

## Original article

## Short break-up time type dry eye has potential ocular surface abnormalities

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## ABSTRACT

**Purpose:** To describe a case series in which corneal fluorescein staining (CFS) development occurred in short break-up time (s-BUT) dry eyes after a short period during prolonged opening of the eye.

**Methods:** The study was designed as a clinical case series. Ocular surface evaluations were performed on 13 individuals with s-BUT dry eye. Tear function examinations included Schirmer's test and BUT evaluation.

**Results:** In all 13 cases, the BUT was short, but the tear quantity was not so bad. In all cases, CFS developed following a single eye opening, and the staining was observed at sites that showed as dark spots. In several cases, the CFS disappeared later.

**Conclusion:** In this study, we demonstrated that CFS could develop following a single eye opening. Based on our findings, CFS is a dynamic phenomenon rather than a stable indicator of ocular surface abnormalities. Moreover, s-BUT dry eye has the potential to show ocular surface abnormalities.

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## 1. Introduction

Dry eye is a common disease that results in symptoms such as eye fatigue, discomfort, stinging, and blurry vision. The disease is multifactorial and commonly associated with aging, hormonal dysfunction, wearing of contact lenses, systemic drug effects, Sjögren's Syndrome, and refractive surgery.<sup>1–5</sup> The Dry Eye Workshop definition and classification subcommittee updated the work of the National Eye Institute Workshop to create a classification system for dry eye. The subcommittee reinforced the concept of two different categories of dry eye: aqueous tear-deficient dry eye and evaporative dry eye.<sup>5</sup>

In the diagnosis of dry eye, the break-up time (BUT) is indicative of tear-film stability and is the simplest clinical test for this condition. BUT is measured by applying fluorescein dye to the eye and

determining the time between a complete blink and the appearance of the first dry spot in the corneal tear film. Recently, a potentially new type of dry eye, termed short BUT (s-BUT) dry eye, has attracted attention.<sup>6</sup> A particular feature of s-BUT dry eye is a decreased tear BUT. Further, the tear quantity is normal in s-BUT dry eye patients, but the tear quality is abnormal, and patients experience a characteristic dry eye sensation. Clarifying whether s-BUT dry eye is another form of dry eye could potentially facilitate its diagnosis and treatment.

The three diagnostic criteria of dry eye syndrome are dry eye symptoms, tear abnormalities, and ocular surface abnormalities. Superficial punctate keratitis (SPK) is a hallmark of corneal epithelial abnormalities. Because s-BUT dry eye sometimes lacks SPK, it satisfies only two of the diagnostic criteria (i.e., dry eye symptoms and tear abnormalities). Thus, as stated earlier, s-BUT type is sometimes not considered to be a definite type of dry eye but rather a potential one. However, we recently observed that during prolonged eye opening, such as during BUT measurements, corneal fluorescein staining (CFS) rapidly developed in some s-BUT patients eyes, revealing ocular surface abnormalities. This CSF may be different from SPK which is generally defined, but the generic

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implication of corneal dyeing positive. This observation may potentially be an important one. In particular, if such a phenomenon is universal, CFS is not necessarily a stable indicator of a chronic dry eye condition, but is a conditional one that changes according to environmental stress, such as the simple desiccation that occurs during the prolonged absence of blinking during visual display terminal (VDT) work.<sup>7</sup>

The purpose of this study was to clarify whether CFS develops in a relatively short period of time during prolonged opening of the eye. To accomplish this aim, we examined patients who showed no CFS at the start of the examination but who developed CFS during BUT measurements. We found that the pattern of CFS matched exactly the pattern of tear break-up, as reflected in the location of the desiccation stress. These observations suggest that in certain dry eye patients, CFS may develop and disappear in a cyclical manner according to environmental factors.

## 2. Methods

### 2.1. Patients

This case series represents data obtained from 13 patients who were treated at Keio University and the Minamiaoyama Eye Clinic, Tokyo, Japan. The participants (10 males and 3 females) had an average age of 41.8 years (range, 20–74 years), and did not exhibit fluorescein staining at the first slit-lamp examination of their eyes. Approval for data collection and analysis was obtained from the Department of Ophthalmology, Keio University School of Medicine, and the Minamiaoyama Eye Clinic, Tokyo. We obtained informed consent from the patients.

### 2.2. Tear function examinations

BUT measurements were performed after instillation of 2  $\mu$ L of 1% fluorescein solution into the conjunctival sac of each patient's eye(s) using a micropipette. A cobalt blue filter was used to measure the BUT. The patients were then instructed to blink several times for a few seconds to ensure adequate mixing of the dye with the tear film. The interval between the last complete blink and the appearance of the first corneal black spot in the stained tear film was measured three times, and the mean value of the measurements was calculated. A BUT value of  $\leq 5$  seconds was considered abnormal. The BUT measurements were obtained by the same doctor each time.

### 2.3. Schirmer's I test

In Schirmer's test, a 35 mm  $\times$  5 mm strip of filter paper was used to measure the amount of tears produced over a period of 5 minutes under ambient light. The strip was then placed at the junction of the middle and lateral thirds of the lower eyelid without anesthetic eye drops, and the patient was instructed to close his/her eyes. Patients were considered to have dry eyes when the wetting values were  $< 5$  mm during the 5-minute period, as defined by Japanese criteria for the diagnosis of dry eye syndrome. This test was performed after obtaining the BUT measurements.

## 3. Results

All of the patients had relatively severe dry eye symptoms. The results of the BUT and Schirmer's tests are shown in Table 1. The tear BUT was  $< 5$  seconds in all of the patients, thus revealing abnormalities in the tear dynamics. In contrast, none of the individuals had wetting values of  $< 5$  mm according to the Schirmer's I test, revealing that the patient's eyes did not have a tear deficiency.

**Table 1**  
Patient descriptions and the results of diagnostic tests for dry eye disease.

	Age (y)/sex	Schirmer's I test (mm)	BUT (s)
Case 1	36/F	8	3
Case 2	36/M	11	3
Case 3	20/M	10	3
Case 4	37/M	9	2
Case 5	50/F	8	3
Case 6	41/M	11	3
Case 7	74/M	9	1
Case 8	45/M	8	2
Case 9	39/M	10	3
Case 10	29/F	8	4
Case 11	50/M	9	3
Case 12	20/M	11	4
Case 13	67/M	7	3

BUT = break-up time.

In all 13 cases, CFS developed in only a single BUT measurement in each case. Some images of representative cases are shown in Figs. 1 and 2. The initial examination showed no CFS (Figs. 1A and 2A). After the patients held their eyes open for several seconds, the eyes developed tear break-up (Figs. 1B and 2B). Strikingly, as seen in Figs. 1C and 2C, CFS developed in only a single BUT measurement in each case, and matched exactly the tear break-up pattern. We also provide a movie of another case (Video 1).

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.tjo.2015.02.004>.

Among the 13 patients, five cases (Cases 9–13) were followed for an additional ~30 minutes and reexamined for CFS. These cases showed weak or nearly absent CFS (Fig. 2D).

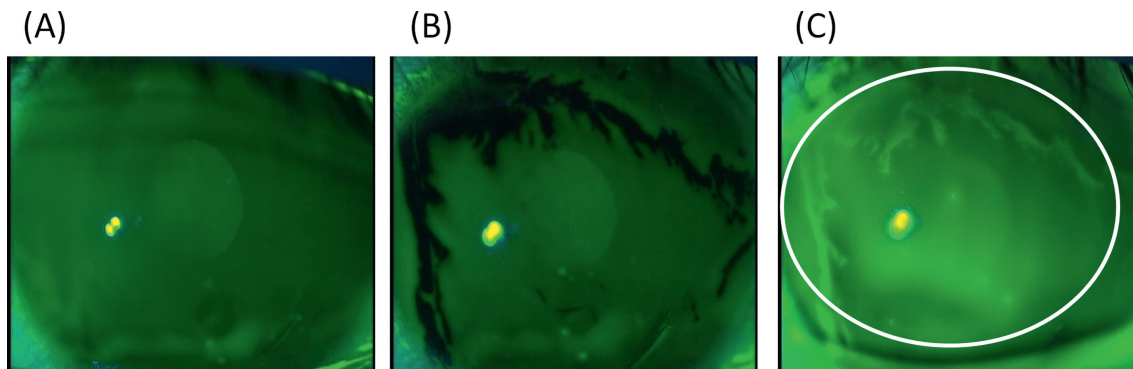
At the first visit, the 13 patients were diagnosed with probable dry eye because they satisfied two out of three diagnostic criteria, the presence of dry eye symptoms and abnormal tear dynamics (s-BUT). However, we were unable to make a definite diagnosis of dry eye because the eye condition of these patients did not satisfy the third criteria of ocular surface abnormalities. However, based on the development of CFS during the BUT examinations, all 13 patients may fulfill the three diagnostic criteria of dry eye syndrome.

## 4. Discussion

To maintain a stable tear film, the ocular surface employs a unique strategy of defense involving both compositional and hydrodynamic factors. Even when normal tear components are present, a stable tear film cannot be formed without the kinetic movement that occurs during blinking. Blinking also facilitates the expression of meibum at the margin of the eyelid and refreshing of the tear fluid. In addition, blinking causes the open-eye state to be intermittently turned off by eyelid closure, thus helping to minimize evaporation of the tear fluid and drying of the eye. Blinking frequency and the completeness of eyelid closure during a blink ensures the establishment of a stable tear film between blinks.

Aqueous tear-deficient dry eye disease is caused by a failure of lachrymal tear secretion.<sup>8,9</sup> Evaporative dry eye disease, by contrast, may be caused by intrinsic factors such as compromised eyelid health or extrinsic factors such as topical medications. These categories of dry eye disease are not mutually exclusive and dry eye beginning as one major type may coexist with the other type or lead to events that cause dry eye by another mechanism.

Different diagnostic tests are best correlated to the subsets of dry eye disease. However, tear osmolality is currently believed to be a global indicator of the disease, independent of its etiology.<sup>5</sup> Unlike disease subset markers, which suffer from excessive scatter (Schirmer's test, meibomian scoring, and ocular surface disease



**Fig. 1.** Representative slit-lamp images of Case 4. (A) No fluorescein staining was observed during the first slit-lamp examination; (B) during break-up time measurements without any blinking; and (C) corneal fluorescein staining (CFS) developed following a single eye opening (white circle).

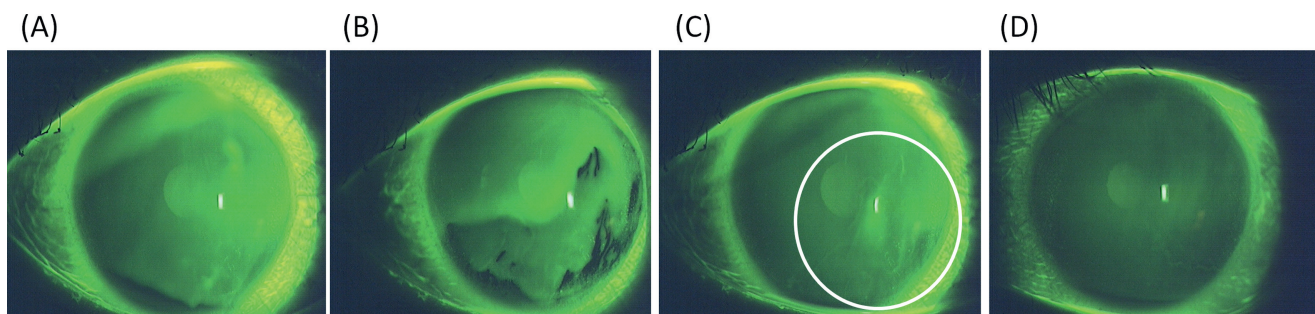
index), bimodality (BUT), or saturation (corneal and conjunctival staining), the relationship between osmolality and disease severity is generally linear.<sup>5,10,11</sup> Although dry eye disease may be diagnosed on the basis of the osmolality of the tear fluid, additional tests are usually performed to determine if injury to the ocular surface has occurred. One of the most common tests involves introducing a dye on to the ocular surface to determine the presence of surface injury. The most commonly used dyes are fluorescein, rose bengal, and lissamine green. Fluorescein is the most prevalently used diagnostic dye due to its ready availability, lack of intrinsic epithelial toxicity, rapid speed of diffusion, and short duration of effect. However, fluorescein is also associated with punctate staining of the eye surface, although the basis of this staining remains controversial.<sup>12</sup> Clinically, a number of factors affect the intensity of corneal surface fluorescence. For example, the intensity of its fluorescence increases with increasing concentration up to ~0.001%, above which it diminishes. This decrease in fluorescence at higher concentrations is termed 'quenching' and may be due to collision of molecules which dissipates the absorbed energy without the emission of light.<sup>12</sup>

In laboratory assessments, the intensity of fluorescence of fluorescein increases with rising pH until approximately pH 8, after which there is a decrease.<sup>12</sup> In acidic conditions, the spectral output moves towards the blue end of the spectrum; at alkaline pH, the fluorescence has a more yellowish appearance.<sup>12</sup> At typical ocular surface pH levels (between pH 6.5 and pH 8), the color of fluorescein remains constant<sup>13</sup> and is seen in its familiar green appearance. Clinically, however, it is possible that differences in local pH across the ocular surface can give rise to different levels of fluorescence intensity.

The amount of fluorescein applied to the ocular surface will affect its appearance. Too high a concentration of fluorescein can cause quenching and delay the time taken to reach peak fluorescence. An important factor in the intensity of fluorescence seen at the ocular surface is the idiosyncratic nature of the human tear film. Essentially, the overall clinical fluorescence presentation will be affected by the quality and quantity of tear fluid present.<sup>14</sup> For example, many practitioners will be familiar with patients in whom there is little initial fluorescence; a situation which improves after exaggerated blinking. This is likely to be due to the initial dose of fluorescein aggregating in a small ocular surface area which does not fluoresce adequately due to its high concentration and the quenching effect. Over time, and especially with increased tear volume caused by frequent forced blinking, fluorescence improves as the fluorescein mixes and spreads over the ocular surface thus reducing its concentration, overcoming the quenching effect, and giving rise to a much better clinical picture.

The number of times that fluorescein is applied to the ocular surface also affects the degree of visible corneal surface fluorescence. Korb and Herman<sup>15</sup> reported an increase in the incidence of corneal staining from 19% of corneas after a single instillation of fluorescein to 42% of corneas after five instillations each separated by 5 minutes. The reason why staining increases with sequential doses is not well understood.

In this study, CFS developed after a single eye opening and then disappeared in several cases, when we examined again. Therefore, CFS appears to be a more dynamic phenomenon than currently believed. The mechanism underlying this dynamic process is not fully understood, but several possibilities are described below.



**Fig. 2.** Representative slit-lamp images of Case 10. (A) No fluorescein staining was observed during the first slit-lamp examination; (B) during break-up time measurements without any blinking; (C) corneal fluorescein staining (CFS) developed following a single eye opening (white circle); and (D) CFS disappeared after the first examination, approximately 30 minutes later.



First, a mucin defect may result in the decreased BUT score for the tears in these individuals. Such a defect could contribute to the loss or weakening of the eye's protective barrier.<sup>16–18</sup> Additionally, mucin abnormalities have been linked with corneal punctate staining in atopic disease.<sup>19</sup> MUC1 and MUC16 proteins are produced by epithelial cells on the ocular surface, a location consistent with the topographical distribution of punctate spots,<sup>17,20,21</sup> and conjunctival expression of MUC16 is known to be decreased in dry eye disease.<sup>22</sup> And, a change in pH with a decrease of the mucin may be seen as a change in the color of the dyeing.

Another mechanism that does not depend on epithelial cellular damage is the potential pooling of fluorescein in small, recessed pockets in the ocular epithelium. The collection of fluorescein in the small indentations on the corneal surface may have resulted in the 'staining' observed in the present study. Ladage et al.<sup>23</sup> reported that these corneal indentations extend to the level of the basal lamina, although no clear evidence of epithelial cellular damage around the indentation was present. In such cases, punctate staining can be observed and is typically transient, appearing and disappearing over a matter of hours.<sup>24,25</sup> However, irrigation does not easily remove the fluorescent punctate stains, suggesting that the pooling of fluorescein in surface irregularities is unlikely.<sup>26,27</sup>

CSF judged from this study may be temporary pooling which has formed by irregular of cornea.

CFS may not develop within a normal eye blink. However, when the number of eye blinks decreases, such as during the extended use of VDT,<sup>28</sup> CFS may develop and then disappear after normal blinking resumes. Thus, the patients who developed CFS after a single eye opening may be a group of people who are at risk of developing dry eyes, particularly if they are working at a VDT for an especially extended period. In addition, a patient with this condition may be variably diagnosed as having and not having dry eye disease because of the dynamic nature of CFS, as observed in this study. These concepts may provide partial explanations for the desiccation stress induced during corneal staining, however, they remain unproven, and additional investigations are required to test these hypotheses and further explore this phenomenon.

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