

Prevalence and Clinical Relevance of Allergic Rhinitis in Patients with Classic Asthma and Cough Variant Asthma

Tomoko Tajiri^a Akio Niimi^{a, b} Hisako Matsumoto^a Isao Ito^a
Tsuyoshi Oguma^a Kojiro Otsuka^{a, c} Tomoshi Takeda^{a, d} Hitoshi Nakaji^{a, e}
Hideki Inoue^a Toshiyuki Iwata^a Tadao Nagasaki^a Michiaki Mishima^a

^aDepartment of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, ^bDivision of Respiratory Medicine, Department of Medical Oncology and Immunology, Nagoya City University School of Medical Sciences, Aichi, ^cDepartment of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, ^dDepartment of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, and ^eDepartment of Respiratory Medicine, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

Key Words

Allergic rhinitis · Classic asthma · Cough variant asthma · Eosinophilic airway inflammation

Abstract

Background: A clinically relevant relationship between classic asthma and allergic rhinitis has been reported. However, the possible link between cough variant asthma (CVA) and allergic rhinitis remains unknown. **Objectives:** To clarify the prevalence and clinical relevance of perennial allergic rhinitis or seasonal allergic rhinitis in CVA patients compared to classic asthma patients. **Methods:** We retrospectively studied adult patients with classic asthma (n = 190) and those with CVA (n = 83). The prevalence of perennial allergic rhinitis or seasonal allergic rhinitis and associations of concomitant perennial or seasonal allergic rhinitis with asthma severity, forced expiratory volume in 1 s (% predicted), fractional exhaled nitric oxide (FeNO) levels, and eosinophil proportions in sputum and blood were analyzed in the two groups. **Results:** The prevalence of perennial allergic rhinitis and/or seasonal allergic rhinitis was significantly higher in classic

asthma patients than in CVA patients (all p < 0.05). Concomitant perennial allergic rhinitis was associated with higher FeNO levels and eosinophil proportions in sputum and blood in classic asthma patients (p = 0.035, p = 0.036, and p = 0.008, respectively) and with higher asthma severity, FeNO levels, and sputum eosinophil proportions in CVA patients (p = 0.031, p = 0.007, and p = 0.010, respectively). Concomitant seasonal allergic rhinitis was only associated with higher sputum eosinophil proportions in CVA patients with active rhinitis symptoms during the sensitized pollen season (p = 0.025). **Conclusions:** Perennial allergic rhinitis may be relevant for CVA patients as well as classic asthma patients by consistently augmenting eosinophilic lower airway inflammation.

© 2013 S. Karger AG, Basel

Introduction

Asthma and allergic rhinitis often coexist. Allergic rhinitis and its impact on asthma guidelines suggest that rhinitis occurs in over 75% of patients with allergic asthma

and in over 80% of patients with nonallergic asthma [1]. In a review examining 12 published studies from 1983 to 2004, Gaugris et al. [2] reported that the point prevalence of allergic rhinitis ranged from 24 to 94%, and the lifetime prevalence ranges from 50 to 100% among adult asthmatic patients in the USA and Europe. In Japan, allergic rhinitis is present in 67.3% of asthmatic patients [3].

A strong link between asthma and allergic rhinitis has been reported in epidemiological and clinical studies. Allergic rhinitis often precedes the development of asthma [4–7], suggesting that it may be a risk factor for asthma. The presence of concomitant allergic rhinitis in asthmatics results in more frequent asthma attacks, emergency room visits [8], and asthma-related hospitalizations [9], as well as higher asthma-related medication costs [9, 10]. Nonasthmatics with allergic rhinitis have elevated numbers of eosinophils in the bronchial mucosa [11–13]. In asthmatics with allergic rhinitis, nasal provocation with specific allergens increases eosinophils in the bronchial mucosa [14] and bronchial responsiveness to methacholine [15]. Conversely, eosinophil infiltration is present in the nasal mucosa of asthmatics without allergic rhinitis [16]. Thus, asthma and allergic rhinitis share a similar inflammatory process, which leads to the concept of ‘one airway, one disease’ [1].

Cough variant asthma (CVA) is one of the most common causes of chronic cough [17]. This variant form of asthma presents solely with cough and is associated with airway hyperresponsiveness and responsiveness to bronchodilators [18] and other antiasthma treatments [19]. Although a relationship between classic asthma and allergic rhinitis has been reported, a possible relationship between CVA and allergic rhinitis is unknown.

In this study, we analyzed the prevalence and clinical relevance of allergic rhinitis in CVA patients compared to classic asthma patients with wheezing.

Materials and Methods

Patients

This was a retrospective study involving consecutive adult patients with classic asthma ($n = 190$) and CVA ($n = 83$) who were newly referred to the asthma clinic of Kyoto University Hospital between September 1, 2007, and August 31, 2009. Patients who had smoked for >5 pack-years or who had smoked within the previous 6 months were excluded. Patients with classic asthma were diagnosed according to American Thoracic Society criteria [20]. The diagnosis of CVA was based on an isolated cough without dyspnea or wheezing, airway hyperresponsiveness to methacholine, and symptomatic improvement of the cough with β_2 -agonists [18]. When patients presented normo-sensitive results to inhaled

methacholine, but responded to bronchodilator therapy, they were diagnosed with CVA. After the minimum medication required to achieve control was determined, the disease severity of classic asthma and CVA was classified according to the Japanese guidelines for asthma [21] as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent). We used this system because no validated severity scores for CVA have been reported, except in our previous report [22]. Patients with allergic rhinitis were diagnosed by otolaryngologists or pulmonologists according to nasal symptoms, questionnaires regarding rhinitis symptoms, a nasal physical examination, and serum-specific IgE antibody results. This study was approved by the Ethics Committee of Kyoto University, and written informed consent was obtained from all participants.

Measurements

Fractional exhaled nitric oxide (FeNO) measurements, spirometry, methacholine challenge, sputum induction, blood tests, and questionnaires were performed during each patient's first visit, as described below.

FeNO Levels

FeNO levels were measured with a chemiluminescence analyzer (NOA 280; Sievers, Boulder, Colo., USA) according to the current guidelines [23]. We measured FeNO levels at an expiratory flow rate of 50 ml/s during a single unobstructed expiration [24].

Pulmonary Function Test

After FeNO measurements, patients underwent spirometry using a Chestac-65V spirometer (Chest™, Tokyo, Japan) according to the guidelines [25]. Prebronchodilator values of forced expiratory volume in 1 s [FEV₁ (% predicted)] were examined.

Methacholine Challenge

We determined the airway responsiveness by measuring the respiratory resistance (cm H₂O/l/s) (Astograph; Chest) under continuous methacholine inhalation as previously described [26]. The index of airway sensitivity was D_{min}, i.e. the cumulative dose of inhaled methacholine at the inflection point where respiratory resistance began to continuously increase. Based on the results of our previous study [22], positivity for airway hyperresponsiveness was defined as a D_{min} <12.5 units.

Sputum Induction and Processing

Sputum was induced and processed as described [27, 28]. Briefly, after premedication with salbutamol, participants inhaled a hypertonic (3%) saline solution for 15 min from an ultrasonic nebulizer. Adequate plugs of sputum were treated with 0.1% dithiothreitol (Sputasol; Oxoid Ltd., Hampshire, UK) followed by Dulbecco's phosphate-buffered saline. After centrifugation, cell differentials were determined by counting at least 400 nonsquamous cells stained with the May-Grünwald-Giemsa method. Correlations between sputum eosinophil proportions and FeNO levels were analyzed.

Blood Tests

Eosinophil proportions and serum IgE levels were determined in blood samples. The serum levels of total and specific IgE antibodies against common aeroallergens [house dust, *Dermatoph-*

Table 1. Characteristics of patients

	Classic asthma	CVA	p value
Patients, n	190	83	
Age, years	49±19	48±18	0.86
Sex (male/female)	54/136	23/60	0.90
Disease duration, years	7±12	2±6	0.007
Use of inhaled corticosteroids at the first visit (yes/no)	43/147	13/70	0.18
Dose of inhaled corticosteroids ^a , µg/day	451±229	442±240	0.6
Use of antihistamines (yes/no)	15/175	12/71	0.09
Use of leukotriene receptor antagonists (yes/no)	20/170	7/76	0.59
Never smoker/ex-smoker	164/26	70/13	0.66
FEV ₁ (n = 271), % predicted	91±23	103±15	<0.0001
Disease severity ^b	2.8±0.1	2.5±0.1	0.0006
Total serum IgE (n = 273), IU/ml	130 (5–2,916)	54 (5–2,600)	0.0001
FeNO level (n = 265), ppb	60±78	32±27	0.001
Sputum eosinophil proportion (n = 140), %	11±21 (n = 95)	3±7 (n = 45)	0.003
Blood eosinophil proportion (n = 273), %	5±5 (n = 190)	3±3 (n = 83)	<0.0001
Dmin (n = 174), units	1.819 (0.011–48.898)	2.77 (0.044–27.705)	0.33
	(n = 117)	(n = 57)	

Values are given as means ± SD or medians (range) unless otherwise stated. ^a Equivalent to fluticasone propionate. ^b Defined as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent) after the minimum medication required to achieve control had been determined in accordance with the Japanese guidelines for adult asthma [21].

goides pteronyssinus, Japanese cedar pollen, mixed gramineae pollen (orchard grass, sweet vernal grass, Bermuda grass, timothy, and reeds), mixed weed pollen (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy), mixed mold (*Candida*, *Alternaria*, *Penicillium*, *Aspergillus*, *Helminthosporium*, and *Cladosporium*), *Trichophyton rubrum*, cat dander, and dog dander] were measured with radioimmunosorbent tests and the CAP method (Pharmacia Diagnostics, Uppsala, Sweden) [29]. Specific IgE antibody results were considered positive if the response levels exceeded 0.35 IU/ml [30].

Questionnaires

The participants answered questionnaires with the following questions: 'Do you start to sneeze, get a runny nose, or get a stuffy nose during the pollen season?' and 'Do you have nasal allergies such as sneezing, a runny nose, and a stuffy nose throughout the year?' The sensitized pollen seasons were defined as February to April for Japanese cedar pollen, April to June and August to October for mixed gramineae pollens, and September to October for mixed weed pollens, according to the Japanese guidelines for allergic rhinitis [31].

Statistical Analysis

JMP system version 6 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. Data are expressed as means ± SD or medians (range). To compare two groups, a χ^2 test or the Wilcoxon rank-sum test was used as appropriate. Spearman's correlation coefficients were used to analyze the relationships among the data. $p < 0.05$ was considered statistically significant.

Results

Characteristics of the Patients

The patient characteristics are shown in table 1. The disease duration was longer and the FEV₁ was lower in classic asthma patients than in CVA patients. Disease severity, total serum IgE levels, FeNO levels, and eosinophil proportions in sputum and blood were higher in classic asthma patients than in CVA patients.

Prevalence of Allergic Rhinitis

A total of 104 classic asthma patients and 32 CVA patients answered that they had rhinitis symptoms during the pollen season, and 96 classic asthma patients and 23 CVA patients answered that they had rhinitis symptoms throughout the year.

The prevalence of perennial allergic rhinitis and/or seasonal allergic rhinitis was significantly higher in classic asthma patients than in CVA patients (fig. 1).

Specific IgE Antibody

Sensitization to house dust, *D. pteronyssinus*, cat dander, and dog dander was significantly higher in classic asthma patients than in CVA patients. Sensitization to pollens did not differ between the two groups. The mean

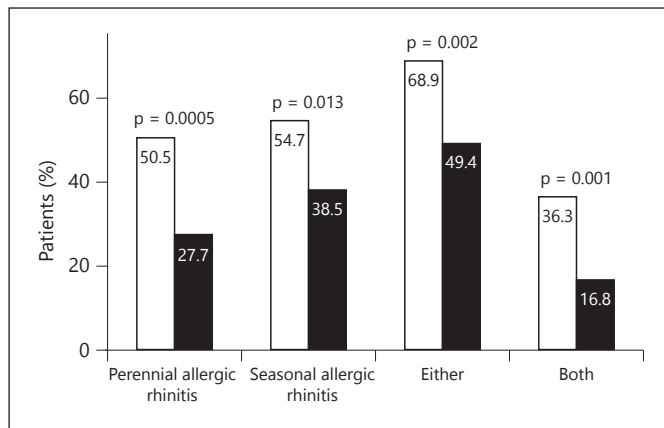


Fig. 1. Prevalence of allergic rhinitis in patients with classic asthma (white bars) or CVA (black bars).

Table 2. Specific IgE antibodies against common allergens

	Classic asthma (n = 190)	CVA (n = 83)	p value
House dust	98 (51.5)	28 (33.7)	0.007
<i>D. pteronyssinus</i>	98 (51.5)	27 (32.5)	0.004
Japanese cedar pollen	115 (60.5)	42 (50.6)	0.12
Mixed gramineae pollen ^a	57 (30)	19 (22.8)	0.22
Mixed weed pollen ^b	25 (13.1)	8 (9.6)	0.41
Mixed mold ^c	27 (14.2)	6 (7.2)	0.10
Cat dander	40 (21.0)	5 (6.0)	0.002
Dog dander	45 (23.6)	4 (4.8)	0.0002
<i>T. rubrum</i>	23 (12.1)	8 (9.6)	0.55
Sensitization to any allergen	138 (72.6)	51 (61.4)	0.065
Sensitized allergens, n	2 (0–9)	1 (0–7)	0.002

Values are given as numbers (%) or medians (range). ^a Orchard grass, vernal grass, Bermuda grass, and timothy grass. ^b Ragweed, mugwort, oxeye daisy, dandelion, and goldenrod. ^c *Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, and *Alternaria*.

number of positive allergens per patient was significantly higher in classic asthma patients than in CVA patients (table 2).

Clinical Relevance of Allergic Rhinitis in Patients with Classic Asthma and CVA

Classic asthma patients with perennial allergic rhinitis had significantly higher FeNO levels and higher eosinophilic proportions in sputum and blood than those without (table 3a). CVA patients with perennial allergic rhinitis had significantly higher asthma severity, FeNO levels,

and sputum eosinophil proportions than those without (table 3b).

Meanwhile, the presence of seasonal allergic rhinitis was not associated with the clinical index in patients with classic asthma (table 3a) and CVA (table 3b). Even when patients with active rhinitis symptoms who were examined during the sensitized pollen season were selected, the presence of seasonal allergic rhinitis was only associated with higher sputum eosinophil proportions in CVA patients than in those without ($8 \pm 10\%$ and $3 \pm 8\%$; $p = 0.025$).

We also reanalyzed the data for a subset of steroid-naïve patients with classic asthma ($n = 147$) and CVA ($n = 70$) and observed similar results (data not shown).

Correlations between FeNO Levels and Sputum Eosinophil Proportions

Regardless of the presence of perennial allergic rhinitis (fig. 2a, b) or seasonal allergic rhinitis (fig. 2c, d), FeNO levels were positively and significantly correlated with sputum eosinophil proportions in the combination of patients with classic asthma and those with CVA who had succeeded in sputum induction ($n = 140$).

Discussion

This study showed that: (1) the prevalence of allergic rhinitis in classic asthma patients was higher than that in CVA patients and (2) concomitant perennial allergic rhinitis was clinically relevant for CVA patients as well as classic asthma patients by augmenting eosinophilic lower airway inflammation. To our knowledge, this is the first study to investigate a possible link between CVA and allergic rhinitis.

In Japan, rhinitis is present in 67.3% of asthmatic patients [3]. Our data for classic asthma patients are consistent with this report. The prevalence of allergic rhinitis in CVA patients was lower than that in classic asthma patients. CVA is a phenotype of asthma that presents solely with coughing [18] and shares several pathophysiological features with classic asthma. Compared to classic asthma, CVA shows similar levels of eosinophilic airway inflammation [22, 32] and a milder degree of airway remodeling [32] and airway hyperresponsiveness [33]. The reason for the difference in prevalence of allergic rhinitis between the two groups remains unclear. Asthma and allergic rhinitis share common risk factors for their onset, including atopic status. In this study as well as in our previous study [30], the degree of atopic status that was assessed with to-

Fig. 2. Relationship between FeNO levels and sputum eosinophil proportions in classic asthma patients (open circles) and CVA patients (closed circles) with (a) or without (b) perennial allergic rhinitis and with (c) or without (d) seasonal allergic rhinitis. Eos = Eosinophils.

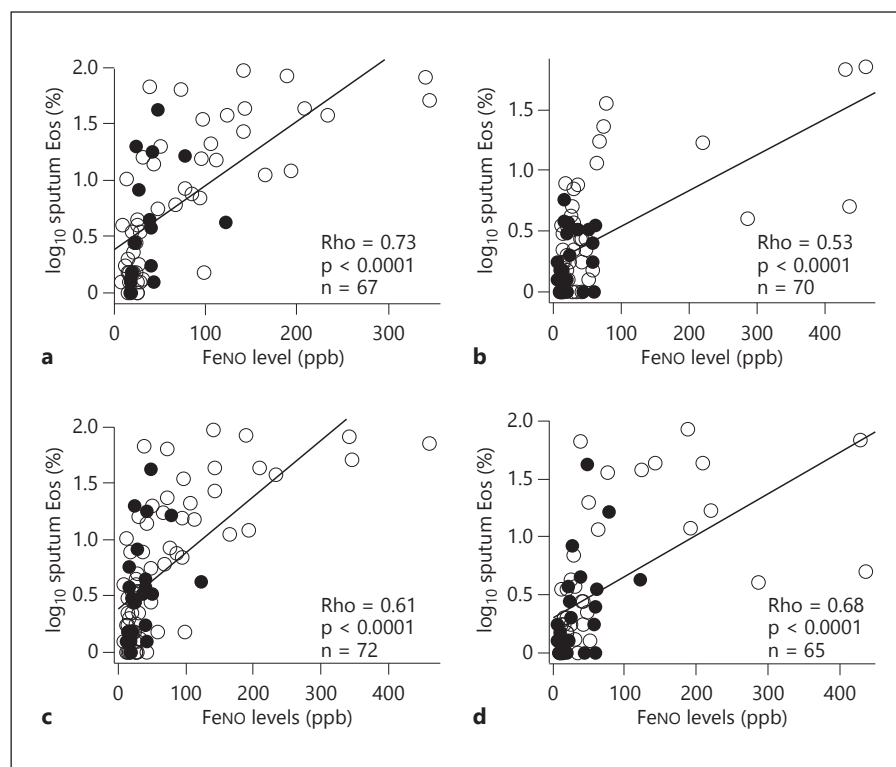


Table 3. Clinical relevance of allergic rhinitis

a Clinical relevance of allergic rhinitis for classic asthma patients

	Perennial allergic rhinitis			Seasonal allergic rhinitis		
	+	–	p value	+	–	p value
	(n = 96)	(n = 94)		(n = 104)	(n = 86)	
FEV ₁ , % predicted	90±20	93±25	0.08	95±19	88±26	0.25
Disease severity ^a	2.9±0.9	2.8±0.9	0.58	2.8±0.9	2.9±0.9	0.48
FeNO level, ppb	69±74	52±83	0.035	60±76	62±83	0.46
Sputum Eos proportion, %	16±24	7±15	0.036	12±21	12±21	0.52
Blood Eos proportion, %	6±5	4±4	0.008	5±5	4±4	0.16

b Clinical relevance of allergic rhinitis for CVA patients

	Perennial allergic rhinitis			Seasonal allergic rhinitis		
	+	–	p value	+	–	p value
	(n = 23)	(n = 60)		(n = 32)	(n = 51)	
FEV ₁ , % predicted	101±14	105±16	0.42	102±12	105±17	0.34
Disease severity ^a	2.7±0.7	2.4±0.8	0.031	2.4±0.8	2.5±0.8	0.61
FeNO level, ppb	41±31	28±26	0.007	33±29	32±27	0.69
Sputum Eos proportion, %	7±11	2±5	0.010	5±8	3±8	0.06
Blood Eos proportion, %	3±2	3±3	0.24	3±2	3±4	0.06

Values are given as means ± SD. Eos = Eosinophils. ^a Defined as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent) in accordance with the Japanese guidelines for adult asthma [21].

tal IgE levels and a specific IgE response was higher in classic asthma patients than in CVA patients. This may partly explain the difference in prevalence of allergic rhinitis in the two groups.

Although an increasing number of studies have shown that perennial allergic rhinitis affects the disease state in classic asthma patients, no study has examined the effects in CVA patients. First, regarding asthma severity, self-reported concomitant allergic rhinitis results in more frequent emergency room visits and asthma attacks in patients with chronic asthma [8]. Another retrospective study showed that asthmatics with concomitant allergic rhinitis visited general practitioners more frequently, had more asthma-related hospitalizations, and had higher asthma-related medication costs than those without [9]. In the present study, concomitant perennial allergic rhinitis was associated with disease severity in CVA patients.

Second, two studies have examined the effects of concomitant allergic rhinitis on pulmonary function in asthmatics. One study showed that concomitant allergic rhinitis was not associated with impaired lung function including FEV₁ (% predicted) in asthmatics [34]. Another study observed no difference in FEV₁ (% predicted) between asthmatics with and without allergic rhinitis [35]. In the present study, concomitant perennial allergic rhinitis was also not associated with FEV₁ (% predicted) in patients with classic asthma and CVA.

Third, several studies have examined lower airway inflammation in patients with nonasthmatic rhinitis, but few have shown the additional effects of allergic rhinitis in asthmatics. Based on examination of cross-sectional data, patients with nonasthmatic rhinitis have significantly higher FeNO levels [36–38], sputum eosinophil counts [39], and eosinophil cationic protein levels [37] than healthy controls. One study compared FeNO levels between asthmatics with and without perennial allergic rhinitis and observed no difference [36]. In the present study, we first showed that FeNO levels and eosinophil proportions in sputum and/or blood were significantly higher in classic asthma patients and CVA patients with perennial allergic rhinitis than in those without. Nasal NO contamination was unlikely because significant correlations were observed between FeNO levels and sputum eosinophil proportions regardless of the presence of allergic rhinitis. These results suggest a link between upper and lower airway inflammation, which may be induced by inflammatory mediators from the initial site of inflammation moving into the systemic circulation [40].

In contrast to perennial allergic rhinitis, the clinical effects of seasonal allergic rhinitis in asthmatics have been reported to vary between during and outside the pollen season. The effects in CVA patients remain unknown. First, the effects of seasonal allergic rhinitis on asthma severity have been inconsistently reported. In a retrospective study, although asthmatics with seasonal allergic rhinitis had significantly higher total asthma symptom scores than those without, the need for a β_2 -agonist as a rescue medication was similar between the two groups [41]. In this study, pollen species and levels were not taken into consideration. In large epidemiological studies that considered pollen species and levels, Tobias et al. [42] and Erbas et al. [43] showed effects of ambient pollen on asthma-related hospital admissions, but Anderson et al. [44] and Rossi et al. [45] did not. These inconsistencies among studies may have resulted from differences in pollen species, levels, and sensitization. In the present study, concomitant seasonal allergic rhinitis was not associated with disease severity in patients with classic asthma and CVA. The most common allergen for seasonal allergic rhinitis in Japan is Japanese cedar pollen [31]. In contrast to grass or birch pollen, the effects of Japanese cedar pollen on asthma severity remain unclear. Further prospective studies on Japanese cedar pollen are needed.

Second, one study has examined the effects of concomitant seasonal allergic rhinitis on pulmonary function in asthmatics. Patients with asthma alone showed lower FEV₁ (% predicted) than those with asthma and seasonal allergic rhinitis [41]. In the present study, concomitant seasonal allergic rhinitis was not associated with the FEV₁ (% predicted) in patients with classic asthma and CVA.

Third, several studies have reported the effects of seasonal allergic rhinitis on lower airway inflammation in patients with nonasthmatic rhinitis. However, none has examined the additional effects of seasonal allergic rhinitis in asthmatics. In previous studies, natural pollen exposure during the pollen season caused a significant elevation of FeNO levels in patients with seasonal allergic rhinitis alone [48–50]. In those with rhinitis, sputum eosinophil counts were also elevated compared to those of healthy controls during the pollen season [51]. No significant difference in sputum eosinophil counts was observed between the two groups outside the pollen season [52]. Collectively, the effects of seasonal allergic rhinitis may depend on whether they are assessed during or outside the pollen season. In the present study, we observed only slight effects of concomitant seasonal allergic rhini-

tis on the sputum eosinophil proportion in CVA patients with active rhinitis symptoms during the sensitized pollen season.

Our study has several limitations. First, the study was retrospective, and we cannot draw definite conclusions regarding the effects of allergic rhinitis on classic asthma and CVA. Additional prospective studies are required. Second, the pollen species, levels, and sensitization were not considered. Instead, we reanalyzed the data for the subset of patients with active rhinitis symptoms during the sensitized pollen season. Third, we included some patients who used inhaled corticosteroids. We therefore reanalyzed the data for the subset of steroid-naïve patients only and confirmed a similar clinical impact of perennial allergic rhinitis or seasonal allergic rhinitis on these patients. Fourth, some patients failed at sputum induction. We did not observe any differences in age, sex, disease duration, use of inhaled corticosteroids, FEV₁, asthma severity, or FeNO levels between patients who failed sputum induction and those who succeeded (all $p > 0.10$; data not shown).

Conclusions

We found consistent associations of concomitant perennial allergic rhinitis with airway inflammation indices, such as sputum and blood eosinophils and FeNO levels, in CVA patients as well as in classic asthma patients. For CVA patients, perennial allergic rhinitis may also be implicated in disease severity. Perennial allergic rhinitis may be involved via augmentation of eosinophilic lower airway inflammation. The clinical relevance of concomitant seasonal allergic rhinitis in airway inflammation was only slight for CVA patients with active rhinitis symptoms during the sensitized pollen season. Further prospective studies are needed to clarify the clinical impact of seasonal allergic rhinitis, and in particular rhinitis induced by Japanese cedar pollen.

Acknowledgements

The authors are grateful to Ms. Aya Inazumi for her help with sputum processing.

References

- ▶ 1 Bousquet J, Van Cauwenberge P, Khaltaev N: Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147–S334.
- ▶ 2 Gaugris S, Sazonov-Kocevar V, Thomas M: Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma* 2006;43:1–7.
- ▶ 3 Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, Ebisawa M, Tamura G, Nagai A, Nishima S, Fukuda T, Morikawa A, Okamoto Y, Kohno Y, Saito H, Takenaka H, Grouse L, Bousquet J: Prevalence and impact of rhinitis in asthma: SACRA, a cross-sectional nation-wide study in Japan. *Allergy* 2011;66:1287–1295.
- ▶ 4 Settipane RJ, Hagy GW, Settipane GA: Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;15:21–25.
- ▶ 5 Guerra S, Sherrill DL, Martinez FD, Barbee RA: Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109:419–425.
- ▶ 6 Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, Johns DP, Abramson MJ, Hopper JL, Dharmage SC: Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007;120:863–869.
- ▶ 7 Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, Wjst M, Cerveri I, Pin I, Bousquet J, Jarvis D, Burney PG, Neukirch F, Leynaert B: Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;372:1049–1057.
- ▶ 8 Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, Bjerner L: Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy (corrected). *Clin Exp Allergy* 2005;35:723–727.
- ▶ 9 Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M: Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;35:282–287.
- ▶ 10 Halpern MT, Schmier JK, Richner R, Guo C, Togias A: Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004;41:117–126.
- ▶ 11 Braunstahl GJ, Fokkens WJ, Overbeek SE, KleinJan A, Hoogsteden HC, Prins JB: Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003;33:579–587.
- ▶ 12 Foresi A, Leone C, Pelucchi A, Mastropasqua B, Chetta A, D'Ippolito R, Marazzini L, Oliveri D: Eosinophils, mast cells, and basophils in induced sputum from patients with seasonal allergic rhinitis and perennial asthma: relationship to methacholine responsiveness. *J Allergy Clin Immunol* 1997;100:58–64.
- ▶ 13 Brown JL, Behndig AF, Sekerel BE, Pourazar J, Blomberg A, Kelly FJ, Sandstrom T, Frew AJ, Wilson SJ: Lower airways inflammation in allergic rhinitis: a comparison with asthmatics and normal controls. *Clin Exp Allergy* 2007;37:688–695.
- ▶ 14 Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ: Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;107:469–476.
- ▶ 15 Corren J, Adinoff AD, Irvin CG: Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;89:611–618.
- ▶ 16 Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S, Sofios C, Rasidakis A, Jordanoglou J: Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000;30:663–669.
- ▶ 17 Niimi A: Geography and cough aetiology. *Pulm Pharmacol Ther* 2007;20:383–387.
- ▶ 18 Corrao WM, Braman SS, Irwin RS: Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;300:633–637.
- ▶ 19 Takemura M, Niimi A, Matsumoto H, Ueda T, Matsuoka H, Yamaguchi M, Jinnai M, Chin K, Mishima M: Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. *Respiration* 2012;83:308–315.

- ▶20 Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma – this official statement of the American Thoracic Society was adopted by the ATS board of directors, November 1986. *Am Rev Respir Dis* 1987; 136:225–244.
- ▶21 Ohta K, Yamaguchi M, Akiyama K, Adachi M, Ichinose M, Takahashi K, Nishimura T, Morikawa A, Nishima S: Japanese guideline for adult asthma. *Allergol Int* 2011;60:115–145.
- ▶22 Niimi A, Amitani R, Suzuki K, Tanaka E, Murayama T, Kuze F: Eosinophilic inflammation in cough variant asthma. *Eur Respir J* 1998;11: 1064–1069.
- ▶23 ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–930.
- ▶24 Matsumoto H, Niimi A, Jinnai M, Nakaji H, Takeda T, Oguma T, Otsuka K, Inoue H, Yamaguchi M, Matsuoka H, Ito I, Hirai T, Chin K, Mishima M: Association of alveolar nitric oxide levels with pulmonary function and its reversibility in stable asthma. *Respiration* 2011;81:311–317.
- ▶25 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J: Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- ▶26 Niimi A, Matsumoto H, Takemura M, Ueda T, Chin K, Mishima M: Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. *Am J Respir Crit Care Med* 2003;168:983–988.
- ▶27 Pin I, Gibson PG, Kolendowicz R, Girgis-Gabardo A, Denburg JA, Hargreave FE, Dolovich J: Use of induced sputum cell counts to investigate airway inflammation in asthma. *Thorax* 1992;47:25–29.
- ▶28 Takemura M, Niimi A, Minakuchi M, Matsumoto H, Ueda T, Chin K, Mishima M: Bronchial dilatation in asthma: relation to clinical and sputum indices. *Chest* 2004;125:1352–1358.
- ▶29 Matsuoka H, Niimi A, Matsumoto H, Ueda T, Takemura M, Yamaguchi M, Jinnai M, Otsuka K, Oguma T, Takeda T, Ito I, Chin K, Amitani R, Mishima M: Specific IgE response to *Trichophyton* and asthma severity. *Chest* 2009;135:898–903.
- ▶30 Takemura M, Niimi A, Matsumoto H, Ueda T, Yamaguchi M, Matsuoka H, Jinnai M, Chin K, Mishima M: Atopic features of cough variant asthma and classic asthma with wheezing. *Clin Exp Allergy* 2007;37:1833–1839.
- ▶31 Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H, Takenaka H, Baba K: Japanese guideline for allergic rhinitis. *Allergol Int* 2011;60:171–189.
- ▶32 Niimi A, Matsumoto H, Minakuchi M, Kitaichi M, Amitani R: Airway remodelling in cough-variant asthma. *Lancet* 2000;356:564–565.
- ▶33 Matsumoto H, Niimi A, Takemura M, Ueda T, Yamaguchi M, Matsuoka H, Jinnai M, Chin K, Mishima M: Features of cough variant asthma and classic asthma during methacholine-induced bronchoconstriction: a cross-sectional study. *Cough* 2009;5:3.
- ▶34 Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG: Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. *Chest* 2006;130:429–435.
- ▶35 Jang AS, Park JS, Lee JH, Park SW, Kim DJ, Uh ST, Kim YH, Park CS: Asthmatics without rhinitis have more fixed airway obstruction than those with concurrent rhinitis. *Allergy Asthma Immunol Res* 2010;2:108–113.
- ▶36 Gratziau C, Lignos M, Dassiou M, Roussos C: Influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis. *Eur Respir J* 1999;14:897–901.
- ▶37 Marcucci F, Passalacqua G, Canonica GW, Frati F, Salvatori S, Di cara G, Petrini I, Bernini M, Novembre E, Bernardini R, Incorvaia C, Sensi LG: Lower airway inflammation before and after house dust mite nasal challenge: an age and allergen exposure-related phenomenon. *Respir Med* 2007;101:1600–1608.
- ▶38 Kostikas K, Papaioannou AI, Tanou K, Koutsokera A, Papala M, Gourgoulis KI: Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. *Chest* 2008;133:906–913.
- ▶39 Alvarez MJ, Olaguibel JM, Garcia BE, Rodriguez A, Tabar AI, Urbiola E: Airway inflammation in asthma and perennial allergic rhinitis: relationship with nonspecific bronchial responsiveness and maximal airway narrowing. *Allergy* 2000;55:355–362.
- ▶40 Braunstahl GJ: The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease. *J Allergy Clin Immunol* 2005;115:142–148.
- ▶41 Bousquet J, Boushey HA, Busse WW, Canonica GW, Durham SR, Irvin CG, Karpel JP, Van Cauwenberge P, Chen R, Iezzoni DG, Harris AG: Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy* 2004;34:897–903.
- ▶42 Tobias A, Galan I, Banegas JR: Non-linear short-term effects of airborne pollen levels with allergenic capacity on asthma emergency room admissions in Madrid, Spain. *Clin Exp Allergy* 2004;34:871–878.
- ▶43 Erbas B, Chang JH, Dharmage S, Ong EK, Hyndman R, Newbiggin E, Abramson M: Do levels of airborne grass pollen influence asthma hospital admissions? *Clin Exp Allergy* 2007;37:1641–1647.
- ▶44 Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Emberlin J, Strachan DP: Air pollution, pollens, and daily admissions for asthma in London 1987–1992. *Thorax* 1998;53:842–848.
- ▶45 Rossi OV, Kinnula VL, Tienari J, Huhti E: Association of severe asthma attacks with weather, pollen, and air pollutants. *Thorax* 1993;48: 244–248.
- ▶46 Ueno K, Minoguchi K, Kohno Y, Oda N, Wada K, Miyamoto M, Yokoe T, Hashimoto T, Minoguchi H, Tanaka A, Kokubu F, Adachi M: Japanese cedar pollinosis is a risk factor for bronchial asthma in Japanese adult asthmatics (in Japanese). *Alerugi* 2002;51:565–570.
- ▶47 Maeda Y, Akiyama K, Shida T: A clinical study of Japanese cedar (*Cryptomeria japonica*) pollen-induced asthma. *Allergol Int* 2008; 57:413–417.
- ▶48 Bergmann-Hug K, Wirth R, Henseler M, Helbling A, Pichler WJ, Schnyder B: Effect of natural seasonal pollen exposure and repeated nasal allergen provocations on elevation of exhaled nitric oxide. *Allergy* 2009;64:1629–1634.
- ▶49 Henriksen AH, Sue-Chu M, Holmen TL, Langhammer A, Bjermer L: Exhaled and nasal no levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999;13:301–306.
- ▶50 Gratziau C, Rovina N, Lignos M, Vogiatzis I, Roussos C: Exhaled nitric oxide in seasonal allergic rhinitis: influence of pollen season and therapy. *Clin Exp Allergy* 2001;31:409–416.
- ▶51 Polosa R, Ciamarra I, Mangano G, Prosperini G, Pistorio MP, Vancheri C, Crimi N: Bronchial hyperresponsiveness and airway inflammation markers in nonasthmatics with allergic rhinitis. *Eur Respir J* 2000;15:30–35.
- ▶52 Spanevello A, Migliori GB, Sharara A, Ballardini L, Bridge P, Pisati P, Neri M, Ind PW: Induced sputum to assess airway inflammation: a study of reproducibility. *Clin Exp Allergy* 1997;27:1138–1144.