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Allergic conjunctivitis and dry eye

Hiroshi Fujishima, Ikuko Toda, Jun Shimazaki, Kazuo Tsubota

Abstract

***Aims*—Differential diagnosis of allergic conjunctivitis or dry eye is sometimes very difficult to diagnose by symptoms and clinical examination alone, especially in older patients. It was hypothesised that clinically allergic patients who were serum antigen specific IgE negative were candidates for dry eye.**

***Methods*—Sixty patients were studied prospectively who were clinically diagnosed with allergic conjunctivitis by their itchy sensation and papilla formation of conjunctiva. They consisted of 30 serum antigen specific IgE positive and 30 IgE negative patients, with no significant differences in age. Dry eye examination and serum total IgE were performed on these two groups.**

***Results*—No significant differences were seen between the two groups with regard to age (p=0.76) and sex ratio. The antibody negative group had lower Schirmer's test scores (p=0.002), lower tear clearance (p=0.0001), lower tear function index (p=0.0001), and lower serum total IgE (p=0.04) than the antibody positive group.**

***Conclusion*—This study suggests that the evaluation of serum antigen specific IgE and tear dynamics are important for the differential diagnosis of patients with allergic conjunctivitis and dry eye. Clinically diagnosed allergic conjunctivitis with negative serum antigen specific and total IgE can be one form of dry eye.**

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Department of Ophthalmology, Tokyo Dental College, Chiba, Japan and Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan
H Fujishima
I Toda
J Shimazaki
K Tsubota

Correspondence to:
Hiroshi Fujishima, MD, Department of Ophthalmology, Tokyo Dental College, 5-11-13 Sugano, Ichikawa-shi, Chiba, Japan 272.

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Allergic conjunctivitis and dry eyes are major ocular surface disorders affecting millions of people. Although neither of them are sight threatening diseases, the chronic discomfort interferes with the quality of life of the patients for a long period of time. A typical clinical symptom of allergic conjunctivitis is 'itching', whereas the symptoms of dry eye are a 'burning sensation', 'irritation', and 'ocular fatigue'.[1 2] The two disorders can be clinically distinguished, however, from the analysis of patients with dry eye. Toda *et al* has reported that 12 out of 80 patients with dry eye complained of an itchy feeling and those with decreased tear break up time had increased papillary formation of the upper tarsal conjunctiva and increased serum antigen specific IgE.[3] This report suggested an overlap syndrome in allergic conjunctivitis and dry eyes. In allergic conjunctivitis, an allergen directly comes in contact with the conjunctiva and induces a type I hypersensitivity reaction.[4] It interacts with the IgE bound to tissue mast cells and leads to a release of chemical mediators.[5 6] Two factors, the mast cell response and the amount of antigen, are thus responsible for the severity of allergic conjunctivitis.[7] Thus, positivity for some antigen specific IgE may be an important factor for the diagnosis of allergic conjunctivitis.[8 9] We hypothesised that some cases of clinically diagnosed allergic conjunctivitis may not be allergic conjunctivitis but dry eye, especially in those patients who were serum antigen specific and total IgE negative. We prospectively studied serum total IgE, tear production, and tear dynamics in 60 patients with clinically diagnosed allergic conjunctivitis to determine whether patients with dry eye occur in the serum antigen specific IgE negative patient group.

Patients and methods

Sixty patients (24 male and 36 female, aged 16 to 64 years; mean age 36.0 (SD 14.1) years) who were clinically diagnosed as having allergic conjunctivitis were enrolled in this study. Allergic conjunctivitis was diagnosed according to past history, clinical symptoms such as ocular itching, redness, tearing, or ocular pain, and slit-lamp examinations showing filamentous (mucous) discharge, chemosis, hyperaemia, or papillae of the palpebral conjunctiva.[8–10] All subjects gave their informed consent for participation in this study. Serum antigen specific IgE was detected using a commercial MAST 16 test (SRL Inc, Tokyo, Japan) based on an enzyme linked immunosorbent assay (ELISA) using 16 monoclonal antibodies.[11–13] The 16 antigens tested were house dust (extracted by Hollister-Siel Co Ltd, USA), mites (*Dermataphagoides farinae*), egg (egg white), soybean (soybean), ragweed mix I (*Ambrosia artemisifolia* and *Ambrosia trifida*), mugwort (*Artenisia vulgaris heterophylla*), sweet vernal (*Phleum pratense*), timothy (*Anthoxanthum odoratum*), Japanese cedar pollen (*Cryptomeria japonica*), *Penicillium* (*Penicillium notatum*), *Cladosporium* (*Cladosporium herbarum*), *Candida* (*Candida albicans*), *Alternaria* (*Alternaria tenuis*), *Aspergillus* (*Aspergillus fumigatus*), and antigens of cats (cat epithelium) and dogs (dog epithelium). A concentration of above 4.41 (100 LC) was positive (MAST class >1).[14] Serum total IgE was assayed by fluoroenzyme immunoassay (FEIA; SRL Co, Tokyo, Japan). Patients who were positive for at least one antigen specific IgE in 16 antigens (MAST class >1), were considered positive.[8 9 11] Older patients with clinical allergic conjunctivitis were recruited, as sometimes the diagnosis of allergic conjunctivitis and dry eye was confused in these patients. Patients over the age of

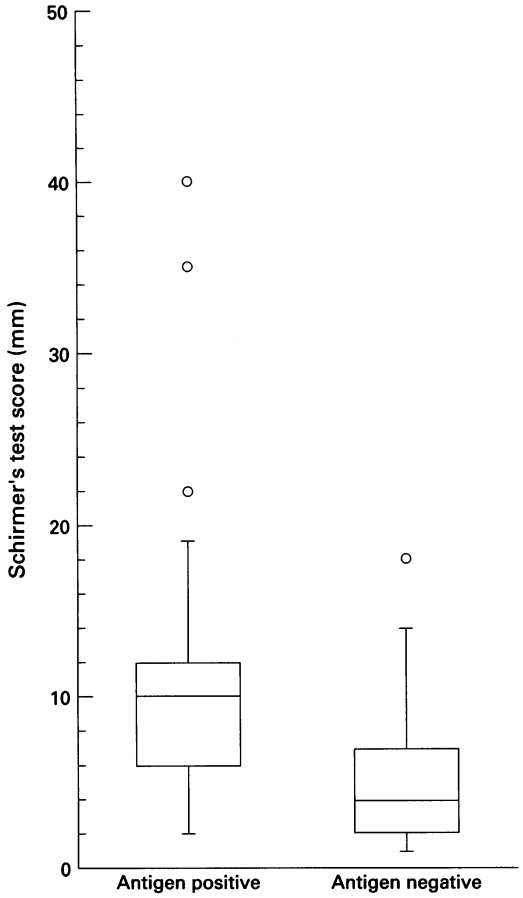

Figure 1 Schirmer's test score in both groups. Box plots show range of interquartile distance (IQD); distance between upper quartile (UQ) and lower quartile (LQ) with the median as the horizontal line; top section shows median + UQ+ (1.5 × IQD) and bottom section shows median − LQ − (1.5 × IQD). Any response outside this range are shown as a circle. Patients positive for antigen specific IgE in serum had significantly higher Schirmer's test scores than those who were negative (p=0.002: Wilcoxon rank sum test).

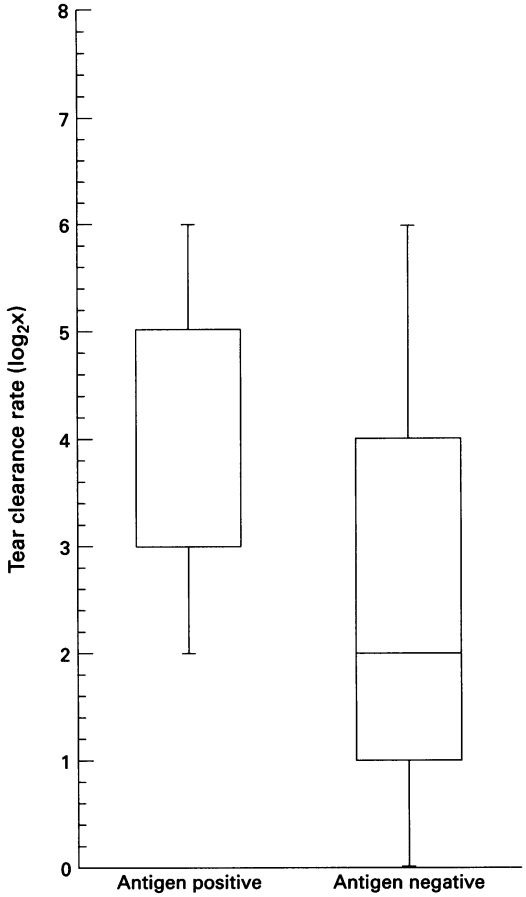

Figure 2 Tear clearance rate (TCR) in both groups. Box plots show the same as in Figure 1. TCR itself was compared with log2x. Patients positive for antigen specific IgE in serum had significantly better clearance than those who were negative (p=0.0001: Wilcoxon rank sum test).

65 or under the age of 15 were excluded from this study for fear of an aging effect on allergic reactions. Patients were divided into serum antigen specific IgE positive group (n = 30) and IgE negative group (n = 30). To evaluate tear production and tear dynamics, the Schirmer's test and tear clearance tests were used.[15 16] The Schirmer's test was performed 5 minutes after instillation of 10 µl of a mixture of preservative free 0.5% fluorescein and 0.4% oxybuprocaine hydrochloride into the cul de sac.[15] Tear clearance rate (TCR) was determined by the intensity of fluorescein dye colour on the Schirmer's test paper strip and was graded as 1 (2^0), 2 (2^1), 4 (2^2), 8 (2^3), 16 (2^4) times, etc (normal > 4 times).[16] Tear function index (TFI) was defined as the Schirmer's test value multiplied by the TCR: TFI = Schirmer's value × TCR (TFI < 96 is consistent with dry eye).[17] All measurements were performed before treatment. Data are shown as mean (SD) and were analysed using the unpaired *t* test for age and Wilcoxon rank sum test for examinations, with a level of $p < 0.05$ accepted as statistically significant.

Results

There were no significant age and sex ratio differences between patients who had antigen specific IgE positive serum (13 males and 17 females; mean age 35.4 (12.5) years) and those who had antigen specific IgE negative serum (11 males and 19 females; mean age 36.5 (15.6) years) (p=0.76; unpaired *t* test). There was a significant difference between the two groups in the Schirmer's test scores (10.7 (8.6) mm compared with 5.6 (4.8) mm, respectively, p=0.002; Wilcoxon rank sum test) (Fig 1). Also, there was a significant difference between the two groups in TCR (log2x: 4.4 (1.2) compared with 2.4 (1.7), respectively, p=0.0001) (Fig 2), in TFI (326.9 (351.0) compared with 35.4 (39.9), respectively, p=0.0001) (Fig 3), and in the total serum IgE (254.5 (268.8) U/ml compared with 124.7 (139.7) U/ml, respectively, p=0.04) (Fig 4) (Tables 1 and 2).

Discussion

A definite diagnosis of allergic conjunctivitis is difficult and complicated by ambiguous criteria and laboratory tests which do not always reflect the clinical diagnosis.[2 18] However, in daily practice, allergic conjunctivitis should be easily diagnosed by itchy symptoms and papilla formation of conjunctiva without the need to measure the serum IgE. Ideally, allergic conjunctivitis should be diagnosed based on the following criteria: (1) history of ocular and other allergic disease, (2) presence of symptoms such as itchiness, (3) papilla formation of conjunctiva, and (4) the presence of antigen specific IgE in serum.[10] However, there are

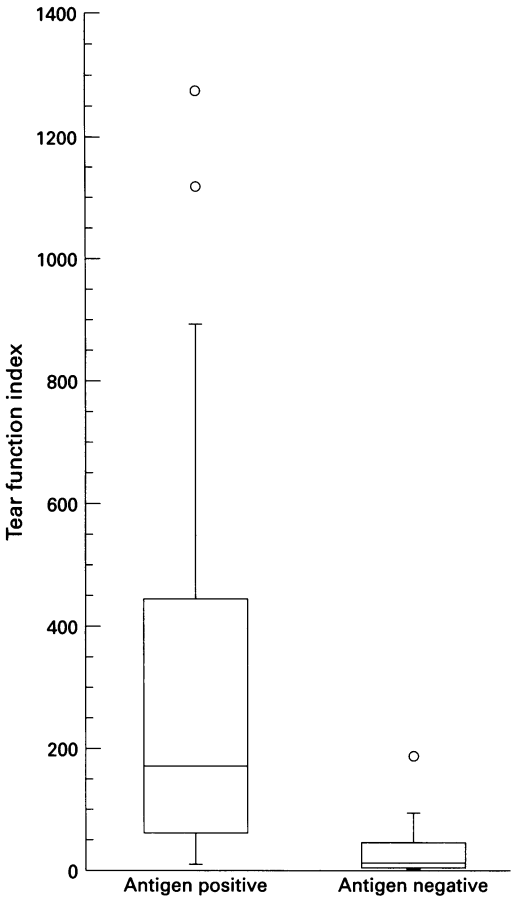

Figure 3 Tear function index (TFI) in both groups. Box plots show the same as in Figure 1. Patients positive for antigen specific IgE in serum had significantly higher TFI than those who were negative (p=0.0001: Wilcoxon rank sum test).

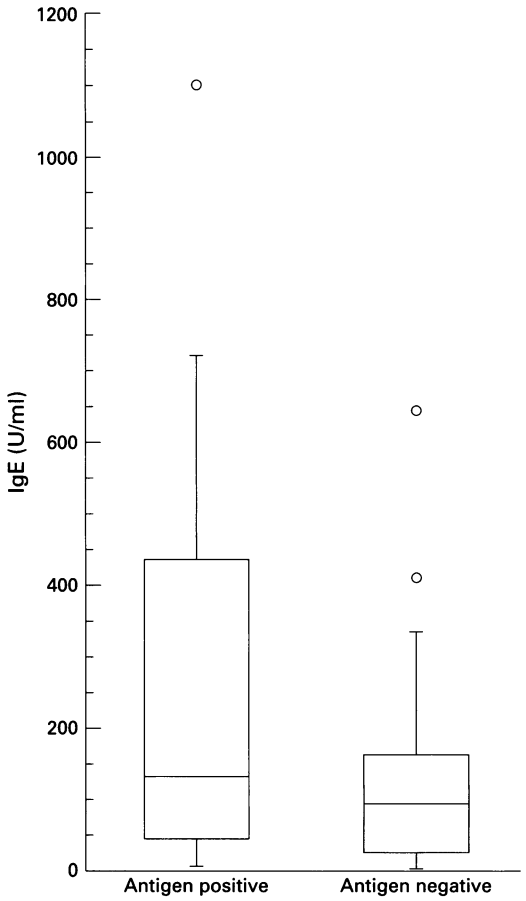

Figure 4 Serum total IgE in the two groups. Box plots show the same as in Figure 1. There was a significant difference between the two groups in the total serum IgE (p=0.04: Wilcoxon rank sum test).

Table 1 Data of patients who were positive for serum antigen specific IgE

Patient No	*Age*	*Schirmer*	*TCR*	*TFI*	*Total IgE*
1	31	8	2	32	118
2	49	10	2	40	6
3	28	5	5	160	41
4	33	6	2	24	44
5	26	3	4	48	478
6	60	5	3	40	16
7	38	14	6	896	594
8	26	10	5	320	148
9	33	5	5	160	156
10	27	8	4	128	32
11	26	10	5	320	47
12	29	2	3	16	22
13	25	12	6	768	41
14	22	35	5	1120	436
15	29	2	5	64	96
16	50	6	4	96	92
17	63	2	5	64	120
18	49	10	5	320	111
19	52	19	5	608	360
20	30	7	6	448	280
21	22	11	5	352	440
22	48	7	3	56	280
23	30	12	6	768	170
24	21	6	5	192	570
25	50	10	3	80	720
26	21	12	6	768	250
27	23	40	5	1280	71
28	50	10	3	80	720
29	44	22	4	352	76
30	27	13	4	208	1100
Mean	35.4	10.7	4.4	326.9	254.5
SD	12.5	8.6	1.2	351.0	268.8

Schirmer=Schirmer's test score; TCR=tear clearance rate; TFI=tear function index; total IgE=serum total IgE (U/ml).

Table 2 Data of patients who were negative for serum antigen specific IgE

Patient No	*Age*	*Schirmer*	*TCR*	*TFI*	*Total IgE*
1	50	9	3	72	25
2	57	7	0	7	25
3	26	18	1	36	25
4	24	1	4	16	189
5	62	1	3	8	332
6	26	2	2	8	645
7	21	3	6	192	22
8	27	4	3	32	210
9	27	2	5	64	156
10	43	14	0	14	99
11	58	4	0	4	163
12	23	10	2	40	55
13	39	3	2	12	89
14	19	2	3	16	156
15	62	2	5	64	220
16	27	5	1	10	52
17	25	11	2	44	110
18	32	2	2	8	110
19	65	12	2	48	410
20	56	3	0	3	11
21	27	2	2	8	52
22	62	1	5	32	220
23	27	18	0	18	30
24	36	6	0	6	11
25	22	2	2	4	130
26	51	3	4	48	13
27	31	6	4	96	38
28	34	4	2	16	75
29	21	5	3	40	94
30	16	6	4	96	69
Mean	36.5	5.6	2.4	35.4	124.7
SD	15.6	4.8	1.7	39.9	139.7

Schirmer=Schirmer's test score; TCR=tear clearance rate; TFI=tear function index; total IgE=serum total IgE (U/ml).

some patients who suffer from the itchiness with papillary formation of conjunctiva who do not have antigen specific IgE. The reason for negative antigen specific IgE might be (1) due to another antigen being involved in the allergic reaction,[11 19] (2) IgG or other factors being involved in the allergic reaction,[12 20] (3) the level of serum IgE being below the threshold of detection, or (4) misdiagnosis of other ocular surface disorders such as dry eye. In any case, the allergic reaction itself may not be as strong as in the patients with a definite allergic conjunctivitis; we focused on reason (4) and hypothesised that the patients without antigen specific IgE did not have allergic conjunctivitis but dry eye.

We could not find IgE in tears in most of the patients in this study (data not shown). Earlier reports imply that there was a correlation between IgE levels in serum and tear in patients with vernal keratoconjunctivitis, but no correlation was found in patients with allergic conjunctivitis.[21 22] Kari *et al* pointed out that tear fluid IgE was sometimes undetectable and local IgE production seemed to occur in some but not necessarily all patients.[23] In severe cases, measuring IgE in tears will be beneficial. However, the interpretation of the results can be difficult in certain situations owing to the dilution factor, technical problems, and presence of reflex tearing.

In the present study, patients with negative serum antigen specific IgE had significantly lower tear flow and poorer tear clearance despite no significant differences in age. The tear clearance test is a new form of fluorescein clearance test to evaluate tear drainage, and is of value both quantitatively and qualitatively. Poor clearance means an abnormality in tear dynamics.

Patients who were negative for antigen specific IgE had lower TFI than the patients who were positive. Xu *et al* pointed out that TFI values below 96 were consistent with dry eye.[17] TFI in the IgE negative group in this study was 35.4, and this result may mean that this group included other diseases such as dry eye.

Although allergic conjunctivitis and dry eye sometimes share very similar symptoms, our findings may also suggest another possibility that an allergic reaction occurs locally in the conjunctiva when an antigen remains longer than usual in the conjunctival sac, even if the antigen is too weak to activate a systemic reaction. Just as an insufficient amount of antigen may fail to cause an allergic reaction, so too poor tear clearance may lead to the accumulation of an antigen until it provokes an allergic reaction.[4 24] In such cases, artificial tears may improve the ocular anterior segment conditions.

From this result and other reports, the patients with negative serum IgE can be considered as having dry eye or a combination of dry eye with other diseases and not allergic conjunctivitis. While allergic conjunctivitis is not a typical manifestation of antigen specific IgE, we have to determine whether abnormalities of tear fluid, such as dry eye, can cause similar symptoms and, in such cases, artificial tears can greatly improve the clinical symptoms of allergic conjunctivitis. As Toda *et al* reported,[3] from the 'dry eye' side, some patients clinically diagnosed as having dry eye had positive serum IgE. Taken with this information, our study suggests an overlap between the diagnosis of dry eye and allergic conjunctivitis, both of which have a significant correlation with tear dynamics.

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