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Ocular Surface Disease in Atopic Dermatitis

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Purpose: To describe the ocular surface disorders of 362 patients with severe active atopic dermatitis (AD) treated in the Ophthalmology Department of Kobe University Hospital and Kobe Rosai Hospital Eye Clinics during the period 1994–1996.

Methods: Routine ophthalmic examinations as well as tear film break-up time (BUT) and Schirmer tests were carried out.

Results: Lid eczema (65.7%), atopic keratoconjunctivitis, and superficial punctate keratopathy (67.5%) were the dominant ocular diseases in these patients. Tear function tests showed a BUT value of less than 10 seconds in 62.4% of the eyes and a Schirmer test value of less than 5 mm in 56.2% of the eyes.

Conclusions: A careful examination of the ocular surface is essential in treating AD patients. We also suggest that the ocular surface disorders in AD may be due to allergic reactions and disorders in tear film quantity or quality. **Jpn J Ophthalmol 1999;43:53–57**

Key Words: Atopic dermatitis, dry eye, keratoconjunctivitis, superficial punctate keratopathy.

Introduction

The word *atopy* describes hypersensitivity directed against common household or environmental allergens in persons with a hereditary background of allergic disease. Atopic diseases are present in 5% to 20% of the general population. Atopic dermatitis (AD) alone affects approximately 3% of the population in the USA.[1] Japan faces a higher incidence of around 8%, together with a steadily increasing frequency of other related ocular complications.[2] Ocular involvement in AD occurs in 25% to 40% of patients. The most severe ocular surface manifestation of this disease has been termed *atopic keratoconjunctivitis* (AKC). Atopic keratoconjunctivitis patients present with typical eczema and keratinization of the lids, cicatrising conjunctivitis, and a keratopathy that ranges in severity from a superficial punctate keratopathy to neovascularization, thinning, ulceration, and perforation.[3–6]

Investigation and thorough understanding of the changes at the ocular surface, including cellular alterations in the cornea and conjunctiva, may help explain the pathogenesis and clinical appearance of this blinding disease. With the aim of emphasizing the ocular surface diseases of AD and related problems, we examined 724 eyes of 362 patients with severe active AD, carrying out tear film break-up time and Schirmer tests in addition to routine ophthalmic examinations.

Materials and Methods

Seven hundred and twenty-four eyes of 362 atopic dermatitis patients (141 men, 221 women; M:F, 5:8); aged between 17 and 35 years (mean = 22.7 years) were examined in the Eye Clinics of Kobe Rosai Hospital and Kobe University Hospital during the period from 1994–1996. All patients had moderate to severe atopic disease that was treated with systemic steroids, psychiatric counseling, or desensitization therapy at least once during the course of their dis-

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ease. None of the patients had a history of Stevens-Johnson syndrome, chemical, thermal, or radiation injury. In addition, none had any other systemic disorder and none had undergone any ocular surgery that would create an ocular surface problem. No patient was being treated with cytotoxic immunosuppressants, topical prostaglandin inhibitors, or topical steroids at the time of tear function tests. A few patients younger than 16 years of age, presenting with limbal or giant papillae, together with a history of seasonal aggravation of ocular symptoms and signs that resolved during puberty, were considered to have vernal keratoconjunctivitis (VKC) and were excluded from the study.

The existence of severe active dermatitis at the time of examination was confirmed by consulting the dermatology departments. All patients also had radioallergosorbent tests (RAST) and scratch tests to confirm their allergic status. At ocular examination, particular attention was paid to signs of keratoconjunctivitis and corneal erosion and to the lid margins. In accordance with the guidelines described by the Allergic Eye Disease Research Committee of the Japan Ophthalmologists Association, those AD patients who had symptoms of allergic conjunctivitis without seasonal aggravation, presenting with small- and middle-sized conjunctival papillae and keratopathy, were diagnosed as having atopic keratoconjunctivitis (AKC). The patients were also questioned about the occurrence of eye fatigue, irritation, and foreign-body sensation.

Landolt visual acuity and fundus examinations were carried out in each patient. The standard tear film break-up time (BUT) measurement was performed. Moistened fluorescein strips were placed in the conjunctival sac with minimal stimulation and were usually undetected by the patients. Immediately afterward, the subjects were instructed to blink several times for a few seconds to ensure adequate mixing of fluorescein. The interval between the last complete blink and the appearance of the first corneal black spot was measured three times, and the mean value of the measurements was calculated. A BUT value less than 10 seconds was regarded as abnormal, as described by Lemp et al[7] and Barsam et al.[8]

For further examination of tears, the standard Schirmer test with topical anesthesia (0.4% oxybuprocaine chloride) was performed. The standardized strips of filter paper (Alcon Labs, Fort Worth, TX, USA) were placed in the lateral lower lid away from the cornea and kept in place for 5 minutes with eyes closed. Readings were reported in millimeters of wetting after 5 minutes. Patients with a BUT value of less than 10 seconds or a Schirmer test reading of less than 5 mm of wetting were diagnosed as having a tear function abnormality.

Statistical Analysis

Tear function parameters in patients with superficial punctate keratopathy (SPK) were compared to those in patients without SPK. Data were processed using StatView software (1988; Abacus Concepts, CA, USA). The analysis of categorized data was carried out by chi-square analysis with the probability level set at 5% for statistical significance.

Results

All patients had active severe AD with pruritus, typical flexural lichenification, papular eruptions, and tendency toward chronically relapsing dermatitis. Personal or family history of atopic disease and "positive" immediate skin reactivity, as confirmed by the consulting dermatologist, were present in all cases at the time of examination. The average duration of AD was 18 years and the average age was 22.7 years with a male:female ratio of 5:8. Biomicroscopy revealed the incidence of AKC to be 67.5% in this series. Conjunctival papillary formation was the dominant feature in the lower lids of 310 eyes, where chemosis and dense injection of the palpebral conjunctiva was also observed (Figure 1). Horner-Trantas dots were observed in 2 cases (Figure 2). All subjects with AKC had SPK, with predilection for the inferior cornea (Figure 3). Keratoconus was rare and observed in only 24 eyes (3.3%). Peripheral corneal neovascularization was present in 16 eyes (2.2%). No patient had complete absence of the palisades of

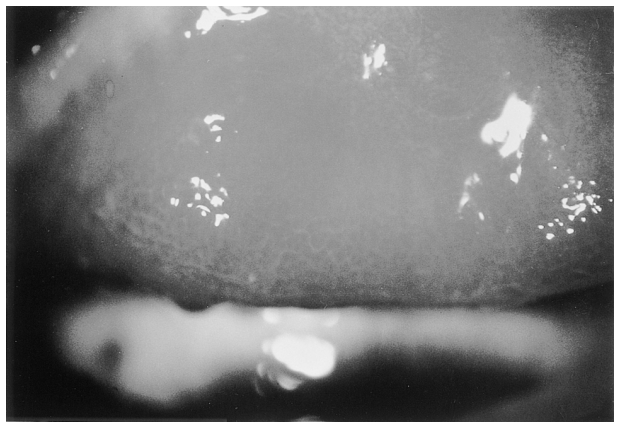

Figure 1. Papillary formation, chemosis, and deep injection of inferior tarsal conjunctiva.

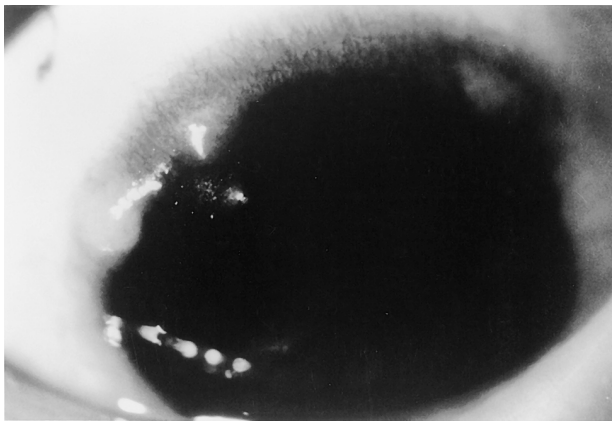

Figure 2. Horner-Trantas dots.

Vogt. All patients with AKC complained of fatigue, irritation, and foreign-body sensation. Clinical findings have been summarized in Table 1. Break-up time values were less than 10 seconds in 452 eyes (62.4%) and Schirmer test values were less than 5 mm in 407 eyes (56.2%). These patients were diagnosed as having a tear function abnormality with a mean BUT value of 6.7 seconds and an average Schirmer test value of 2.4 mm. Two hundred and forty-two eyes (33.4%) had both a BUT value less than 10 seconds and a Schirmer test value less than 5 mm. The average BUT value for these eyes was 4.3 ± 1.2 seconds and the mean Schirmer test value was 2.2 ± 1.6 mm. In addition, 81% of the eyes with SPK had BUT values of less than 10 seconds, and 78% had Schirmer test values of less than 5 mm. On the other hand, 24% of the eyes without SPK had BUT values less than 10 mm, and 11% had Schirmer test values less than 5 mm. This difference was statistically significant, as shown in Table 2 ($P < 0.05$).

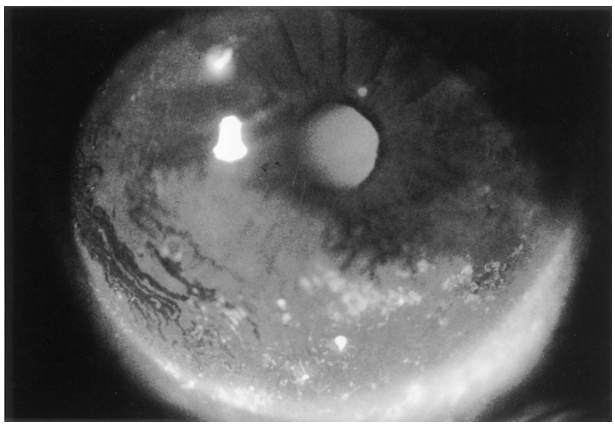

Figure 3. Superficial punctate keratopathy of lower cornea.

Table 1. Clinical Signs in Atopic Dermatitis Patients

Clinical Signs	No. of Eyes	(%)
Lid		
Eczema	476	(65.7)
Trichiasis	14	(1.9)
Ectropion	2	(0.2)
Conjunctiva		
Atopic keratoconjunctivitis	489	(67.5)
Conjunctival papillary formation		
Upper tarsal	179	(24.7)
Lower tarsal	310	(42.8)
Chemosis	489	(67.5)
Deep hyperemia	489	(67.5)
Symblepharon	2	(0.2)
Limbus		
Trantas dots	2	(0.2)
Cornea		
Superficial punctate keratopathy	489	(67.5)
Epithelial defect	9	(1.2)
Keratoconus	24	(3.3)
Peripheral neovascularization	16	(2.2)
Tear function abnormality		
BUT < 10 s	452	(62.4)
Schirmer test < 5 mm	407	(56.2)
BUT < 10 s and Schirmer test < 5 min	242	(33.4)

BUT: break-up time (tear film).

Discussion

Atopic dermatitis is a common skin disorder that usually begins at puberty and involves eye lids, flexor limbs, and the trunk in the form of lichenification or exudative plaques.[9] Ocular complications are serious and include eczema of the eyelids, blepharitis, keratoconus, bacterial corneal ulcer, keratoconjunctivitis, ocular herpes simplex, superficial punctate keratopathy, corneal ulcer, trichiasis, ptosis,

Table 2. Relation of Tear Function Abnormality to Superficial Punctate Keratopathy

Presence of SPK	No. of Eyes	BUT < 10 s		Schirmer < 5 mm	
SPK (+)	489	396 (81%)	*	381 (78%)	*
SPK (−)	235	56 (24%)		26 (11%)	
Total	724	452		407	

BUT: break-up time (tear film), SPK: superficial punctate keratopathy.
*$P < 0.05$, chi-square analysis.

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madorosis, cataract, and retinal detachment.[1,3,4] Hogan[10] initially described the association of bilateral keratoconjunctivitis with AD. Later, Karel et al[11] reported eyelid eczema, mild conjunctivitis, and keratitis in 41/128 AD patients. In 1981, Jay[12] described atypical tarsal or limbal VKC in 9 patients, which Foster believed to be an atypical presentation of AKC. In 1990, Foster and Calonge[3] described their series of 45 patients with AD in whom AKC was the dominant feature, affecting mainly the inferior forniceal and palpebral conjunctiva. However, they did not distinguish between AKC and VKC, and some of their patients did not have AD.

The present study is the broadest series of active AD patients to our knowledge. Atopic keratoconjunctivitis was the most common ocular finding in 67.5% of the patients. Following the criteria of the Allergic Eye Disease Research Committee of the Japan Ophthalmologists Association, we have tried to describe a patient population with AKC that we believe to have resulted only from AD, with the exclusion of VKC. Although the precise classification of chronic ocular allergic disease is difficult, several authors have tried to differentiate AKC from VKC on clinical grounds.[13,14] An important differential feature is the natural history; VKC affects younger people and often regresses after puberty, whereas AKC has a more protracted course. Atopic keratoconjunctivitis usually develops after the onset of other atopic symptoms, whereas VKC can be the first sign of atopy. Jay[12] reported the similarities between the clinical signs of AKC and VKC and noted that 9/17 patients with AKC had changes typical of tarsal or limbal VKC. However, only 4 of these patients had been documented as having had VKC during childhood.[10] All patients with AKC in this report were older than 17 years of age. The symptoms of AKC, which started after the onset of dermatitis, lasted throughout the year and were almost always bilateral. None of our patients had documented VKC from childhood. Atopic keratoconjunctivitis was associated with mid- to small-sized papillae, deep hyperemia, and chemosis of the conjunctiva. Cicatricial ocular complications were relatively rare in this series, but we would like to emphasize that the practicing ophthalmologist should always consider AKC in the differential diagnosis of chronic cicatrizing conjunctivitis. All patients with AKC had superficial punctate keratopathy with predilection to the inferior cornea, similar to Allansmith and Ross's report.[13] We believe that this predilection is due to papillary formations involving mainly the lower lids. Although SPK could have been caused by mechanical contact with the papillae, one cannot rule out the possibility that the release of allergic inflammatory mediators might have had a detrimental effect on the cornea.

We also carried out tear film break-up time and Schirmer tests believing that SPK might be related to a disorder of tear film function. Break-up time was less than 10 seconds in 62.4% and Schirmer test value was less than 5 min in 56.2% of the subjects, with mean values of 6.7 seconds and 2.4 mm, respectively. The percentage of patients who had poor results in both BUT and Schirmer tests was 33.4%, with an average BUT value of 4.3 ± 1.2 seconds and mean Schirmer test value of 2.2 ± 1.6 mm. These results indicate that a tear function abnormality existed in one third of the AD patients in this study. Analysis of the relationship between tear function abnormality and SPK revealed that 81% of the cases with SPK had a BUT value less than 10 seconds, and 78% had a Schirmer test value less than 5 mm. The differences in tear function parameters between patients presenting with SPK and patients without SPK were statistically significant. Furthermore, all patients with AKC complained of symptoms of chronic dry eye. These results suggest that the coexistence of dry eye in patients with AKC is a strong possibility.

Lemp et al[7] described a category of dry-eye patients with decreased tear secretion, normal goblet cell density, and normal or slightly decreased tear BUT. They concluded that ocular surface desiccation may occur, despite normal tear volume, and is caused by mucin deficiency. Barsam et al[8] reported a form of dry eye similar to that described by Toda et al[15] in which tear film breaks up in less than 10 seconds with the appearance of corneal dry spots. Both authors noted an association with allergic conjunctivitis. Yukari et al[16] also suggested that shortening of BUT might be strongly associated with palpebral conjunctival papillary formations. Toda et al[15] hypothesized that the decrease in BUT is related to goblet cell damage caused by an allergic reaction. How AKC relates to tear function disorders in AD remains unclear. Nelson and Wright[17] described an 81% goblet cell loss in 6 eyes from AD patients in 1984. It is generally believed that goblet cells are the main source of tear mucin and that this mucin plays an important role in increasing the tear film stability. It is also accepted that BUT, when performed carefully, is a direct test of tear film stability. The percentage of eyes in this study that had BUT values of less than 10 seconds was 62%. Whether this is due to goblet cell loss or mucin deficiency cannot be answered by the present report because we did not

look for pathological alterations at the cellular level or quantify the tear mucin content. We believe that impression cytology or tissue biopsies establishing the pathogenesis of tear function disorders in AD, together with determination of tear mucin content and surface activity of tears, should resolve the current conflicts about tear film stability and aid in effective management of this disorder. Patients with chronic dry-eye symptoms and poor performance in tear function tests in this study were managed conventionally by artificial tear substitutes containing no preservatives and also sodium hyaluronate eye drops. Atopic keratoconjunctivitis was treated by antiallergic eye drops alone or in conjunction with steroid eye drops.

We believe that a careful ocular surface examination is mandatory in AD patients, and also suggest that ocular surface disease in AD may be due to allergic reactions and disorders in tear film quality and quantity. We are concerned that a number of our patients may seek advice about undergoing surgery for atopic cataract eventually. A careful study of the ocular surface and tear function will be helpful in the decision to choose contact lenses or intraocular lens implants for aphakic correction. We believe that atopic dermatitis deserves more attention because it is a potentially blinding disorder. Thus, the need for further clinical, pathological, and experimental studies should be recognized.

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