

RESEARCH ARTICLE

Evaluation of the tear film instability in children with allergic diseases

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Abstract

Context: The presence of dry eye syndrome (DES) in ocular allergic diseases was evaluated in several studies. Despite this, little exists about the tear film instability in atopic children including patients with allergic rhinitis (AR), allergic conjunctivitis (AC) and asthma. This is a study which presents intriguing findings regarding the relationship of tear film instability with clinical aspects in atopic children.

Objective: To determine the tear film instability in children with AR, AC and asthma.

Materials and methods: One hundred and thirty-five consecutive children with AR, AC and asthma as study group and 45 children without any systemic and ocular abnormality as control group were included in the study. Skin prick tests, measurement of tear film breakup time (TFBUT), serum immunoglobulin E and eosinophil counts were performed in all patients. Also four subgroups of patients were designated as AR group (Group I), AC group (Group II), asthma group (Group III) and control group (Group IV).

Results: Socio-demographic characteristics were similar except for family atopy between the groups ($p > 0.05$). The mean TFBUT was significantly lower in the study group (15.5 ± 4.4 s) than the control group (18.4 ± 2.9 s; $p = 0.000$). Also, there was no significant differences in the percentage of the patients who has TFBUT < 10 s ($p = 0.066$). In logistic regression analysis, atopy was found to be the determinant of lower TFBUT (OR = 16.33, 95%; CI = 1.17 to 228.05, $p = 0.03$).

Conclusion: The presence of tear film instability was higher in children with AC, AR and asthma. This finding should be taken in consideration in atopic children.

Keywords

Allergic conjunctivitis, allergic rhinitis, asthma, tear film break-up time, tear film instability

History

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Introduction

Tear film instability has been a well-known mechanism in the development of dry eye syndrome (DES). Other causes of DES mainly included tear deficiency and excessive evaporation from ocular surface. Allergic conjunctivitis (AC) plays a role in the development of evaporative DES by revealing an extrinsic exposure to ocular surface. Basically, allergic eye disease can damage the tear film instability due to the disturbance of conjunctival epithelial and goblet cells in which a reduction in mucin production eventually arises. Although several methods have been applied in DES diagnosis, lower degrees of tear film break-up time (TFBUT) was associated with tear film instability^{1,2}.

Atopic syndrome is a systemic inflammatory response which mostly encompasses allergic rhinitis (AR) and asthma. Chronic airway inflammation is the main pathogenic

mechanism in both diseases³. Although several studies reported on the association between DES and AC^{4–8}, little is known about such relationship in AR and asthma^{9–11}. Thus, in consideration of the effect of such conditions on ocular surface, we aimed to evaluate tear film instability in AC, AR and asthma among pediatric population.

Materials and methods

One hundred and thirty-five consecutive children diagnosed as AR, AC and asthma in Immunology and Allergy clinic of Zeynep Kamil Maternity and Children's Disease Training and Research Hospital between January 2013 and November 2013 were included as study group in the current cohort. A local approval was taken from the same institute and the study was carried out due to the tenets of Helsinki Declaration. Written and oral informed consents were taken from all parents and/or participants regarding the procedures in the study. Forty-five children without any systemic and ocular abnormality were designated as a control group. Patients who had undergone intraocular or corneal refractive surgery and who had atopic keratoconjunctivitis, vernal conjunctivitis, pterygium, corneal

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degeneration, cataract, glaucoma or those with any active ocular infection were excluded from the study.

Study protocol

A questionnaire including details regarding patient demographics and medical history were completed. “Atopy” was defined as a positive reaction to any one of the allergens determined in skin prick test (SPT). Family atopy was accepted as positive when having allergic disease in first degree relatives. The diagnosis of AC, AR and asthma were made according to the international guidelines^{12–14}. The patients were divided into four subgroups as; AR group (Group I), AC group (Group II), asthma group (Group III) and control group (Group IV).

Skin prick test

Skin prick tests with common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternaria*, cockroaches (*Blatella germanica*), cat dander and dog dander, mixture of grass pollens (*Lolium perenne*, *Dactylis glomerata*, *Phleum pratense*, *Anthoxanthum odoratum*, *Poa pratensis*, *Festuca eliator*, *Agrostis vulgaris*, *Holcus lanatus*, *Cynodon dactylon*, *Avena sativa*, *Avena fatua*, *Lotus Corniculatus*), a mixture of grain pollens (oats, wheat, barley, corn), a mixture of tree pollens (*Acer pseudoplatanus*, *Aesculus hippocastanum*, *Robinia pseudoacacia*, *Tilia platyphyllos*, *Platanus vulgaris*), weed-mix pollens (*Medicago sativa*, *Trifolium pratense*, *Brassica nigra*, *Urtica dioica*, *Rumex acetosa*; Stallergenes SA, Antony, France) were performed using lancet. Skin prick tests were applied on the anterior surface of the forearm. Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. Skin reactions were evaluated 20 min after the application of the skin test, and indurations of ≥ 3 mm were considered as indicative of a positive reaction.

The measurement of TFBUT

All participants were subjected to a full ophthalmic examination in Ophthalmology Department of Zeynep Kamil Maternity and Children’s Disease Training and Research Hospital. After examining conjunctiva and cornea under slit-lamp biomicroscopy, TFBUT measurements were performed pursuant to the literature¹. After waiting 3 min following the instillation of the topical anesthetic drop (proparacaine hydrochloride 5%), a fluorescein strip was wetted by a drop

of physiological saline and touched to the inferior fornix to perform the TFBUT measurement. Then, the patients were asked to blink three times and look straight ahead without blinking. The precorneal tear film was examined under blue-light illumination and the first time break of this layer was noted. The same procedure was carried out in all patients.

Serum total immunoglobulin E and eosinophil counts

Serum total IgE levels were analyzed with the nephelometry system (Siemens Healthcare Diagnostics Inc., Deerfield, Germany) and values of over 100 IU/ml were considered high. Total eosinophil counts and the percentage of blood eosinophils were measured with an automated blood analyzer-ABX Pentra 80 (HORIBA Medical, Montpellier, France) and values more than 4% were considered high.

Statistical analysis

Data was analyzed by using the program Statistical Package for Social Sciences (SPSS for Windows 11.0, Chicago, IL). Values for continuous variables were given as either mean $\pm$ standard deviation or as median, based on the normality of distribution. ANOVA and Kruskal–Wallis test were used in the comparison of parametric values. Chi-square test was used to compare non-parametric values. To determine which factors were independently associated with presence of DES, logistic regression models were developed. Age, gender, presence of asthma, presence of conjunctivitis, presence of rhinitis, atopy, the number of sensitization, IgE level, eosinophilia were included in model. Results were expressed as odds ratios. Levels of $p < 0.05$ were considered as statistically significant.

Results

Totally 180 children were evaluated during the study period. The socio-demographic characteristics were similar in all groups except for family atopy (Table 1).

The TFBUT was a mean of 15.5 ± 4.4 s (range between 5–25 s) in study group, while, it was 18.4 ± 2.9 s (range between 13–25 s) in control group ($p = 0.000$). The TFBUT was < 10 s in 15 (11.1%) patients in study group. All subjects in control group had a TFBUT of > 10 s ($p = 0.011$). There was also statistically significant difference of TFBUT in between

Table 1. Comparison of socio-demographic characteristics of the groups.

	Group I (N:45)	Group II (N:45)	Group III (N:45)	Group IV (N:45)	p
Gender (M/F)	27/18	30/15	28/17	30/15	0.885 ^a
Age (mean $\pm$ SD; years)	7.8 ± 2.8	8.4 ± 2.8	7.8 ± 2.3	8.1 ± 2.5	0.232 ^b
Consanguineous marriages	5 (11.1%)	3 (6.7%)	7 (15.6%)	5 (11.1%)	0.407 ^a
Family atopy	25 (55.6%)	24 (53.3%)	26 (57.8%)	10 (22.2%)	0.019 ^a
Exposure to smoke	13 (28.9%)	16 (35.6%)	16 (35.6%)	14 (31.1%)	0.741 ^a

M: male; F: female; SD: standart deviation; group I: children with allergic rhinitis; group II: children with allergic conjunctivitis; group III: children with asthma; group IV: healthy children.

^aChi-square test.

^bKruskal–Wallis test.

group I, group II, group III and group IV ($p < 0.05$; Table 2). The laboratory results were similar in all groups (Table 3).

An inquiry was performed on children regarding ocular allergy symptoms. It was found that the presence of itching, burning and foreign body sensation were significantly higher in patients with TFBUT of under 10 s ($p = 0.011$, 0.006, 0.007, respectively). Furthermore, there was no significant difference in terms of lacrimation between patients with TFBUT of < 10 s and TFBUT of > 10 s ($p = 0.567$).

A logistic regression model was developed to determine which factors were independently associated with lower TFBUT (< 10 s). Age, gender, presence of asthma, presence of AC, presence of AR, atopy, the number of sensitization, IgE levels and eosinophilia were included. Logistic regression analysis revealed that atopy was found to be determinant for lower TFBUT (OR = 16.33; 95%, CI = 1.17–228.05, $p = 0.03$).

Discussion

Previous reports showed tear film dysfunction in patients with ocular allergy. Furthermore, various factors were suggested to be related to this mechanism including, reduced conjunctival goblet cell density^{5,7}, decreased TFBUT and conjunctival mucins^{4–8,15}. Several other investigators demonstrated lower TFBUT in children with AC and also revealed that number of DES symptoms were higher in patients with AC than those without AC⁴. In addition, Suzuki et al. showed a decrease in TFBUT with an increase in tear film lipid layer in patients with seasonal and perennial AC⁶. Levels of TFBUT in our

study were found to be similar to the literature as well. The TFBUT was significantly lower in patients with AC than control group. Besides, ocular allergy symptoms such as, itching and burning, were also seemed to be associated with lower TFBUT in this study.

The anatomical connection between eye and nose with lacrimal duct was proven to play an important role in interactivity of blood vessels, lymphatic tissue and the neurogenic networks where they both share several common properties. Allergic reactions which occur primarily in nasal mucosa due to exposure to an inhalant allergen may affect the conjunctiva, cornea or other ocular tissues by various mechanisms^{16,17}. Such connection of nasal area with the eye may lead to allergy related abnormalities on ocular surface. To the best of our knowledge, this was not investigated well enough previously. The values of TFBUT were similar in patients with AR (15.0 ± 4.2 s) and AC (15.7 ± 4.4 s) in our study. These findings indicate that TFBUT measurement might be a predictable parameter in patients with AR without any accompanying AC symptoms.

Allergy is a systemic response to allergens in which such response can be observed in several target organs irrespective of the local contact sites of the allergen. Some authors found allergy as a risk factor for DES and suggested that the association of atopy with tear film dysfunction may also be due to the development of hyperosmolar tear film layer associated with chronic inflammation^{9–11}. Wang et al.¹⁰ described the comorbidities of DES in their study and they reported that asthma was one of the disorder that patients with DES were more likely to have. Lindgren et al.¹⁸ found atopy

Table 2. Comparison of TFBUT measurements.

	Group I (n:45)	Group II (n:45)	Group III (n:45)	Group IV (n:45)	p
TFBUT (Mean $\pm$ SD)	15.0 $\pm$ 4.2	15.7 $\pm$ 4.4	15.2 $\pm$ 4.5	18.4 $\pm$ 2.9	0.001 ^a
TFBUT < 10 s (N)	6 (13.3%)	6 (13.3%)	3 (6.7%)	0 (0%)	0.066 ^b

TFBUT: tear film break-up time; group I: children with allergic rhinitis; group II: children with allergic conjunctivitis; group III: children with asthma; group IV: healthy children.

^aKruskal–Wallis test.

^bChi-square test.

Table 3. Comparison of laboratory findings of the patients in the study.

	Group I (n:45)	Group II (n:45)	Group III (n:45)	p
Eosinophilia	48.9%	57.8%	57.8%	0.620 ^a
The percentage of eosinophils (Mean $\pm$ SD)	3.9 $\pm$ 2.5	4.9 $\pm$ 3.0	4.3 $\pm$ 2.7	0.191 ^c
Immunoglobulin E (Mean $\pm$ SD)	260 $\pm$ 60	376 $\pm$ 51	364 $\pm$ 65	0.626 ^b
Sensitivity in SPT	28 (62.2%)	34 (75.6%)	31 (68.9%)	0.393 ^a
The number of sensitivity (Mean $\pm$ SD)	1.09 $\pm$ 1.12	1.29 $\pm$ 0.99	1.35 $\pm$ 1.13	0.449 ^c
Sensitivity to house dust	26 (57.8%)	31 (68.9%)	28 (62.2%)	0.547 ^a
Sensitivity to pollens	8 (17.8%)	12 (26.7%)	15 (33.3%)	0.240 ^a
Sensitivity to <i>A. alternata</i>	2 (4.4%)	1 (2.2%)	2 (4.4%)	0.812 ^a
Sensitivity to dander	11 (24.4%)	7 (15.6%)	9 (20%)	0.574 ^a
Sensitivity to cochrach	2 (2.2%)	7 (15.6%)	9 (20%)	0.082 ^a
TFBUT (Mean $\pm$ SD)	15.0 $\pm$ 4.2	15.7 $\pm$ 4.4	15.2 $\pm$ 4.5	0.739 ^c
TFBUT < 10 s	6 (13.3%)	6 (13.3%)	3 (6.7%)	0.509 ^a

SPT: skin prick test; TFBUT: tear film break-up time; SD: standart deviation; group I: children with allergic rhinitis; group II: children with allergic conjunctivitis; group III: children with asthma; group IV: healthy children.

^aChi-square test.

^bKruskal–Wallis test.

^cANOVA test.

as an important predictor for working environment among international airline crewmembers and showed that symptoms related to tear film deficiency were higher in atopic patients without any contribution from age, gender or smoking. Pan et al.¹⁹ studied the exposure to perennial allergens in an environmental chamber and showed that office dusts might lead to irritation in eyes, nose, throat as well as significantly decreased TFBUT. We assessed TFBUT in this study and found lower levels of TFBUT in asthma group than the control group. In addition, there was no significant difference of TFBUT among the percentage of the children with AR, AC and asthma. In our opinion, this could be related to relatively lower number of patients with TFBUT of under 10 s in AR, AC and asthma groups, so as, we did not reveal a statistically difference in the study. However, these findings indicated that whether a child has AR, AC or asthma, TFBUT evaluation would be required to search for tear film instability. In addition, antihistamine agents have anticholinergic properties due to their intrinsic high muscarinic receptor binding sites where they can cause tear film abnormalities eventually²⁰. Hence, frequent use of antihistamines in atopic patients might be one of the reasons for tear film instability in our study.

There are some limitations which could be attributed to the current work. We did not evaluate Schirmer test in our cohort. Actually, Schirmer test mainly measures aqueous tear deficiency, yet, our primary aim was to assess tear film instability in the study. Furthermore, it was not applicable to apply Schirmer test in our study due to possible querulosity during the tests in such relatively smaller-age cohort in which optimal results could not be achieved. Also, tear film osmolarity was not performed and this was an important weak point of the study. Although we revealed significant lower TFBUT in atopic children, tear film osmolarity needs to be performed in order to better understand the effect of inflammation on ocular surface in patients with AR, AC and asthma.

In conclusion, the current study showed that the presence of tear film instability (revealed by TFBUT measurements) was higher in children with allergic diseases such as AR, AC and asthma. Atopic children should be carefully monitored to avoid any deterioration on ocular surface during the course of the disease and to provide the prompt treatment. However, larger series prospective studies are necessitated to corroborate the relationship of tear film instability and atopy among pediatric population.

Declaration of interest

The authors have no proprietary interests about the subject matter through the manuscript.

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