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ORIGINAL ARTICLE

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Cough Triggers and Their Pathophysiology in Patients with Prolonged or Chronic Cough

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ABSTRACT

Background: The character or timing of chronic cough is considered to be unpredictable for diagnosing its cause. However, the associations of cough triggers with cough pathophysiology remains unknown.

Methods: We developed a closed questionnaire listing 18 triggers that were reported by ≥1% of 213 patients in a retrospective survey. Using this questionnaire, patients with cough-predominant or cough-variant asthma (n = 140) and those with non-asthmatic cough (54) were asked whether their cough was induced by the listed triggers. Associations of triggers with causes of cough, airway sensitivity to inhaled methacholine, exhaled nitric oxide (NO) levels, number of sensitizing allergens, and scores from gastroesophageal reflux (GER) questionnaires were examined. Factor analysis was used to categorize variables, including the 12 most common cough triggers, diagnosis of asthmatic cough, airway sensitivity, and exhaled NO levels.

Results: "Cold air" and "fatigue/stress" induced cough more often in asthmatic coughers than in non-asthmatic coughers. "Spices" and "meals" induced cough more frequently in GER-coughers (n = 19). Patients who marked "cold air" as the trigger were more sensitive to inhaled methacholine and showed higher exhaled NO levels than those who did not mark this trigger. The "post-nasal drip" trigger was associated with elevated exhaled NO levels, and this association was mainly exhibited by patients with cough-predominant asthma. The triggers "pollen" and "mold smell" were associated with a number of sensitizing allergens. The number of triggers was weakly associated with GER scores. By factor analysis, "cold air," "fatigue/stress," asthmatic cough, airway hypersensitivity, and elevated NO levels were categorized into the same factor.

Conclusions: Several cough triggers may reflect the pathophysiology of prolonged or chronic cough.

KEY WORDS

allergens, chronic cough, cough triggers, cough variant asthma, gastroesophageal reflux

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INTRODUCTION

Prolonged or chronic cough is a troublesome symptom for which patients seek medical consultation. Recent methodological progress in the measurements of airway pathophysiology, such as exhaled nitric oxide (NO) levels, has provided a better understanding of airway diseases, including chronic cough.[1] However, obtaining a meticulous clinical history remains a basic, key tool for the diagnosis and management of patients in general practice. Information on any associations of clinical history, such as cough triggers, with pathophysiological findings would be helpful for physicians who cannot easily access specialized or expensive equipment.

Cough variant asthma (CVA) is one major cause of prolonged or chronic cough which solely presents cough that is relieved with bronchodilators.[2-4] Hannaway *et al*. reported that among 32 children with CVA, 25 reported exercise-induced cough and 14 reported cold air-induced cough, and a majority of these patients experienced worsening of cough during specific seasons.[5] Among patients with cough associated with gastroesophageal reflux disease (GER-coughers), 90%, 87%, and 74% experienced worsening of cough on phonation, rising, and eating, respectively, and 83% of GER-coughers experienced throat clearing.[6] However, the specificity of these triggers or associated symptoms to patients with CVA or GER-coughers remains unclear.

A prospective study reported that the character or timing of chronic cough was not very useful for diagnosing its cause.[7] The positive predictive value of symptoms, such as nocturnal cough, precipitation by cold air, exercise, and aerosols, for the diagnosis of CVA was 56% in a study comprising 10 CVA patients.[8] In a retrospective survey, we found that cold air was more frequently reported as a cough trigger by CVA patients (n = 126) than by non-asthmatic chronic coughers (n = 87; p = 0.044).[9] We also demonstrated that bronchoconstriction caused by methacholine inhalation induced cough in CVA patients.[10] Thus, we hypothesized that some triggers may reflect the cough pathophysiology in patients with prolonged or chronic cough.

In this study, we developed a closed questionnaire listing 18 triggers that were reported by ≥1% of 213 patients in our retrospective survey.[9] Using this questionnaire, the associations of cough-inducing factors with causes of cough and pathophysiological findings were examined.

METHODS

STUDY DESIGN AND SUBJECTS

We cross-sectionally studied 194 adults with cough that continued for 3 or more weeks; asthmatic coughers (n = 140) and non-asthmatic coughers (n = 54) who visited our asthma and chronic cough clinic of Kyoto University Hospital from December 2006 to August 2009 and completed a structured diagnostic approach. Asthmatic coughers were comprised of patients with cough-predominant asthma whose chief complaint was cough but who also experienced minimal wheeze or dyspnea (n = 57 including 2 patients with GER), and those with CVA [n = 83 including those with GER 7, sinobronchial syndrome (SBS) 2, concomitant infection with pertussis 2]. Non-asthmatic coughers were comprised of patients with post-infectious cough (n = 24), GER (n = 9), atopic cough (n = 7 including 1 patient with GER), SBS (n = 4), smoking related (chronic bronchitis) (n = 4), and unexplained (idiopathic) (n = 6).

Diagnosis of prolonged or chronic cough was made according to the criteria proposed by the Japanese Respiratory Society.[11] Specifically the diagnosis of CVA was based on the following criteria; an isolated prolonged or chronic cough without dyspnea or wheezing not audible on auscultation; airway hypersensitivity to inhaled methacholine and symptomatic improvement of cough with the use of bronchodilators; no past history of asthma, or upper respiratory tract infection within the past 8 weeks. When patients presented normo-sensitive results to inhaled methacholine but responded to bronchodilator therapy, they were diagnosed as having probable CVA. Diagnosis of SBS was made on a positive result of sinus images and improvement of cough as well as the symptoms related to chronic sinusitis with antibiotics. Diagnosis of GER-cough was made on the basis of the presence of gastrointestinal symptoms of GER such as heartburn and acid regurgitation; no response to bronchodilators, histamine H1 antagonists, and inhaled corticosteroids; relief of cough with proton-pump inhibitors. Scores from questionnaires for GER were also taken into account. Diagnosis of atopic cough was made on the basis of cough resistant to the use of bronchodilators; presence of one or more findings indicative of an atopic predisposition, including a history and/or complications of allergic disease excluding asthma, peripheral blood eosinophilia, elevated total serum IgE levels, positive specific IgE antibody to aeroallergens and/or induced sputum eosinophilia; resolution of cough with histamine H1 antagonists and/or inhaled and/or oral corticosteroids. Diagnosis of post-infectious cough was made based on a preceding history of upper airway infection and spontaneous remission of cough; exclusion of other causes of cough. Diagnosis of smoking related cough (chronic bronchitis) was made when a patient was a current smoker, and the patient's cough was productive and improved with cessation of smoking. If examinations and intensive therapeutic trials for CVA, GER-cough, SBS, and atopic cough including inhaled corticosteroids and anti-reflux treatment were failed, the cough was considered unexplained (idiopathic). All the patients showed normal chest ra-

Table 1 Questionnaire for cough triggers (originally in Japanese)

Please check the factors that induce cough in you (You can choose as many as you think apply).

☐ Common cold	☐ Meals
☐ Cold air	☐ Alcohol
☐ Talking	☐ Heartburn
☐ Smoke/ fragrance	☐ Humidity
☐ Mold smell	☐ Dry air
☐ Fatigue/stress	☐ Changing position particularly when lying down
☐ Spices such as curry or chili	☐ Contact with pets
☐ Post-nasal drip (nasal discharge dripping down your throat)	☐ Pollen
☐ Exercise	☐ Others ( )
☐ Itchy throat	

Table 2 Patients' backgrounds

	Asthmatic coughers		Non-asthmatic coughers (n = 54)	3-group comparison p value*
	Cough predominant (n = 57)	CVA (n = 83)		
Male/Female	22/35	35/48	24/30	0.84
Age (year)	52.3 ± 17.5	49.7 ± 18.9	49.3 ± 17.1	0.58
Smoking history current/past/never	4/12/41	7/24/52	10/9/35	0.14
Disease duration (mo)	34.9 ± 88.0†	18.5 ± 40.7‡	8.5 ± 20.2§	0.030
Blood eosinophils (%)	4.7 ± 4.5‡	2.9 ± 2.7	2.5 ± 1.8	0.002
Serum IgE (IU)	110 (4-8700)‡	96 (4-2600)‡	41 (4-1000)§	0.023
Exhaled NO (ppb)	55.9 ± 60.4‡	30.9 ± 20.3†	25.3 ± 22.3§	0.002
Sputum eosinophils‖ (%)	17.5 ± 27.9‡¶	3.4 ± 8.2†	0.9 ± 1.3§	0.0008
FEV_1 (%predicted)	95.6 ± 18.9	101.6 ± 15.4	100.8 ± 15.8	0.14
Dmin (unit)	1.4 (0.045-11.3)‡	3.1 (0.033-50)‡	6.5 (0.039-50)§	<0.0001
C5 (μmol/L)#	9.77 (0.61-156.3)	9.77 (0.61-156.3)	3.66 (0.61-78.1)	0.48
FSSG scores	7.1 ± 7.0	7.3 ± 7.3	7.7 ± 5.8	0.50
QUEST scores	2.7 ± 3.6	2.0 ± 3.6	2.4 ± 4.0	0.28

Mean ± SD or median (ranges), *by Kruskal-Wallis, †$p < 0.05$ vs. non-asthmatic coughers, ‡$p < 0.016$ vs. non-asthmatic coughers, §$p < 0.05$ vs. asthmatic cough (cough predominant + cough variant) by Mann-Whitney test, ¶$p < 0.016$ vs. CVA. ‖Cough-predominant asthma (n = 40) , CVA (n = 47) , Non-asthmatic coughers (n = 27). #Cough-predominant asthma (n = 16) , CVA (n = 49), Non-asthmatic coughers (n = 25).

CVA, cough-variant asthma; NO, nitric oxide; Dmin, the cumulative dose of inhaled methacholine at the inflection point where which Rrs began to increase; C5, concentration of capsaicin solution when 5 or more coughs were first induced. FSSG and QUEST are questionnaires for gastroesophageal reflux.

diographs.

The ethics committee of our institution approved the study protocol. Written informed consent was obtained from each participant and patient anonymity was preserved.

BLOOD EXAMINATION

Total and specific serum IgE antibody titers were measured by radioimmunosorbent testing (Pharmacia, Upjohn, Tokyo, Japan). Patients were considered atopic when one or more specific IgE antibodies against cat dander, dog dander, weeds, grass pollen, cedar pollen, mold and house dust mite were positive. Blood eosinophil percentage was also measured.

PULMONARY FUNCTION TEST AND METHACHOLINE CHALLENGE TEST

Prebronchodilator FEV_1 was tested using a spirometer (Chestac-65V, Chest, Tokyo, Japan) according to the standards of the American Thoracic Society.[12] Airway sensitivity was tested by directly recording a dose-response curve of respiratory resistance (Rrs) ($cmH_2O/L/sec$) during continuous inhalation of methacholine in two-fold incremental concentrations (49 to 25,000 μg/ml) under tidal breathing from nebulizers with an output of 0.15 ml/minute (Asto-

Table 3 Frequencies of cough triggers

Average frequency (%) Among all cases (n = 194)		Asthmatic coughers (n = 140)		Non-asthmatic coughers (n = 54)	3-group comparison p-value*
		Cough predominant	CVA		
Itchy throat	52.1	50.9 ± 50.4	49.4 ± 50.3	57.4 ± 49.9	0.64
Cold air	38.7	50.9 ± 50.4†	38.6 ± 49.0	25.9 ± 44.2§	0.027
Common cold	37.1	36.8 ± 48.7	33.7 ± 47.6	42.6 ± 49.9	0.58
Dry air	32.0	35.1 ± 48.1	32.5 ± 47.1	27.8 ± 45.2	0.71
Smoke/fragrance	27.8	40.4 ± 49.5	21.7 ± 41.5‡	24.1 ± 43.2	0.042
Talking	26.8	21.1 ± 41.1	33.7 ± 47.6	22.2 ± 42.0	0.17
Changing position	22.7	22.8 ± 42.3	20.5 ± 40.6	25.9 ± 44.2	0.76
Fatigue/stress	19.6	31.6 ± 46.9†	18.1 ± 38.7	9.3 ± 29.3§	0.012
Post-nasal drip	16.5	19.3 ± 39.8	16.9 ± 37.7	13.0 ± 33.9	0.66
Exercise	13.9	17.5 ± 38.4	15.7 ± 36.6	7.4 ± 26.4	0.26
Spices	11.9	15.8 ± 36.8	6.0 ± 23.9	16.7 ± 37.6	0.095
Meals	11.3	7.0 ± 25.8	13.3 ± 34.1	13.0 ± 33.9	0.47
Pollen	9.3	15.8 ± 36.8	8.4 ± 28.0	3.7 ± 19.1	0.086
Mold smell	6.7	10.5 ± 31.0	7.2 ± 26.1	1.9 ± 13.6	0.18
Alcohol	3.6	5.3 ± 22.5	2.4 ± 15.4	3.7 ± 19.1	0.67
Humidity	3.1	3.5 ± 18.6	2.4 ± 15.4	3.7 ± 19.1	0.89
Heartburn	2.6	3.5 ± 18.6	2.4 ± 15.4	1.9 ± 13.6	0.85
Contact with pets	2.6	3.5 ± 18.6	2.4 ± 15.4	1.9 ± 13.6	0.85
Number of triggers (n)	3.4	3.9 ± 2.1†	3.3 ± 1.9‡	3.0 ± 1.8	0.024

Mean ± SD, *by Kruskal-Wallis; †$p < 0.016$ vs. non asthmatic coughers, ‡$p < 0.05$ vs. cough-predominant asthma, §$p < 0.05$ vs. asthmatic cough (cough predominant + cough variant), by Mann-Whitney test.

graph™; Chest), as described previously in detail.[10,13] The index of airway sensitivity that we adopted was Dmin: the cumulative dose of inhaled methacholine at the inflection point where which Rrs began to increase continuously. One unit of Dmin is equivalent to dose of 1 mg/ml of methacholine inhalation for one minute.

MEASUREMENT OF NO

NO levels were measured with a chemiluminescence analyzer (NOA 280, Sievers, Boulder, CO, USA) according to the current guideline.[14,15] The analyzer was calibrated daily with gas without NO generated by exposing ambient air to NO scavengers and a standard concentration of 640 ppb NO. The lower detection limit for NO was 2 ppb. The signal output from the NO analyzer was fed to a computer data acquisition program, and concentrations were measured using a data analysis program (NOA Analysis™ Software, Sievers). Seated subjects inserted a mouthpiece, inhaled orally to total lung capacity, exhaled at 50 ml/s immediately against a resistance, and maintained mouth pressure at 20 cmH_2O, displayed on a pressure gauge. The steady-state NO plateau was taken as the fraction of exhaled NO (FeNO) value.

SPUTUM INDUCTION

Sputum induction and processing were performed according to the methods of Pin[16] with a slight modification.[17] Briefly, subjects inhaled a hypertonic (3%) saline solution from an ultrasonic nebulizer (MU-32, Azwell Inc., Osaka, Japan) for 15 minutes and adequate plugs of sputum were separated from saliva. After treatment with 0.1% dithiothreitol (Sputasol™, OXOID Ltd, Hampshire, UK), the sample was cytocentrifuged and cells were stained by May-Grünwald-Giemsa method. Inflammatory cell differentials were determined by counting at least 400 nonsquamous cells on each sputum slide. Data of 40 patients with cough-predominant asthma, 47 with CVA, and 27 with non-asthmatic coughers in whom sputum was successfully induced was analyzed.

GER QUESTIONNAIRES

We used two questionnaires for GER. One was a frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) developed by Kusano *et al.*.[18] The other was a questionnaire for the diagnosis of reflux esophagitis (QUEST) developed by Carlsson *et al.*.[19] The presence of GER was suspected when 8 or more points from FSSG and/or 4 or more points from QUEST were recorded.

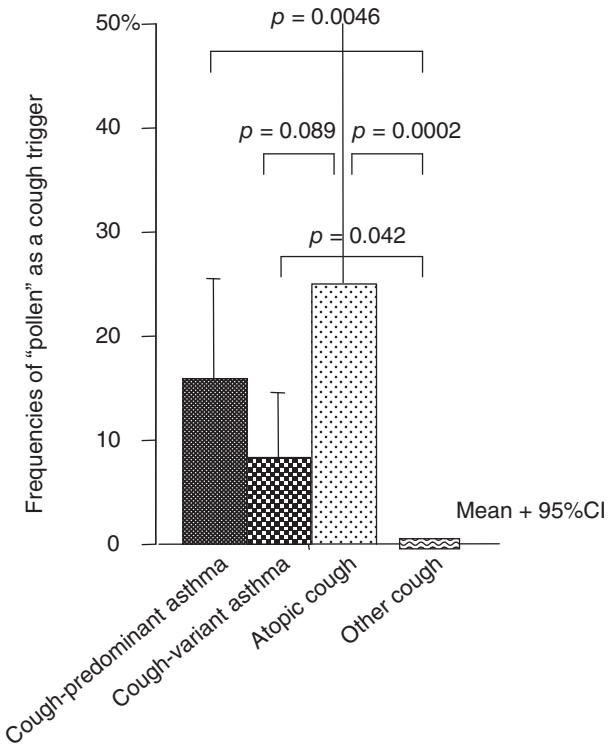

Fig. 1 Frequencies of patients who answered "pollen" as a cough trigger in cough-predominant asthma (n = 57), cough-variant asthma (83), atopic cough (7), and other cough group (47). p = 0.013 by Kruskal-Wallis test.

CAPSAICIN COUGH SENSITIVITY TEST

In 16 patients with cough-predominant asthma, 49 with CVA, and 25 with non-asthmatic coughers, cough sensitivity test in addition to methacholine inhalation test was done one to two weeks apart. Cough sensitivity was tested by a continuous inhalation method of capsaicin solution using the Astograph™ as described previously.[20] Ten doubling concentrations of capsaicin solution (0.61-312 μM) were inhaled until 5 or more coughs were induced (cough threshold, C5). C2 indicates a concentration of capsaicin solution when 2 or more coughs were first induced. Each concentration of capsaicin was inhaled for 15 seconds during tidal breathing every 60 seconds. Remaining patients were not examined for this test because informed consents for the test were not obtained mostly due to time constraint.

CLOSED QUESTIONNAIRE LISTING 18 TRIGGERS

We developed a closed questionnaire listing 18 triggers (Table 1). These were reported by ≥1% of 213 patients with chronic cough in a retrospective survey. In that survey, medical charts of the patients were thoroughly reviewed with respect to their cough triggers. Among these patients, "common cold" was reported by 45.7%, "cold air" by 22%, "talking" by 14.1%, "smoke/fragrance" by 10.3%, "fatigue/stress" by 5.2%, "spices" by 4.2%, "itchy throat" by 4.2%, "post-nasal drip (PND)" by 2.3%, "exercise" by 2.3%, "pollen/contact with pets" by 2.3%, and 7 other triggers by ≥1% each. The 213 patients who visited our asthma and chronic cough clinic included 126 patients with CVA (average age = 45.6 yr; 83 females) and 87 with non-asthmatic chronic cough (average age = 48.6 yr; 59 females).

In the current study, answers to the closed questionnaires were not taken into account during the diagnoses. In addition to the 18 triggers, patients were asked whether they had any other cough triggers and any specific seasons during which their cough worsened.

FOLLOW-UP STUDY

In addition to the cross-sectional study, we retrospectively examined medical charts of patients who were followed up at our hospital and who were maintained on standard medications as proposed by the Japanese Respiratory Society[11] six months after obtaining the questionnaire responses. Any associations of cough triggers with maintenance medication doses were investigated.

STATISTICAL ANALYSIS

Data were analyzed using StatView software 5.0 (SAS Institute Inc., Cary, NC, USA). Mann-Whitney test or χ^2 test were used for the 2-group comparison, and Kruskal-Wallis test was used for 3- or 4-group comparison tests followed by Mann-Whitney test with Bonferroni/Dunn's correction. To test the correlation of two parameters, Spearman's correlation test was used. To test for independent effects on the number of cough triggers, stepwise multivariate regression analysis was performed. For inclusion of variables into multivariate analysis, the F value, a measure of the extent to which a variable makes a unique contribution to the prediction of the dependent variable, was set at 4.0.

Factor analysis was used to determine the dimensions underlying the pattern of interrelationships between variables and to reduce a large number of variables to smaller sets of factors. We used principal components extraction with varimax rotation to categorize variables. These included the 12 most common triggers that were reported by ≥10% of patients, diagnosis of asthmatic cough, airway sensitivity, and exhaled NO levels. A response of "yes" was assigned a value of 1 and "no" was assigned a value of 0. Factor loadings were the correlation coefficients between variables and factors. Variables with factor loadings >0.4 were considered to represent the factor.

Results are expressed as means ± SDs. We considered p values of <0.05 to indicate statistical significance.

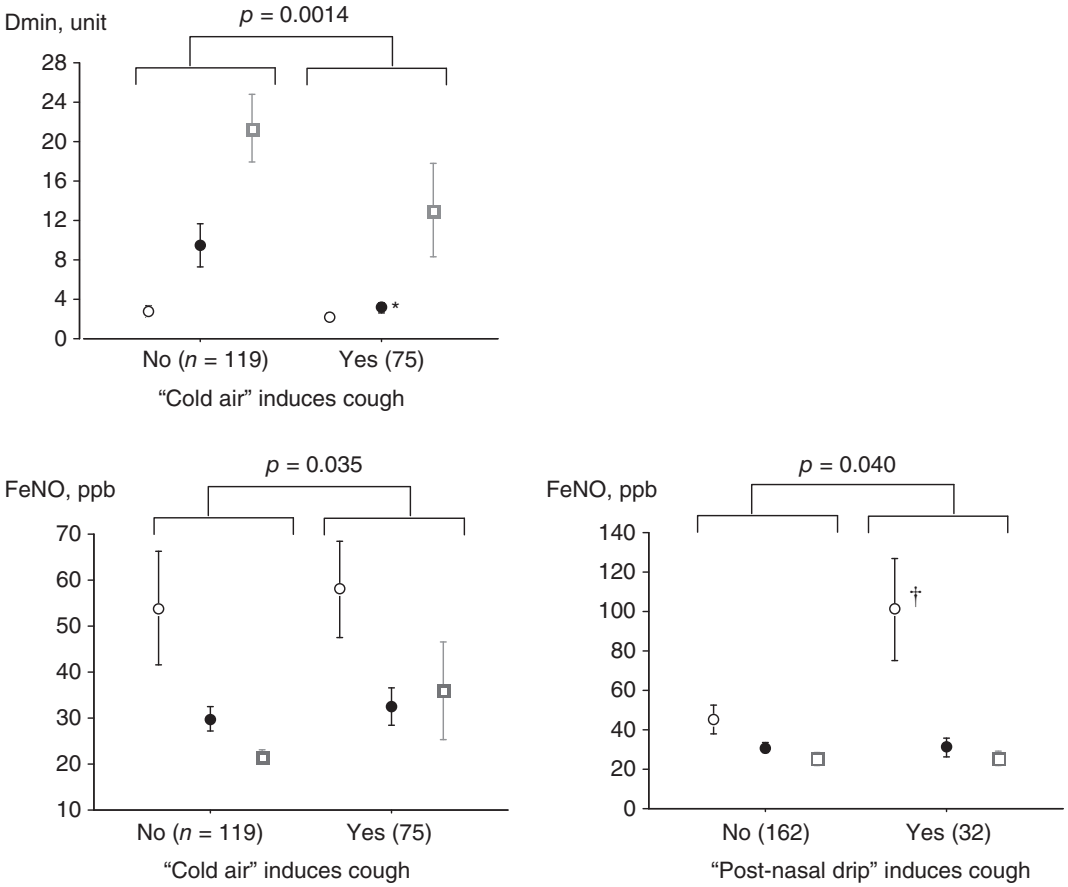

Fig. 2 Associations of "cold air" and "post-nasal drip" as cough triggers with airway hypersensitivity and exhaled nitric oxide levels. *p = 0.042 for patients with cough-variant asthma who marked "cold air" as a trigger vs. those who did not. †p = 0.020 for patients with cough-predominant asthma who marked "post-nasal drip" as a trigger vs. those who did not. ○ indicates mean ± SD values of pathophysiological findings for patients with cough-predominant asthma, ● for those with cough-variant asthma, □ for non-asthmatic coughers.

RESULTS

PATIENTS' CHARACTERISTICS

The characteristics of patients with cough-predominant asthma (n = 57), CVA (n = 83), and non-asthmatic coughers (n = 54) are shown in Table 2. Patients with probable CVA (n = 8) were categorized as CVA.

When compared with non-asthmatic coughers, asthmatic coughers were more frequently sensitized to dog dander (1.9 ± 13.6% vs. 11.4 ± 31.9%; p = 0.035) and mold (1.9 ± 13.6% vs. 10.7 ± 31.0%; p = 0.045).

COUGH TRIGGERS AND CAUSES OF COUGH

The frequencies of cough triggers for all the patients are listed in Table 3. The most common triggers (>20%) were "itchy throat," "cold air," "common cold," "dry air," "smoke/fragrance," "talking," and "changing position," in that order. Reports of "other" triggers included dust exposure, eye drops, singing, menstruation, vapor, and changes in air. Eleven patients answered that they had no specific triggers. There were no seasonal differences in the frequencies when answering "common cold," "cold air," or "pollen."

When the frequencies of triggers were compared between asthmatic coughers and non-asthmatic coughers, "cold air" and "fatigue/stress" induced cough more often in asthmatic coughers, particularly in those with cough-predominant asthma, than in non-asthmatic coughers (Table 3). The positive predictive values of "cold air" for differentiating asthmatic coughers and CVA patients from non-asthmatic coughers were 81.3% and 69.6%, respectively, and the negative predictive values were 33.6% and 56.0%, respectively. Addition of "fatigue/stress" to "cold air" did not increase these predicted values (data not shown). "Smoke/fragrance" was most frequently reported by patients with cough-predominant asthma among the 3 patient groups (Table 3). Marginally

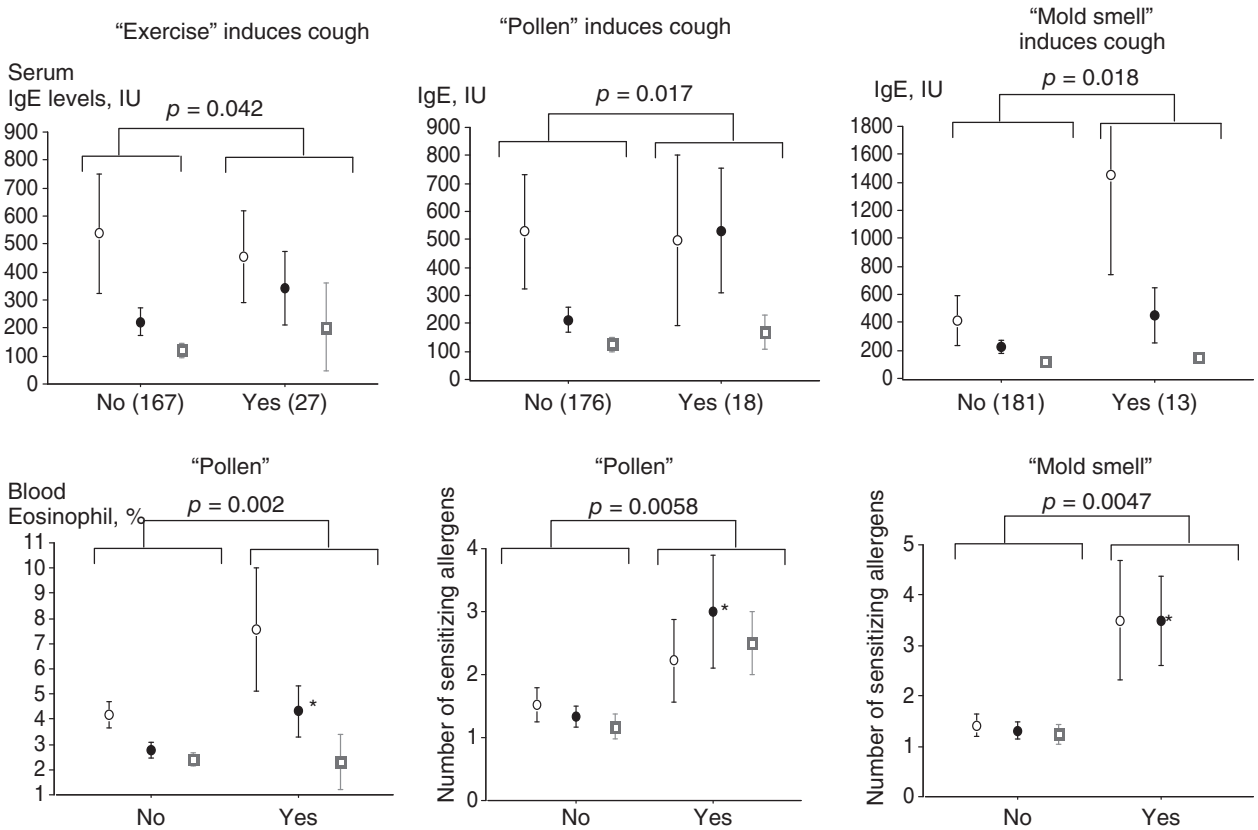

Fig. 3 Associations of "exercise," "pollen," and "mold smell" as cough triggers with serum IgE levels, blood eosinophil percentages, and number of sensitizing allergens. *$p < 0.05$ for patients with cough-variant asthma who marked these as cough triggers vs. those who did not.

more asthmatic coughers answered that their cough worsened in specific seasons than the non-asthmatic coughers ($p = 0.055$).

When patients were divided into GER coughers ($n = 19$) and others ($n = 175$), "spices" induced cough more often in GER coughers (26.3 ± 45.2% vs. 10.3 ± 30.5%; $p = 0.041$), as did "meals" (31.6 ± 47.8% vs. 9.1 ± 28.9%; $p = 0.004$). When patients were divided into 4 groups (cough-predominant asthma, CVA, atopic cough, and other cough), patients with atopic cough and those with cough-predominant asthma answered "pollen" as a cough trigger more frequently than other coughers (Fig. 1).

NUMBER OF TRIGGERS

The number of triggers for asthmatic coughers was greater than those for non-asthmatic coughers (Table 3). Females reported more triggers (3.7 ± 2.0) than males (2.9 ± 1.8; $p = 0.004$). The number of triggers was weakly associated with GER questionnaire scores (Rho = 0.23, $p = 0.002$ for QUEST; Rho = 0.16, $p = 0.023$ for FSSG). Stepwise multiple regression analysis showed that females and GER questionnaire scores were independently associated with a greater number of triggers (data not shown).

ASSOCIATIONS OF COUGH TRIGGERS WITH PATHOPHYSIOLOGICAL FINDINGS

We investigated possible associations of cough triggers with pathophysiological findings such as airway sensitivity (Dmin), exhaled NO levels, sputum eosinophil percentages, blood eosinophil percentages, serum IgE levels, number of sensitizing allergens, and capsaicin cough sensitivity (C2 and C5). Only the significant associations that were found are shown in Figure 2, 3. When these significant associations were sub-analyzed according to disease groups, i.e., cough-predominant asthma, CVA, and non-asthmatic cough, the decrease in Dmin in patients who marked "cold air" as a trigger was significant among patients with CVA, and an increase in exhaled NO in patients who marked "PND" as a trigger was significant among patients with cough-predominant asthma (Fig. 2). Patients who answered "pollen" or "mold smell" as triggers, were more frequently sensitized to cat dander, dog dander, grass pollen, cedar pollen, and weeds than those who did not mark these triggers. In particular, patients who marked "mold smell" were more frequently sensitized to mold than those who did not mark this trigger. In addition to the associations shown in the figures, patients who

answered "alcohol" as a trigger had higher sputum eosinophil percentages (n = 5, 39.5 ± 35.9%) than those without this trigger (n = 109, 6.3 ± 16.4%; p = 0.006). Cough sensitivity to capsaicin inhalation (C5) was weakly correlated with the scores of the QUEST questionnaire (Rho = -0.23; p = 0.037), but was not associated with any cough triggers or the number of triggers.

ASSOCIATIONS OF COUGH TRIGGERS WITH MAINTENANCE MEDICATION DOSES

Six months later, 99 patients were followed up at our hospital: 40 patients had cough-predominant asthma, 46 had CVA, and 13 were non-asthmatic coughers (including 5 with GER, 3 with atopic cough, 1 with SBS, and 4 with idiopathic cough). Among the 93 patients followed up at 6 months who had cough-predominant asthma, CVA, atopic cough, or idiopathic cough, 28 patients reported "smoke/fragrance" as a trigger and were maintained on higher doses of inhaled corticosteroids (ICS) as opposed to 65 patients did not report this trigger (539 ± 360 μg daily vs 333 ± 312 μg daily, p = 0.012).

FACTOR ANALYSIS

By factor analysis, "cold air," "fatigue/stress," asthmatic cough, airway hypersensitivity, elevated NO levels were categorized as an "asthmatic factor." "Itchy throat," "dry air," "spices," and "PND" were categorized as another "non-specific factor."

DISCUSSION

To the best of our knowledge, this is the first study that comprehensively investigated the associations of cough triggers with its cough pathophysiology. "Cold air" and "stress/fatigue" were associated with asthmatic cough. "Spices" and "meals," but not "itchy throat" or "talking," induced cough more often in GER coughers than in other coughers. "PND" as a cough trigger was associated with elevated exhaled NO levels, and this association was mainly exhibited by patients with cough-predominant asthma. "Pollen" and "mold smell" were associated with elevated serum IgE levels and a number of sensitizing allergens.

"Cold air" as a cough trigger was associated with airway hypersensitivity and elevated exhaled NO levels that are major pathophysiological features of asthma. These findings from univariate analysis were confirmed by factor analysis, and were consistent with our findings from a retrospective survey[9] and those of Hannaway *et al.*.[5] Cold air causes airway smooth muscle contraction directly[21] or *via* neural activation.[22] Constriction or deformation of the airways may induce cough by activating mechanosensitive receptors, such as rapidly adapting receptors.[23] Although it remains speculative, transient receptor potential (TRP) channels, such as a thermosensor of noxious cold sensation TRPA1[24] may also be involved in cold air-induced cough in asthmatic cough, because an agonist of TRPA1 provokes cough in healthy volunteers[25] and its threshold is lowered under inflammatory conditions.[26,27] A role for the thermosensor of cool sensation TRPM8[28] in the cough reflex has not been demonstrated,[26] though. Despite these associations with pathophysiological indices, "cold air" should be carefully interpreted as a trigger while differentiating CVA from non-asthmatic coughers because its positive (69.6%) and negative (56.0%) predictive values were not satisfactorily high.

"Stress/fatigue" was also associated with asthmatic cough. Psychological stress is a known factor that constricts airways *via* cholinergic pathways[29] and modulates immune system responses.[30,31] A persistent sense of tiredness or fatigue is frequently associated with psychological factors[32] and exacerbates asthma, possibly *via* pathways similar to psychological stress.[33] These proposed mechanisms may underlie "stress/fatigue-" triggered cough in patients with asthmatic cough.

"Smoke/fragrance" was most frequently reported by patients with cough-predominant asthma. In addition, in a follow-up study, maintenance doses of ICS for patients who had reported "smoke/fragrance" as a trigger were higher than doses for patients who did not report this trigger. Smoke,[27] scents,[34] and odors[27] are believed to activate TRPA1, as well as TRPV1 and other TRP channels. We speculate that the most frequent recording of "smoke/fragrance" by those with cough-predominant asthma may have been due to the presence of the most severe level of inflammation in this patient group, because TRPA1 in particular is activated by reactive oxygen species and nitrative stress.[27] Higher maintenance doses of ICS for patients who had reported "smoke/fragrance" trigger may support this speculation.

As expected, "spices" and "meals," which are risk factors for GER, were more frequent complaints of GER-coughers than of non GER-coughers, which is consistent with the findings of Everett *et al.*.[6] In previous reports that studied only GER-coughers, cough on phonation,[6] itchy throat,[3] and throat clearing[6] which had a moderate relationship with itchy throat in patients with laryngopharyngeal reflux disease,[35] were also common symptoms of GER-coughers. In contrast, the current study found that "itchy throat" and "talking" were not unique triggers for GER-coughers, but were common triggers in all coughers. We may have missed some patients with GER because we did not perform pH monitoring for the diagnosis of GER-cough in this study. Our findings, however, were based on a population that included non GER-coughers. Therefore, complaints of "itchy throat" or "talking" may not be simply associated with GER-cough.

The number of cough triggers was associated with asthmatic coughers, FSSG and QUEST scores, and

female gender. After multiple regression analysis, scores from GER questionnaires and females remained as independent factors associated with a greater number of cough triggers. Although the number of triggers was not correlated with cough hypersensitivity, it is noteworthy that the number of cough triggers may share some features with cough sensitivity because GER-coughers[36] and females[37] show cough hypersensitivity to tussive agents.

Until date, causal associations between prolonged or chronic cough and PND have not been clearly demonstrated. In this study, "PND" as a trigger of cough was associated with elevated exhaled NO levels. However, this association was mainly exhibited by patients with cough-predominant asthma, suggesting that when patients with cough-predominant asthma complain of "PND" as a trigger of cough, they may have severe lower airway eosinophilic inflammation. On the other hand, "PND" may not be necessarily accompanied with such inflammation in other coughers. Further studies are needed to clarify the mechanisms underlying PND-related cough, currently referred to as upper airway cough syndrome.[38]

"Pollen" and "mold smell" as triggers were associated with elevated serum IgE levels and a greater number of sensitizing allergens, but not with airway hypersensitivity. Most of the aeroallergens examined were associated with both "pollen-" and "mold smell-" triggered cough. In addition, sensitization to mold was only associated with "mold smell." These findings may suggest that IgE-related inflammation is one of the important mechanisms of prolonged or chronic cough. Indeed, "pollen" as a trigger was associated with the diagnosis of atopic cough.

Unexpectedly, cough sensitivity to capsaicin was not correlated with any cough triggers. Capsaicin inhalation activates TRPV1[27] and is a robust test to measure cough sensitivity. The lack of an association with cough sensitivity to capsaicin may imply the complexity of relationships between cough triggers and their receptors. Several common triggers, such as "dry air," "talking," or "changing position" were not associated with cough pathophysiology in this study. Dry air is a known stimulus that induces airway constriction, but responsiveness to dry air is weaker than that to cold air.[39] The weaker response to dry air may explain the lack of association of airway hypersensitivity with "dry air" in this study. Theoretically, mechanical stimuli could be involved in "talking-" or "changing position-" triggered cough. However, there is currently no clinically accessible indicator of mechanical stimuli and this remains speculative. Further research on non-specific cough triggers and cough pathophysiology is warranted.

One limitation of our study is the method used for questioning. Each trigger frequency that was obtained with a closed-end questionnaire in this study was greater than that in our retrospective survey. In the closed-end questionnaire, we did not rank triggers to assess the strength of patients' preferences. Ranking triggers might have added more relevant information. In addition, a questionnaire is a subjective and self-reporting measure. We may need challenge tests using the reported triggers to strengthen the current findings.

In conclusion, we identified several triggers associated with cough pathophysiology. Asking about cough triggers using a questionnaire may be clinically informative, particularly when specialized measurements are not accessible. With methodological progress in the measurements of airway pathophysiology, asking about cough triggers may provide additional insights for this research field.

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