

ORIGINAL PAPER

Atopic features of cough variant asthma and classic asthma with wheezing

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Summary

Background Cough variant asthma is a phenotype of asthma solely presenting with coughing. It involves airway inflammation and remodelling as does classic asthma with wheezing, and a subset of patients may progress to classic asthma. The atopic features of cough variant asthma remain unclear.

Objective To compare atopic features between patients with cough variant asthma and those with classic asthma, and to examine the possible correlation of these features with the future development of wheezing in the former group.

Methods Total and specific IgE levels of seven common aeroallergens [house dust mite (HDM), Gramineae/Japanese cedar/weed pollens, moulds, cat/dog dander] were examined in 74 cough variant asthma patients and in 115 classic asthma patients of varying severity. Forty of the former patients were prospectively observed for 2 years to determine whether cough variant asthma progressed to classic asthma despite inhaled corticosteroid treatment.

Results Patients with classic asthma had higher total IgE ($P < 0.0001$), larger numbers of sensitized allergens ($P = 0.03$), and higher rates of sensitization to dog dander (24% vs. 3%, $P < 0.0001$), HDM (46% vs. 28%, $P = 0.02$), and moulds (17% vs. 7%, $P = 0.047$) than did patients with cough variant asthma. Wheezing developed in six (15%) patients with cough variant asthma, who were sensitized to larger numbers of allergens ($P = 0.02$) and had higher rates of sensitization to HDM ($P = 0.01$) and dog dander ($P = 0.02$) than the 34 patients in whom wheezing did not develop. Among the patients with classic asthma, total and specific IgE variables were similar in the subgroup with mild disease ($n = 60$) and the subgroup with moderate-to-severe disease ($n = 55$), as reported previously.

Conclusions Atopy may be related to the development of wheezing in patients with cough variant asthma. To prevent the progression of cough variant asthma to classic asthma, avoidance of relevant allergens may be essential.

Keywords allergen, atopy, classic asthma, cough, cough variant asthma, dog dander, phenotype, specific IgE, total IgE, wheezing

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Introduction

Sensitization to indoor and outdoor allergens is a risk factor for the development of asthma. Exposure to sensitized allergens may exacerbate asthma by promoting airway inflammation, airflow obstruction, and airway hyper-responsiveness (AHR). Conversely, the elimination of exposure to allergens, such as house dust mites (HDMs), may remarkably improve subjective as well as objective markers of asthma severity in sensitized individuals [1].

Cough variant asthma (CVA) is a phenotype of asthma solely presenting with persistent coughing [2]. It is con-

sidered one of the most common causes of chronic cough world-wide [3–7]. CVA shares several pathophysiologic features with classic asthma with wheezing, including AHR, eosinophilic airway inflammation, and airway remodelling [8–11]. However, the underlying mechanism(s) leading to phenotypic differences between CVA and classic asthma, i.e. the presence or absence of wheezing, remains poorly understood, although several mechanisms have been proposed [12, 13].

Up to 30–40% of adults with CVA may progress to classic asthma with wheezing [2, 14, 15]. Such progression is much less common in other eosinophilic airway

disorders such as non-asthmatic eosinophilic bronchitis and atopic cough, both of which lack AHR or responsiveness of coughing to bronchodilators [7, 11, 14]. Retrospective studies have indicated that early treatment with inhaled corticosteroids may prevent this phenomenon in patients with CVA [14, 15]. Other factors potentially related to the development of classic asthma from CVA include the degrees of AHR [14, 16] and airway inflammation [17] at diagnosis. The roles of allergen sensitization in baseline phenotypic differences between CVA and classic asthma or in the future progression of CVA to classic asthma remain unknown.

To gain an insight into factors related to the progression of CVA to classic asthma, we examined atopic status, assessed on the basis of total IgE levels and specific IgE titre against common aeroallergens, in patients with CVA and those with classic asthma. A subset of patients with CVA treated with inhaled corticosteroid was prospectively observed for 2 years to clarify the role of atopy in the development of wheezing. Moreover, the patients with classic asthma were separately analysed to investigate the relation of atopy to the severity of full-blown asthma.

Methods

Subjects

A total of 74 consecutive outpatients with CVA and 115 with classic asthma were recruited from the asthma and cough clinic of Kyoto University Hospital. None of the patients were current smokers.

CVA was diagnosed on the basis of a chronic cough persisting for longer than 8 weeks, the absence of wheezing or dyspnoea, the presence of AHR to methacholine, and a symptomatic response of coughing to bronchodilators such as inhaled β_2 -agonists (used as needed or four times per day), sustained-release theophylline (taken twice daily), or both [2, 5, 8, 18]. Wheezing or rhonchi were not audible on chest auscultation, even with forced expiration. The patients had normal chest radiographs and no history of asthma, upper respiratory infection within the past 8 weeks, or other respiratory diseases. None had signs or symptoms of chronic sinusitis, post-nasal drip or gastroesophageal reflux, or had been taking angiotensin-converting enzyme inhibitors. Coughing subsided in all patients with the addition of inhaled corticosteroids without using other medications such as histamine H1 receptor antagonists, antibiotics, and proton pump inhibitors. CVA was thus considered the single cause of chronic cough in all patients.

Patients with classic asthma had a history of episodic dyspnoea and wheezing with or without coughing. Asthma was diagnosed and disease severity was classified according to the 2004 version of Global Initiative for Asthma (GINA) guidelines [19]. Sixty patients had mild

asthma (steps 1 and 2 of the GINA guidelines), and 55 had moderate-to-severe asthma (steps 3 and 4) [19].

The research protocol was approved by the Institutional Review Board of Kyoto University Hospital, and written informed consent was obtained from all subjects.

Immunoglobulin E measurements

The serum levels of total and specific IgE antibodies against common aeroallergens were measured by radio-immunosorbent tests and the CAP method (Pharmacia Diagnostics, Uppsala, Sweden). Specific IgE antibodies were considered to be positive if the response level exceeded 0.35 IU/mL [20]. Specific IgE antibody responses were measured to seven allergens: HDM, Japanese cedar pollen, mixed Gramineae pollens (orchard grass, sweet vernal grass, Bermuda grass, timothy, reeds), mixed weed pollens (ragweed, mugwort, goldenrod, dandelion, oxeye daisy), mixed moulds (*Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, *Alternaria*), cat dander, and dog dander.

Methacholine challenge

In patients with CVA, airway responsiveness to methacholine was measured as described previously [21, 22]. Briefly, twofold-increasing concentrations of methacholine in 10 dose steps (49–25 000 μ g/mL) were inhaled during tidal breathing from nebulizers with an output of 0.15 mL/min. After recording the baseline respiratory resistance (R_{rs} , cm H₂O/L/s) during inhalation of physiologic saline, methacholine was given sequentially, starting with the lowest concentration, at 1-min intervals. D_{min} , the cumulative dose of methacholine at the inflection point at which R_{rs} began to increase, was used as a measure of airway sensitivity. The slope of the methacholine– R_{rs} dose–response curve (SR_{rs}) was used as a measure of airway reactivity [22]. Airway responsiveness of the patients with classic asthma was only available for a subset of patients and was therefore not included in the analysis.

Study protocol

The study was conducted in a cross-sectional fashion. Total and specific IgE levels and other clinical variables, including pulmonary function, were assessed. Ownership of dog or cat at home at the onset of disease was inquired. The data were compared between the 74 patients with CVA and 115 patients with classic asthma. Clinical variables were also compared between patients with classic asthma who had mild disease ($n = 60$) and those who had moderate-to-severe disease ($n = 55$).

Forty of the patients with CVA were prospectively observed for 2 years after diagnosis to determine whether

wheezing developed. Wheezing was diagnosed by auscultation, symptoms reported by the patients, or both [15]. Inhaled corticosteroids, which may inhibit the development of wheezing [14, 15], were administered to all patients throughout the course of the study. Daily doses of fluticasone propionate 200–400 µg via Diskhaler™ or Diskus™ (GlaxoSmithKline, Middlesex, UK), budesonide 400–800 µg via Turbuhaler™ (AstraZeneca, London, UK), or HFA-beclomethasone dipropionate (BDP) 200–400 µg via pMDI, were given according to the recommendation of Japanese Respiratory Society Guidelines for Management of Cough [5]. Ownership of dog or cat at home during the 2-year follow-up was inquired. The characteristics of patients in whom wheezing developed were compared with those of patients without wheezing. The remaining 34 patients had discontinued their visits to our clinic midway from whom the follow-up data were unavailable.

Statistical analysis

Values are expressed as means ± SD, medians (range), or numbers (percentage). Comparisons between two groups were made with Mann–Whitney *U*-tests or Fisher's exact probability tests. *P*-values of <0.05 were considered to indicate statistical significance.

Results

Comparison between patients with cough variant asthma and those with classic asthma

The backgrounds and outcomes of the 74 patients with CVA and 115 with classic asthma are presented in Table 1. Patients with CVA were significantly younger, had a shorter disease duration, and included a lower percentage of former smokers than patients with classic asthma. Airflow obstruction and blood eosinophilia were significantly greater in classic asthma than in CVA.

The total IgE levels were significantly higher in classic asthma than in CVA. Sensitization to HDM, dog dander, and mixed moulds were significantly more prevalent in classic asthma than in CVA. The difference in the prevalence of sensitization was especially marked for dog dander. Consistent with this finding, a higher proportion of patients with classic asthma owned dogs at disease onset, as compared with those who had CVA. Sensitization to cat dander showed an insignificant trend towards a higher prevalence in the classic asthma group, whereas cat ownership at disease onset was similar in the groups. The median number of positive allergens per patient was significantly higher in classic asthma than in CVA. The prevalence of sensitization to at least one of the seven allergens did not differ between the two groups (Table 1).

Table 1. Characteristics of CVA and classic asthma patients

	CVA	Classic asthma	<i>P</i> -value
<i>n</i>	74	115	
Age (years)	44 ± 17	51 ± 17	0.008
Sex (male : female)	28 : 46	41 : 74	0.76
Duration of disease (years)	5 ± 7	11 ± 11	0.0001
Life time nonsmoker : exsmoker	63 : 11	72 : 43	0.0009
FEV ₁ (% pred)	102 ± 14	86 ± 20	<0.0001
FEV ₁ /FVC (% pred)	83 ± 8	74 ± 16	<0.0001
Blood eosinophils (cells/µL)	195 ± 190	380 ± 416	<0.0001
Log IgE* (IU/mL)	1.9 ± 0.7	2.3 ± 0.6	<0.0001
Sensitization to specific allergens*			
House dust mite	21 (28)	53 (46)	0.022
Japanese cedar pollen	32 (43)	58 (50)	0.37
Mixed gramineae pollens	16 (21)	24 (21)	>0.99
Mixed weed pollens	5 (7)	13 (11)	0.45
Cat dander	8 (11)	25 (22)	0.08
Dog dander	2 (3)	28 (24)	<0.0001
Mixed moulds	5 (7)	20 (17)	0.047
Number of positive allergens	1 (0–5)	2 (0–7)	0.033
Sensitization to any allergen	45 (61)	77 (67)	0.44
Dog ownership at the onset	8 (13)	29 (26)	0.035
Cat ownership at the onset	5 (8)	15 (14)	0.33

*Number and percentage (in parentheses) of patients with positive results.

CVA, cough variant asthma; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Association of sensitized allergens with the development of wheezing in patients with cough variant asthma

Wheezing developed and progressed to classic asthma in six (15%) of the 40 patients with CVA who were followed up for 2 years after the diagnosis. The characteristics of these patients and the 34 patients in whom wheezing did not develop are presented in Table 2.

Age, sex distribution, disease duration, smoking history, initial and final doses of inhaled corticosteroids (equivalent of CFC-BDP), blood eosinophil count, and airway sensitivity did not differ significantly between the two groups. The patients with CVA in whom wheezing developed had a significantly lower forced expiratory volume in 1 s (FEV₁) value at diagnosis than those in whom wheezing did not develop. Moreover, these patients had significantly higher rates of sensitization to HDM and dog dander, as well as a significantly greater median number of positive allergens than did the patients without wheezing. Only two patients showed a positive IgE response to dog dander, both of whom developed wheezing. Total IgE levels and airway reactivity differed slightly but not significantly. Dog or cat ownership during the follow-up was similar in the two groups.

Table 2. Characteristics of CVA patients with and without development of wheezing

	Wheezing (-)	Wheezing (+)	P-value
<i>n</i>	34	6	
Age (years)	48 ± 18	35 ± 13	0.08
Sex (male : female)	8 : 26	4 : 2	0.055
Duration of disease (years)	5 ± 6	2 ± 2	0.20
Life time nonsmoker : exsmoker	30 : 4	4 : 2	0.21
FEV ₁ (% pred)	105 ± 16	88 ± 9	0.006
FEV ₁ /FVC (% pred)	83 ± 8	82 ± 6	0.76
Initial dose of inhaled corticosteroid (µg/day)	603 ± 446	467 ± 301	0.52
Final dose of inhaled corticosteroid (µg/day)	618 ± 342	633 ± 512	0.70
Blood eosinophils (cells/µL)	234 ± 287	149 ± 36	0.61
Log IgE (IU/mL)	0.7 ± 0.1	1.1 ± 0.5	0.099
Airway sensitivity (log Dmin) (µg/mL)	0.5 ± 0.7	0.2 ± 0.6	0.26
Airway reactivity (SR ₁₅) (cmH ₂ O/L/s/min)	1.5 ± 1.5	2.3 ± 1.4	0.074
Sensitization to specific allergens [†]			
House dust mite	8 (24)	5 (83)	0.010
Japanese cedar pollen	12 (35)	4 (67)	0.20
Mixed gramineae pollens	8 (24)	1 (17)	>0.99
Mixed weed pollens	2 (6)	2 (34)	0.10
Cat dander	4 (12)	2 (34)	0.21
Dog dander	0 (0)	2 (34)	0.019
Mixed moulds	3 (9)	1 (17)	0.49
Number of sensitized allergen	1 (0-4)	3 (0-5)	0.020
Sensitization to any allergen	19 (56)	6 (100)	0.07
Dog ownership during follow-up	6 (18)	1 (17)	>0.99
Cat ownership during follow-up	3 (9)	1 (17)	0.49

[†]Number and percentage (in parentheses) of patients with positive results.

CVA, cough variant asthma; wheezing (-), CVA patients who did not develop wheezing; wheezing (+), CVA patients who developed wheezing; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Association of sensitized allergens with the severity of classic asthma

The characteristics of the patients with classic asthma are shown according to disease severity in Table 3. Age and pulmonary function differed significantly between the patients with mild asthma and those with moderate-to-severe asthma, as expected. However, atopic status assessed on the basis of variables such as total IgE levels, rates of sensitization to different allergens, or the number of positive allergens was similar in the two groups.

Table 3. Characteristics of classic asthma patients with mild and moderate-to-severe disease

	Classic asthma		
	Mild	Moderate- to-severe	P-value
<i>n</i>	60	55	
Age (years)	47 ± 18	55 ± 14	0.020
Sex (male : female)	21 : 39	20 : 35	>0.99
Duration of asthma (years)	10 (0.0-60)	5 (0.1-37)	0.62
Life time non- smoker : exsmoker	43 : 17	31 : 24	0.12
FEV ₁ (% pred)	90 ± 15	81 ± 24	0.08
FEV ₁ /FVC (% pred)	79 ± 17	68 ± 12	0.0003
Blood eosinophils (cells/µL)	356 ± 410	407 ± 426	0.17
Log IgE (IU/mL)	2.3 ± 0.7	2.3 ± 0.6	0.88
Sensitization to specific allergens*			
House dust mite	32 (53)	21 (38)	0.13
Japanese cedar pollen	35 (58)	23 (42)	0.09
Mixed gramineae pollens	15 (25)	9 (16)	0.36
Mixed weed pollens	6 (10)	7 (13)	0.77
Dog dander	17 (28)	11 (20)	0.39
Cat dander	12 (20)	13 (24)	0.66
Mixed moulds	12 (20)	8 (15)	0.47
Number of sensitized allergen	2 (0-7)	1 (0-7)	0.27
Sensitization to any allergen	43 (72)	34 (62)	0.32
Dog ownership at the onset	11 (18)	17 (31)	0.13
Cat ownership at the onset	7 (12)	8 (15)	0.78

*Number and percentage (in parentheses) of patients with positive results. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Discussion

We have shown that patients with classic asthma who present with wheezing had significantly higher total IgE levels, higher rates of sensitization to HDM, dog dander, and moulds, and a greater number of allergens to which they were sensitized than patients with CVA, who present solely with coughing. Dog ownership at disease onset was more common among patients with classic asthma than among those with CVA. Progression of CVA to classic asthma, which occurred in six of 40 patients during the 2 years after diagnosis, was associated with marginally higher total IgE levels, significantly higher rates of sensitization to HDM and dog dander, and a significantly greater number of sensitized allergens. Total and specific IgE variables did not differ, however, between patients with classic asthma who had mild disease and those who had moderate-to-severe disease.

Several mechanisms have been proposed for phenotypic differences between classic asthma and CVA. A higher wheezing threshold [12] and lower airway reactivity to inhaled methacholine [13] have been demonstrated in children with CVA, as compared with those with classic asthma. A small study immunohistochemically showed increased expression of substance P in the airway epithelium of patients who have CVA, as compared with those who have classic asthma or healthy controls [23]. These results may explain why patients with CVA present with coughing, but not wheezing. The degree of basement membrane thickening is more prominent in classic asthma than in CVA [9], whereas the severity of eosinophilic inflammation is similar [8]. These phenomena are apparently not involved in the different presentations of CVA and classic asthma. The development of wheezing in patients with CVA has been associated with more pronounced airway responsiveness or maximal airway response [14, 16], as well as with eosinophilic inflammation as assessed using sputum [17]. Inhaled corticosteroids may prevent the development of wheezing [14, 15] by inhibiting airway responsiveness and airway inflammation. In our study, airway reactivity at baseline was only marginally higher in the patients with CVA who later developed wheezing than in those without wheezing.

The main findings of our study, presented in Tables 1 and 2, indicated a consistent trend. Namely, total IgE levels, rates of sensitization to common allergens, and the total number of sensitized allergens were higher in patients with classic asthma than in those with CVA. These values were also higher in patients with CVA who developed wheezing than in those without wheezing. Our results convincingly indicate that the degree of atopic status, evaluated on the basis of indices such as sensitization to several specific allergens, is associated with the development of classic asthma with wheezing. The development of wheezing in 15% of the patients with CVA was consistent with the prevalence in patients treated with inhaled corticosteroids in our previous study [15]. This ratio may become higher unless patients were treated with this anti-inflammatory medication [14, 15]. Treatment with inhaled corticosteroids may thus have altered the natural history of these 40 patients over 2 years.

Indoor allergens, such as HDM and domestic pets (dogs and cats), and outdoor allergens, such as moulds, are recognized as major risk factors for asthma world-wide [24–26]. HDM is ubiquitous and acknowledged to be a common sensitizing and deleterious allergen. This notion is supported by a dose–response relation between HDM exposure and sensitization [25]. A causal relationship between exposure to pets or pet allergens and sensitization or the development of asthma has been proposed on the basis of intriguing but conflicting evidence and therefore remains more controversial [25, 27, 28]. Pet allergens have different effects at different stages of life. Early

exposure, either indirect or direct, to endotoxin associated with pets might cause a protective shift from a T-helper type 2 (Th2) cell to a Th1 cell response in the immune system, whereas exposure to pets later in life might be positively associated with asthma [29, 30]. McConnell et al. [27] have reported that the development of asthma positively correlates with dog exposure in a prospective study of adolescents, whereas studies in infants refute such a relation [31]. In adults, a pet in the home has been associated with an increased risk of pet-specific sensitization [32], and direct or even indirect exposure to cat or dog allergens triggers symptoms in already sensitized individuals with asthma [28, 33, 34]. In our study, the rate of sensitization to dog dander was significantly higher in patients with classic asthma than in those with CVA; it was also higher in patients with CVA who progressed to classic asthma than in those who did not. Moreover, the rate of dog ownership at the onset was significantly higher in patients with classic asthma than in those with CVA. Because disease developed after adolescence in all patients with CVA, as well as in most patients with classic asthma (104 out of 115), our results are consistent with the findings of previous studies, including two performed by Gerada et al. [29, 30]. It is unclear, however, why sensitization to dog dander, but not to cat dander was associated with classic asthma. Lack of difference in dog ownership between the patients with CVA who progressed to classic asthma and those who did not during follow-up may be attributed to a small sample size, but might indicate an importance of indirect rather than direct exposure to dogs.

A higher total number of sensitized allergens in classic asthma than in CVA was also in agreement with the results of a previous study demonstrating a direct relation between the number of positive skin prick tests and the prevalence of asthma symptoms [35]. We hypothesized that some specific allergens may show higher rates of sensitization in patients with CVA than in those with classic asthma. We had also assumed that some allergens might specifically induce coughing rather than wheezing by causing more intense inflammation in larger airways, which may be richer in 'cough receptors' than smaller airways. This assumption, however, was not supported by our findings.

In our study, atopic profiles were not associated with the severity of classic asthma. Several groups of investigators have obtained similar results in adult asthmatic patients. Inouye et al. [36] failed to find a difference in the severity of asthma between patients with positive skin tests and those with negative skin tests. Cline et al. [37] also found no association of skin test positivity with FEV₁ or asthma severity. Subjects with severe asthma in the ENFUMOSA study were even less atopic than a control group with milder asthma [38, 39]. Taken together, these results suggest that allergic responses are seen at all levels of asthma severity and do not play a direct role in

determining disease severity [40]. Collectively, atopic/allergic reactions may be an important inducer or trigger of asthma or wheezing, while remaining disassociated from the severity of asthma.

Our study may involve limitations. The follow-up of patients with CVA was incomplete. We could follow 40 out of 74 patients with CVA for 2 years. The remaining 34 patients had discontinued their visits to our clinic. After confirming the diagnosis of CVA, we informed each patient that CVA may be considered a pre-asthmatic state but may involve airway inflammation and remodelling [8–10], and that long-term treatment with inhaled corticosteroid is desirable, which may prevent the progression to classic asthma with wheezing [14, 15]. Subsequently, we kept trying our best to prevent patients from being lost to follow-up. However, coughing of patients with CVA usually improves within weeks after commencement of treatment including inhaled corticosteroids [41], and therefore dropout may be inevitable in a subset of patients. The small sample size of patients who completed the follow-up, and those who developed wheezing, might have lessened the power of the study.

In conclusion, atopy is an important determinant of the development of wheezing in patients with CVA. Coughing annoys patients with CVA, but physiologic abnormalities such as airflow limitation and airway responsiveness are more marked in classic asthma than in CVA [2, 5, 8, 13]. Severe airway narrowing complicated by hypoxaemia and a potential risk of death may develop in patients with classic asthma, but rarely occurs in patients with CVA. It is therefore important to prevent the progression of CVA to classic asthma. One essential strategy may be the avoidance of relevant allergens, such as HDM and dog dander, in addition to treatment with inhaled corticosteroids [14, 15]. However, future studies involving a larger number of patients may be required to address these issues in more detail.

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