Corneal Sensitivity and Tear Function in Recurrent Corneal Erosion Syndrome

Eugene Yu-Chuan Kang,[1,2] Hung-Ta Chen,[3] Yi-Jen Hsueh,[1,4] Hung-Chi Chen,[1,2,4] Hsin-Yuan Tan,[1,2] Ching-Hsi Hsiao,[1,2] Lung-Kun Yeh,[1,2] and Wei-Chi Wu[1,2]

[1]Department of Ophthalmology, Chang Gung Memorial Hospital, Linkou, Taiwan
[2]Department of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[3]Department of Internal Medicine, Taipei City Hospital-Heping Branch, Taipei, Taiwan
[4]Center for Tissue Engineering, Chang Gung Memorial Hospital, Taoyuan, Taiwan

PURPOSE. To determine the association of corneal sensitivity and tear functions on the prognosis of eyes after posttraumatic recurrent corneal erosion syndrome (RCES).

METHODS. Patients were enrolled retrospectively and had unilateral RCES and a history of ocular surface trauma. A corneal sensitivity test and tear function test (tear break-up time and Schirmer test) were performed at three time points (month 1 to month 3, month 3 to month 6, and month 6 to month 12). Depending on the number of recurrences during the follow-up, patients were divided into group A (n > 2) or group B (n = 2). A comparison between diseased and normal fellow eyes in each patient was performed.

RESULTS. A total of 31 patients were enrolled and divided into group A (n = 14) and group B (n = 17). The mean age was 40.3 ± 12.2 years, whereas the mean follow-up was 28.0 ± 3.6 months. During the study period, corneal sensitivity, tear break-up time, and the Schirmer test results were all lower in diseased eyes than in normal fellow eyes in both groups. Compared to the first time point, recovery of corneal sensitivity and the Schirmer test values were observed in diseased eyes in group B at the second and third time points.

CONCLUSIONS. Poor corneal sensitivity and tear function are associated with posttraumatic RCES. Recovery of corneal sensitivity and tear function may be associated with a reduction of recurrence in eyes with posttraumatic RCES.

Keywords: recurrent corneal erosion syndrome, corneal sensitivity, tear functions, recurrence

Recurrent corneal erosion syndrome (RCES) has long been recognized as a common disorder of the corneal epithelium and characterized by repeated episodes of a sudden onset of eye pain, usually at night or upon awakening, accompanied by redness, photophobia, and tearing.[1–3] Most patients presenting with RCES have a history of a previous superficial trauma to the cornea (posttraumatic RCES)[4] or evidence of diabetes mellitus or epithelial basement membrane dystrophy (EBMD).[5,6] Typically, the pathology features ultrastructural change, including loosened adhesion of the corneal epithelium, which includes a deficiency of the epithelial basement membrane,[5,7] absence and abnormality of hemidesmosomes,[7–9] and loss of anchoring fibrils.[5,10,11] Although the epidemiology, natural history, and pathogenesis of RCES have been widely studied,[1,2,12,13] the factors governing the progression and prognosis of RCES are largely unknown.

For decades, knowledge of corneal sensation and tear functions in ocular surface disorders has accumulated.[14,15] Nevertheless, the neural basis for various ocular surfaces disorders is not well understood,[16] notably for RCES. Corneal innervation has pivotal trophic influences on the corneal epithelium and is essential for the maintenance of a healthy ocular surface, both structurally and functionally.[17] Many ocular surface disorders present with neurotrophic phenomena, either primarily or secondarily, and most of them are classified as a neurotrophic keratopathy, one of the most difficult and challenging diseases among all corneal diseases.[18] Recently, in vivo confocal microscopy (IVCM) of corneas with RCES has shown damaged sub-basal nerves.[19,20] More recently, substance P-derived peptide and insulin-like growth factor have been successfully used to treat a patient with nonhealing traumatic corneal erosion.[21] These reports highlighted the role of corneal sensory innervation in RCES. Herein, we aimed to review patients with posttraumatic RCES and to investigate the roles of corneal sensation and tear functions in RCES eyes versus normal eyes.

METHODS

Patients and Methods

A retrospective chart review was performed on 39 patients who had unilateral RCES (macroform)[22] and were consecutively attended by one ophthalmologist for a follow-up of at
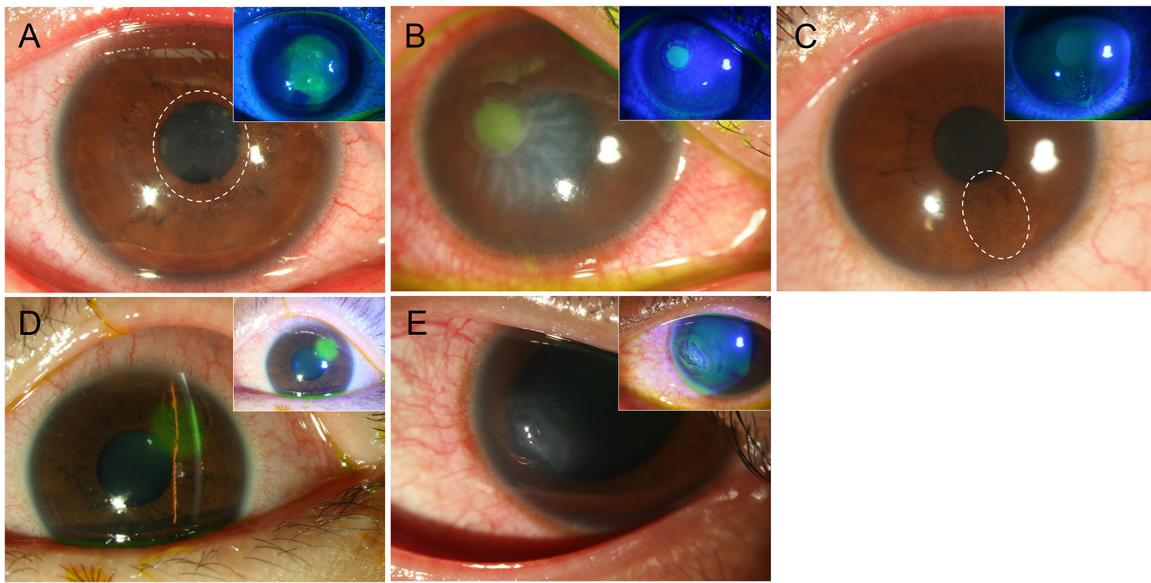
Figure 1. Representative external images of eyes with recurrent corneal erosion. The locations of the erosions were carefully detected and recorded as central (**A**, area within 3 mm of visual axis) or noncentral (**B**, superonasal; **C**, inferonasal; **D**, superotemporal; **E**, inferotemporal areas). We used the right eye to demonstrate the location of the lesions. The most common location of the lesions was the central area (n = 11), followed by inferotemporal (n = 7), inferonasal (n = 6), superotemporal (n = 4), and the superonasal (n = 3) quadrant.

least 2 years. The study protocol adhered to the Declaration of Helsinki and was approved by the Chang Gung Medical Hospital Institutional Review Board (96-0036B).

A diagnosis of RCES was made based on a history of ocular surface trauma with at least two additional episodes of corneal erosion and the presence of a spontaneously occurring focal epithelial defect or an area of loosely adherent epithelium, confirmed by staining or pooling of fluorescein. All eyes were evaluated for the causes, frequency, and presenting symptoms of corneal erosion and underwent ophthalmologic examinations. The follow-up frequency was weekly or biweekly for 1 month, monthly or bimonthly for 6 months, and then quarterly or semiannually indefinitely. Three time points were used: month 1 to month 3 (first time point), month 3 to month 6 (second time point), and month 6 to month 12 (third time point) after the last RCES episode. The inclusion criteria were patients with (1) a memorable episode of an ocular surface trauma within 2 years, (2) a minimum of two episodes of corneal erosion after the trauma, (3) a minimum follow-up of 2 years, (4) final best-corrected visual acuity (BCVA) better than 20/40, and (5) final intraocular pressure (IOP) < 22 mm Hg. The exclusion criteria were patients with (1) a history of wearing contact lenses or diabetes mellitus, (2) evidence of EBMD or previous corneal inflammation, (3) prior or subsequent ocular surgery, (4) dry eye syndrome (tear break-up time [TBUT] < 5 mm or Schirmer test < 5 mm), (5) meibomian gland dysfunction (crust, telangiectasias, or greasy secretion at the lid margin), or (6) a presumed neurological impairment, such as lagophthalmos, absent Bell phenomenon, or corneal esthesiometry < 55 mm, which may be associated with surgical injury, herpes zoster ophthalmicus, diabetic keratopathy, antiglaucoma medical therapy, and aging.[23]

Routine ophthalmic examinations, corneal sensitivity measurements, TBUT, and the Schirmer test with topical anesthesia were performed on both eyes at least once at each time point. For those who failed to be followed at our clinics after 12 months, information on their ocular health status was acquired by a telephone questionnaire to achieve a minimum of 2 years' observation without any RCES event. For all patients, conservative management was adopted using topical lubricants, oral doxycycline, a pressure gauze patch, or therapeutic soft contact lenses. No surgical intervention was performed on any patient during the study period. Routine ophthalmic examinations were documented, including BCVA, slit-lamp biomicroscopy, and intraocular pressure IOP. BCVA was determined from the Snellen chart and calculated as the logarithm of the minimal angle of resolution (logMAR). A broad, angled slit-beam examination and retroillumination examination after dilation of the pupil were used to aid in the detection of signs of EBMD (Haag-Streit, Knoitz, Switzerland). The location of the erosions was carefully detected and recorded as central (area within 3 mm of visual axis) or noncentral (i.e., superonasal, inferonasal, superotemporal, and inferotemporal areas other than the central 3 mm area) (Fig. 1). Pneumotonometry was used to measure IOP (Topcon c60, Topcon Corp, Tokyo, Japan).

Measurement of corneal sensitivity was performed using a Cochet-Bonnet esthesiometer (Luneau Ophthalmologia, Chartes Cedex, France), which was equipped with an adjustable 60-mm-long nylon monofilament. The filament was soft when fully extended and became firm when retracted into the handpiece, creating a pressure gradient that ranged from 11 to 200 mg/mm². To measure corneal sensation, the nylon monofilament was smoothly and perpendicularly applied toward the corneal surface, avoiding touching the eyelashes, and contact was detected by the slightest bend of the nylon. If a patient did not notice the touch at the 60-mm length, the monofilament was downward adjusted at intervals of 5 mm until sensation was perceived. Patient reliability was tested by bringing the filament close to the cornea without actually touching it. The length was recorded in millimeters. Measurements were

taken from the lesion location of the cornea with RCES after complete recovery of the epithelial defect and the corresponding point on the fellow cornea. For example, if the primary lesion was located on the inferonasal cornea of the right eye, the corresponding point would be the inferonasal cornea of the left eye.

Tear function tests consisted of TBUT and the Schirmer test. TBUT was performed before the corneal sensitivity test. A strip of moistened fluorescein paper (Haag-Streit) was used to touch the inferior fornix shortly to instill fluorescein. Patients were asked to blink several times to facilitate an even distribution of the stain. The interval (seconds) from the last complete blink to the first emergence of negative staining was recorded, as described elsewhere.[24] For the Schirmer test, which is a measurement of basal tear secretion and was performed after the corneal sensitivity test, topical 0.5% proparacaine HCl (Alcon Laboratory, Fort Worth, TX) was instilled. Standardized strips of filter paper (Alcon Laboratory) were placed in the lateral canthus away from the cornea and left in place for 5 minutes with the eyes closed. Readings were recorded in millimeters of wetting for 5 minutes (mm/5 min).

Statistical Analysis

To further analyze the aforementioned data, patients were allocated into two groups, groups A and B. In group A, the number of recurrences was at least three, whereas in group B, the number of recurrences was two. Unless otherwise specified, data are presented in the form of the means ± standard deviations or frequencies. To compare differences in ages, recurrences, follow-up length, and final BCVA (in logMAR) between patients of groups A and B, a *t*-test was used for quantitative variables. Categorical variables, such as gender and eye laterality, of both groups were compared using a χ^2 test. To compare the differences in either corneal sensitivity or the tear function levels between diseased eyes and fellow eyes, a generalized linear mixed model was used. For chronological analyses of corneal sensitivity and tear functions at the three time points in the two groups, the group x time interaction was obtained using generalized linear mixed model for intraindividual comparisons between the diseased and fellow eyes of the patients. All of these data were analyzed using SPSS software, version 22.0 (IBM corp. Armonk, NY), where $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, eight patients were excluded (two with obscure memory and six who received a prior aggressive therapy), leaving a total of 31 patients, for whom gender, laterality of eye, cause of trauma, location of erosion, number of recurrence, follow-up (months), and final BCVA are listed in Table 1. Of the 31 patients, 18 were male (58.1%) and 13 were female (42.9%). The mean age of the patients was 40.3 ± 12.2 years (range 18-62), whereas the mean follow-up length was 28.0 ± 3.6 months (range 24-35). Five patients (14, 18, 20, 22, and 30), who were free of further recurrence at the twelfth month from the first visit, chose to discontinue the follow-up and were interviewed by telephone thenceforth to update their final ocular examinations recorded during the last outpatient follow-up.

The most common type of trauma was from a fingernail (n = 10), followed by paper (n = 7) and other minor causes.

During the whole course of the follow-up, a slit-lamp biomicroscopic examination of both eyes of all patients showed no evidence of EBMD. None of our patients presented with positive lagophthalmos or a negative Bell phenomenon, nor did they have obvious dry eye syndrome or meibomian gland dysfunction. The most common location of the lesion was the central area (n = 11), followed by the inferotemporal (n = 7), inferonasal (n = 6), superotemporal (n = 4), and superonasal (n = 3) quadrants. Fourteen patients experienced at least three episodes of RCES (group A), whereas 17 patients experienced 2 episodes (group B). All patients had a final BCVA better than 20/40 and IOP less than 22 mm Hg, whereas none sustained any adverse events related to our examinations. Table 2 presents comparisons of the demographic and clinical characteristics of groups A and B on. We could not find any significance in terms of gender, age, inflicted eye laterality, follow-up length, final BCVA, or final IOP. Only the number of recurrences was different between the two groups, given the subdivision by recurrence frequency.

Among the three time points, the change of the corneal sensitivity test values, TBUT, and Schirmer test values in group A and group B are shown in Figures 2–4, respectively. In both group A and group B, diseased eyes had lower values for corneal sensitivity (group A effect: $B = -1.64$, $P < 0.001$; group B effect: $B = -6.24$, $P < 0.001$), TBUT (group A: $B = -1.07$, $P = 0.001$; group B: $B = -0.82$, $P = 0.044$), and the Schirmer test (group A: $B = -0.93$, $P = 0.007$; group B: $B = -3.59$, $P < 0.001$) than the fellow eyes during the entire study period.

In the corneal sensitivity test (Fig. 2), there was no significant longitudinal change in diseased and fellow eyes in group A and fellow eyes in group B among the three time points, whereas recovery of corneal sensitivity was observed in diseased eyes in group B at the second and third time points (group x time interaction of second to first time point, $B = 4.47$, $P < 0.001$; third to first, $B = 5.59$, $P < 0.001$). In TBUT (Fig. 3), no change of values was observed in either group at the three time points. As for the Schirmer test (Fig. 4), increased values in diseased eyes in group B were observed at the second and third time point (group x time interaction of second to first time point, $B = 2.88$, $P < 0.001$; third to first, $B = 2.00$, $P = 0.004$). The findings suggest an association between corneal sensitivity and tear function in the tendency for recurrence.

DISCUSSION

Numerous studies have demonstrated alterations in tear functions or corneal sensitivity at the ocular surface under abnormal conditions, such as dry eye disease,[25] diabetic keratopathy,[26] wearing contact lenses,[27,28] or after refractive surgery.[29–32] However, no research has investigated the longitudinal changes in tear functions and corneal sensitivity in patients with RCES. In this study, corneal sensitivity and tear functions were both significantly decreased in the eyes of patients with RCES compared with the fellow eyes, implying a relationship between RCES and corneal sensory neuropathy.

The Schirmer test and TBUT, which have been in widespread clinical use for more than a century, are criticized for their variability and tendency to exhibit wide intrasubject, day-to-day, and visit-to-visit variations.[33] The

TABLE 1. Clinical Characteristics of 31 Eyes With Recurrent Corneal Erosion Syndrome

Patient/Gender/Age/Eye	Etiology	Location of Erosion	Number of Recurrence	Follow-up (Months)	Final BCVA
1/M/57/L	Paper	ST	2	34	20/30
2/M/36/R	Paper	IT	5	27	20/20
3/M/33/R	SCL	CN	7	31	20/30
4/M/38/L	Pencil	IT	2	30	20/25
5/M/44/L	Paper	IN	7	32	20/20
6/M/59/L	Chopstick	IN	10	33	20/20
7/F/62/R	Wire	SN	6	32	20/20
8/M/59/L	Wire	IT	4	29	20/25
9/F/57/R	Fingernail	CN	7	31	20/20
10/F/50/R	Fingernail	IT	2	35	20/25
11/M/22/R	SCL	CN	2	24	20/20
12/F/30/R	Needle	SN	2	27	20/20
13/M/18/L	Fingernail	IN	2	31	20/20
14/F/39/L[a]	Fingernail	CN	2	24	20/30
15/F/44/L	Paper	ST	7	26	20/20
16/F/45/L	Needle	CN	7	28	20/20
17/F/39L	Fingernail	CN	8	32	20/20
18/F/49/L[*]	Glasses	ST	2	24	20/20
19/F/50/R	Chopstick	CN	2	33	20/25
20/M/44/R[*]	Glasses	SN	2	24	20/20
21/M/36/L	Reed	IN	2	28	20/20
22/F/56/R[*]	Fingernail	CN	2	24	20/20
23/F/44/L	Needle	IN	2	24	20/20
24/M/23/L	Fingernail	CN	4	27	20/25
25/M/26/R	Fingernail	ST	2	24	20/20
26/M/24/R	Reed	IT	2	25	20/20
27/M/34/L	Fingernail	IT	7	30	20/20
28/M/36/R	Paper	CN	4	32	20/20
29/F/26/R	Paper	IT	2	29	20/20
30/M/33/R[*]	Fingernail	CN	2	24	20/20
31/M/35/R	Paper	IN	3	24	20/20

BCVA, best-corrected visual acuity; CN, central; F, female; IN, inferonasal; IT, inferotemporal; L, left; M, male; R, right; SN, superotemporal; ST, superotemporal; SCL, soft contact lens.
[*] Lost to follow-up since the second year, but interviewed by telephone thereafter.

TABLE 2. Comparisons Between Group A and B of 31 Eyes With Recurrent Corneal Erosion Syndrome

	Group A (n = 14)	Group B (n = 17)	P Value
Gender (male/female)	9/5	9/8	0.524
Age (years)	43.3 ± 11.9	37.8 ± 12.2	0.214
Eye laterality (OD/OS)	6/8	10/7	0.376
Number of recurrences[*]	6.1 ± 1.9	2.0 ± 0.0	<0.001
Follow-up (months)	29.6 ± 2.8	27.3 ± 4.0	0.071
Final BCVA (logMAR equivalent)	20/30 (1.4 ± 0.1)	20/25 (1.5 ± 0.1)	0.605

BCVA, best-corrected visual acuity (compared via logMAR equivalent).
[*] Group A > 2; group B = 2.

Schirmer test has never been tested on patients with RCES, except in one study.[34] Interestingly, the Schirmer I test used in that study was not performed to make a tear secretion assessment but to check the expression of gelatinase in a tear sample collection, and hence, no data regarding secretion volume were recorded. The meaningfully lower Schirmer test results in our study group can be explained by the concept of the lacrimal gland functional unit to address the importance of sensory innervation,[35] given our assumption that RCES can be viewed as a neuropathic disorder. In a previous study surveying 30 patients with recalcitrant RCES, TBUT was surprisingly reduced in all patients.[36] The over-

all value of TBUT found in our study was not very low (8-12 seconds); however, the value of diseased eyes substantially decreased throughout the entire follow-up. The tear film instability (low TBUT) may be attributed to a possible ocular surface irregularity (topographic change), which still requires future scientific support. The major drawbacks of the Cochet-Bonnet esthesiometer include a restricted stimulus range and invasiveness. Luckily, the fluctuation amplitude of sensitivity in our patients fell in an acceptable range (52 mm to 60 mm), and no iatrogenic injury was found from contact. As for other minor physiologic variations of the esthesiometer,[37] our "mirror-image" measurement
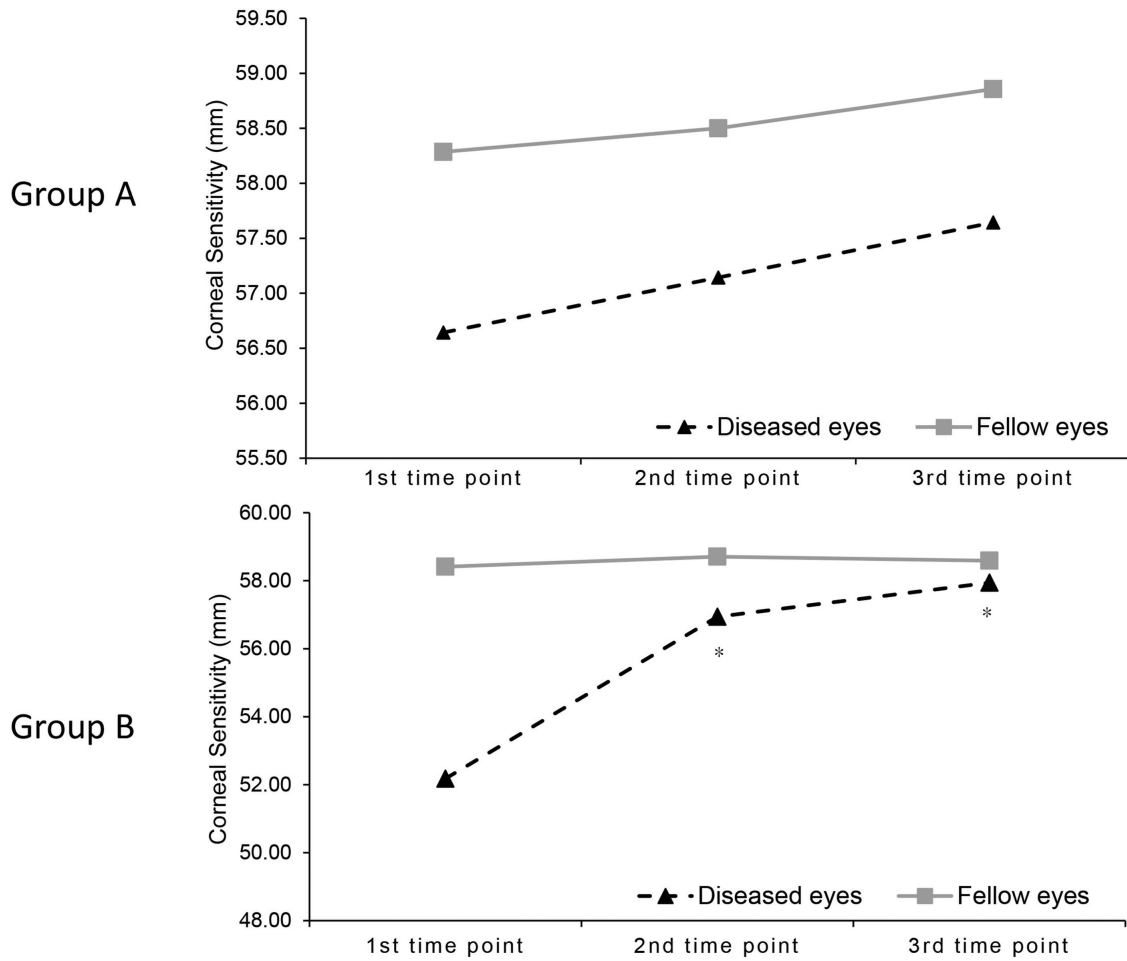
FIGURE 2. Corneal sensitivity in recurrent corneal erosion syndrome eyes and fellow eyes. Longitudinal changes of corneal sensitivity in group A (n = 14) and group B (n = 17) at three time points (first time point: month 1 to month 3; second time point: month 3 to month 6; third time point: month 6 to month 12). The group effect was analyzed by a generalized linear mixed model showing lower corneal sensitivity in diseased eyes than in fellow eyes in group A ($B = -1.64$, $P < 0.001$) and group B ($B = -6.23$, $P < 0.001$). The group × time interaction was analyzed by a generalized linear mixed model showing increased corneal sensitivity in diseased eyes in group B at the second and third time points (second to first time point, $B = 4.47$, $P < 0.001$; third to first, $B = 5.59$, $P < 0.001$). * $P < 0.05$.

protocol and incidental match in age, gender, and laterality may compensate for technical or systematic errors to some extent.

Although corneal sensitivity was similar in corneas with superficial punctate keratopathy and normal controls,[38] decreased corneal sensitivity was reported in corneas following cataract surgery, penetrating keratoplasty, lamellar keratectomy, or refractive surgery.[16] Excimer laser surgery is not only the most popular refractive surgery, but is also reciprocally related to posttraumatic RCES. Despite the proven therapeutic effect of phototherapeutic keratectomy on RCES,[39–41] there have been few reports of RCES after PRK or LASIK.[42,43] We take the large body of relevant studies on PRK and LASIK as a model, even though there are subtle differences in the cleavage planes between corneal specimens from patients with RCES and following refractive surgery.[11] Evidence from imaging (IVCM) studies indicates that sub-basal nerve regeneration may be incomplete for up to 1 year after PRK and 5 years after LASIK.[44] On the other hand, evidence from functional (corneal sensitivity) studies indicates that incomplete recovery of the mechanical threshold may take up to 1 year in PRK and 6 months

in LASIK.[16] Therefore, in this study, it is reasonable that the corneal sensitivity and Schirmer test were at a satisfactory level in eyes from group B with only two episodes of recurrence. Whether and how long it will take for aggressively treated eyes with RCES to regain sensory function remain unknown.

In a seminal paper presenting the diagnostic use of IVCM, four of seven patients with RCES were shown to have sub-basal nerve plexus abnormalities.[19] For the remaining three patients without IVCM evidence of nerve involvements, two were not receiving any treatment, suggesting a status of quiescence or cure. Because the imaging examinations of each patient were only performed once and there was no severity grading or grouping of patients, it is hard to arbitrarily correlate the evolving change of corneal sensitivity found in our study to their clinical morphological findings. In a more recent work using IVCM, an absence or reduced number of sub-basal nerves was observed in four of six patients with posttraumatic RCES.[20] Intriguingly, the remaining two "neuroanatomically normal" patients had suffered many more (>twofold) attacks than the other four patients, which was explained as regeneration of the damaged nerves
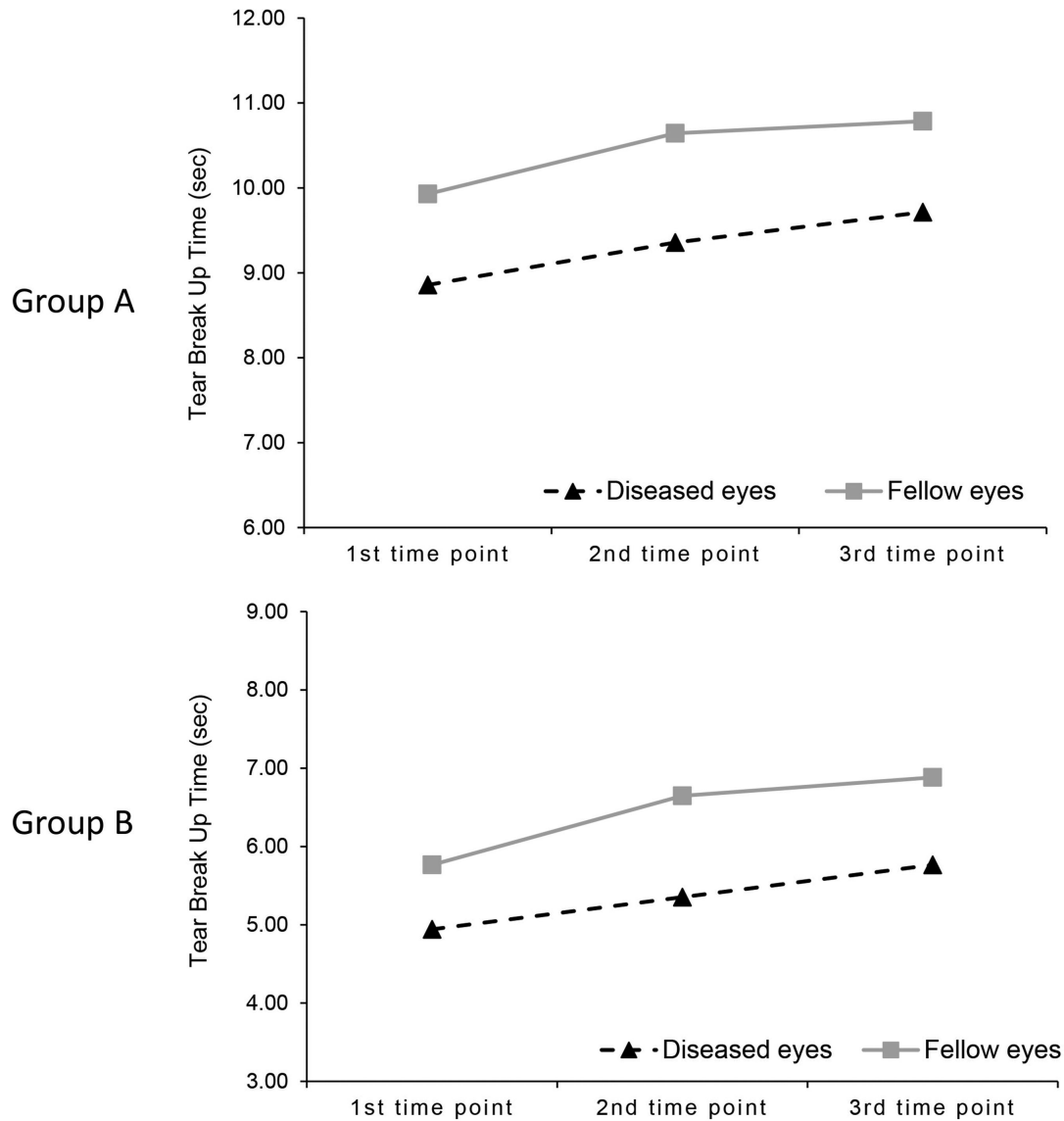
FIGURE 3. Tear break-up time in recurrent corneal erosion syndrome eyes and fellow eyes. ongitudinal changes of the tear break up time in group A (n = 14) and group B (n = 17) at three time points (first time point: month 1 to month 3; second time point: month 3 to month 6; third time point: month 6 to month 12). The group effect was analyzed by a generalized linear mixed model showing a shorter tear break-up time in diseased eyes than in fellow eyes in group A ($B = -1.07$, $P = 0.001$) and group B ($B = -0.82$, $P = 0.044$). The group × time interaction was analyzed by the generalized linear mixed model showing no significant changes in both groups at different time points.

with a prolonged examination time after erosion. Judging by our functional data of corneal sensitivity (recovered after 6 months), we are skeptical as to whether regenerated nerves would be functional according to esthesiometry approximately 1 month after onset. Nonetheless, these findings could provide an anatomical basis for our novel speculation that RCES may be related to neuropathic disorders.

There were some limitations in this study. First, the design was a retrospective investigation recruiting a nonrandomized case series, and the only observer was not masked, rendering bias inevitable. That all patients were treated and followed by only one ophthalmologist partly explains the small case number, whereas on the other hand, it strengthens the homogeneity of our data. Second, we only studied RCES patients with a previous ocular trauma, which makes it

difficult to extrapolate our results to other populations, such as those with EBMD. Patients with a single erosion event were not studied. The results of the tear function and corneal sensitivity tests in those patients require further investigation. Third, without an advanced facility, we could not provide information concerning IVCM; otherwise, we would be confident to conclude that RCES is a form of sensory neuropathy. Fourth, with the use of contact esthesiometers, we could only explore the response of mechano-nociceptors other than chemical or thermal receptors. Fifth, the role of ocular surface changes (e.g., staining pattern, topographic data) was not addressed and merits further investigation. Finally, in future studies, both biochemical and molecular analyses of tear fluids or debrided epithelia may provide more basic evidence for our preliminary findings.
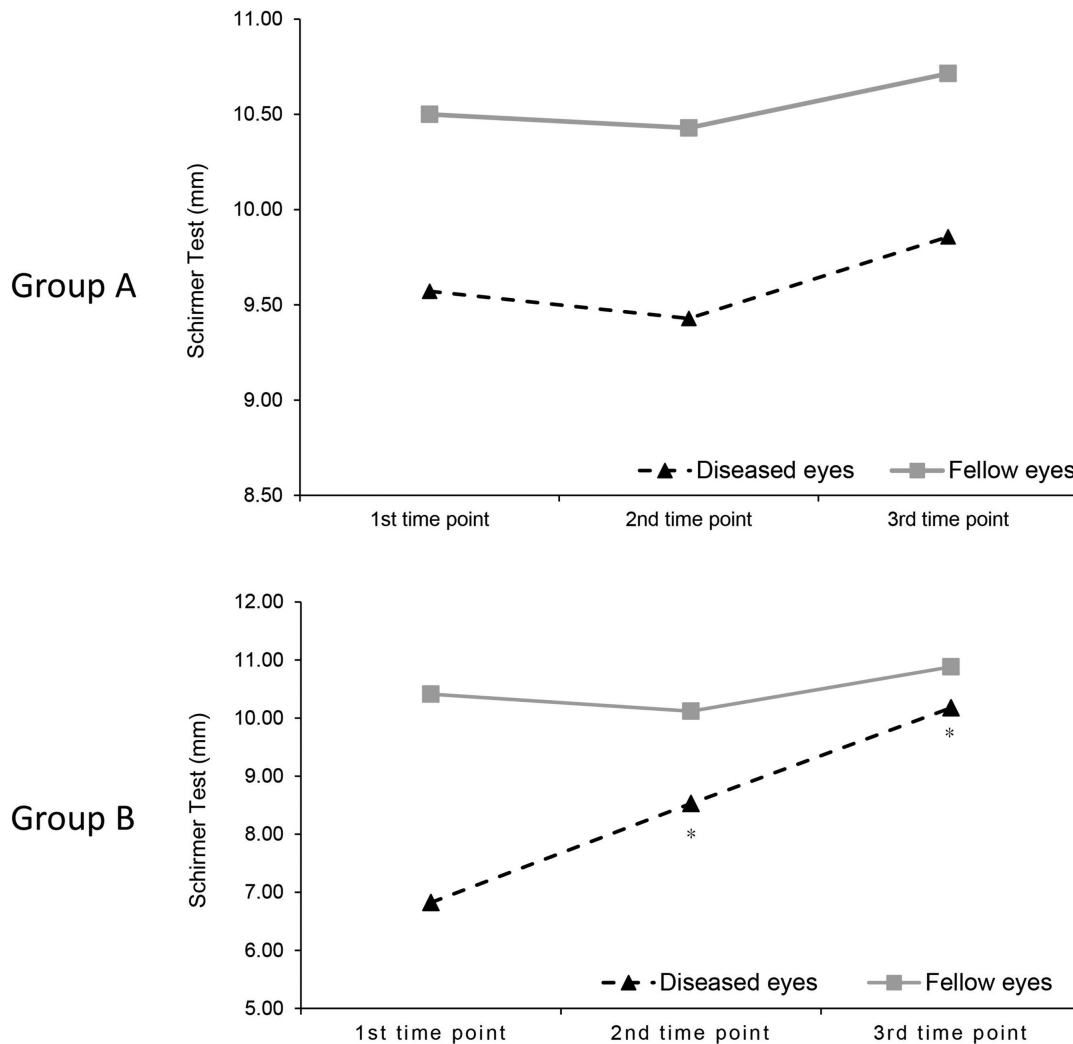
FIGURE 4. Schirmer test level in recurrent corneal erosion syndrome eyes and fellow eyes. Longitudinal changes in the Schirmer test level in group A (n = 14) and group B (n = 17) at three time points (first time point: month 1 to month 3; second time point: month 3 to month 6; third time point: month 6 to month 12). The group effect was analyzed by a generalized linear mixed model showing a lower Schirmer test level in diseased eyes than in fellow eyes in group A ($B = -0.93$, $P = 0.007$) and group B ($B = -3.59$, $P < 0.001$). The group $\times$ time interaction was analyzed by generalized linear mixed models showing increased corneal sensitivity in diseased eyes in group B at the second and third time points (second to first time point, $B = 2.88$, $P < 0.001$; third to first, $B = 2.00$, $P = 0.004$). * $P < 0.05$.

In summary, our clinical findings suggest that both corneal sensitivity and tear functions are impaired in RCES eyes. Our chronological analysis further confirms that corneal sensitivity and the Schirmer test results gradually recover over 12 months in diseased eyes of patients who suffered from two recurrences. Accordingly, the corneal sensitivity test and Schirmer test level, which are significantly related to the number of recurrences, merit future prospective studies to establish their role as prognostic indicators in patients with RCES. In addition, patients with persistently diminished corneal sensitivity and Schirmer test levels should be treated aggressively to avoid unpleasant recurrences.

References

1. Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. *Eye.* 2006;20:635–44.
2. Das S, Seitz B. Recurrent corneal erosion syndrome. *Surv Ophthalmol.* 2008;53:3–15.
3. Ewald M, Hammersmith KM. Review of diagnosis and management of recurrent erosion syndrome. *Curr Opin Ophthalmol.* 2009;20:287–291.
4. Hykin PG, Foss AE, Pavesio C, Dart JK. The natural history and management of recurrent corneal erosion: a prospective randomised trial. *Eye.* 1994;8:35–40.

5. Fogle JA, Kenyon KR, Stark WJ, Green WR. Defective epithelial adhesion in anterior corneal dystrophies. *Am J Ophthalmol.* 1975;79:925–940.

6. Brown N, Bron A. Recurrent erosion of the cornea. *Br J Ophthalmol.* 1976;60:84–96.

7. Goldman JN, Dohlman CH, Kravitt BA. The basement membrane of the human cornea in recurrent epithelial erosion syndrome. *Trans Am Acad Ophthalmol Otolaryngol.* 1969;73:471–481.

8. Tripathi RC, Bron AJ. Ultrastructural study of non-traumatic recurrent corneal erosion. *Br J Ophthalmol.* 1972;56:73–85.

9. Mencucci R, Paladini I, Brahimi B, Menchini U, Dua HS, Romagnoli P. Alcohol delamination in the treatment of recurrent corneal erosion: an electron microscopic study. *Br J Ophthalmol.* 2010;94:933–939.

10. Aitken DA, Beirouty ZA, Lee WR. Ultrastructural study of the corneal epithelium in the recurrent erosion syndrome. *Br J Ophthalmol.* 1995;79:282–289.

11. Chen YT, Huang CW, Huang FC, Tseng SY, Tseng SH. The cleavage plane of corneal epithelial adhesion complex in traumatic recurrent corneal erosion. *Mol Vis.* 2006;12:196–204.

12. Reidy JJ, Paulus MP, Gona S. Recurrent erosions of the cornea: epidemiology and treatment. *Cornea.* 2000;19:767–771.

13. Heyworth P, Morlet N, Rayner S, Hykin P, Dart J. Natural history of recurrent erosion syndrome–a 4 year review of 117 patients. *Br J Ophthalmol.* 1998;82:26–28.

14. Belmonte C, Aracil A, Acosta MC, Luna C, Gallar J. Nerves and sensations from the eye surface. *Ocul Surf.* 2004;2:248–253.

15. Bron AJ, Yokoi N, Gafney E, Tiffany JM. Predicted phenotypes of dry eye: proposed consequences of its natural history. *Ocul Surf.* 2009;7:78–92.

16. Belmonte C, Acosta MC, Gallar J. Neural basis of sensation in intact and injured corneas. *Exp Eye Res.* 2004;78:513–525.

17. Muller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003;76:521–542.

18. Bonini S, Rama P, Olzi D, Lambiase A. Neurotrophic keratitis. *Eye.* 2003;17:989–995.

19. Rosenberg ME, Tervo TM, Petroll WM, Vesaluoma MH. In vivo confocal microscopy of patients with corneal recurrent erosion syndrome or epithelial basement membrane dystrophy. *Ophthalmology.* 2000;107:565–573.

20. Chikama T, Takahashi N, Wakuta M, Morishige N, Nishida T. In vivo biopsy by laser confocal microscopy for evaluation of traumatic recurrent corneal erosion. *Mol Vis.* 2008;14:2333–2339.

21. Benitez-Del-Castillo JM, Rodriguez-Bayo S, Fontan-Rivas E, Martinez-de-la-Casa JM, Garcia-Sanchez J. Treatment of recurrent corneal erosion with substance P-derived peptide and insulin-like growth factor I. *Arch Ophthalmol.* 2005;123:1445–1447.

22. Dua HS, Lagnado R, Raj D, et al. Alcohol delamination of the corneal epithelium: an alternative in the management of recurrent corneal erosions. *Ophthalmology.* 2006;113:404–411.

23. Yang AY, Chow J, Liu J. Corneal innervation and sensation: the eye and beyond. *Yale J Biol Med.* 2018;91:13–21.

24. Lemp MA, Hamill JR, Jr. Factors affecting tear film breakup in normal eyes. *Arch Ophthalmol.* 1973;89:103–105.

25. Xu KP, Yagi Y, Tsubota K. Decrease in corneal sensitivity and change in tear function in dry eye. *Cornea.* 1996;15:235–239.

26. Rosenberg ME, Tervo TMT, Immonen IJ, Muller LJ, Gronhagen-riska C, Vesaluoma MH. Corneal structure and sensitivity in type 1 diabetes mellitus. *Invest Ophthalmol Vis Sci.* 2000;41:2915–2921.

27. Millodot M. Effect of long-term wear of hard contact lenses on corneal sensitivity. *Arch Ophthalmol.* 1978;96:1225–1227.

28. Polse KA. Etiology of corneal sensitivity changes accompanying contact lens wear Invest. *Ophthalmol Vis Sci.* 1978;17:1202–1206.

29. Koenig SB, Berkowitz RA, Beuerman RW, McDonald MB. Corneal sensitivity after epikeratophakia. *Ophthalmology.* 1983;90:1213–1218.

30. Shivitz IA, Arrowsmith PN. Corneal sensitivity after radial keratotomy. *Ophthalmology.* 1988;95:827–832.

31. Campos M, Hertzog L, Garbus JJ, McDonnell PJ. Corneal sensitivity after photorefractive keratectomy. *Am J Ophthalmol.* 1992;114:51–4.

32. Ishikawa T, Park SB, Cox C, del Cerro M, Aquavella JV. Corneal sensation following excimer laser photorefractive keratectomy in humans. *J Refract Corneal Surg.* 1994;10:417–422.

33. Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol.* 2008;146:350–356.

34. Sakimoto T, Shoji J, Yamada A, Sawa M. Upregulation of matrix metalloproteinase in tear fluid of patients with recurrent corneal erosion. *Jpn J Ophthalmol.* 2007;51:343–346.

35. Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the pathophysiology of dry eye. *Eye Res.* 2004;78:409–416.

36. Hope-Ross MW, Chell PB, Kervick GN, McDonnell PJ. Recurrent corneal erosion: clinical features. *Eye.* 1994;8:373–377.

37. Millodot M. A review of research on the sensitivity of the cornea. *Ophthalmic Physiol Opt.* 1984;4:305–318.

38. Nishida T, Chikama T, Sawa M, Miyata K, Matsui T, Shigeta K. Differential contributions of impaired corneal sensitivity and reduced tear secretion to corneal epithelial disorders. *Jpn J Ophthalmol.* 2012;56:20–25.

39. Kremer I, Blumenthal M. Combined PRK and PTK in myopic patients with recurrent corneal erosion. *Br J Ophthalmol.* 1997;81:551–554.

40. O'Brart DP, Muir MG, Marshall J. Phototherapeutic keratectomy for recurrent corneal erosions. *Eye.* 1994;8:378–383.

41. Morad Y, Haviv D, Zadok D, Krakowsky D, Hefetz L, Nemet P. Excimer laser phototherapeutic keratectomy for recurrent corneal erosion. *J Cataract Refract Surg.* 1998;24:451–455.

42. Puk DE, Probst LE, Holland EJ. Recurrent erosion after photorefractive keratectomy. *Cornea.* 1996;15:541–542.

43. Ti SE, Tan DT. Recurrent corneal erosion after laser in situ keratomileusis. *Cornea.* 2001;20:156–158.

44. Patel DV, McGhee CN. In vivo confocal microscopy of human corneal nerves in health, in ocular and systemic disease, and following corneal surgery: a review. *Br J Ophthalmol.* 2009;93:853–860.