophthalmol.* 2009;54:226–234.
13. Tsubota K, Fujihara T, Saito K, et al. Conjunctival epithelium expression of HLA-DR in dry eye patients. *Ophthalmologica*. 1999;213:16–19.
14. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. *Cornea*. 2006;25: 900–907.
15. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. *Arch Ophthalmol.* 2012;130:90–100.
16. Lin H, Liu ZG, Li W, et al. Preliminary investigation on tear film alterations in latent herpes stromal keratitis [in Chinese]. *Zhonghua Yan Ke Za Zhi.* 2010;46:785–790.

17. Simard-Lebrun A, Boisjoly H, Al-Saadi A, et al. Association between unilateral quiescent stromal herpetic keratitis and bilateral dry eyes. *Cornea*. 2010;29:1291–1295.
18. Pflugfelder SC, Jones D, Ji Z, et al. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjogren's syndrome keratoconjunctivitis sicca. *Curr Eye Res.* 1999;19:201–211.
19. Holly FJ, Beebe WE, Esquivel E. Lacrimation kinetics in humans as determined by a novel technique. In: Holly FJ, Lamberts DW, MacKeen DL, eds. *Preocular Tear Film in Health, Disease and Contact Lens Wear*. Lubbock, TX: The Dry Eye Institute; 1986:76–88.
20. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*. 2003;22:640–650.
21. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007;5:75–92.
22. Stern ME, Pflugfelder SC. Inflammation in dry eye. *Ocul Surf.* 2004;2:124–130.
23. Choudhary A, Hiscott P, Hart CA, et al. Suppression of thrombospondin 1 and 2 production by herpes simplex virus 1 infection in cultured keratocytes. *Mol Vis.* 2005;11:163–168.
24. M'Garrech M, Rousseau A, Kaswin G, et al. Impairment of lacrimal secretion in the unaffected fellow eye of patients with recurrent unilateral herpetic keratitis. *Ophthalmology*. 2013;120:1959–1967.
25. Keijser S, van Best JA, Van der Lelij A, et al. Reflex and steady state tears in patients with latent stromal herpetic keratitis. *Invest Ophthalmol Vis Sci.* 2002;43:87–91.
26. Gilbard JP, Farris RL. Tear osmolarity and ocular surface disease in keratoconjunctivitis sicca. *Arch Ophthalmol.* 1979;97:1642–1646.
27. Anthony JB, Yokoi N, Gouveia MS. Using osmolarity to diagnose dry eye: a compartmental hypothesis and review of our assumptions. In: Sullivan DA, Stern ME, Tsubota K, et al, eds. *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3*. Springer; 2002:1087–1095.
28. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol.* 2011;151:792–798.e791.
29. Hamrah P, Cruzat A, Dastjerdi MH, et al. Unilateral herpes zoster ophthalmicus results in bilateral corneal nerve alteration: an in vivo confocal microscopy study. *Ophthalmology*. 2013;120:40–47.
30. Kumar M, Hill JM, Clement C, et al. A double-blind placebo-controlled study to evaluate valacyclovir alone and with aspirin for asymptomatic HSV-1 DNA shedding in human tears and saliva. *Invest Ophthalmol Vis Sci.* 2009;50:5601–5608.
31. van Gelderen BE, Van der Lelij A, Treffers WF, et al. Detection of herpes simplex virus type 1, 2 and varicella zoster virus DNA in recipient corneal buttons. *Br J Ophthalmol.* 2000;84:1238–1243.
32. Liesegang TJ, Melton LJ III, Daly PJ, et al. Epidemiology of ocular herpes simplex. Incidence in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol.* 1989;107:1155–1159.
33. Battat L, Macri A, Dursun D, et al. Effects of laser in situ keratomileusis on tear production, clearance, and the ocular surface. *Ophthalmology*. 2001;108:1230–1235.
34. Gilbard JP, Rossi SR. Tear film and ocular surface changes in a rabbit model of neurotrophic keratitis. *Ophthalmology*. 1990;97:308–312.
35. Gallar J, Tervo TM, Neira W, et al. Selective changes in human corneal sensation associated with herpes simplex virus keratitis. *Invest Ophthalmol Vis Sci.* 2010;51:4516–4522.
36. Jordan A, Baum J. Basic tear flow. Does it exist? *Ophthalmology*. 1980;87:920–930.
37. Townsend JJ. The demyelinating effect of corneal HSV infections in normal and nude (athymic) mice. *J Neurol Sci.* 1981;50:435–441.
38. Oaklander AL, Brown JM. Unilateral nerve injury produces bilateral loss of distal innervation. *Ann Neurol.* 2004;55:639–644.
39. Hamrah P, Cruzat A, Dastjerdi MH, et al. Corneal sensation and subbasal nerve alterations in patients with herpes simplex keratitis: an in vivo confocal microscopy study. *Ophthalmology*. 2010;117:1930–1936.
40. Oaklander AL, Romans K, Horasek S, et al. Unilateral postherpetic neuralgia is associated with bilateral sensory neuron damage. *Ann Neurol.* 1998;44:789–795.
41. Jacquin MF, Chiaia NL, Rhoades RW. Trigeminal projections to contralateral dorsal horn: central extent, peripheral origins, and plasticity. *Somatosens Mot Res.* 1990;7:153–183.
42. Pfaller K, Arvidsson J. Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. *J Comp Neurol.* 1988;268:91–108.