Clinical Presentation and Causes of Recurrent Corneal Erosion Syndrome: Review of 100 Patients

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Purpose: To study the clinical features and etiology of recurrent corneal erosion syndrome (RCES).

Methods: We examined a total of 100 patients (117 eyes) with the diagnosis of RCES who presented at our institution (Instituto Clinico Quirúrgico de Oftalmología, Bilbao, Spain). Studied data included demography, etiology, corneal location, and association with meibomian gland dysfunction (MGD).

Results: The mean age of patients was 44.5 (range, 14–80) years. Attributed causes of RCES were previous minor trauma (46 eyes, 39.3%), epithelial basement membrane corneal dystrophy (20 eyes, 17.1%), photorefractive keratectomy (20 eyes, 17.1%), laser-assisted in situ keratomileusis (9 eyes, 7.7%), and of unknown origin (22 eyes, 18.8%). The most frequent site of RCES was the inferior paracentral cornea (68.4%), followed by the upper cornea (21.3%) and widespread location (21.3%). An association with MGD was found in 59% of patients.

Conclusions: RCES has various etiologies, which explains the variety in the clinical presentation of the disorder. Interestingly, a significant number of RCES patients begin to manifest the syndrome after keratorefractive surgery, and a high percentage of patients also present with MGD.

Key Words: recurrent corneal erosion syndrome, corneal erosion, meibomian gland dysfunction, photorefractive keratectomy, epithelial basement membrane dystrophy

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Recurrent corneal erosion syndrome (RCES) is a relatively common disorder, which is associated with intense ocular pain and chronic discomfort. This syndrome was first described in 1872 by Hansen,[1] who called it *intermittent neuralgic vesicular keratitis*. Occasionally, it can go unrecognized because the patient can be asymptomatic on examination. The most frequent symptoms include pain, eye watering, and photophobia on waking, and it is not unusual that the pain wakes the patient during the night.[2] Symptoms usually decline or even disappear during the day. These patients may present with serious episodes of spontaneous epithelial erosion, which cause intense pain and normally require treatment in hospital emergency services. It is not uncommon that these emergency visits are the only care that the patients receive, and this leads to a sensation of anxiety and vulnerability because the patient is unsure whether the episode will occur again or what should be done to avoid its recurrence.

RCES affects men and women equally, and it can occur at any age.[3] Normally, it affects only 1 eye, but it can also occur bilaterally.[4] The most common clinical sign is the lack of adherence of the epithelium to the anterior stroma, which is the cause of the pain and frequent erosions. In addition, microcysts and alterations to the basement membrane of the epithelium can occur; these are apparent on slit-lamp examination.[2,5] The disorder is frequently associated with minor trauma of the affected eye, such as small epithelial erosions, which do not affect the stroma. These are normally caused by objects with moderately sharp edges, such as nails or plastic, and they usually cure without further complications.[6] However, occasionally symptoms of RCES can appear from weeks to years later. The disorder also occurs frequently in patients with dystrophy of the basement membrane of the epithelium, and in such cases, it can occur bilaterally.[2] The etiology of the disease is unknown, and treatment is usually successful, but only for acute episodes of erosion. Nevertheless, despite the multiple medical and surgical treatments, which have been reported, a significant percentage of these patients continue with the symptoms for protracted periods of time.[7]

This retrospective study of 100 cases corroborates most of the previous descriptions of RCES, although we have observed a different age distribution depending on the etiology. Two different location patterns for the affected corneal epithelium were also noted, and these were found to be etiology dependent. Keratorefractive surgery was discovered to be a risk factor for RCES, especially after photorefractive keratectomy (PRK). Finally, a high incidence of meibomian gland dysfunction (MGD) in RCES patients was detected.

METHODS

Patients diagnosed with RCES had enrolled between May 2012 and June 2013 at the Cornea Clinic at the Instituto

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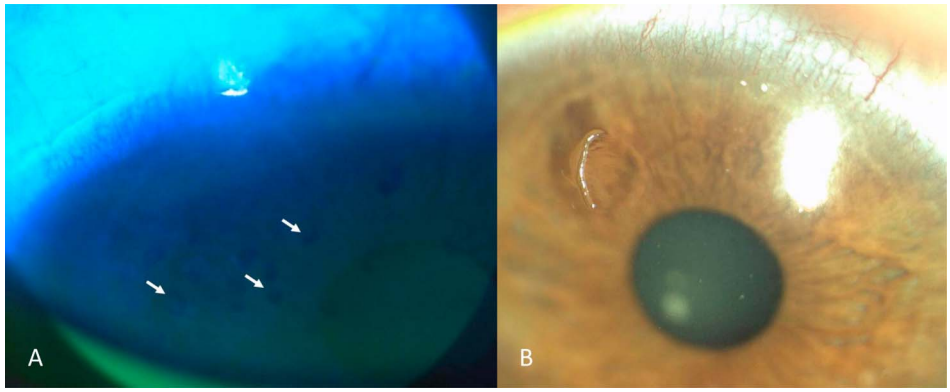

FIGURE 1. Image of the corneal surface showing black spots (arrows) that represent the areas of tear film irregularity. These black spots are apparent after fluorescein staining of the tear film of patients with RCES (A). Image of the same anterior ocular segment, illustrating loosely adherent epithelium of the upper cornea. The epithelium was found to slide easily when tested with a weck-cel (B).

Clinico Quirúrgico de Oftalmología (Bilbao, Spain). The diagnosis of RCES was based on the presence of typical symptoms in addition to clinical signs on examination. Symptoms consisted of repeated episodes of pain at night or on first awakening with redness and watering of the eye. Some patients had previously experienced repeated episodes of epithelial erosions that required emergency consultation. When previous minor eye trauma or surgery was reported, we examined whether these correlated with the onset of symptoms. The principal sign apparent with slit-lamp examination consisted of loosely adherent epithelium. Affected areas of the epithelium were identified as black spots after fluorescein staining of the tear film (Fig. 1A). Adherence of the epithelium was tested with a weck-cel sponge after topical anesthesia of the cornea. Sliding of the epithelium was demonstrated by folds created with the weck-cel sponge (Fig. 1B). We looked for signs of epithelial basement membrane corneal dystrophy (EBMD) in all patients. EBMD was defined as the presence of microcystic or map–dot–fingerprint changes in the epithelium of both eyes.

Relevant epidemiological data included sex, age (at the time of the diagnosis), affected eye, a history of surgery or trauma, presence of MGD, and localization of the affected epithelium. The diagnosis of MGD was positive only when the clinician decided to treat the condition with at least 1 of the following: daily hygiene of the lids margins, topical antibiotics, or oral tetracycline.

The affected areas of the cornea were recorded on a chart in 6 different possible locations (Fig. 2). In some cases, more than one area was involved. Patients were excluded when the epithelial erosions were associated with Reis–Buckler dystrophy, Salzmann nodular degeneration and band keratopathy, any stromal dystrophy, bullous keratopathy, and keratoconjunctivitis sicca.

RESULTS

One hundred patients (117 affected eyes) were finally included in the study. Forty-six patients (46%) were male, and 54 (54%) were female; the average patient age was 44.5 (range, 14–80) years. The modal age was 33 years (6 patients). Patient ages exhibited a Gaussian distribution, with mild differences between the male and female profiles. Men and women are affected at almost any age during their lifetime. Middle-aged patients are more often affected, creating a Gaussian distribution. The mean age was similar in both groups: 46.6 years for men (range, 23–82 years) and 46.3 years for women (range, 15–75 years). Most frequently affected males were in their 30s, whereas most frequently affected females were in their 40s.

Differences in age distribution were observed between the different etiology groups (Fig. 3). Seventeen patients presented bilateral RCES, 56 eyes were right eyes (47.4%), and 61 were left eyes (52.6%).

The most frequent causal factor was a previous minor trauma in 46 eyes (39.3%). The most common trauma was due to fingernail damage (45.2%), especially from a child. Other causes included EBMD (20 eyes or 17.1%), PRK (20 eyes or 17.1%), laser-assisted in situ keratomileusis (LASIK, 9 eyes or 7.7%), and of unknown cause (22 eyes or 18.8%). Among the 17 bilateral cases, 6 were caused by EBMD, 6 by PRK, 2 by LASIK, 2 were spontaneous, and 1 experienced a different trauma in each eye before developing RCES. All LASIK patients with RCES were female. Patients with RCES after refractive surgery did not have symptoms or signs of dry eye, Schirmer test findings were normal, as were the cornea sensitivity when tested with a cotton tip.

MGD was observed in 59 patients (59%), of whom 30 were male and 29 were female. In 11 of these patients, RCES was bilateral. MGD was observed in every etiological group (Table 1). Seventy-five percent of the patients with spontaneous RCES also presented with MGD.

Affected epithelium was most frequently found in the lower part of the cornea (68.4% of all cases) (Fig. 2). Differences were observed when data were analyzed in terms of location and causal factor. The traumatic group and the group of unknown origin had the lower part of the cornea affected in more than 60% of cases, whereas the EBMD, PRK, and LASIK groups presented a more varied location, affecting any area, and occasionally being widespread over the entire corneal surface (Fig. 4).

DISCUSSION

RCES is a relatively common disorder affecting the structures that attach the epithelium to its basement

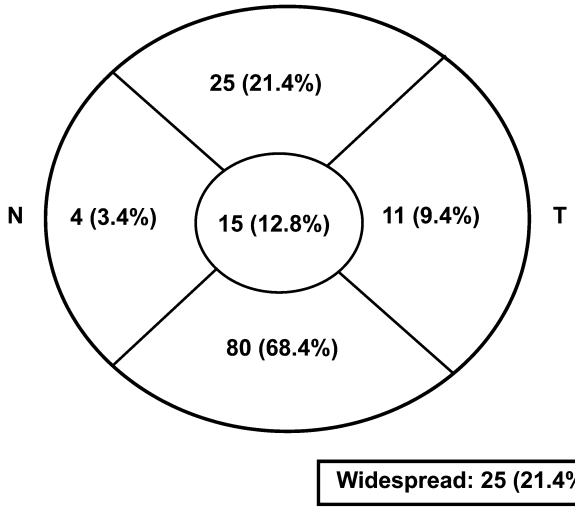

FIGURE 2. Chart used to record the location of the affected epithelium. Six possible locations were defined: upper , central, lower, nasal (N), temporal (T), and widespread. More than one location was possible in any case. The numbers indicate the mean number of eyes and the corresponding percentage of cases.

membrane and the anterior stroma.[3,8] This instability of the epithelium is the cause of the eye discomfort and of the recurrent erosions. It has been reported to occur at all ages and with the same incidence in both sexes, and it is most frequently associated with previous ocular trauma and with dystrophy of the basement membrane (EBMD).[4]

Our series of 100 patients coincides in age and sex with that reported previously (54% men and 46% women; mean age, 44.5 years; and range, 15–85 years).[3] It is noteworthy that despite the ample age range, most patients were middle aged (70% were aged between 30 and 60 years). In addition, this apparently normal age distribution exhibited differences in terms of the cause of RCES. The most frequent cause in our series was trauma (45% of patients). These were minor traumas due to small objects causing epithelial erosions, which normally resolved within days. The most frequent traumatic object was the nail, especially those of children with their parents or caretakers. However, other reported traumatic objects included a sheet of paper or plastic, a nut, a toy soldier, a straw hat, or even the antenna of a shrimp. The resulting erosions did not leave corneal opacities, and interestingly, they did not seem to be correlated with the location of the epithelium affected by the disease.

Another common cause of RCES is EBMD (17.1% of patients). This percentage is somewhat lower than that reported in other series (Hykin et al,[2] 19.7% and Reidy et al,[9] 29%). This apparent discrepancy may be because we used very stringent criteria for EBMD. Frequently, the affected eye in RCES presents microcysts and alterations of the epithelium basement membrane. However, we only included patients in the EBMD group who presented these features in both eyes. We consider that alterations in the basement membrane of the affected eye can be a consequence of the pathology, which often presents repeated erosions, and thus, it is not clear whether these changes in the basement membrane are primary or a consequence of previous erosions.

It was surprising to find that previous PRK treatment of 20 eyes (17.1% of patients) was a frequent cause of RCES, that is, the same percentage as for EBMD. The association between keratorefractive surgery (PRK, LASIK, and Intra-LASIK) and RCES has already been reported in the

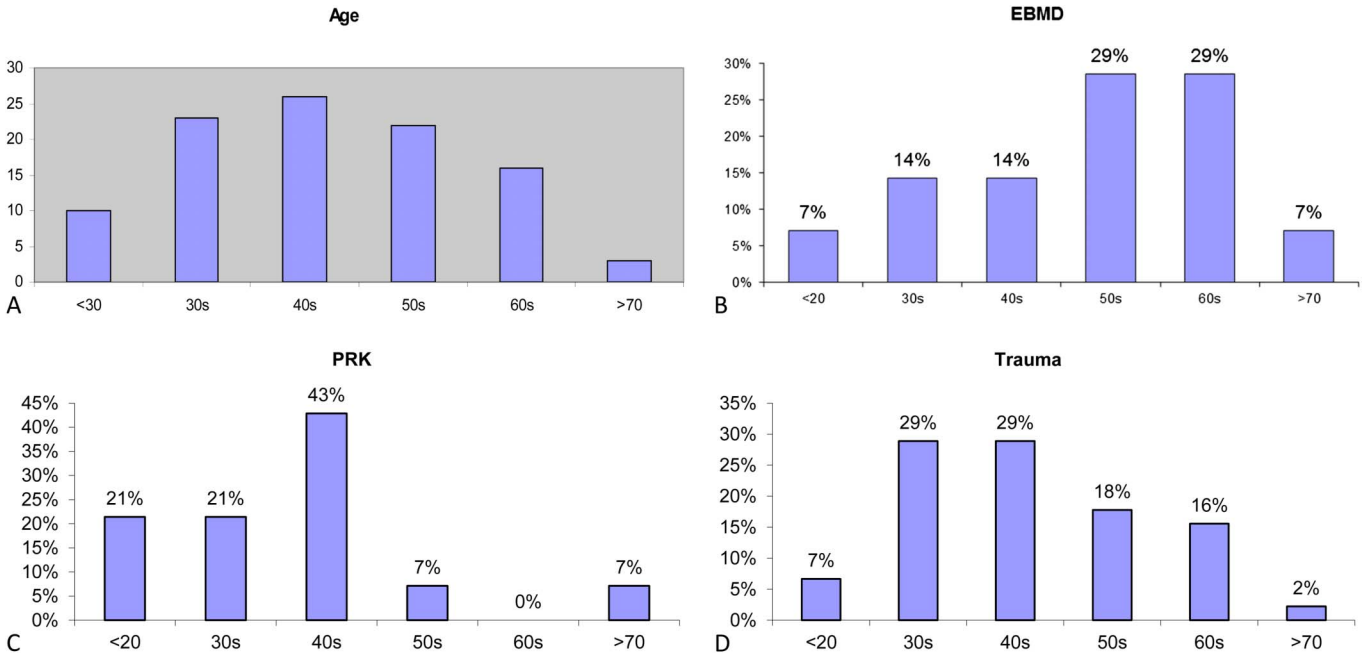

FIGURE 3. Etiology and age distribution. We observed how the Gaussian distribution of ages (A) is skewed toward older patients when the cause is EBMD (B) or toward younger patients when the etiology is PRK (C) or trauma (D).

TABLE 1. Causative Factor in 117 Eyes of 100 patients With RCES and Association With MGD

	No. Eyes (%)	No. Patients	Bilateral	MGD (%)
Trauma	46 (39.31)	45	1	28 (62.20)
EBMD	20 (17.09)	14	6	5 (35.70)
PRK	20 (17.09)	14	6	6 (42.82)
LASIK	9 (7.69)	7	2	5 (71.42)
Unknown	22 (18.80)	20	2	15 (75)

We observed a high prevalence of MGD in traumatic cases and in the group with unknown etiology.

literature.[10–13] Among these techniques, in our study, PRK is more frequently associated with RCES. This difference could in principle be due to a sampling bias, for example, in a clinic in which a larger number of surgeries are performed through PRK than through LASIK. However, LASIK is more frequently performed than PRK in our setting. On the basis of our findings, PRK treatment should be considered as a risk factor for RCES. This is somewhat more paradoxical when we consider that PRK in its phototherapeutic keratectomy (PTK) variant has been reported to be one of the treatments with the best outcome for the management of RCES. Treatment through PTK or the recently reported alcohol debridement technique[14] is based on the finding that the induction of a new process of epithelial repair can create new binding structures that bind firmly to the stroma.[15] However, according to the present data, the creation of a new stromal bed can also be the triggering cause of RCES. Thus, the same process may be both the cause and the treatment, and this paradox cannot yet be explained on the basis of our current understanding of the pathophysiology of this disorder. It could be of interest to know how alcohol debridement, laser technique, or mechanical scraping of the epithelium may favor or prevent RCES after PRK. In our series of patients, most of the PRK patients had their epithelium removed by 20% alcohol, but still in some cases, the epithelium was removed by scrapping.

There were also 22 eyes (20% of patients) in our series for which no specific cause could be identified. These patients did not report any history of trauma despite our directed anamnesis. We did not find any signs of EBMD or of previous surgery, which could have triggered the symptoms. Neither did we find any association between RCES and diabetes, a known risk factor for this disorder.

In contrast, a high incidence of MGD was found in our sample. The increased levels of matrix metalloproteinases reported in MGD have been postulated to be one of the causal agents, or at least an agent that favors the structural changes in the basement membrane of patients with RCES.[16,17] We carefully examined for the presence of MGD in each case because of the importance it has in the management of the disease. Sixty percent of our patients presented moderate-to-severe MGD, which required treatment. This percentage is apparently high, but it is difficult to compare with a healthy population because of the scarcity of prevalence studies, in part due to the variability with which MGD presents itself.[18] Recently, a prevalence of 30% has been reported in a healthy population and in a study conducted in a population in Spain, 45% of patients with dry eye were reported to have MGD.[19] Thus, our finding of a prevalence of 60% could be interpreted as being clearly above the norm and would support the association between MGD and RCES, which is frequently observed in the clinical setting. Nevertheless, we consider that more population studies of MGD and its relationship with the various ocular surface pathologies are necessary. It is noteworthy that in our series, the presence of MGD rises to 75% in the "unknown" group of patients, whereas it decreases to almost 35% among patients with EBMD.

On considering the age of our patients in terms of causal groups, we observed clear differences in the distribution of ages among the distinct groups. Thus, we found that patients whose cause of RCES was keratorefractive surgery were younger than average and much younger than patients diagnosed with EBMD. The difference between PRK and EBMD is illustrative because 85% of patients with PRK as the cause of RCES were younger than 50 years, whereas 64% of the EBMD group were older than 50 years (Fig. 3). This difference can be explained by the mean age of patients subjected to this surgery and to the mean age of appearance of EBMD. EBMD can appear from 30 years of age onward, especially in women, but it is more frequent from 50 years onward. Patients whose cause was traumatic were also slightly younger than the mean age of all cases. In this

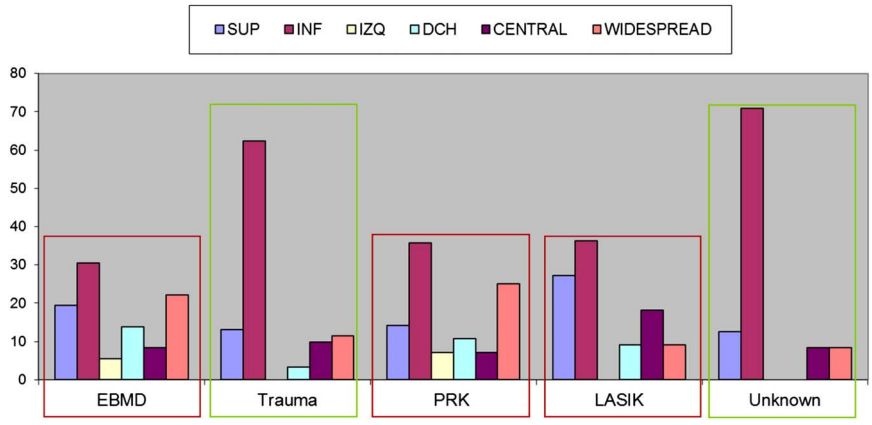

FIGURE 4. Location of the affected epithelium depending on etiology. We observed 2 different patterns: PRK, LASIK, and EBMD patients presented a much more scattered location. In contrast, in the trauma group and in the group with unknown etiology, the location of the lesion was much more concentrated in the inferior part of the cornea. DCH, right; INF, lower; IZQ, left; SUP, upper.

way, the normal distribution of age for our series of cases, which is consistent with what has previously been reported for this pathology, can be divided into groups of patients, who are older or younger, as a function of the cause of the RCES (Fig. 3).

Regarding the location of the lesions, our series corroborates previous reports,[2,9] with the inferior paracentral cornea being the most frequently affected zone (68.4% cases, 50.4% as the only affected zone). According to both our data and those of others, there is a predominance of cases in this specific zone of the cornea, yet the reasons for this remain elusive. It should be remembered that this is precisely the zone in which the tear film first breaks in healthy patients when tear film break-up time is measured.[20] The second most frequently affected location, which often passes unnoticed on examination, is the upper cornea, the zone that is normally covered by the upper eyelid. In our series, 21.4% of cases presented affected epithelium in this location. This is the same frequency found for cases in which the lesion is widespread. What is different about this zone with respect to the rest is its permanent contact with the upper eyelid margin. It is possible that this area is more affected by the aggression from MGD, such as, for example, increased levels of matrix metalloproteinases.[17] Both the upper and lower zones of the cornea are those which are most affected in severe MGD. Curiously, it is precisely in these zones in which epithelial hypertrophy or infectious keratitis are present in severe MGD.[20] Contact of the rest of the cornea with the eyelid in a continuous manner only occurs during the night, thus coinciding with the worsening of patient symptoms. The temporal or nasal zones were less affected, representing 9% of cases (Fig. 2).

On analyzing the location of lesions as a function of the cause of the pathology, we also found revealing differences. Thus, although the most frequent location in all cases was the lower corneal zone, the degree of its predominance differs according to the cause. In the group of patients with RCES caused by trauma, the inferior location appears in 63% of cases, in contrast to the EBMD group, in which it is affected in only 31% of cases. In the EBMD group, the affected location is more widespread, in keeping with what is frequently observed in clinical practice. The epithelial zones that are affected in EBMD are much more variable.

In addition, we observed 2 patterns of distribution of the affected epithelium. One consists of the clear predominance of the lower location (more than 60% of cases present with lesions in the lower zone). This distribution pattern is found with the group for which we could not find a cause for the RCES. In these cases, the lower location rises to 70.8% of all cases. The other distribution pattern consists of a more variable location, in which the percentages are shared more among the different possibilities. This is the "EBMD-type" pattern that was found in the groups whose attributed cause is refractive surgery, both PRK and LASIK (Fig. 4). We consider it likely that these 2 patterns may reflect different physiopathologies of the disease. It is also possible that a large proportion of the cases of unknown origin may be due to ocular trauma that had been forgotten or went unnoticed.

In this study, we have described the different patterns of location of RCES according to its etiology. We have also found that refractive surgery in its PRK and LASIK forms may trigger RCES, despite the fact that PTK is also a treatment of choice for this pathology. Finally, we report a correlation between RCES and MGD, which should be taken into account during the clinical management of this pathology. Further research to investigate the mechanisms by means of which MGD can favor RCES is also warranted.

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