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Mediators and Some Cytokines in Tears During the Late Conjunctival Response Induced by Primary Allergic Reaction in the Nasal Mucosa

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1. Introduction

The allergic conjunctivitis (AC) consists of five clinical types, a seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC), having a common causal background, namely the involvement of allergic component, but different clinical features. [1-5] The five clinical types of AC can occur in 2 basic forms, a primary and a secondary form, with respect to the locality of the initial antigen-antibody/sensitized Th1 cells interaction with following steps, called initial allergic reaction. [6-12] In the primary AC forms, the initial allergic reaction with all subsequent steps, due to the direct exposure of conjunctivae by an external allergen, is localized in the conjunctival tissue. In these, classical, AC forms, the conjunctival tissue is the primary site of allergic reaction and together the primary target tissue affected directly by the allergic reaction and displaying the characteristic clinical symptoms. In the secondary AC forms, the initial allergic reaction taking place in the nasal mucosa, due to exposure to an external allergen, induces subsequently the secondary form of AC through various possible mechanisms and pathways. In this case, the conjunctival tissue is affected by factors released and generated by allergic reaction in the nasal mucosa and the conjunctival response displaying characteristic clinical symptoms may be considered as a consequence of the primary allergic reaction in the nose. [6-12]

In both the basic forms of AC as well as all five clinical types, various hypersensitivity mechanisms, such as immediate type (IgE-mediated Type I), late (Type III) or delayed (cell-mediated Type IV), may be involved.[1, 2, 5, 9-19] The involvement of various hypersensitivity types in AC results then in development of various types of conjunctival response (CR) to allergen exposure (challenge), an immediate (ICR), a late (LCR), a dual late (DLCR, being a combination of an immediate and a late type), a delayed (DYCR) and a dual delayed (DDYCR, being a combination of an immediate and a delayed type). [1- 3, 5-14, 20] The primary forms of AC can be demonstrated by direct conjunctival provocation tests with allergens (CPTs), whereas the secondarily induced AC forms can only be confirmed by nasal provocation tests with allergens (NPTs) in combination with registration of the conjunctival signs and subjective symptoms.

Nevertheless, there is a great dearth of data concerning both the clinical and the immunologic features of the secondary CR and the mechanism(s) through which the allergic reaction initiated in the nasal mucosa induces the secondary CR types. [1-3, 5-42] The purpose of this study was to investigate: (1) the appearance and possible concentration changes of some important mediators, such as histamine, tryptase, eosinophil cationic protein (ECP), leukotrienes, myeloperoxidase (MPO) and cytokines, such as, interferon-γ (IFN-γ), IL-2, IL-4 and IL-5 in tears during the secondary late CR; (2) the possible significance of these mediators in tears for the mechanism(s) underlying the secondary late CR.

2. Material and methods

2.1 Patients

Thirty-one patients suffering from allergic conjunctivitis (SAC, n=13 and PAC, n=18) for more than 3 years, showing insufficient therapeutic compliance to the standard topical ophthalmologic treatment, having been referred to our Department of Allergology & Immunology (Institute of Medical Sciences "De Klokkenberg", Breda, The Netherlands), for more extensive diagnostic analysis of their AC complaints, and developing the secondary late conjunctival response(SLCR) to nasal provocation tests with allergens (NPTs),were randomly selected and volunteered to participate in this study.

These patients, 12 males and 19 females, 18-47 years of age (Table 1), have previously been treated with various topical and oral H1-receptor-antagonists, ophthalmic cromolyn formulation, topical ocular glucocorticosteroids, decongestant, topical vasoconstrictors and incidentally with NSAID drugs, without significant therapeutic effects. None of these patients suffered from other ocular disorders, infection, systemic diseases or immunodeffociency or had previously been treated with nasal cromolyn, nasal or systemic glucocorticosteroids, immunosuppressive drugs or immunotherapy. All of them demonstrated normal intraocular pressure. In 14 of these patients 19 conjunctival provocation tests (CPT) with inhalant allergen, performed previously, were negative.

The patients underwent a routine diagnostic procedure consisting of: a detailed disease history, general physical examination, basic laboratory tests, bacteriological screening of tears, nasal secretions, sputum and blood, roentgenogram of chest and paranasal sinuses in Water's projection, nasoscopy and cytologic examination of nasal secretions, skin tests with basic and supplementary inhalant and food allergens, determination of serum immunoglobulins, and ophthalmologic examination including ophthalmoscopy, slit-lamp evaluation, vital staining with fluorescein and cytologic examination of the tears. The routine diagnostic procedure performed in these 31 patients revealed positive or suspect history for nasal allergy (93%), positive skin (intracutaneous) tests with various inhalant allergens (100%), hyperaemic /livid and edematic nasal mucosa (97%), increased eosinophil and neutrophil counts in nasal secretions (87%), conjunctival hyperaemia and tearing to a slight degree (100%), appearance of incidental eosinophils and conjunctival epithelial cells in the tear specimens (84%), increased blood eosinophil counts (23%), positive specific IgE in the serum (ImmunoCAP) for some inhalant allergens (19%) and non-increased nasal responsiveness to histamine determined by means of nasal challenge with histamine (93%) (Table 1). No other abnormalities were found in these patients.

In these 31 patients, 54 nasal provocation tests (NPTs) with various inhalant allergens (Table 2)and 31 control challenges with PBS (phosphate-buffered saline)were performed using rhinomanometry in combination with simultaneous recording of the ocular signs and

subjective symptoms (Tables 1, 2). The ocular signs and relevant subjective symptoms were evaluated by means of the Pelikan's scoring (grading) system (Table 3). [7, 9-12] The patients were investigated in a period without acute ocular and/or nasal complaints, without symptoms of an acute infection, outside the allergen-relevant period (season) and during. hospitalization. The long-acting H1-receptor antagonists, topical cromolyn and glucocorticosteroids were withdrawn 4 weeks, topical and oral short-acting H1 receptor antagonists, topical decongestants and other treatments were withdrawn 48 hours before each of the NPTs.

	Patients		Control subjects
	SAC (n=13)	PAC (n=18)	n=14
Age (years)	25 ± 7	31 ± 12	29 ± 9
Sex (M/F)	5/8	7/11	6/8
Disease history (years)	3.9±1.5	4.6±0.7	5.2 ± 1.1
Blood leukocyte count (x 10^9 /L) °	8.3±0.6	9.1±1.4	7.9±0.8
-increased	0	0	0
Blood eosinophil count (x 10^6 /L) °°	263±21	285±13	255±29
-increased	2	5	4
Increased total IgE in the serum ▫	0	0	0
Positive specific IgE in the serum ▫▫	1	5	2
Positive skin response •			
-Immediate type	4	7	8
-Late type	9	10	5
-Delayed type	0	1	1
Nasal provocation tests			
-positive	13	18	21
-negative	10	13	15

SAC= seasonal allergic conjunctivitis; PAC= perennial allergic conjunctivitis; ° = normal value 4.0-10.0 x 10^9/L; °° = normal value < 300 x 10^6/L; ▫ = normal value <500 IU/mL; ▫▫ = normal value <0.70 U/mL; • = positive skin response to the relevant allergen (=allergen producing positive nasal and conjunctival or nasal response only)

Table 1. Characteristics of the patients

The 31 positive NPTs producing the secondary late conjunctival response (SCLR) in these patients and 31 PBS control challenges were repeated 2-3 weeks later. The repeated NPTs and PBS control challenges were supplemented with a collection of the tears for the mediator determination (Table 4). A 4-day interval was always inserted between the end of the preceding test and the begin of the following test to prevent the carry-over effects and to allow the patient recovery. The study protocol was approved by the local ethical committee and informed consent was obtained from all study participants.

Allergen	Concentration	Nasal responses positive (n=31)	Conjunctival responses (n=31)		Nasal responses negative (n=23)
			SAC (n=13)	PAC (n=18)	
Dermatophagoides pteron	1000 BU/mL	5		5	3
Dermatophagoides farinae	1000 BU/mL	1		1	1
Animal danders					
-dog	3000 BU/mL	3		3	2
-horse	2000 BU/mL	2		2	0
-cat	2000 BU/mL	2		2	3
-guinea pig	2000 BU/mL	1		1	0
Feathers					
-parrot	3000 BU/mL	1		1	0
-parakeet	3000 BU/mL	1		1	1
Aspergillus fumigatus	1000 BU/mL	2		2	1
Pollen					
-grass mix I	1000 BU/mL	4	4		2
-grass mix II	1000 BU/mL	2	2		1
-flower mix	5000 BU/mL	1	1		2
-tree mix	3000 BU/mL	2	2		3
-weed mix	1000 BU/mL	1	1		2
-poplar	2000 BU/mL	1	1		0
-ragweed short	1000 BU/mL	1	1		1
-ragweed giant	1000 BU/mL	1	1		1

SAC = seasonal allergic conjunctivitis; PAC = perennial allergic conjunctivitis; BU/mL = biologic units per mL
Grasspollen mix I = *Dactylis glomerata, Lolium perenne, Phleum pratensis, Poa pratensis*;
Grasspollen mix II = *Festuca pratensis, Holcus lanatus, Agrostis alba, Anthoxanthum odoratum*
Flower pollen mix = *Dahlia variabilis, Solidago virgaurea, Primula variabilis, Forsythia suspensa*
Tree pollen mix = *Betula pendula, Corylus avellana, Juniperus communis, Salix alba*
Weed pollen mix = *Artemisia vulgaris,Plantago lanceolata, Rumex acetosa, Taraxacum officinale*

Table 2. Survey of the allergens used for nasal challenge

2.2 Allergens

Dialyzed and lyophilized allergen extracts (Allergopharma, Reinbek, Germany) were diluted in phosphate-buffered saline (PBS) and used for skin tests in concentrations of 100-500 BU/mL and for NPTs in concentrations of 1000-5000 BU/mL (Table 2), as recommended by the manufacturer. If indicated, higher dilutions of the allergen extracts were used both for the skin tests and for the NPTs.

2.3 Skin tests

Scratch tests with allergenic extracts in concentrations of 500 BU/mL were performed and the results evaluated after 20 minutes. If the results were negative, then intracutaneous tests in concentrations of 100 BU/mL and 500 BU/mL were carried out and evaluated 20 minutes and 6, 12, 24, 36, 48, 56, 72 and 96 hours after the intradermal injection. A skin wheal (>7.0 mm in diameter) occurring after 20 minutes was qualified as a positive immediate skin response, the skin infiltration appearing between 6 and 12 hours as a late skin response, and the skin induration recorded later than 48 hours as a delayed skin response.[8-13, 42-46]

2.4 Nasal provocation tests (NPTs)

Nasal challenges with allergens were performed using rhinomanometry, already described in our previous studies. [6-13, 23, 43-47] The nasal obstruction due to the edema of the nasal mucosa was evaluated by means of nasopharynx-nostril pressure gradient (NPG) parameters, which are the pressure differences (ΔP) between the nasopharyngeal cavity and the outside air, expressed in cm H_2O. NPTs were performed using the following schedule: (1) baseline values recorded at 0, 5 and 10 minutes before the challenge; (2) PBS control values recorded at 0, 5 and 10 minutes after a 3-minute application of PBS to the nasal mucosa of the non-intubated nasal cavity by means of a saturated wad of cotton wool on a nasal probe inserted under the middle turbinate; (3) post-challenge values recorded after a 3-minute challenge with allergen, carried out in the same manner as the challenge with PBS, at 0, 5, 10, 20, 30, 45, 60, 90 and 120 minutes, then every hour up to the 12th hour, and every second hour during the time-periods between the 24th-38th and 48th – 56th (60th) hour.[9-13] The allergens used for the NPTs were chosen with respect of the disease history and positive skin tests (Tables 1, 2). The nasal response (NR) was assessed to be positive when the post-challenge mean NPG values increased by at least 2.0 cm H_2O (1.2 ± 0.3, mean± SE) with respect to the mean baseline values, recorded at least at three consecutive time intervals[14, 23-26]. The NPG changes recorded within 60-120 minutes after the allergen challenge were considered to be an immediate NR (INR), those recorded within 4-12 hours to be a late NR (LNR), and the changes measured later than 24 hours to be a delayed NR (DYNR) [9-13, .43-45]

2.5 Control tests with phosphate-buffered saline (PBS)

The control nasal challenge with PBS was performed in each patient studied by the same schedule as that used for the NPTs with allergen, however 3 days later.

2.6 Conjunctival response

The objective conjunctival signs and relevant subjective symptoms were registered before and during all NPTs with allergens and PBS at the same time-points as the nasal NPG values. The features of the conjunctiva were assessed by ophthalmoscopy including a slit lamp. The conjunctival signs, hyperaemia (injection), chemosis, hyperlacrimation, and palpebral edema, and the subjective symptoms, such as itching (burning), blurred vision and photophobia, were registered and evaluated by means of the scale suggested by Abelson, however, modified by us (Pelikan's scale). [10-12] The evaluation criteria of the individual signs and symptoms were as follows: 0=absent, 1=mild (present to a slight degree), 2=moderate, 3= pronounced (moderately severe), 4=severe (Table 3). The

differences in total sign score of 4 points or more (3 ± 1, mean ± SE), recorded at least at three consecutive time-intervals, were found to be statistically significant (p<0.05).

	Abelson I*	Abelson II**	Pelikan
I. OBJECTIVE SIGNS			
-Hyperemia (injection, redness)	0 - 4	0 - 3	0 - 4
-Chemosis		0 - 3	0 - 4
-Hyperlacrimation (tearing)		0 - 3	0 - 4
-Palpebral edema			0 - 4
II. SUBJECTIVE SYMPTOMS			
-Itching (burning)	0 - 4	0 - 4	0 - 4
-Photophobia			0 - 4
-Blurred vision			0 - 4

* = References 27, 28, 29; ** = References 21, 30

Abelson's grading scale: 0=None; 1=Mild (intermittent); 2=Moderate; 3=Severe;
4= extremely severe (or "incapacitating "itching); [Significant threshold: ≥+2]

Pelikan's grading scale: 0=Absent; 1=Mild (present to a slight degree or intermittent);
2=Moderate; 3= Pronounced (moderately severe); 4=Severe; [Significant difference: ≥4 points (p<0.05), with respect to the pre-challenge value, recorded at least at 3 consecutive time-points].

Table 3. Survey of Abelson's and our "modified" conjunctivitis grading scale and symptom score ("Pelikan's modified grading scale")

2.7 Collection and processing of tears

The tear specimens were collected from each of eyes separately by means of a micropipette from the inferior conjunctival fornix and/or lacus lacrimalis, before, 30 and 60 minutes, every second hour up to 12 hours and 24 hours after the allergen challenge. If necessary, a gentle pressure on the lacrimal sac from outside was applied. The tear samples (1-4 mL) were stored at -8^{o}C and processed within 1 hours. The concentrations of appropriate factors in tears were measured by using commercially available kits, following the manufacturer's recommendations. The measurements of the factors were performed separately in tear samples from each of the eyes on each occasion, and the results were then calculated as the mean of both the eyes.

All measurements were performed in duplicate by a double-blind schedule. The intra-assay as well as the inter-assay coefficients of variations for all the assay kits employed were less than 10 %.

a. *Histamine* Histamine concentrations, so-called "blanks", were measured by the Siraganian's fluorometric method [48] Detection limits (DL): 1.0 ng/mL
b. *Tryptase* -ImmunoCAP (Pharmacia, Uppsala, Sweden). DL: 1.0 µg/L
c. *Eosinophil cationic protein (ECP)*-ImmunoCAP (Pharmacia Diagnostics, Uppsala, Sweden). DL: 2µg/L

d. *Leukotrienes B4, C4, E4* -EIA kits (Cayman Chemical Company, Ann Arbor/MI, USA). Detection limits (DL): LTB_4 = 4.8 pg/mL; LTC_4 = 2 pg/mL; LTE_4 = 3.7 pg/
e. *Myeloperoxidase (MPO)* - ELISA kit (Oxis International Inc, Portland /OR, USA). DL: 25 ng/mL
f. *Interferon-gamma (IFN-γ)* - ELISA kit (Bender MedSystems, Wien, Austria). DL: 1.0 pg/mL
g. *Interleukin 2 (IL-2)* - ELISA kit (R & D System (Minneapolis/MN, USA). DL: < 3.0 pg/mL
h. *Interleukin 4 (IL-4)* - ELISA kit (Bender MedSystems , Wien, Austria).DL: 0.6 pg/mL
i. *Interleukin 5 (IL-5)* - ELISA kit (R & D System (Minneapolis/MN, USA). DL: 3.0 pg/mL

2.8 Control group

Fourteen adults suffering from allergic rhinitis, confirmed by positive history, skin tests and positive NPTs with inhalant allergens, but without history of any ocular disease and with normal ophthalmologic findings, volunteered to participate as control subjects. In these patients 14 positive late nasal responses (LNR)with inhalant allergens were repeated and supplemented with registration of the conjunctival features and subjective symptoms and estimation of the above mentioned mediators in tears.

2.9 Statistical analysis

1. Nasal and conjunctival responses (mean total scores of conjunctival signs and subjective symptoms) to the allergen challenge as well as to the PBS control challenge in individual patients were statistically analyzed by Wilcoxon matched-pair signed rank test, comparing the post-challenge values at each of the time-points with the mean pre-challenge (baseline) values.
2. The mean NPG values and the mean total conjunctival score values were compared with corresponding PBS control values at each of the time-points and analyzed by the Mann-Whitney *U* test.
3. The post-challenge mediator values measured at each of the time points during the repeated SLCRs and PBS control in individual patients were compared with their pre-challenge values and statistically analyzed by Wilcoxon matched-pair signed rank test.
4. The mean post-challenge mediator values during the repeated SLCRs were compared with corresponding PBS values and statistically evaluated by Mann-Whitney *U* test. Statistical evaluation of the CR was performed separately for each of the eyes and then the mean from both the eyes was calculated. A *P* value < 0.05 was considered to be statistically significant.

3. Results

3.1 Nasal responses (NRs)

In the 31 patients 54 nasal provocation tests (NPTs) with various inhalant allergens (Tables 1, 2) and 31 PBS control challenges were performed. The 31 patients developed 31 late nasal responses (LNRs; $p<0.01$) and 23 negative nasal responses (NNRs; $p>0.1$)(Table 2). The LNR

began between 4-6 hours, reached its maximum between 6-8 hours and resolved within 12 hours after the nasal challenge with allergen.
The 31 PBS control tests were all negative ($p>0.1$). No significant differences were found in the appearance of the LNRs with respect to the individual allergens ($p>0.1$). The LNRs were associated with significant changes ($p<0.05$) in the counts (mostly temporary increase) of the neutrophils, eosinophils, epithelial and goblet cells, and to a lesser degree of the lymphocytes, in the nasal secretions. The counts of basophils, mast cells, monocytes and plasma cells were relatively low and without significant changes.
The repeated NPTs resulted in the development of similar and statistically significant LNRs as comparing the post-challenge with the pre-challenge (baseline) values ($p<0.001$) and with the PBS control values ($p<0.001$) (Fig. 1C). No statistical significant differences were found between the initial and the repeated LNRs ($p>0.2$).

3.2 Conjunctival responses (CRs)

The 31 positive LNRs, recorded in 31 patients, were associated with significantly positive secondary conjunctival responses of the late type (SLCR; $p<0.01$)(Table 2). The positive SLCR began between 5-6 hours, reached its maximum between 8-10 hours and resolved usually within 12, sometimes within 24 hours after the allergen challenge. The SLCR was represented by significant changes of the objective conjunctival signs ($p<0.01$) as well as subjective symptoms ($p<0.05$). No significant corneal signs were recorded in any SLCR. No conjunctival changes were recorded during the 23 negative nasal responses ($p>0.05$) or during the 31 PBS control challenges ($p>0.1$). The 31 repeated NPTs , have induced similar and statistically significant SLCRs , both as comparing the post-challenge with the pre-challenge (baseline) values ($p<0.01$) and as comparing with the PBS control challenge ($p<0.01$). (Fig. 1B). No statictically significant difference were found between the initial and the repeated SLCRs ($p>0.2$). No significant differences in the conjunctival changes recorded both during the initial and during the repeated SLCRs were observed between the right and left eye ($p>0.1$).

3.3 Changes of mediators and other factor in the tears during the SLCRs

The SLCRS were associated with significant changes in the concentrations ($p<0.05$) of histamine, EPC, LTC_4 , LTB_4 , MPO, IL-4 and IL-5 in the tears (Table 4; Fig. 1A). The pre-challenge concentrations of most of these factors were either very low or under the detection limit, whereas their post-challenge concentrations usually increased to various degrees at various time-points, followed by their decrease and disappearance from the tears within 24 hours after the allergen challenge (Table 4 ; Fig.1A). The concentrations of tryptase in tears was very low, sometimes under the detection limit and without significant changes ($p>0.05$). The INF-γ and IL-2 were recorded in the tears during the SLCRs irregularly and without any significant changes ($p>0.05$ and $p>0.05$, respectively). The LTE_4 was not detected in the tears during the positive SLCRs. No significant concentration changes of the investigated factors were recorded in tears during the 31 PBS control challenges and 23 negative CRs. Moreover, the concentrations of most of these factors were under the detection limits (Table 4). No significant differences in the concentrations of particular factors and their changes in tears have been found between the right and left eye, both during the SLCRs and during the PBS controls ($p>0.1$ and $p>0.2$, respectively).

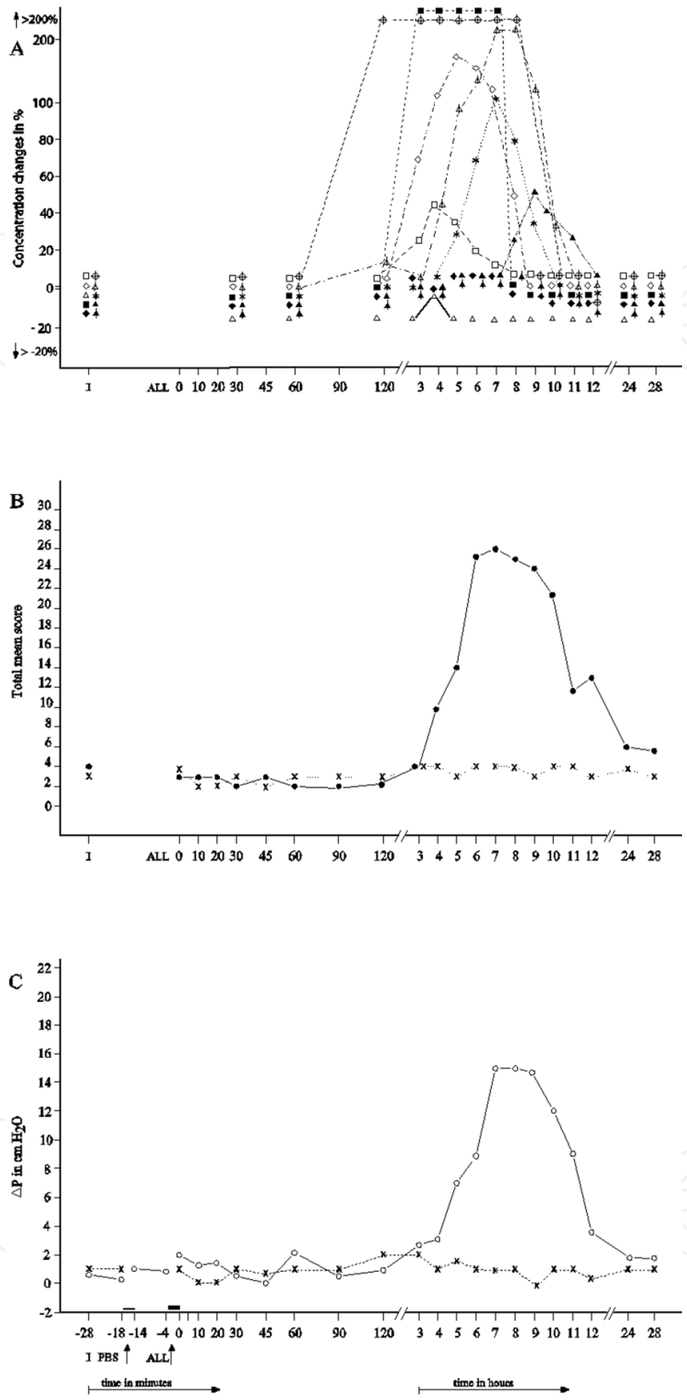

Fig. 1. The secondary late conjunctival responses (SLCRs; n=31) accompanying the isolated late nasal responses (ILNRs; n=31). **A.** The mean score of particular factors during the SLCR: □ = histamine, Δ = tryptase, ⌖ = EPC, ⍋ = LTB_4, ◇ = LTC_4, ✶ = MPO, ■ = IL-4, ▲ = IL-5, ◆ = IFN-γ, ⍋ = IL-2. **B.** The total mean score of conjunctival signs and symptoms during the SLCR (●) and PBS (**x**). **C.** The mean rhinomanometric values (NPG) recorded during ILNR (○) and PBS (x), I = Initial (baseline) values; PBS = Phosphate buffered saline; ALL = Allergen challenge

	Before the challenge	After the challenge (hours)														
		½	1	2	3	4	5	6	7	8	9	10	11	12	24	28
Histamine *ng/mL*																
- *SLCR*	< 1.0	< 1.0	< 1.0	< 1.0	2.6 ± 0.3*	4.7 ± 0.5*	3.4 ± 0.7*	1.9 ± 0.6+	1.2 ± 0.1	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	1.3 ± 0.2
- *PBS*	< 1.0	< 1.0	< 1.0	< 1.0	<1.0	<1.0	1.1 ± 0.1	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Tryptase *µg/L*																
- *SLCR*	1.3±0.3	<1.0	<1.0	1.1 ± 0.1	<1.0	1.3 ± 0.2	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
- *PBS*	< 1.0	<1.0	<1.0	<1.0	1.2 ± 0.2	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
EPC µg/L																
- *SLCR*	2.3±0.2	2.5 ± 0.4	2.2 ± 0.1	4.5 ± 0.7+	5.3 ± 1.1+	9.5 ± 2.3*	13.8 ± 3.2**	15.6 ± 2.0**	7.3 ± 1.8*	6.0 ± 1.4*	2.4 ± 0.2	<2.0	<2.0	<2.0	<2.0	<2.0
- PBS	2.7±0.6	<2.0	<2.0	2.4 ± 0.4	2.5 ± 0.3	<2.0	<2.0	2.8 ± 0.5	2.3 ± 0.3	2.5 ± 0.2	2.1 ± 0.1	2.2 ± 0.1	<2.	2.4 ± 0.3	<2.	<2.
LTB4 pg/mL																
- *SLCR*	<4.8	<4.8	<4.8	5.5 ± 0.6	4.9 ± 0.1	6.8 ± 1.0+	9.3 ± 2.1*	11.2 ± 3.1*	23.0 ± 2.6**	28.5 ± 1.4**	10.7 ± 1.9*	6.6 ± 0.5+	5.1 ± 0.4	5.0 ± 0.2	<4.8	<4.8
- PBS	<4.8	<4.8	<4.8	5.1 ± 0.2	<4.8	<4.8	<4.8	<4.8	5.0±0.2	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8
LTC4 pg/mL																
- *SLCR*	2.2±0.1	<2.0	<2.0	2.3 ± 0.3	3.8 ± 0.7+	5.2 ± 0.5*	6.1 ± 0.4*	5.8 ± 0.3*	4.9 ± 0.8*	3.3 ± 0.2	2.3 ± 0.2	<2.0	<2.0	<2.0	<2.0	<2.0
- *PBS*	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0	2.2 ± 0.2	2.1 ± 0.1	<2.0	<2.0	<2.0	<2.0	<2.0
MPO *ng/mL*																
- *SLCR*	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0	31.9 ± 5.5+	43.8 ± 3.6*	51.5 ± 4.0**	45.1 ± 2.8*	34.2 ± 1.7*	26.3 ± 1.0	<25.0	<25.0	<25.0	<25.0
- PBS	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0	28.6 ± 2.7	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0	<25.0
IFN-γ *pg/mL*																
- *SLCR*	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	1.2 ± 0.1	1.2 ± 0.2	<1.0	<1.0
- PBS	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
IL-2 pg/mL																
- *SLCR*	< 3.0	< 3.0	3.2 ± 0.2	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	3.3 ± 0.3	<3.0	<3.0	<3.0	3.2 ± 0.1	<3.0	<3.0
- PBS	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	3.1 ± 0.1	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0
IL-4 *pg/mL*																
- *SLCR*	<0.6	<0.6	<0.6	<0.6	2.4 ± 1.0+	5.7 ± 0.8*	7.9 ± 1.5**	4.0 ± 0.6*	1.8 ± 0.5	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6
- PBS	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	1.3 ± 0.4	<0.6	<0.6	<0.6

	Before the challenge	After the challenge (hours)														
		½	1	2	3	4	5	6	7	8	9	10	11	12	24	28
IL-5 *pg/mL*																
- *SLCR*	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	3.7 ± 0.6	4.6 ± 0.4*	4.3 ± 0.7*	3.8 ± 0.2	<3.0	<3.0	<3.0
- PBS	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	<3.0	3.1 ± 0.1	<3.0

SLCR = Secondary late conjunctival response; PBS = Phosphate-buffered saline; Significance of mean post-challenge values with respect to the mean pre-challenge (baseline) value:
+ = p≤0.05; * = p<0.05; ** = p<0.01

Table 4. Concentration of particular factors in tears during the secondary late conjunctival response (SLCR)

3.4 Control patients

The 14 control patients developed an isolated late nasal response (ILNR) during the initial as well as the repeated NPTs ($p<0.001$ and $p<0.001$ respectively). No significant conjunctival signs or subjective symptoms were recorded during the 14 repeated LNRs ($p>0.2$). No significant changes in concentrations of the investigated factors were recorded in tears during the repeated LNRs in these control patients.

4. Discussion

The relationship between the conjunctivae and the nose includes both the anatomical and the functional aspect. [1, 10-12] The conjunctiva is connected with the nasal cavity not only by means of the naso-lacrimal duct, being a part of lacrimal ways, through which opening the tear drainage into the nasal cavity is facilitated, but also by means of the blood vessel network, lymphatic tissue system and neurogenic network. All of them express a number of mutual links and share various common properties.[1, 10-12] Allergic reactions taking place primarily in the nasal mucosa due to the intranasal exposure to inhalant allergen may affect the conjunctiva and subsequently also other ocular tissues, such as the cornea, in various ways and upon involvement of various mechanisms.[9-12, 33, 49-58] These mechanisms may include: (1) Various cell types participating in the allergic reaction occurring in the nasal mucosa, such as mucosal mast cells, eosinophils, basophils, neutrophils, B-lymphocytes/plasma cells, particular subsets of T-lymphocytes (Th`1, Th2, Th 17, T-regulatory cells, natural killer cells), dendritic cells, monocytes thrombocytes, macrophages, epithelial and endothelial cells, and mucosal goblet cells, can migrate into the bloodstream and/or lymphatic system, and under extreme conditions also into lacrimal ways, and thereby attain the conjunctiva; (2) The various cell types, activated and/or inhibited during the allergic reaction in the nasal mucosa, generate and release a number of factors (classical mediators, eicosanoids, cytokines, chemokines, adhesion molecules, chemotactic and other factors), which could then reach conjunctiva either directly by the retrograde penetration through the naso- lacrimal duct and lacrimal ways or indirectly through the related blood and/or lymphatic vessel system; (3) The allergic

reaction could also activate the local neurogenic system (sensory nerves, sympathetic and parasympathetic fibres) releasing then the neuropeptides which can reach the conjunctiva either along or through the related nerves, such as nervus trigemini, nervus nasociliaris and ganglion pterygopalatinum; (4) The allergic reaction or its particular stages and parts can also stimulate the local nasal mucosal lymphatic system called "nose-associated lymphatic tissue" (NALT), being a part of the"mucosa- associated lymphatic system" (MALT). The MALT system facilitates a multiple and mutual communication among the particular lymphatic organ-related sub-systems, in this case between the NALT on one hand and the "eye-associated lymphatic tissue "(EALT), "conjunctiva- associated lymphatic tissue"(CALT), "tear-associated lymphatic tissue "(TALT) and "lacrimal drainage-associated lymphatic tissue"(LDALT) on the other hand. The abundance of the relationship and communication among the individual parts of lymphatic system allow not only a multiple transmission of various signals (e.g. cell-cell, cell-receptor, receptor-receptor), but also a reciprocal (both- directional) traffic of various types of circulating cells, such as B-lymphocytes/plasma cells producing immunoglobulins of individual classes and sub-classes, particular sub-sets of T-lymphocytes (Th1- and Th2-cells, cytotoxic, regulatory and natural killer cells), antigen-presenting cells (APC), other cell types, or finally, under certain circumstances, of some cells resident in the mucosal membrane.

The cell traffic can be effectuated not only through various attraction mechanisms governed by chemotactic factors, cytokines, chemokines and adhesion molecules, but also through a special, so-called, "homing mechanism" of B- and T-lymphocytes, controlled by a number of homing factors.[10-12, 55, 56]

The disturbed homing mechanism leads to migration of particular cell types (e.g. B- or T-lymphocytes) to locations different from the predetermined destinations. By this way, the particular sub-sets of lymphocytes having been initially activated in a certain tissue (mucosal locality), after migrating into the bloodstream and/or lymphatic network to finish their maturation process, do not return to this original tissue, but due to the disturbed homing factors they terminate their route by entering into another tissue, different from the original one. This process is called "wrong homing". [10-12, 45-56]

The occurrence and possible role of various mediators, cytokines, chemokines and adhesion molecules in tears has already been extensively studied in patients suffering from various forms of allergic conjunctivitis. [14-16, 18, 20, 26, 32-35, 37-42, 57-83]

The mediators having been most frequently studied in tears included histamine,[20, 37, 40, 41,59-62, 64, 66] tryptase,[14, 26, 35, 37, 62, 66, 67] ECP,[14, 26, 32, 63, 66, 68, 69] LTB_4,[20, 64, 70-74] LTC_4,[20, 37, 41, 73, 74] LTD_4,[73] MPO,[63, 66] Prostaglandins (PGD_2, PGE_2) [41, 60, 62, 72] and various cytokines [1, 3, 5, 12, 16-18, 26, 36, 62, 63, 66, 76-83]

In most of these studies a single determination of the mediators in tears of patients suffering from primary forms of allergic conjunctivitis (SAC, PAC) or keratoconjunctivitis (VKC, AKC) has been performed. The papers addressing the determination of the mediators during the conjunctival provocation tests with allergens (CPTs) are not numerous.[14, 20, 26, 32, 35, 37, 38, 40, 60, 66, 83] Studies following the concentration changes of the above mentioned mediators in tears for a longer period of time as a serial determination during the particular types of conjunctival response (immediate/ early and/or late) due to the conjunctival challenge with allergen are relatively rare.[14, 20, 32, 37, 61-63, 83] The primary immediate/early conjunctival response (ICR) to conjunctival challenge with allergen (CPT) has been reported to be accompanied by concentration changes (mostly increase) of histamine, [14, 20, 26, 37, 38, 40, 41,

[60-62, 66, 83] tryptase, [14, 35, 37, 62] ECP,[63] LTB_4 ,[20, 73] LTC_4 ,[20, 37, 41, 73] MPO, [63] PGD_2, [41, 60, 83] kinin, [41, 60] TAME-esterase [41, 60] and various cytokines [62, 63] in tears. The primary late conjunctival response (LCR) to conjunctival challenge with allergen (CPT) has been reported to be associated with increased concentrations of histamine, [14, 20, 61, 83] ECP,[14, 32, 63] LTB_4 ,[20] LTC_4 [20]and some cytokines [16, 62] in tears. Our results demonstrating increased concentrations of histamine, EPC, LTB_4 , LTC_4 , MPO in tears during the secondary late conjunctival response (SLCR) would indicate their active role in the development of this type of CR. However, they were most probably released by the eosinophils, neutrophils and mast cells or basophils in the nasal mucosa, the place of the primary allergic reaction due to the initial allergen exposure. This fact may be supported by results of our other studies,[7, 9, 84] demonstrating only limited numbers of these cell types in tears during the later stages of SLCR. Moreover, these cells were in a non-activated condition, which means their cytoplasmic granules were not degranulated. In contrast, the primary LCR due to the direct conjunctival challenge with allergen is usually accompanied by the abundant appearance of eosinophils and neutrophils and sporadical mast cells, all of them having been exhausted and demonstrating empty cytoplasmic granules (=degranulation) (our not yet published data).

Another interesting result was evidence of slightly increased concentrations of cytokines IL-4 and IL-5 in the tears, whereas IFN-γ and IL-2 appeared in the tears only irregularly and without any concentration changes. This finding may suggest an involvement of Th_2 – lymphocytes in the mechanism leading to the SLCR, however, during the initial phase of this mechanism taking place in the nasal mucosa.

An interesting, but also somewhat conflicting, result was the absence of specific allergen-IgE antibody in serum of most the patients developing the SLCR. Moreover, in another supplementary pilot study, which results are not shown, we did not record any allergen-specific IgE antibody in the nasal secretions or even in the tears during the SLCR. This finding is then partly in contrast to the increased histamine concentrations in the tears during this CR type. The absence of specific IgE antibody in the serum as well as in the nasal secretions and tears of the patients developing the SLCR would suggest either that the concentration of IgE both in the serum and in the nasal secretions and tears were under the detection limits, or a possible involvement of topical IgE being limited to the nasal mucosa only and without any migration outside the nasal mucosa, or finally involvement of non-IgE mechanism in the SLCR. Unfortunately, at this moment we have no acceptable explanation for these phenomena. Further investigation, such as biopsy and immunohistochemical methods of the conjunctival and adjacent tissues will be necessary to provide more clarity on this field.

The results of this study would also stress the importance of provocation tests with allergens. The conjunctival provocation tests with allergens (CPTs), performed directly on the conjunctiva, confirm the role of allergic reaction taking place in the conjunctiva due to a direct exposure of conjucntival tissue to an inhalant allergen. The CPTs result in the manifestation of various types of primary conjunctival response, such as immediate, late or delayed, characterized by various conjunctival signs and subjective symptoms. The CPTs are therefore suitable for demonstrating and confirming the primary types of CR. Nevertheless, the secondary or secondarily induced CR types can only be demonstrated and confirmed by means of nasal provocation tests with allergens (NPTs) combined with simultaneous registration of the conjunctival signs and subjective symptoms. An important requirement for both the CPTs and NPTs is registration of the particular representative

parameters before and repeatedly after the allergen challenge, thus for a sufficiently long period of time, allowing measurement of the particular response type in its whole and dynamic course.

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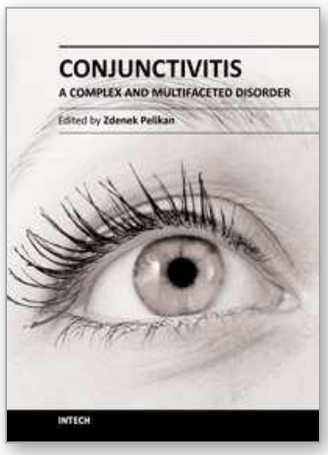

Conjunctivitis - A Complex and Multifaceted Disorder
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This book presents a number of interesting and useful aspects and facets concerning the clinical features, properties and therapeutical management of this condition. Dr. H. Mejía-López et al. present an interesting survey of the world-wide epidemiologic aspects of infectious conjunctivitis. Dr. U. Ubani evaluates conjunctival symptoms/signs participating in the clinical features of this disorder. Dr. A. Robles-Contreras et al. discuss immunologic aspects underlying possibly the conjunctivitis. Dr. Z. Pelikan presents the cytologic and concentration changes of some mediators and cytokines in the tears accompanying the secondary conjunctival response induced by the nasal challenge with allergen. Dr. S. Sahoo et al. summarize the treatment and pharmacologic control of particular clinical forms of conjunctivitis in general practice. Dr. S. Leonardi et al. explain the basic pharmacologic effects of leukotriene antagonists and their use for the treatment of allergic conjunctivitis. Dr. J.A. Capriotti et al. evaluate the therapeutical effects of various anti-adenoviral agents on the acute conjunctivitis caused by adenovirus. Dr. V. Vanzzini-Zago et al. assess the prophylactic use and efficacy of "povidone-iodium solution", prior the ocular surgery. Dr. F. Abazi et al. present the clinical features, diagnostic and therapeutical aspects of "neonatal conjunctivitis". Dr. I.A. Chaudhry et al. review the special sub-form of conjunctivitis, being a part of the "Trachoma". Dr. B. Kwiatkowska and Dr. M. Maślińska describe the clinical, pathophysiologic and immunologic features of conjunctivitis. Dr. S. Naem reviews the conjunctivitis form caused by Thelazia nematodes, occurring principally in animals.

How to reference
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