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Original article

Diagnostic utility of fractional exhaled nitric oxide in prolonged and chronic cough according to atopic status

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Abbreviations:
AC, asthmatic cough; AUC, area under the curve; BMI, body mass index; CVA, Cough-variant asthma; CPA, cough-predominant asthma; FEF_{25-75}, forced expiratory flow between 25 and 75%; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; NAC, non-asthmatic cough

ABSTRACT

Background: Cough-variant asthma (CVA) and cough-predominant asthma (CPA) are the major causes of persistent cough in Japan. The utility of fractional exhaled nitric oxide (FeNO) measurement in the differential diagnosis of persistent cough has been reported, but the influence of atopic status, which is associated with higher FeNO levels, on the diagnostic utility of FeNO has been unknown.
Methods: We retrospectively analyzed 105 non-smoking patients with prolonged and chronic cough that were not treated with corticosteroids and anti-leukotrienes.
Results: CPA was diagnosed in 37 patients, CVA in 40, and non-asthmatic cough (NAC) in 28. FeNO levels were significantly higher in the CPA [35.8 (7.0–317.9) ppb] and CVA [24.9 (3.1–156.0) ppb] groups than in the NAC group [18.2 (6.9–49.0) ppb] ($p < 0.01$ by Kruskal–Wallis test). The optimal cut-off for distinguishing asthmatic cough (AC; CPA and CVA) from NAC was 29.2 ppb [area under the curve (AUC) 0.74, $p < 0.01$]. Ninety-one percent of subjects with FeNO levels ≥29.2 ppb had AC. Meanwhile, 40% of AC patients had FeNO levels <29.2 ppb. Stratified cut-off levels were 31.1 ppb (AUC 0.83) in atopic subjects vs. 19.9 ppb (AUC 0.65) in non-atopic subjects ($p = 0.03$ for AUC).
Conclusions: Although high FeNO levels suggested the existence of AC, lower FeNO levels had limited diagnostic significance. Atopic status affects the utility of FeNO levels in the differential diagnosis of prolonged and chronic cough.

Introduction

Cough is one of the most common symptoms for which patients seek medical attention.[1] Almost all guidelines have consistently classified cough into three categories according to its duration: acute cough lasting for less than 3 weeks, prolonged or subacute cough lasting for a period of 3–8 weeks, and chronic cough persisting for more than 8 weeks.[2,3] Generally, as cough duration becomes longer, the prevalence of non-infectious causes of cough becomes higher.[2] In Japan, the most prevalent causative diseases of isolated chronic cough have been reported to be cough-variant asthma (CVA), atopic cough, and sinobronchial syndrome, followed by gastroesophageal reflux disease (GERD).[4,5] A recent multicenter study involving isolated cough patients and also those coughed predominantly but complicated by wheeze/dyspnea revealed a high prevalence of CVA and cough-predominant asthma (CPA), accounting for more than 70% of both prolonged and chronic cough.[1]

Fractional exhaled nitric oxide (FeNO) measurement is considered a useful surrogate marker of Th2-driven airway inflammation.[6,7] FeNO levels correlate with sputum eosinophil count,[8] and higher FeNO levels have been reported in asthmatic patients

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compared with non-asthmatic subjects.[9,10] Since FeNO levels are affected by the presence of allergic rhinitis and smoking, Matsunaga *et al.* proposed four cut-off levels for FeNO, stratified by these two factors, to discriminate asthma from non-asthma.[11]

Atopy, which is common in CPA and CVA,[8,12] is also known as one of the factors that affect FeNO levels.[13,14] Although the utility of FeNO measurements in the differential diagnosis of prolonged or chronic cough has been reported,[12,15–18] no study has taken into account the atopic status, which may affect the results. In the present study, we investigated the utility of FeNO measurement in distinguishing asthmatic cough from non-asthmatic cough, in consideration of the atopic status.

Methods

Subjects

We retrospectively analyzed consecutive patients with prolonged and chronic cough lasting for more than 3 weeks. These patients were newly referred to our asthma and chronic cough clinic at Nagoya City University (Nagoya, Japan) and underwent FeNO measurements, from March 2013 to April 2015. Exclusion criteria were 1) prior treatment with inhaled corticosteroids or anti-leukotriene agents; 2) abnormal chest radiograph findings that may explain the cough; 3) fever, blood-stained sputum, or active respiratory infection; and 4) current smokers or former smokers of more than five pack-years or those who quited smoking within for less than 3 months preceding the study. Patients with shortness of breath or wheezing and those with multiple causes of cough were included, as in our previous study.[1] The study was approved by the ethics committee of Nagoya City University Hospital (44-12-0004).

Cough-predominant asthma (CPA) was diagnosed when patients had cough as the predominant symptoms while together with wheeze and/or dyspnea, and either positive airway hyperresponsiveness to methacholine[2] assessed by the continuous methacholine inhalation method (Astograph®; Chest, Tokyo, Japan),[19] or reversible airflow obstruction.[20,21] A diagnosis of CVA was based on an isolated cough, which was relieved by β_2-agonists, and positive airway hyperresponsiveness.[2] Patients with CPA and CVA were combined into the asthmatic cough (AC) group for further analysis.

A diagnosis of non-asthmatic cough (NAC) was made as follows. GERD-related cough was suspected by the presence of 1) classic reflux symptoms of heartburn, indigestion, chest discomfort, throat clearing, dysphonia, dysphagia, and belching and/or 2) typical characteristics of cough that is triggered by phonation, rising, lying, eating, and intake of certain food.[22] A diagnosis was confirmed when cough was relieved by proton pump inhibitors with or without gastrointestinal prokinetic agents.[22,23]

Post-infectious cough was diagnosed when cough was preceded by an acute respiratory tract infection that was not complicated by pneumonia and eventually resolved spontaneously.[2] Sinobronchial syndrome was diagnosed based on findings of chronic sinusitis on sinus imaging and improvement of cough and symptoms related to chronic sinusitis with macrolide antibiotics.[2,24] Atopic cough was diagnosed based on the presence of atopic status and response of coughing to histamine H1 receptor antagonist, but not to inhaled β_2-agonist.[2,25]

Overlapping cases of AC and various causes of non-asthmatic cough (NAC) were categorized as AC subgroups (CPA or CVA).

As previously described, the biological diagnosis of atopy was made by positive specific immunoglobulin E (IgE) against at least one prevalent allergen (>0.70 kU/l), regardless of the level of total IgE.[20] These allergens included house dust mite, mixed Japanese cedar pollen, graminea pollens, mixed weed pollen (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy), Trichophyton, mixed molds (*Candida*, *Penicillium*, *Alternaria*, *Aspergillus*, *Helminthosporium*, and *Cladosporium*), cat dander, and dog dander.[26]

Measurement of study variables

Spirometry was measured with Chestac-8900® (Chest; Tokyo, Japan), according to the American Thoracic Society/European Respiratory Society recommendation.[27]

FeNO measurement

FeNO was measured by Sievers NOA280i chemiluminescence analyzer (GE Analytical Instruments; Boulder, Colorado, USA) at a flow rate of 50 ml/s, according to ERS/ATS recommendations.[6]

Statistical analysis

Statistical analysis was performed with JMP10 Start Statics (SAS Institute Inc., Cary, North Carolina, USA). Normally distributed variables were described as mean (SD) and non-normally distributed variables were described as median (range). Comparison of three groups was made using Chi-square test, ANOVA followed by Tukey–Kramer test, or Kruskal–Wallis analysis followed by Steel–Dwass analysis, as appropriate. Comparison of two groups was made using Mann–Whitney U test. The cut-off value for distinguishing AC from NAC was determined by receiver operating characteristic (ROC) curve analysis. Comparison of area under the curve (AUC) of ROC between atopic subjects and non-atopic subjects was made by DeLong's test.

Univariate analysis was done to evaluate the patient characteristics that were significantly associated with higher FeNO levels; specifically, these factors were age, sex, body mass index (BMI), former smoking status (%), cough duration, diagnosis, atopy, blood eosinophil (/mm^3), total serum IgE (IU/ml), and % predicted forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC), and forced expiratory flow between 25 and 75% (FEF_{25-75}). Variables that had a p value of <0.10 in the univariate analysis were included in the multivariate logistic regression analysis to evaluate which one predict higher FeNO levels (more than the cut-off value calculated by the ROC curve analysis). Correlations between FeNO levels and blood eosinophil count and serum IgE levels were analyzed by Spearman's rank correlation test.

Results

A total of 105 patients were analyzed; final diagnosis was CPA in 37 (35.2%); CVA in 40 (38.1%); and NAC in 28 (26.7%), including 14 patients with GERD (Table 1). Comparison of the patient in the CPA, CVA, and NA groups is shown in Table 2. The CPA group had

Table 1
Etiology of prolonged and chronic cough in our study population (N = 105).

Diagnosis		Number (%)	
Asthmatic cough	Cough-predominant asthma[†]	37 (35%)	77 (73.3%)
	Cough-variant asthma[‡]	40 (38%)	
Non-asthmatic cough	Gastroesophageal reflux disease	14 (13%)	28 (26.7%)
	Sinobronchial syndrome	8 (8%)	
	Post-infectious cough	4 (4%)	
	Atopic cough	2 (2%)	

[†] 32 isolated, 4 with concomitant gastroesophageal reflux disease, 1 with concomitant sinobronchial syndrome.
[‡] 30 isolated, 10 with concomitant gastroesophageal reflux disease.