



Tear cytokine levels in allergic rhinitis without ocular symptoms

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ABSTRACT • RÉSUMÉ

Objective: To compare cytokine levels in the pre-corneal tear film between patients with allergic rhinitis, allergic rhinoconjunctivitis and the normal population.

Design: A comparative cross sectional study.

Participants: Patients were divided into Group 1 (allergic rhinitis without conjunctivitis), Group 2 (allergic rhinoconjunctivitis), and Group 3 (normal population).

Methods: A comparative cross-sectional study was conducted. Patients were divided into; Group 1 (allergic rhinitis without conjunctivitis), Group 2 (allergic rhinoconjunctivitis), and Group 3 (normal controls). Tears were collected using Schirmer strips and cytokine analysis performed using enzyme linked immunosorbent assay.

Results: There were a total of 68 subjects. Median values of cytokines in the allergic rhinitis group were as follows; TNF α (45.34 pg/ml), IL-4 (61.91 pg/ml), IL-5 (8.92 pg/ml), IL-6 (538.37 pg/ml) and IL-8 (1438.72 pg/ml). Cytokine levels in the group with allergic rhinoconjunctivitis were approximately two-fold higher than in the group with allergic rhinitis only. The median cytokine level in the control group was lowest. A significant inter-group difference was observed for TNF- α , IL-4, IL-6 and IL-8 levels, with allergic rhinoconjunctivitis patients demonstrating significantly elevated cytokines compared to those with allergic rhinitis only ($p < 0.001$). These four cytokines were also significantly higher in those with allergic rhinitis than in controls ($p < 0.005$). Although the group with allergic rhinoconjunctivitis had the highest levels of IL-5, no statistically significant inter-group difference was noted ($p = 0.479$).

Conclusion: This study demonstrated the presence of raised tear film inflammatory cytokines even in allergic rhinitis patients without ocular symptoms. These patients may be at increased risk of developing allergic conjunctivitis. These findings not only substantiate the immunological theory of the naso-ocular reflex, but have clinical and therapeutic implications for the holistic management of allergic rhinitis and conjunctivitis.

Objectif: Comparer le taux de cytokines du film lacrymal précornéen chez le sujet présentant une rhinite allergique, chez le sujet souffrant de rhinoconjunctivite allergique et chez le sujet sain.

Nature: Étude transversale comparative.

Participants: Les 68 sujets ont été répartis en 3 groupes: rhinite allergique sans conjonctivite, rhinoconjunctivite allergique et population saine.

Méthodes: On a procédé à une étude transversale comparative au cours de laquelle les patients ont été répartis en 3 groupes: groupe 1 (rhinite allergique sans conjonctivite), groupe 2 (rhinoconjunctivite allergique) et groupe 3 (sujets témoins). On a recueilli des larmes au moyen d'un ruban de papier filtre afin de réaliser un test de Schirmer. L'analyse des cytokines a été réalisée par essai immuno-enzymatique ELISA (*enzyme linked immunosorbent assay*).

Résultats: Chez l'ensemble des 68 sujets, le taux médian de cytokines dans le groupe rhinite allergique se chiffrait comme suit: TNF- α (45,34 pg/mL), IL-4 (61,91 pg/mL), IL-5 (8,92 pg/mL), IL-6 (538,37 pg/mL) et IL-8 (1438,72 pg/mL). Le taux de cytokines dans le groupe rhinoconjunctivite allergique était approximativement 2 fois plus élevé que le taux enregistré dans le groupe rhinite allergique seule. Le taux médian de cytokines était le moins élevé dans le groupe témoin. On a noté une différence inter-groupe significative quant au taux de TNF- α , d'IL-4, d'IL-6 et d'IL-8; le taux de cytokines était significativement plus élevé chez les patients du groupe rhinoconjunctivite allergique comparativement à ceux du groupe rhinite allergique seule ($p < 0,001$). Le taux de ces 4 cytokines était en outre significativement plus élevé chez les sujets qui souffraient de rhinite allergique comparativement aux sujets témoins ($p < 0,005$). Bien que le taux d'IL-5 ait été le plus élevé dans le groupe rhinoconjunctivite allergique, on ne note aucune différence inter-groupe statistiquement significative à ce chapitre ($p = 0,479$).

Conclusion: Cette étude met au jour une hausse du taux des cytokines inflammatoires dans le film lacrymal même chez les patients souffrant de rhinite allergique sans symptômes oculaires. Ces sujets sont peut-être exposés à un risque plus élevé de conjunctivite allergique. Nos résultats étayaient la théorie immunologique du réflexe naso-oculaire, sans compter qu'ils font ressortir les répercussions cliniques et thérapeutiques de la prise en charge globale de la rhinite et de la conjunctivite allergique.

Allergic rhinitis is a common condition within the spectrum of atopy, with conjunctivitis frequently coexisting with rhinitis.¹ Significant morbidity has been attributed to this condition, termed “allergic rhinoconjunctivitis,” due to the effect of symptoms on school or work productivity.² The pathogenesis of both allergic rhinitis and

allergic rhinoconjunctivitis is a predominantly Th2-mediated mechanism, with cytokines like IL-4 prominently involved.³

Measurement of tear film cytokine levels via enzyme-linked immunoassays (ELISA) is gaining popularity as an objective, noninvasive method not only of exploring the

Table 1—Demographic and clinical features of patients with allergic rhinitis, allergic rhinoconjunctivitis, and controls

Parameter	Allergic Rhinitis	Allergic Rhinoconjunctivitis	Control	P
Age (mean, SD)	41.83 (19.56)	27.56 (14.90)	29.75 (10.20)	0.005*
Sex (n, %)				
Male	7 (30.4%)	10 (40.0%)	7 (35.0%)	0.786 [†]
Female	16 (69.6%)	15 (60.0%)	13 (65.0%)	
Systemic disease	12 (52.2%)	14 (56.0%)	5 (25.0%)	0.214 [†]
Papillary reaction	0.0 (0%)	10.0 (40%)	0.0 (0%)	<0.001 [†]
Superficial punctate keratitis	0.0 (0%)	9.0 (30%)	0.0 (0%)	<0.001 [†]

*1-way analysis of variance test.

[†]Pearson χ^2 test.

underlying immunologic mechanisms in various ocular diseases, but in assessing the response to treatment.^{4–7} An increase in tear film cytokines in an asymptomatic patient may suggest ongoing subclinical inflammation.⁴ We hypothesized that conjunctival inflammation may be present not only in patients with allergic rhinoconjunctivitis, but also in those with allergic rhinitis without ocular symptoms. This study thus aims to compare the cytokine levels in the tear film of those with allergic rhinitis, allergic rhinoconjunctivitis, and nonatopic individuals.

MATERIALS AND METHODS

After obtaining approval from the Universiti Sains Malaysia Ethical Committee, data collection was performed according to the approved study protocol. Informed written consent was obtained from all subjects. A case report form was used to document demographic features, symptoms, frequency of attacks, and medical history, such as hypertension and diabetes.

Inclusion criteria were patients with allergic rhinitis aged 5–70 years attending the Ophthalmology Clinic and Otorhinology Clinic Hospital Universiti Sains Malaysia during the study period. These patients were divided into 2 groups; group 1 had allergic rhinitis only, without any clinical evidence of allergic conjunctivitis. Group 2 had allergic rhinitis and allergic conjunctivitis. The diagnosis of allergic rhinitis was made by an otorhinolaryngologist, based on the guidelines developed by the Allergic Rhinitis and its Impact on Asthma (ARIA) organization, which collaborates with the World Health Organization to educate and implement evidence-based management for allergic rhinitis and asthma. Based on ARIA, allergic rhinitis is clinically defined as a disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation, characterized by symptoms including rhinorrhea, nasal obstruction, nasal itching, and sneezing.⁸ A history of symptoms of allergic conjunctivitis, such as eye itching, redness, tearing, and photophobia, over the past year was used as the inclusion criteria for group 2.

A control group (group 3) was added, in which patients had no allergic rhinitis or allergic conjunctivitis. All subjects were assessed by an ophthalmologist to look for clinical evidence of allergic eye disease (e.g., conjunctival injection, papillae, corneal epithelial erosions) and to rule out other ocular pathology.^{9,10} Exclusion criteria were severe ocular surface disease (e.g., shield ulcer), chronic ocular surface inflammation (e.g., keratoconjunctivitis sicca, glaucoma or

topical medication), autoimmune disease or a history of topical antihistamine or topical/systemic/nasal steroid use within the past 1 month, a history of ocular trauma, or ocular surgery in the past 6 months.

One eye of each patient in the 3 groups was used for sample collection. After instillation of local topical anaesthetic (G. proparacaine 0.05%), a Schirmer strip (Contacare, Baroda, India) was placed in the lower conjunctival cul-de-sac and tears were allowed to diffuse into the strip over a period of 5 minutes. The subjects were allowed to blink freely during this time. The Schirmer strip was then placed into a plain tube and frozen to -80°C within 1 hour of collection. Tear samples were diluted 1:25 in phosphate-buffered saline (Immunoconcepts, Sacramento, Calif.) containing 1 mg/mL bovine serum albumin to a final volume of 100 μL , and ELISA was performed using cytokine detection kits according to protocols supplied by the manufacturer (Biolegend, San Diego, Calif.). The ELISA kits used for cytokine detection were as follows: Legend Max Human TNF- α Elisa Kit with Pre-coated Plates (CAT# 430207), Legend Max Human IL-4 Elisa Kit with Pre-coated Plates (CAT# 430307), Legend Max Human IL-5 Elisa Kit with Pre-coated Plates (CAT# 430404), Legend Max Human IL-6 Elisa Kit with Pre-coated Plates (CAT# 430507), and Legend Max Human IL-8 Elisa Kit with Pre-coated Plates (CAT# 431507). Based on the standard curves, the detection sensitivity for TNF, IL-4, IL-5, IL-6, and IL-8 were 3.5, 0.6, 2.0, 1.6, and 4.4 pg/mL, respectively.

Table 2—Comparison of tear film cytokine levels in patients with allergic rhinitis, allergic rhinoconjunctivitis, and controls

Parameter	Group	Mean Rank	Median	IQR	χ^2 Statistic*	p
TNF	AR	30.98	45.34	97.93	32.42	<0.001
	ARC	51.04	110.64	181.88		
	Control	17.88	11.79	14.07		
IL-4	AR	29.24	61.91	91.50	21.12	<0.001
	ARC	48.52	150.11	250.68		
	Control	23.03	1.723	7.343		
IL-5	AR	31.70	8.92	17.85	1.47	0.479
	ARC	38.24	10.41	10.41		
	Control	33.05	6.70	13.38		
IL-6	AR	35.09	538.37	588.41	36.00	<0.001
	ARC	50.00	1018.62	1492.09		
	Control	14.45	74.36	164.12		
IL-8	AR	36.37	1438.72	1543.5	31.30	<0.001
	ARC	48.22	2353.9	1553.09		
	Control	15.20	492.20	302.16		

AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis.

*Kruskal-Wallis test.

p value significant at <0.001.

Table 3—Post-hoc comparisons for cytokine levels between groups

Cytokine	Comparison	Z Statistic*	p [†]
TNF- α	AR vs ARC	3.57	<0.001
	AR vs control	2.25	<0.005
	ARC vs control	5.49	<0.001
IL-4	AR vs ARC	-3.463	<0.001
	AR vs control	-3.153	<0.005
	ARC vs control	-4.189	<0.001
IL-5	AR vs ARC	-4.189	0.251
	AR vs control	-1.15	0.825
	ARC vs control	-0.22	0.385
IL-6	AR vs ARC	-3.23	<0.001
	AR vs control	-4.14	<0.001
	ARC vs control	-5.27	<0.001
IL-8	AR vs ARC	-2.40	<0.001
	AR vs control	-3.87	<0.001
	ARC vs control	-5.19	<0.001

AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis.

*Mann-Whitney test.

†Bonferroni correction (p value significant at <0.01).

Data analysis was performed using SPSS version 22.0. As the distribution curve of mean values showed the outcome variable to be skewed, statistical medians were used in this study to estimate the level of cytokines in each group. Kruskal-Wallis test and Mann-Whitney test with Bonferroni correction were used to compare the distribution of cytokines between groups based on median value.

RESULTS

A total of 68 participants were included in this study. Their demographic and clinical features (based on the worse eye) are shown in Table 1. The mean age of the group with allergic rhinitis (41.83 ± 19.56 years) was significantly higher than that of the group with allergic rhinoconjunctivitis (27.56 ± 14.90 years) and the control group (29.75 ± 10.20 years) ($p = 0.005$). The 3 groups were otherwise comparable in their sex distribution, with females being predominant. The group with allergic rhinoconjunctivitis demonstrated more signs of allergic eye disease than their counterparts, with papillary reaction and superficial punctate keratitis being significantly absent in the latter ($p < 0.001$).

The levels of TNF- α , IL-4, IL-6, and IL-8 were higher in the group with allergic rhinoconjunctivitis than the group with allergic rhinitis only, with the control group demonstrating the lowest level of tear film cytokines (Table 2). A significant intergroup difference was noted with these 4 cytokines ($p < 0.001$ for each).

Post-hoc analysis revealed that the median tear film cytokine levels of TNF- α , IL-4, IL-6, and IL-8 in patients with allergic rhinoconjunctivitis were significantly higher than the levels observed in patients with allergic rhinitis only. More interestingly, all these tear film cytokine levels were also significantly higher in patients with isolated allergic rhinitis than in the control group (Table 3). Although the group with allergic rhinoconjunctivitis had the highest levels of IL-5, no statistically significant intergroup difference was noted ($p = 0.479$).

DISCUSSION

Allergic rhinitis and allergic rhinoconjunctivitis are part of a systemic inflammatory process, and the relationship between them has long been a subject of investigation.¹¹ Besides the obvious anatomical connection between the nose and the eye via the nasolacrimal apparatus, both these organs share a common pathway of parasympathetic innervation at the pterygo-palatine ganglion, while at the pterygoid plexus and cavernous sinus, venous communication exists, allowing a pathway for the spread of allergens.¹² The nasal-ocular reflex has often been considered clinical evidence of the link between these 2 entities. This reflex, in which a nasal antigen challenge causes conjunctival inflammation, ocular pruritus, and lacrimation, is postulated to be due to the stimulation of nasal afferent nerves by released histamine, leading to an efferent parasympathetic response that culminates in conjunctival mast cell degranulation.^{13,14} Increased cytokine levels have previously been demonstrated in the serum and nasal mucosa of allergic rhinitis patients.^{15,16} However, to the best of our knowledge, this is the first study comparing tear film cytokine levels among patients with allergic rhinoconjunctivitis, allergic rhinitis, and normal patients.

The ability to detect cytokines in different body fluids has facilitated our understanding of the pathogenesis of allergic rhinitis.^{17,18} As a key mediator of allergic rhinitis and a common target of immunotherapy, increased concentrations of IL-4 have been observed in T helper cells in the peripheral blood,^{17,19,20} while reduction of IL-4 concentrations has been observed in the nasal fluid of immunotherapy-treated patients.²¹ This cytokine is responsible for inducing B-lymphocytes to produce IgE, which binds to receptors on mast cells.¹¹ In type 1 hypersensitivity-mediated disease, crosslinking of the IgE on these receptors in response to an allergen causes activation of mast cells, with release of a variety of proinflammatory mediators, including histamine, IL-4, IL-6, IL-8, and TNF- α .²² Histamine gives rise to the acute symptoms of allergic rhinitis like sneezing and rhinorrhoea, while TNF- α drives the late allergic response by directing inflammatory cells like eosinophils to the target mucosa, culminating in nasal obstruction.¹¹ IL-8 is elevated in the nasal mucosa of patients with chronic rhinosinusitis and has likewise been found to regulate the migration of circulating leukocytes to target sites.²³ The concentrations of both TNF- α and IL-8 are higher in the serum of allergic rhinitis than controls and decrease significantly in response to specific immunotherapy.²⁴

The cytokines discussed above are characteristically increased not only in allergic conjunctivitis, but in atopic and vernal keratoconjunctivitis,^{18,24–26} indicating that they may be useful markers of ongoing inflammation. We chose to analyze the levels of these cytokines in patients with isolated allergic rhinitis as we hoped to demonstrate similar cytokine elevations in the tear fluid of these patients. We found that IL-4, IL-6, IL-8, and TNF levels were predictably higher in the tear film of allergic rhinoconjunctivitis patients compared to those with allergic rhinitis, which correlates with the

clinical features of ocular inflammation seen in the former group. A more interesting point of note is that patients with allergic rhinitis without evidence of conjunctival inflammation demonstrated significantly higher levels of these cytokines compared to normal patients. This suggests that these patients have significant subclinical ocular inflammation despite being asymptomatic. Although IL-5 has traditionally been associated with allergic disease, we found no significant elevation in its levels between the different subgroups. We postulate that this is because most patients were not experiencing any acute allergic attack at the point of sampling; IL-5 has been postulated to be a hallmark not of atopy itself, but rather of current, symptomatic disease.²⁷

The results of this study contribute to the body of evidence suggesting that the management of allergic rhinitis is inextricably intertwined with that of allergic conjunctivitis and therefore requires a 2-pronged approach: management of both the nasal and ocular inflammatory processes. Some treatments that have started to utilize this concept include using wraparound spectacles to improve the symptoms of seasonal allergic rhinitis²⁸ and utilizing intranasal corticosteroids and nasal filters to manage the ocular symptoms of allergic rhinoconjunctivitis.^{29–35} The interrelatedness of allergic rhinitis and rhinoconjunctivitis may tempt the clinician to consider monotherapy (treating either the nasal or the ocular inflammation) in the hope that the less severely affected organ will respond also, but we advise caution in this matter, as the results obtained thus far are variable.^{32,36,37}

Although we are limited by our small sample size, no other previously published work has demonstrated increased levels of inflammatory cytokines in the tear film of patients with isolated allergic rhinitis without evidence of allergic conjunctivitis. The clinical and therapeutic implications of these findings have yet to be explored; whether treatment of nonsymptomatic allergic conjunctivitis in patients with isolated allergic rhinitis is cost-effective or whether combination treatment of allergic rhinoconjunctivitis achieves better control than just targeting the site of allergic symptoms are just some of the future questions to be addressed.

CONCLUSION

The concentration of tear film cytokines in patients with allergic rhinitis alone is significantly higher than that of the normal population, although not as high as in those with allergic rhinoconjunctivitis. These findings substantiate the naso-ocular reflex hypothesis and provide immunological evidence of the similar pathophysiologic processes underlying these 2 diseases. Further research is required to determine if patients with allergic rhinitis alone will benefit from being managed as allergic rhinoconjunctivitis.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2018.12.003.

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