

Original Article

Seasonal and perennial allergic conjunctivitis: the possible role of nasal allergy

Zdenek Pelikan MD PhD

Allergy Research Foundation, Breda, the Netherlands

ABSTRACT

Background: There is a link between conjunctiva and nose. Nasal allergy is suspected to be involved in some cases of conjunctivitis. This work aims to investigate the possible role of nasal allergy in seasonal (SAC) and perennial (PAC) allergic conjunctivitis and the value of nasal challenges with allergens (nasal provocation tests [NPTs]) for the diagnostic procedures of the conjunctivitis.

Methods: In 61 adults suffering from SAC or PAC with a positive history and skin tests, but responding insufficiently to the local treatment, 122 NPTs and 61 control nasal challenges with phosphate-buffered saline (PBS) were performed using rhinomanometry combined with recording of ocular response. In 16 control subjects suffering only from allergic rhinitis without a history of conjunctivitis, 16 positive NPTs were repeated and supplemented with registration of ocular features.

Results: Of the 61 patients, 55 developed 103 positive nasal responses of various types ($P < 0.01$), 82 of which were accompanied by significant conjunctival response ($P < 0.01$) without any corneal involvement. No significant ocular responses were recorded during 61 control PBS challenges ($P > 0.05$) as well as during 16 challenges in control subjects ($P > 0.1$).

Conclusions: These results illustrate a possible involvement of nasal allergy in some patients with allergic conjunctivitis (SAC and PAC) and the value of the nasal challenges with allergen combined with registration of the ocular features in the diagnostic approach to these disorders.

Key words: conjunctival response, nasal allergy, nasal challenge with allergen, perennial allergic conjunctivitis (PAC), seasonal allergic conjunctivitis (SAC).

INTRODUCTION

Disorders of the conjunctiva, where an allergic component plays an important causal role are very common.^{1–5} However, the estimations of incidence of ‘allergic conjunctivitis’ and its particular forms vary.^{1–8} Seasonal allergic conjunctivitis (SAC) occurs most frequently, followed by atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and perennial allergic conjunctivitis (PAC), whereas giant papillary conjunctivitis (GPC) may be seen only sporadically.^{1–8} SAC and PAC appear in relatively milder form, whereas AKC and VKC occur in a more severe bilateral form, where the conjunctivae and cornea may also be affected.^{1–8}

The diagnostic approach to allergic conjunctivitis usually consists of history, ophthalmologic examination, scraping of conjunctiva, examination of tears, skin tests with allergens and estimation of specific immunoglobulin E in the serum by means of the radioallergosorbent test (RAST) or its modification (ImmunoCAP).^{1–10}

Although conjunctival provocation tests (CPTs) with allergens are an established diagnostic procedure for showing the primary allergic reaction in the eye and the particular types of conjunctival response (CR), they are usually not included in the routine diagnostic procedure of this disorder.^{1,6,9–19} Moreover, regarding the technical aspects, required experience and relative risks, the CPTs are not performed at every department.^{1,9–19}

The relationship between the conjunctiva and the nose is a well-known entity.^{1,2,5–8} The coexistence of allergic rhinitis and conjunctivitis has repeatedly

■ **Correspondence:** Dr Zdenek Pelikan, Allergy Research Foundation, Effenseweg 42, 4838 BB Breda, the Netherlands. Email: zpelikan@casema.nl

Received 8 October 2008; accepted 2 April 2009.

© 2009 The Author

Journal compilation © 2009 Royal Australian and New Zealand College of Ophthalmologists

been reported in the literature.^{1,3,5–11} However, few data are available to show a direct causal role of the allergic reaction occurring primarily in the nasal mucosa in the development of the secondarily induced CR and its particular types.^{20–24} The purpose of this study, being a continuation of our previous work,^{20–24} was to investigate: (i) the possible role of nasal allergy in the SAC and PAC of patients responding insufficiently to the topical ophthalmologic treatment; (ii) the existence of a CR induced by a primary allergic reaction in the nasal mucosa, and its clinical features; (iii) the diagnostic value of the nasal challenges with allergen combined with recording of the CR in such patients.

METHODS

Patients

Sixty-one patients, 27 men and 34 women, 18–52 years of age, suffering from allergic conjunctivitis for longer than 3 years and responding insufficiently to the topical ophthalmologic treatment, referred to our Department of Allergology and Immunology (Institute of Medical Sciences 'De Klokkenberg', Breda, the Netherlands), volunteered to participate in this study. Of the 61 patients, 29 suffered from SAC and 32 from PAC.

All these patients showed subjective symptoms and objective signs of conjunctivitis and positive skin tests to various inhalant allergens. The intraocular pressure was normal in all patients. Fourteen patients had previously undergone 19 CPTs with various inhalant allergens, which were, however, negative. They had previously been treated with topical and systemic H₁-receptor antagonists, topical cromolyn and glucocorticosteroids, but without significant improvement in their conjunctival complaints. None of them received immunotherapy, nasal or systemic glucocorticosteroids or nasal cromolyn. A routine diagnostic procedure performed in these patients consisted of: a detailed history, general examination to exclude systemic or other diseases, ophthalmological examination including split-lamp evaluations and vital staining with fluorescein, nasoscopy, cytological examination of the nasal secretions, tears and conjunctival scraping specimens, basic laboratory tests and bacteriological screening of the conjunctiva.

Diagnostic testing revealed a positive history for nasal allergy, positive skin tests with various inhalant allergens, hyperaemic and oedemic nasal mucosa, and increased eosinophil count in nasal secretions and conjunctival scrapings, in all these patients. In these 61 patients, 122 nasal challenges (nasal provocation tests [NPTs]) with various inhalant allergens were performed by means of rhinomanometry combined with recording of the ocular signs

and symptoms (Table 1). The patients were investigated in a period without acute ocular and nasal symptoms, without symptoms of an acute infection and outside the appropriate season.

Long-acting H₁-receptor antagonists and topical glucocorticosteroids were withdrawn 6 weeks before this study and topical and oral short-acting H₁-receptor antagonists, topical decongestants and other treatments were withdrawn 48 h before this study. The study protocol was approved by the local ethical committee and informed consent was obtained from all participants.

Allergens

Dialysed 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 1). If indicated, higher dilutions of the allergen extracts were used both for the skin tests and for the NPTs.

Skin tests

Intracutaneous tests were evaluated 20 min after intradermal allergen injection. A skin wheal reaction >7.0 mm in diameter appearing within 20 min after the injection was considered to be a positive immediate skin response.

Nasal provocation tests (NPTs)

Nasal challenges with allergens were performed by the rhinomanometric technique, described already in our previous papers.^{14,23–26} The nasal mucosa response (= nasal obstruction) was evaluated by means of nasopharyngeal-nostril pressure gradient (NPG) parameters, which are the pressure differences (ΔP) between the nasopharyngeal cavity and the external air, expressed in cm H₂O. NPTs were performed using the following schedule: (i) baseline values recorded at 0, 5 and 10 min before the challenge; (ii) PBS control values recorded at 0, 5 and 10 min after a 3-min 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 concha media; and (iii) postchallenge values recorded after a 3-min 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 min, and subsequently every hour up to the 12th hour, and then every second hour during the time periods between the 24th–38th and 48th–56th (60th) hour.^{14,23–26} The allergens used for the NPTs were chosen with respect of the disease history and

Table 1. Survey of the allergens used for nasal challenge

Allergen	Concentration (BU/mL)	n = 122	Nasal responses		Conjunctival responses			
			Positive (n = 103)	Negative (n = 19)	Positive (n = 87)		Negative (n = 35)	
					SAC (n = 42)	PAC (n = 45)	SAC (n = 16)	PAC (n = 19)
<i>Dermatophagoides pteron</i>	1000	23	21	2	1	15	3	4
<i>Dermatophagoides farinae</i>	1000	5	4	1	0	5	0	0
Animal danders								
Dog	3000	4	3	1	0	2	0	2
Cat	2000	9	8	1	2	4	1	2
Horse	2000	2	2	0	0	1	0	1
Hamster	2000	3	3	0	0	2	0	1
Guinea pig	2000	2	2	0	0	1	0	1
Feathers								
Pigeon	3000	3	3	0	0	2	0	1
Canary	3000	3	2	1	0	3	0	0
Parrot	3000	2	2	0	0	1	0	1
Parakeet	3000	4	3	1	1	0	1	2
<i>Aspergillus fumigatus</i>	1000	6	5	1	1	5	0	0
Pollen								
Grass mix I	1000	17	14	3	13	2	1	1
Grass mix II	1000	11	9	2	6	1	3	1
Flower mix	5000	7	6	1	5	0	1	1
Tree mix	3000	9	8	1	5	1	3	0
Weed mix	1000	3	2	1	1	0	2	0
Birch	1000	4	3	1	4	0	0	0
Poplar	2000	1	1	0	1	0	0	0
Ragweed short	1000	1	1	0	1	0	0	0
Ragweed giant	1000	3	1	2	1	0	1	1

Grass pollen mix I: *Dactylis glomerata*, *Lolium perenne*, *Phleum pratensis*, *Poa pratensis*; Grass pollen 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*. PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis.

positive skin tests (Table 1). The nasal response (NR) was assessed to be positive when the postchallenge mean NPG values increased by at least 2.0 cm H₂O (1.2 ± 0.3 , mean $\pm$ 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 min after the allergen challenge were considered to be an immediate NR, those recorded within 4–12 h to be a late NR and the changes measured later than 24 h to be a delayed NR.^{14,23–26}

Control tests with 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. A time interval of 3 days was always inserted between the NPT with allergen and the PBS control test.

Conjunctival response (CR)

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 split lamp. The conjunctival signs, hyperaemia (injection), chemosis, hyperlacrimation and palpebral oedema, and the subjective symptoms, such as itching (burning), blurred vision and photophobia, were registered and evaluated by means of the Abelson's scale, modified by us.^{8,13,16,18} 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. The differences in total sign score of 4 points or more (3 ± 1 , mean $\pm$ SE), recorded at least at three consecutive time intervals, were found to be statistically significant ($P < 0.05$).

Control group

Sixteen young adults suffering from allergic rhinitis, confirmed by positive history, skin tests and NPTs with inhalant allergens, but without history of any ocular disease and with normal ophthalmological

Table 2. Survey of nasal and conjunctival responses

Patients <i>n</i> = 61; NPT <i>n</i> = 122	Nasal response (<i>n</i> = 122)	Conjunctival response			
		Positive (<i>n</i> = 87)		Negative (<i>n</i> = 35)	
		SAC (<i>n</i> = 42)	PAC (<i>n</i> = 45)	SAC (<i>n</i> = 16)	PAC (<i>n</i> = 19)
IINR	38	11	16	4	7
ILNR	45	22	19	1	3
DLNR	6	4	1	0	1
IDYNR	11	3	5	1	2
DDYNR	3	0	1	1	1
NNR	19	2 [†]	3 [‡]	9	5
Control subjects <i>n</i> = 16; NPT <i>n</i> = 16					
IINR	7	0	0	2	5
ILNR	9	0	0	3	6

[†]2 = 2 isolated immediate conjunctival responses. [‡]3 = 2 isolated late conjunctival responses, 1 isolated delayed conjunctival response. DDYNR, dual delayed nasal response; DLNR, dual late nasal response; IDYNR, isolated delayed nasal response; IINR, isolated immediate nasal response; ILNR, isolated late nasal response; NNR, negative nasal response; NPT, Nasal provocation test; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis.

findings, volunteered to participate as control subjects. In these patients 16 positive NPTs with inhalant allergens were repeated and supplemented with registration of the conjunctival features and subjective symptoms.

Statistical analysis

- 1 NR and CR (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 analysed by Wilcoxon matched-pair signed rank test, comparing the postchallenge values with the mean prechallenge (baseline) values at each of the time points.
- 2 The mean NPG values and the mean total conjunctival score values of the same type of response were compared with corresponding PBS control values at each of the time points and analysed by the Mann–Whitney *U*-test.
- 3 The dynamic course of the NR as well as the CR of the same type and their correlation were statistically evaluated by means of generalized multivariate analysis of variance model (MANOVA), proposed by Potthoff and Roy,²⁷ modified by and presented by Timm.²⁸ The polynomials were fitted to the mean curves over time (eight time points within 120 min, six time points between 3 and 12 h and eight time points between 24 and 52 h after the allergen challenge), and the appropriate hypotheses were tested by the modified MANOVA computerized system.²⁹ 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.

RESULTS

Nasal responses (NRs)

Of the 61 patients in whom 122 NPTs were performed, 55 patients developed 103 positive NRs (*P* < 0.01) (Table 2): 38 isolated immediate (*P* < 0.001), 45 isolated late (*P* < 0.01), 6 dual late (= immediate + late; *P* < 0.01 respectively *P* < 0.05), 11 isolated delayed (*P* < 0.05), 3 dual delayed (= immediate + delayed; *P* < 0.01 respectively *P* < 0.05) and 7 negative (*P* > 0.05) (Table 2; Figs 1c,2c,3c). The remaining six patients developed only 12 negative NRs (*P* > 0.1). No statistically significant differences in the NPG values were found during the 61 PBS control tests (*P* > 0.2). The differences between the positive and negative NRs were highly significant (*P* < 0.001). No significant difference was found in the appearance of the particular NR types with respect to the individual allergens (*P* > 0.1).

Conjunctival responses (CR)

Eighty-two of the 103 positive NRs (recorded in 55 patients) and 5 of the 19 negative NRs (1 recorded in 55 patients and 4 in remaining 6 patients) were accompanied by significant CR (*P* < 0.01). The significant changes in the conjunctival signs and subjective symptoms were recorded during 27 of 38

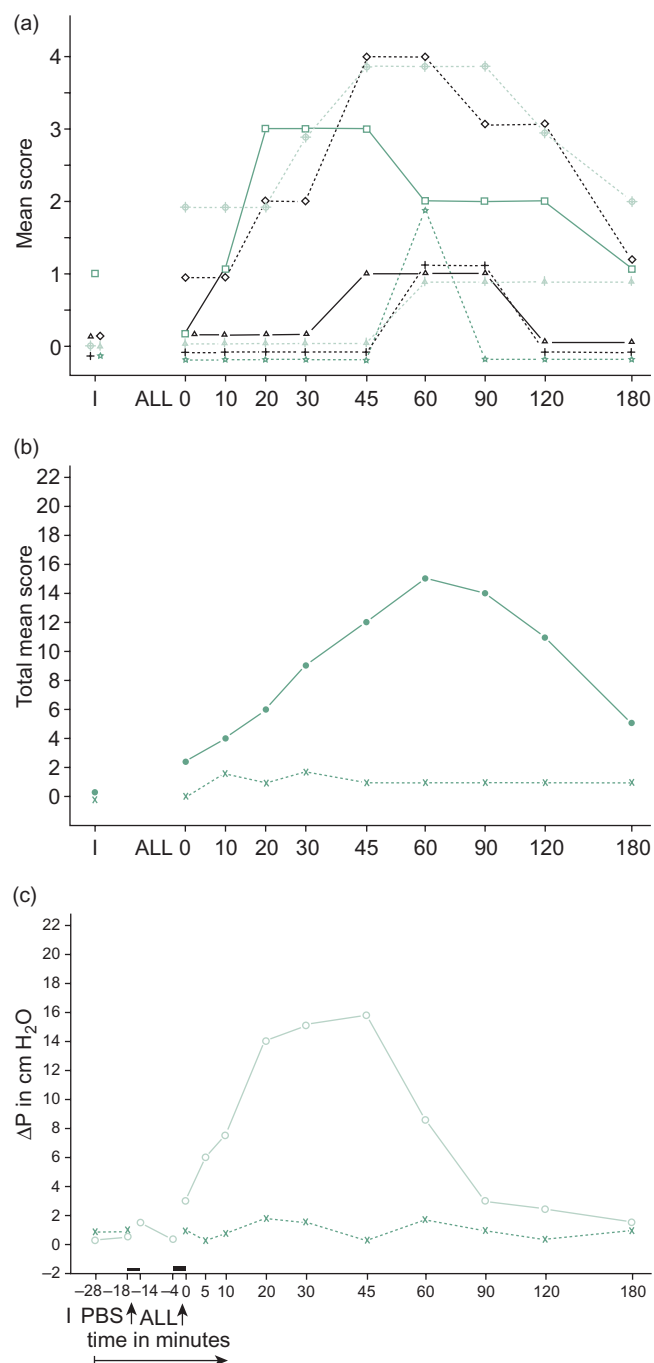


Figure 1. The conjunctival responses accompanying the isolated immediate nasal responses (IINR; $n = 27$). (a) The mean score of conjunctival signs and symptoms during IINR: hyperaemia (□); chemosis (Δ); hyperlacrimation (⊕); palpebral oedema (⬆); itching (◇); photophobia (☆); blurred vision (+). (b) The mean total score of conjunctival signs and symptoms during IINR (●) and phosphate-buffered saline (PBS) (x). (c) The mean rhinomanometric values (NPG) recorded during IINR (○) and PBS (x). ALL, allergen challenge; I, initial (baseline) value; NPG, nasopharyngeal-nostril pressure gradient; ΔP , pressure differences.

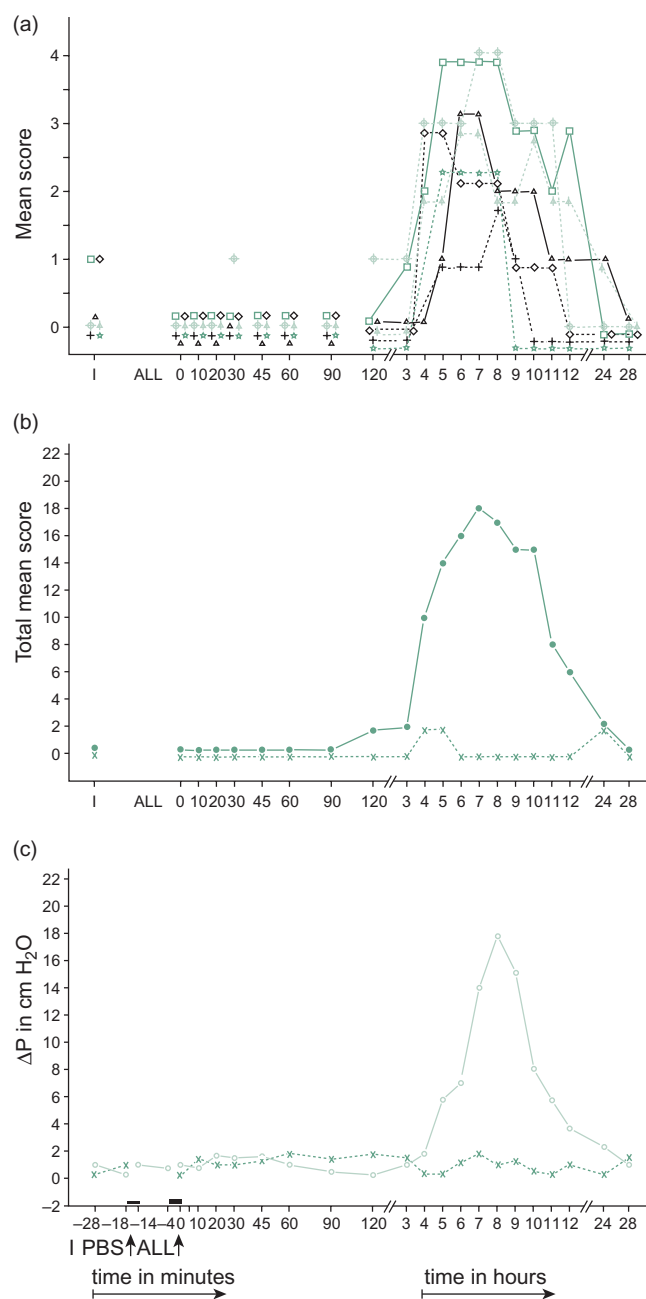


Figure 2. The conjunctival responses accompanying the isolated late nasal response (ILNR; $n = 41$). (a) The mean score of conjunctival signs and symptoms during ILNR: hyperaemia (□); chemosis (Δ); hyperlacrimation (⊕); palpebral oedema (⬆); itching (◇); photophobia (☆); blurred vision (+). (b) The mean total score of conjunctival signs and symptoms during ILNR (●) and phosphate-buffered saline (PBS) (x). (c) The mean rhinomanometric values (NPG) recorded during ILNR (○) and PBS (x). I, initial (baseline) value; ALL, allergen challenge. ALL, allergen challenge; I, initial (baseline) value; NPG, nasopharyngeal-nostril pressure gradient; ΔP , pressure differences.

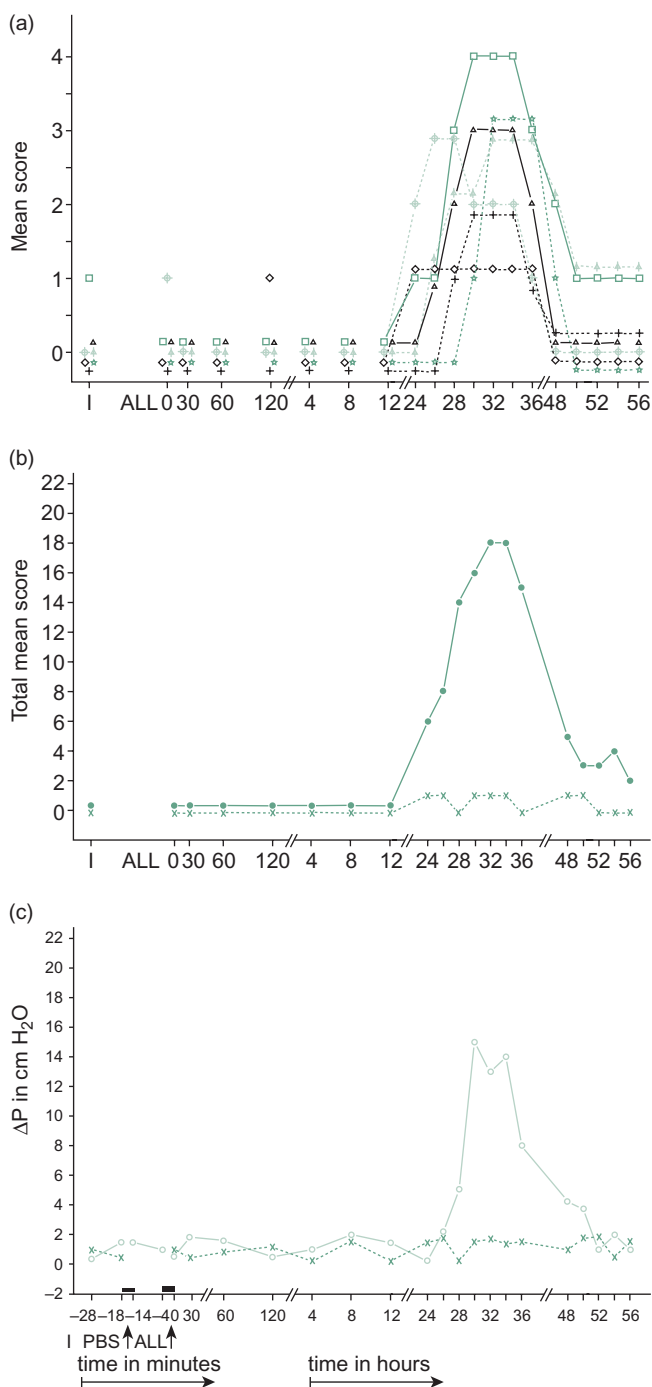


Figure 3. The conjunctival responses accompanying the isolated delayed nasal responses (IDYNR; $n = 8$). (a) The mean score of conjunctival signs and symptoms during IDYNR: hyperaemia ($\square$); chemosis (Δ); hyperlacrimation ($\diamond$); palpebral oedema ($+$); itching ($\diamond$); photophobia ($\star$); blurred vision ($+$). (b) The mean total score of conjunctival signs and symptoms during IDYNR ($\bullet$) and phosphate-buffered saline (PBS) ($\times$). (c) The mean rhinomanometric values (NPG) recorded during IDYNR ($\circ$) and PBS ($\times$). I, initial (baseline) value; ALL, allergen challenge. ALL, allergen challenge; I, initial (baseline) value; NPG, nasopharyngeal-nostril pressure gradient; ΔP , pressure differences.

isolated immediate NRs ($P < 0.05$), 41 of 45 isolated late NRs ($P < 0.01$), 5 of 6 dual late NRs ($P < 0.01$ respectively $P < 0.05$), 8 of 11 isolated delayed NRs ($P < 0.05$), 1 of 3 dual delayed NRs ($P < 0.05$ respectively $P < 0.05$) and 5 of 19 negative NRs ($P < 0.05$) (Tables 2,3, Figs 1a,b,2a,b,3a,b). No CR has been accompanied by significant corneal signs. In most cases of CR accompanying the immediate NRs, the objective signs as well as the subjective symptoms appeared 10–20 min later than the corresponding NRs, whereas CRs accompanying the late and delayed NRs displayed a parallel course with the NRs. No significant conjunctival changes were recorded during the 61 PBS control tests ($P > 0.05$). No significant differences in the conjunctival changes were found between the right and left eye ($P > 0.1$).

Control group

No significant differences were recorded between the first and the repeated NRs in the 16 control subjects developing seven isolated immediate NRs and nine isolated late NRs ($P > 0.05$). No significant conjunctival changes were recorded during the 16 repeated NRs ($P > 0.1$).

DISCUSSION

The pathogenesis underlying allergic conjunctivitis in both the forms (SAC, PAC) differs substantially from that involved in keratoconjunctivitis (VKC, AKC), as it has already been repeatedly described in the literature.^{1,3–9,11,15,30–36} Clinically, allergic conjunctivitis (SAC, PAC) is characterized by a number of objective signs and subjective symptoms, related almost exclusively to the conjunctiva, whereas cornea-related signs are usually absent.^{1,3–8,11–19,20–22,36} The objective conjunctival signs include hyperaemia (injection), chemosis, tearing (hyperlacrimation) and sometimes palpebral oedema. The subjective conjunctiva-related symptoms consist of itching, burning and sometimes blurred vision and photophobia. The most prominent and the diagnosis determining features are considered hyperaemia, itching and watery discharge (hyperlacrimation).^{1–8,11,22,24,36} Under certain conditions, such as massive allergen exposure and/or longer duration, papillary hypertrophy may also be observed.^{1,3,6–8} These objective signs and subjective symptoms have also been recorded during all three types of the secondarily induced CR to nasal challenge with allergen presented in this study. However, the appearance and participation of particular signs and symptoms in the clinical picture exhibited some differences with respect to the individual types of CR (Figs 1a,2a,3a).

In contrast, all three types of the secondarily induced ocular response to nasal challenge with

Table 3. Significance of the correlation between the conjunctival responses (total mean conjunctival sign and symptom score values) and particular types of nasal response (NPG values)

Nasal response	Total ocular symptom score																						
	Minutes									Hours													
	0	10	20	30	45	60	90	120	180	4	6	8	10	12	24	26	28	30	32	34	36	48	52
IINR	-	-	-	*	**	**	*	-	-														
ILNR									-	-	**	***	**	*	-	-							
IDYNR															-	-	**	**	**	*	*	-	-

- $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. IDYNR, isolated delayed nasal response; IINR, isolated immediate nasal response; ILNR, isolated late nasal response; NPT, Nasal provocation test.

Table 4. Survey of Abelson's and our 'modified' conjunctivitis grading scale and symptom score ('Pelikan's modified grading scale')

Conjunctival features	Abelson I ³⁸⁻⁴⁰	Abelson II ^{12,41}	Our score
Objective signs			
Hyperaemia (injection, redness)	0-4	0-3	0-4
Chemosis		0-3	0-4
Hyperlacrimation (tearing)		0-3	0-4
Palpebral oedema			0-4
Subjective symptoms			
Itching (burning)	0-4	0-4	0-4
Photophobia			0-4
Blurred vision			0-4

Abelson's grading scale: 0 = none; 1 = mild (intermittent); 2 = moderate; 3 = severe; 4 = extremely severe or 'incapacitating' itching; significant threshold: $\geq +2$. Our evaluation 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 prechallenge value, recorded at least at three consecutive time points.

allergen in patients suffering from allergic keratoconjunctivitis (VKC, AKC) were characterized by different clinical pictures, as it has already been reported in our previous paper.³⁷ The clinical features of these ocular responses included both the conjunctival and the corneal components. However, these clinical features were dominated by the cornea-related signs and symptoms.³⁷

Generally, it can be presumed that SAC and PAC represent a functional and almost fully reversible process, whereas the keratoconjunctivitis forms (VKC, AKC) may be characterized as a functional-morphological process, associated with reversible damage to the corneal epithelium, and in some cases, corneal scarring. In this study, the CRs (subjective symptoms and objective signs) were recorded and evaluated by means of a modification of the scoring (grading) system proposed by Abelson *et al.*^{12,18,38-41} (Table 4). Initially, Abelson *et al.* presented two types of such scoring systems, differing not only by the individual parameters (signs and symptoms) registered, but also by numbers of the grading points (0-3 vs. 0-4)^{12,38-41} (Table 4). Nevertheless, their scoring system did not include all objective conjunctival signs and subjective symptoms, typical for allergic conjunctivitis.^{12,38-41} This was the reason for us to optimize this grading system. Our modification

includes additional conjunctival signs and subjective symptoms into the final evaluation, such as chemosis, palpebral oedema, burning, blurred vision and photophobia (Table 4).

In our group of patients the following parameters were registered: (i) objective signs: hyperaemia (injection), chemosis, hyperlacrimation, palpebral oedema; and (ii) subjective symptoms: itching, burning, photophobia to a slight degree, blurred and 'vague' vision (Table 4). In our system, predominantly the differences between the postchallenge mean sign and symptom scores and their prechallenge values as well as the dynamic course of these changes have been considered to be basic parameters for the assessment of the CRs. Using our model, the statistically significant difference in the total sign and symptom score has been calculated to be at least four points ($P < 0.05$) (Figs 1-3). We are aware of some aspects that may influence evaluation of the clinical parameters of conjunctivitis and their interpretation. These aspects include the subjective attitude of the evaluating person, relatively high variation of the clinical signs and subjective symptoms of the patient, and the complexity of the processes underlying the immunological events leading to the clinical presentation of the conjunctivitis. The classification of the particular conjunctivitis forms is

to a certain extent an arbitrary measure, which does not discriminate transient or intermediate forms. Nevertheless, the relative comparison of the postchallenge sign and symptom values with their prechallenge values may increase the credibility of the results.

The CPTs with allergen performed directly on the conjunctiva showed the existence of different clinical types of CR, such as immediate (early) and late CR probably due to different immunological mechanisms.^{1,4-6,13,15,17,19,22,30,31,42,43} In addition, some evidence may also support a possible involvement of delayed hypersensitivity mechanisms in the conjunctiva.^{3,6,11,15,21,22,24,30-36,44-47} Nasal allergy could cohere with conjunctivitis in various ways. An allergic reaction occurring initially in the nasal mucosa may affect the conjunctiva in different ways upon involving diverse mechanisms: (i) this reaction leads to release of mediators, cytokines and other factors, which can then penetrate to the conjunctiva through the nasolacrimal duct;^{5,6,11,48,49} (ii) the released factors can also be transported to the conjunctiva by the local haematogenic ways (*a. maxillaris- pars pterygopalatina*, *v. facialis*, *plexus pterygoideus*);^{6,24,33} (iii) allergic reactions in the nasal mucosa can stimulate the local neurogenic network and released neuropeptides may reach conjunctiva along and/or through the appropriate nerves (*n. trigemini*, *n. nasociliaris*, *pterygopalatine ganglion*);^{24,45,50-52} and (iv) this reaction and released factors can stimulate the local nasal mucosal lymphatic system, 'nose-associated lymphatic tissue' (NALT), which is able to communicate with the lymphatic tissue of the lacrimal system, 'tear duct-associated lymphatic tissue' (TALT), 'lacrimal drainage-associated lymphoid tissue' (LDALT), 'eye-associated lymphatic tissue' (EALT) and that of the conjunctiva, called 'conjunctiva-associated lymphatic tissue' (CALT).^{24,45,48,49,53-56} In this way not only transmission of certain signals but also cellular traffic of various cell types, for example, T lymphocytes (Th₁ and Th₂) and B cells (plasma cells), can also be realized.^{1,8,11,13,15,17,22,24,32-34,43,44,46,47} An additional mechanism that could also play a role in the cellular traffic among the particular organ-associated lymphatic tissues is the 'defective homing' of the B lymphocytes.^{24,57-59}

Diagnostic confirmation of hypersensitivity mechanism(s) in the nasal mucosa can be performed by various methods, such as skin tests and *in vitro* estimation of the specific immunoglobulin E antibody.^{6,8-10} However, these tests provide only general evidence for the possible existence of an allergic component somewhere in the body and not specifically in a particular organ or tissue. Moreover, these tests do not reflect the possible participation of local antibodies in the particular organ and do not provide data on the dynamic aspects of the hypersen-

sitivity mechanism(s).²¹⁻²⁴ NPTs combined with registration of the conjunctival parameters are able not only to show the causal role of a certain allergen in the nasal mucosa and subsequently in the conjunctiva, but also to record quantitatively responses in their dynamic and time-related course.²⁰⁻²⁶ Although the NPTs are a laborious, time-consuming technique and require special apparatus and facilities, they generate important clinical data that cannot be gathered by other tests.²⁰⁻²⁶ By combining of the recorded parameters, NPTs are also able to confirm a causal role of one organ in a response of another organ, in this case the causal relationship of nasal mucosa and nasal allergy in the reactions of the conjunctiva.²⁰⁻²⁶ Significant correlation of the first and repeated NPTs confirms reliable reproducibility of this technique. NPTs can also discriminate between the participation of the allergy and the non-specific hypereactivity in the patient's complaints.^{21,23,26} Another advantage of NPTs is their ability to follow relative parameter values, by comparing the postchallenge with the prechallenge results.²⁰⁻²⁶ From this point of view the NPTs are independent of the absolute parameter values that regularly show high variability.²⁵ Similar motivation is applicable for the CPTs with allergens showing an allergic reaction directly in the conjunctiva and its causal participation in the conjunctival complaints.^{5,8-19} Our results emphasize some important clinical implications. As nasal allergy can induce a secondary CR, allergic rhinitis may not always be seen only as a coexisting disorder to allergic conjunctivitis, but in some patients as a causal trigger for the allergic conjunctivitis. This fact would implicate existence of two forms of allergic conjunctivitis, a 'primary or classical form' in which the initial allergic reaction and the subsequent steps (clinical symptoms) take place exclusively in the conjunctiva, whereas the 'secondary form' may be induced by an allergic reaction occurring initially in the nasal mucosa and only the consequences (clinical symptoms) are displayed by the conjunctiva.^{20-22,24} The involvement of various types of hypersensitivity in allergic conjunctivitis^{1,3,5,6,11,17,19-24,30-32,34-36,42-44,46} may result in three types of CR, immediate, late and delayed, analogous to the three basic types of NR.²³⁻²⁶ The particular types of CR showed significant correlation with the corresponding NR types. The following correlation has been found: immediate CR and NR ($P < 0.01$), late CR and NR ($P < 0.01$), delayed CR and NR ($P < 0.05$).

Nasal provocation tests with allergen performed by rhinomanometry in combination with registration of conjunctival objective signs and subjective symptoms may be a useful supplement to diagnostic procedure in patients suffering from SAC and PAC with insufficient compliance to the usual ophthalmological treatment.

REFERENCES

1. Bielory L, Friedlaender MH. Allergic conjunctivitis. *Immunol Allergy Clin North Am* 2008; **28**: 43–57.
2. Uchio E, Kimura R, Migita H, Kozawa M, Kadonosono K. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. *Graefes Arch Clin Exp Ophthalmol* 2008; **246**: 291–6.
3. Bielory L. Ocular allergy overview. *Immunol Allergy Clin North Am* 2008; **28**: 1–23.
4. Dart JK, Buckley RJ, Monnickendan M, Prasad J. Perennial allergic conjunctivitis: definition, clinical characteristics and prevalence. A comparison with seasonal allergic conjunctivitis. *Trans Ophthalmol Sci UK* 1986; **105**: 513–20.
5. McGill JI, Holgate ST, Church MK, Anderson DF, Bacon A. Allergic eye disease mechanisms. *Br J Ophthalmol* 1998; **82**: 1203–14.
6. Bielory L. Allergic and immunologic disorders of the eye; Part II: ocular allergy. *J Allergy Clin Immunol* 2000; **106**: 1019–32.
7. Ziskin A. Allergic conjunctivitis. *Curr Allergy Clin Immunol* 2006; **19**: 56–9.
8. Barney NP, Graziano FM. Allergic and immunologic diseases of the eye. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FE, eds. *Middleton's Allergy, Principles and Practice*, 6th edn. Philadelphia: Mosby Inc., 2003; 1599–617.
9. Leonardi A. In-vivo diagnostic measurements of ocular inflammation. *Curr Opin Allergy Clin Immunol* 2005; **5**: 464–72.
10. Radcliffe MJ, Lewith GT, Prescott P, Church MK, Holgate ST. Do skin prick and conjunctival provocation tests predict symptom severity in seasonal allergic rhinoconjunctivitis? *Clin Exp Allergy* 2006; **36**: 1488–93.
11. Ono SA, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol* 2005; **115**: 118–22.
12. Abelson MB, Chambers WA, Smith LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol* 1990; **108**: 84–8.
13. Helintö M, Renkonen R, Tervo T *et al.* Direct in vivo monitoring of acute allergic reactions in human conjunctiva. *J Immunol* 2004; **172**: 3235–42.
14. Melillo G, Bonini S, Cocco G *et al.* Provocation tests with allergens. *Allergy* 1997; **52** (Suppl. 35): 5–36.
15. Bonini S, Bonini S, Berruto A *et al.* Conjunctival provocation test as a model for the study of allergy and inflammation in humans. *Int Arch Allergy Appl Immunol* 1989; **88**: 144–8.
16. Friedlaender MH. Conjunctival provocation testing: overview of recent clinical trials in ocular allergy. *Int Ophthalmol Clin* 2003; **43**: 95–104.
17. Bacon AS, Ahluwalia P, Irani AM *et al.* Tear and conjunctival changes during the allergen-induced early- and late-phase responses. *J Allergy Clin Immunol* 2000; **106**: 948–54.
18. Abelson MB, Loeffler O. Conjunctival allergen challenge: models in the investigation of ocular allergy. *Curr Allergy Asthma Rep* 2003; **3**: 363–8.
19. Anderson DF. The conjunctival late-phase reaction and allergen provocation in the eye. *Clin Exp Allergy* 1996; **26**: 1105–7.
20. Pelikan M, Pelikan Z. The role of the nasal mucosa in some cases of allergic conjunctivitis and the effects of Disodium Cromoglycate (DSCG). *J Allergy Clin Immunol* 1985; **75** (1 Suppl.): 186.
21. Pelikan Z. Allergic conjunctivitis: primary and secondary role of the allergy reaction in the nose. *Dutch J Med (Ned Tijdschr Geneesk)* 1988; **132**: 561–3.
22. Pelikan Z. The causal role of the nasal allergy in some patients with allergic conjunctivitis. *Allergy* 2002; **57** (Suppl. 73): 230.
23. Pelikan Z. Late nasal response-its clinical characteristics, features, and possible mechanisms. In: Dorsch W, ed. *Late Phase Allergic Reactions*. Boca Raton, FL, Ann Arbor, MI, Boston, MA: CRC Press, 1990; 111–55.
24. Pelikan Z. The late nasal response. Thesis. The Free University of Amsterdam, Amsterdam, 1996.
25. Pelikan Z, Feenstra L, Barree GOF. Response of the nasal mucosa to allergen challenge measured by two different methods of rhinomanometry. *Ann Allergy* 1977; **38**: 263–7.
26. Pelikan Z. Late and delayed response of the nasal mucosa to allergen challenge. *Ann Allergy* 1978; **41**: 37–47.
27. Potthoff RF, Roy SN. A generalized multivariate analysis of variance model, useful especially for growth curve problems. *Biometrika* 1964; **51**: 313–26.
28. Timm NH. *Multivariate Analysis with Application in Educations and Psychology*. Monterey, CA: Brooks Cole, 1975.
29. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. New York: Harper Collins College Publishers, 1996.
30. Bonini S, Lambiasi A, Sachhetti M, Bonini S. Cytokines in ocular allergy. *Int Ophthalmol Clin* 2003; **43**: 27–32.
31. Cook EB. Tear cytokines in acute and chronic ocular allergic inflammation. *Curr Opin Allergy Clin Immunol* 2004; **4**: 441–5.
32. Calder VL, Jolly G, Hingorani M *et al.* Cytokine production and mRNA expression by conjunctival T-cell lines in chronic allergic eye disease. *Clin Exp Allergy* 1999; **29**: 1214–22.
33. Dua HS, Gomes JA, Donoso LA, Laibson PR. The ocular surface as part of the mucosal immune system: conjunctival mucosa-specific lymphocytes in ocular surface pathology. *Eye* 1995; **9**: 261–7.
34. Calder VL. Cellular mechanisms of chronic cell-mediated allergic conjunctivitis. *Clin Exp Allergy* 2002; **32**: 814–17.
35. Leonardi A, Fregona IA, Plebani M, Secchi AG, Calder VL. Th1- and Th2-type cytokines in chronic ocular allergy. *Graefes Arch Clin Exp Ophthalmol* 2006; **244**: 1240–5.
36. Stahl JL, Barney NP. Ocular allergic disease. *Curr Opin Allergy Clin Immunol* 2004; **4**: 455–9.

37. Pelikan Z. The possible involvement of nasal allergy in allergic keratoconjunctivitis. *Eye* 2008. doi: 10.1038/eye.2008.341
38. Abelson M, Howes J, George M. The conjunctival provocation test model of ocular allergy: utility for assessment of an ocular corticosteroid, Loteprednol etabonate. *J Ocul Pharmacol Ther* 1998; **14**: 533–42.
39. Abelson MB, Spitalny L. Combined analysis of two studies using the conjunctival allergen challenge model to evaluate Olopatadine hydrochloride, a new ophthalmic antiallergic agent with dual activity. *Am J Ophthalmol* 1998; **125**: 797–804.
40. Abelson MB. Evaluation of Olopatadine, a new ophthalmic antiallergic agent with dual activity, using the conjunctival allergen challenge model. *Ann Allergy Asthma Immunol* 1998; **81**: 211–18.
41. Abelson MB, George MA, Schaefer K, Smith LM. Evaluation of the new ophthalmic antihistamine, 0.05% levocabastine in the clinical allergen challenge model of allergic conjunctivitis. *J Allergy Clin Immunol* 1994; **94**: 458–64.
42. Leonardi A, Curnow SJ, Zhan H, Calder VL. Multiple cytokines in human tear specimens in seasonal and chronic allergic eye disease and in conjunctival fibroblast cultures. *Clin Exp Allergy* 2006; **36**: 777–84.
43. Magone MT, Whitcup SM, Fukushima A, Chan CC, Silver PB, Rizzo LV. The role of IL-12 in the induction of late-phase cellular infiltration in a murine model of allergic conjunctivitis. *J Allergy Clin Immunol* 2000; **105**: 299–308.
44. Metz DP, Hingorani M, Calder VL, Buckley RJ, Lightman SL. T-cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* 1997; **100**: 817–24.
45. Zoukhri D. Effect of inflammation on lacrimal gland function. *Exp Eye Res* 2006; **82**: 885–98.
46. Baudouin Ch, Liang H, Bremond-Gignac D *et al*. CCR4 and CCR5 expression in conjunctival specimens as differential markers of TH1/TH2 in ocular surface disorders. *J Allergy Clin Immunol* 2005; **116**: 614–19.
47. Stern ME, Siemasko KF, Niederkorn JY. The Th1/Th2 paradigm in ocular allergy. *Curr Opin Allergy Clin Immunol* 2005; **5**: 446–50.
48. Paulsen F. The human nasolacrimal ducts. *Adv Anat Embryol Cell Biol* 2003; **170**: 1–106.
49. Sirigu P, Maxia C, Puxeddu R, Zucca I, Piras F, Perra MT. The presence of a local immune system in the upper blind and lower part of the human nasolacrimal duct. *Arch Histol Cytol* 2000; **63**: 431–9.
50. Motterle L, Diebold Y, De Salamanca AE *et al*. Altered expression of neurotransmitter receptors and neuro-mediators in vernal keratoconjunctivitis. *Arch Ophthalmol* 2006; **124**: 462–8.
51. Calonge M, De Salamanca AE, Siemasko KF *et al*. Variation in the expression of inflammatory markers and neuroreceptors in human conjunctival epithelial cells. *Ocul Surf* 2005; **3** (4 Suppl.): 145–8.
52. Fujishima H, Takeyama M, Takeuchi T, Saito T, Tsubota K. Elevated levels of substance P in tears of patients with allergic conjunctivitis and vernal keratoconjunctivitis. *Clin Exp Allergy* 1997; **27**: 372–8.
53. Knop E, Knop N. Lacrimal drainage-associated lymphoid tissue (LDALT): a part of the human mucosal immune system. *Invest Ophthalmol Vis Sci* 2001; **42**: 566–74.
54. Knop N, Knop E. Conjunctiva-associated lymphoid tissue in the human eye. *Invest Ophthalmol Vis Sci* 2000; **41**: 1270–9.
55. Paulsen FP, Paulsen JL, Thale AB, Schaudig U, Tillmann BN. Organized mucosa-associated lymphoid tissue in human nasolacrimal ducts. *Adv Exp Med Biol* 2002; **506**: 873–6.
56. Paulsen FP, Schaudig U, Thale AB. Drainage of tears: impact on the ocular surface and lacrimal system. *Ocul Surf* 2003; **1**: 180–91.
57. O'Sullivan NL, Montgomery PC, Sullivan DA. Ocular mucosal immunity. In: Mestecky J, Bienenstock J, Lamm M, Strober W, McGhee J, Mayer L, eds. *Mucosal Immunology*, 3rd edn. Burlington, MA, San Diego, CA, London: Elsevier-Academic Press, 2005; 1477–1496.
58. Mikulowska-Mennis A, Xu B, Berberian JM, Michie SA. Lymphocyte migration to inflamed lacrimal glands is mediated by vascular cell adhesion molecule-1/ $\alpha 4\beta 1$ integrin, peripheral node addressin/L-selectin, and lymphocyte function-associated antigen-1 adhesion pathways. *Am J Pathol* 2001; **159**: 671–81.
59. Youngman KR, Lazarus NH, Butcher EC. Lymphocyte homing: chemokines and adhesion molecules in T cell and IgA plasma cell localization in the mucosal immune system. In: Mestecky J, Bienenstock J, Lamm M, Strober W, McGhee J, Mayer L, eds. *Mucosal Immunology*, 3rd edn. Burlington, San Diego, London: Elsevier-Academic Press, 2005; 667–680.