A History of Recurrent Episodes of Prolonged Cough as a Predictive Value for Determining Cough Variant Asthma in a Primary Care Setting

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ABSTRACT

Background   Many patients visit primary care clinics with a complaint of cough. General practitioners (GPs) developed a list of the causative diseases of cough that can produce a patient's symptoms and signs. Then, the patients' medical histories were evaluated to determine whether the diagnosis of cough variant asthma (CVA) or post-infectious cough (PIC) could have been predicted.

Methods   We retrospectively investigated 195 outpatients with a complaint of cough. Medical histories of "recurrent episodes of prolonged cough" and "upper respiratory infection" were obtained during the initial visit. The accuracy of medical histories in predicting CVA and PIC was calculated on the area under the curve (AUC).

Results   Among eligible patients with cough, PIC was diagnosed in 99 patients (50.8%), CVA in 40 patients (20.5%), upper airway cough syndrome in 28 patients (14.4%), and chronic obstructive pulmonary disease in 11 patients (5.6%). Among the patients with CVA and those with PIC, 93% and 12%, respectively, had a history of recurrent episodes of prolonged cough. For the diagnosis of CVA, having a history of recurrent episodes of prolonged cough showed a moderately accurate AUC (0.76, 95% CI: 0.71–0.82). On the other hand, for the diagnosis of PIC, having no history of recurrent episodes of prolonged cough also showed a moderately accurate AUC (0.87, 95% CI: 0.82–0.92).

Conclusion   The medical history of recurrent episodes of prolonged cough is useful for the prediction of CVA as well as PIC.

Key words   cough variant asthma; post-infectious cough; prolonged cough; recurrent episodes

A cough is the most common complaint when patients visit their primary care physician, accounting for around 8% of all consultations.[1, 2]

In most cases, it is difficult to diagnose the cause of the cough. The first step in making a differential diagnosis of the cough is to confirm the duration of the cough.[3–6] Generally, the classification of cough based on duration is as follows: acute cough, within 3 weeks of onset; sub-acute cough, from 3 to 8 weeks; and chronic cough, more than 8 weeks. This classification system is a useful tool for narrowing down the potential causes of cough.[3–6]

In adults, causes of acute cough include acute upper respiratory infection, acute rhinosinusitis, and allergic rhinitis.[7] Post-infectious cough (PIC), which is defined as a self-limiting cough that persists after viral or virus-like infections, is the most common etiology of subacute cough.[8, 9] Approximately 12%–48% of adult patients with subacute cough have PIC.[8, 10]

Chronic cough is caused by cough variant asthma (CVA), upper airway cough syndrome (UACS), and gastro-esophageal reflux disease (GERD).[11] In Japan, CVA is common among diseases that cause of subacute and chronic cough.[12] The only symptom of CVA is cough with no wheezing or dyspnea, which is defined as a subtype of asthma that manifests only as a cough. In CVA, respiratory function tests are almost normal; airway hyperreactivity is mildly increased; and bronchodilator (β2-agonist) is effective.[6, 13] In adults, CVA evolves into typical asthma in 30%–40% of cases, but the rate of transition to typical asthma is reduced by using inhaled steroids at the time of early diagnosis.[14, 15] Therefore, accurate diagnosis and early therapeutic intervention are important for improving treatment efficacy and the resolution of symptoms of cough.

General practitioners can generally diagnose patients accurately based on their pattern of symptoms, response to medications, and family history. There is recent evidence that clinicians can make an accurate diagnosis of the cause of cough for most patients by

using their medical history alone.[16] Tomita and colleagues reported that patients with a high probability of asthma were those with nocturnal cough/wheezing and/or recurrent episodes of cough/wheezing.[17] The medical history often provides important initial clues about patients with subacute or chronic cough. According to a diagnostic algorithm for the approach to adults with cough, all patients should be questioned about the use of angiotensin-converting enzyme (ACE) inhibitors and the presence of an upper respiratory tract infection at the onset of coughing.[18] The aim of this study was to investigate the utility of typical histories of "recurrent episodes of prolonged cough" and "upper respiratory infection" as diagnostic indicators of causes of cough in a primary care setting.

MATERIALS AND METHODS
Patient population
The subjects were 230 consecutive patients (aged 18–91 years) with a chief complaint of cough who were referred to our clinic as outpatients between January 2012 and December 2019. We first performed a plain chest X-ray test, blood test, spirometry, sputum eosinophilia, and chest and sinus computerized tomography as needed. Respiratory infections, such as pneumonia, tuberculosis, and nontuberculous mycobacteriosis, and other pulmonary diseases, including lung cancer, metastatic lung tumor, rheumatic lung, malignant lymphoma, and heart failure, were excluded from this study. Cases of bronchial asthma with wheezing were also excluded from this study.

Medical records of patients who met the inclusion criteria were investigated. These records included the medical history, smoking history, presence or absence of upper respiratory tract infection, atopic diseases, recurrent episodes of prolonged cough, total duration of cough, characteristics of cough and sputum, postnasal drip, heartburn, medication with an ACE inhibitor, previous visits to other clinics, and previous medical treatment. Regarding the history of prolonged cough, we asked questions such as, "Have you ever had a prolonged cough similar to this episode?"

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the Tottori Prefecture Medical Association Ethics Committee (accession number: 2020-01). Written informed consent was obtained from all subjects.

Definition of acute/subacute/chronic cough
Current cough was divided into subtypes. Acute cough was defined as cough lasting less than 3 weeks; subacute cough was defined as cough lasting between 3 and 8 weeks; and chronic cough was defined as cough lasting for more than 8 weeks.

Diagnosis of causative diseases
In our approach to diagnosing causative diseases, we followed the American College of Chest Physicians Guidelines for the management of cough.[19]

CVA was diagnosed in patients who experienced a cough without wheezing for more than 3 weeks but did not have wheezing on auscultation. A sputum eosinophil test, respiratory tract reversibility test, and fractional exhaled nitric oxide measurement, which was measured using NIOX VERO® (Aerocrine, Sweden) with a cutoff of 30 ppb,[20] were evaluated as additional diagnostic tools. Based on these examinations, patients with suspected CVA were treated with long-acting β2-agonist for 1–2 weeks and were observed for signs of improved cough. If improvement was observed, a treatment with an inhaled corticosteroid/long-acting β2-agonist (ICS/LABA) combination was started. Diagnosis of CVA was confirmed after the patient presented with a complete release of cough.

PIC was identified as a continuous cough after experiencing an upper respiratory tract infection, and a final diagnosis was performed if the administration of cough suppressants, histamine H1 antagonist, and/or Chinese herbal medicine[21] effectively improved cough at a follow-up of 1–2 weeks.

Upper airway cough syndrome (UACS) was defined as cough with nasal blockage or nasal discharge (anterior or posterior nasal drip) and either facial pain/pressure or reduction/loss of smell.[22]

Esophageal reflux disease was identified if there was heartburn and/or regurgitation at least one day per week for the past 3 months.[23]

Atopic cough was diagnosed following the diagnostic criteria for general clinical settings: (1) dry cough for at least 3 weeks without wheezing or dyspnea, (2) no response to bronchodilator therapy, (3) one or more findings suggesting an atopic predisposition or induced sputum eosinophilia, and (4) relief of cough with histamine H1 antagonists and/or steroids.[24] Atopy was also defined as a self-reported allergy to pollens, animals, or food.

To reach an accurate diagnosis in situations where an empirical treatment of PIC or UACS did not improve symptoms and CVA was strongly suspected, an inhaled corticosteroid (ICS) treatment was performed.

Only cases for which there was a total resolution of cough after a follow-up period of 3 months or more were examined in this study. We thoroughly inquired about the symptoms by phone or other means for cases

Table 1. Diagnosis classified by the duration of cough (*n* = 195)

Diagnosis	Total (*n* = 195)	Acute (*n* = 29)	Subacute (*n* = 114)	Chronic (*n* = 52)
	n (%)	*n* (%)	*n* (%)	*n* (%)
PIC	99 (50.8)	22 (75.9)	72 (63.2)	5 (9.6)
CVA	40 (20.5)	0 (0.0)	27 (23.7)	13 (25.0)
UACS	28 (14.4)	6 (20.7)	9 (7.9)	13 (25.0)
CB/COPD	11 (5.6)	1 (3.0)	2 (1.8)	8 (15.4)
AC	7 (3.6)	0 (0.0)	3 (2.6)	4 (7.7)
GERD	6 (3.1)	0 (0.0)	0 (0.0)	6 (11.5)
OSAS	2 (1.0)	0 (0.0)	0 (0.0)	2 (3.8)
ACE-induced	2 (1.0)	0 (0.0)	1 (0.9)	1 (1.9)

AC, Atopic cough; ACE, Angiotensin-converting enzyme inhibitor; CB/COPD, Chronic bronchitis/Chronic obstructive pulmonary disease; CVA, Cough variant asthma; GERD, Gastro-esophageal reflex disease; OSAS, Obstructive sleep apnea syndrome; PIC, Post-infectious cough; UACS, Upper airway cough syndrome.

that did not return to the clinic for a 3-month follow-up. After confirmation that the cough had resolved, the etiologic treatment was judged to be effective, so a final diagnosis was made.

Statistical analysis

One-way analysis of variance (ANOVA) was used to determine whether there were any statistically significant differences in the continuous data among groups. A post-hoc analysis was performed using Scheffé's test. Differences in categorical variables between clusters were statistically assessed using Fisher's exact test, and the Benjamini–Hockberg procedure was performed to correct for multiple comparisons.[25]

Next, the accuracy of medical histories in predicting PIC and CVA was calculated in terms of sensitivity and specificity. Positive likelihood hood ratios (LR+) and negative likelihood ratios (LR−) were the primary measures of diagnostic accuracy. An LR+ greater than 10 (an estimated shift in probability of at least 45%) is strong evidence to rule in a disease, whereas an LR+ between 5 and 10 is moderate (estimated shift of at least 30%) and between 2 and 5 is weak (estimated shift 15%).[26, 27] A plot of specific receiver operating characteristic (ROC) curves was used as a graphic presentation of the relationship between both sensitivity and specificity; it helped to decide the optimal model. An area under the curve (AUC) of more than 0.9 was defined as high accuracy, between 0.9 and 0.7 as moderate accuracy, and less than 0.7 as low accuracy.[28]

For all statistical tests, the significance level was set at 0.05. Analyses were conducted using R statistical software (version 3.5.2; R Foundation for Statistical Computing Vienna, Austria).

RESULTS

Among the 230 patients with cough who visited our clinic between January 2012 and December 2019, 16 presented with cases of organic diseases (8 cases of pneumonia, 2 of nontuberculous mycobacteriosis, 1 of lung cancer, 1 of metastatic lung tumor, 1 of sequela of pulmonary tuberculosis, 1 of rheumatic lung, 1 of malignant lymphoma, and 1 of heart failure); 2 presented with bronchial asthma; and 17 were undiagnosed cases, which were subsequently excluded from this study. Among these were 82 males and 113 females with an average age of 49.7 ± 18.2 years old; 21.5% were smokers. Cough was classified as acute in 29 patients, subacute in 114 and chronic in 55. The total duration of cough was 50.3 days on average (17.0 days for acute cough, 36.6 days for subacute cough, and 99.3 days for chronic cough). Out of the patients who complained of cough, 15% had a history of treatment at other medical institutions. Among those who had been treated at other medical institutions, no one was being treated with inhaled steroids at the time of their visit to our clinic.

The causes of cough in 195 outpatients are listed in Table 1. PIC was the most common etiology of cough in 50.8% of cases, followed by CVA in 20.5%, and UACS in 14.4%. When the distributions of duration were analyzed, PIC was the cause of acute cough in 75.9% of patients, subacute cough in 63.2%, and chronic cough in 9.6%. On the other hand, CVA was the second cause of subacute cough in 23.7% and chronic cough in 25.0% of cases. Table 2 provides details on differences in characteristics between PIC and CVA. Compared with CVA, patients with PIC had a more recent and shorter duration of cough, shorter treatment period, lower prevalence of having a history of recurrent episode of prolonged cough, higher prevalence of preceding upper respiratory

Table 2. Clinical characteristics of total patients (*n* = 195)

	PIC	CVA	Others	*P*-value
Number of patients	99	40	56	
Age, years	46.5 ± 17.6*	51.8 ± 17.5	53.8 ± 183	0.04
% Female	65.7%*	62.5%	41.1%	0.01
% Smoker	18.2%	15.0%*	32.1%	0.08
Duration of cough, days	32.5 ± 13.5**	50.8 ± 2 1.1**	81.9 ± 79.2	< 0.01***
Duration of cough before the visit, days	17.8 ± 10.0**	23.7 ± 17.3**	49.7 ± 71.6	< 0.01
Period of cough treatment, days	14.7 ± 9.0**	26.5 ± 12.5*	32.2 ± 21.1	< 0.01***
% Atopy	37.4%	87.5%**	44.6%	< 0.01***
% Recurrent episodes of prolonged cough	12.1%**	92.5%	85.7%	< 0.01***
% Upper respiratory infection	100.0%**	62.5%	64.3%	< 0.01***
% Previous treatment	16.8%**	11.4%**	22.0%	< 0.01***

CVA, cough variant asthma; PIC, post-infection cough. Others include AC, ACE induced cough, CB/COPD, GERD, OSAS and UACS. *P < 0.05 vs. others, **P < 0.01 vs. others, and ***P < 0.01 between PIC and CVA. Differences in numerical variables between groups were analyzed by using one-way analysis of variance (ANOVA) and Scheffe's post-hoc test. Differences in categorical variables between groups were statistically tested by using Fisher's exact test, and correction for multiple comparisons was performed using the Benjamini–Hochberg procedure.[25]

infection, and lower atopic predisposition. There was no significant difference between PIC and CVA in the duration of cough before the visit to our clinic.

As AUC is an effective way to summarize the overall diagnostic accuracy of the test, we analyzed AUC to predict PIC and CVA while using the medical history as a clue (Fig. 1). In patients with CVA, having a history of recurrent episode of prolonged cough showed 93% sensitivity and 60% specificity [AUC: 0.76, 95% CI (0.71–0.82)] (Fig. 1A). Additionally, the positive likelihood ratio was 2.3, and the negative likelihood ratio was 0.16. In patients with PIC, having no history of recurrent episode of prolonged cough showed an 86% sensitivity and 89% specificity [AUC: 0.87, 95% CI (0.82–0.92)] (Fig. 1B). The positive likelihood ratio was 7.8, and the negative likelihood ratio was 0.16. In patients with PIC, having a history of "upper respiratory infection" showed a 100% sensitivity and 37% specificity [AUC: 0.67, 95% CI (0.63–0.73)] (Fig. 1C). The positive likelihood ratio was 1.6. In patients with CVA, having no history of upper respiratory infection showed a 38% sensitivity and 86% specificity [AUC: 0.62, 95% CI (0.54–0.70)] (Fig. 1D). The positive likelihood ratio was 2.7, and the negative likelihood ratio was 0.72.

DISCUSSION

It is a common consensus in many previous studies that respiratory tract infection and PIC accounts for the highest proportion of acute cough cases[10, 29–31] and is a minor cause of chronic cough.[10, 12, 30, 32] In our study, PIC was the specified cause of acute cough and chronic cough, occurring with 75.8% and 8.0% prevalence, respectively, in patients with cough.

The prevalence of causes of subacute cough depends on the sample size and specialty of the institution.[8, 10, 12, 31] Multicenter studies have demonstrated that the prevalence of CVA (46.9%–58.3%) was higher than that of PIC (11.6%–12.2%).[10, 12] On the other hand, Kwon and colleagues demonstrated that the prevalence of CVA (15.8%) was lower than that of PIC (48.4%) in single center studies.[8] Our results, demonstrating a high prevalence of PIC in diseases causing subacute cough, were in concordance with Kwon's study. We speculated that the main reason for this might be that our enrolled patients had no history of treatment with inhaled steroids in other institutions, as this was a similar characteristic in Kwon's patients. In situations where an empirical treatment of PIC did not improve symptoms and CVA was strongly suspected, a steroid treatment was performed. This procedure allowed us to accurately diagnose PIC and CVA.

In primary care clinics, medical history is the most useful tool in clinical reasoning for the diagnosis of diseases. In this study, we showed the utility of some medical histories, such as "recurrent episodes of prolonged cough" and "upper respiratory infection" as a diagnostic approach to identifying the causes of a cough. In patients with asthma, Tomita and colleagues[17] demonstrated that recurrent episodes of symptoms of cough and/or wheezing is a useful indicator for predicting asthma, with an LR+ of 3.22 and LR− of 1.28. Our study revealed that the recurrent episodes of prolonged

(A) (B)

(C) (D)
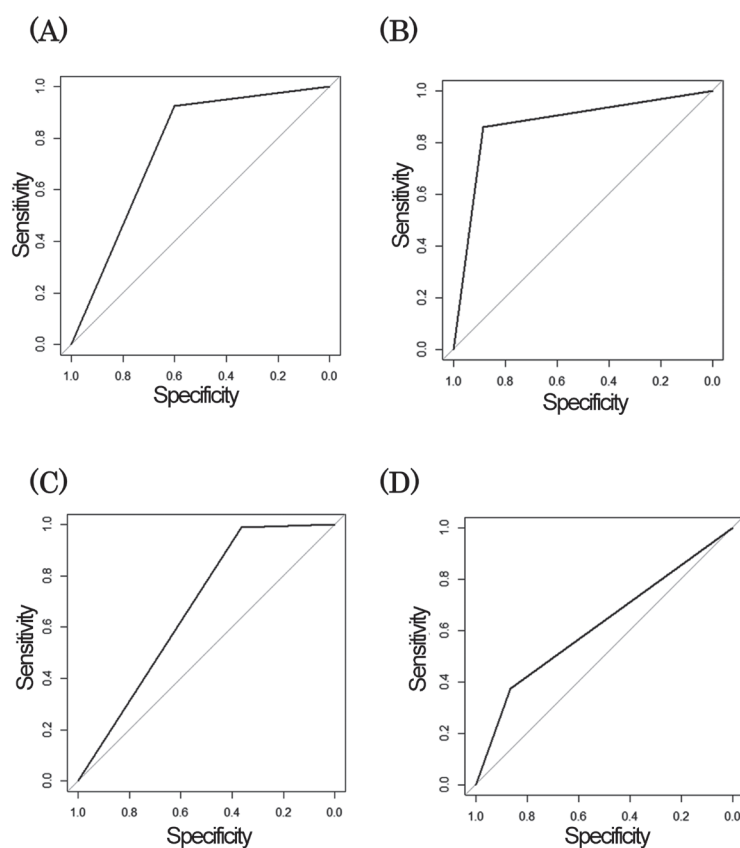
Fig. 1. The ROC curve for a diagnostic test of a patient with a medical history of (**A**) "recurrent episode of prolonged cough" and its discrimination between CVA and non-CVA; (**B**) "no recurrent episode of prolonged cough" and its discrimination between PIC and non-PIC; (**C**) "upper respiratory infection" and its discrimination between PIC and non-PIC; and (**D**) "no upper respiratory infection" and its discrimination between CVA and non-CVA.

cough noted in the medical history are useful in diagnosing the causative diseases of a cough. Patients with CVA were more likely to have a history of recurrent episodes of prolonged cough (LR+ of 2.3); this result supports Tomita's research. In addition, patients with PIC were more likely to have no history of recurrent episodes of prolonged cough (LR+ of 7.8), which is useful to distinguish PIC from non-PIC.

There are some limitations to this study. First, a relatively small number of patients with cough were examined at a single center. Although the sample size was small, the homogeneity of subjects was preserved, which eliminated any assumption bias. However, a larger study without selection bias is still needed. Another limitation is that we did not assess all potential causes of cough. Some studies reported that chronic cough may have overlapping diseases among asthma, UACS, and GERD, alone or in combination,[33] as well as overlapping etiologies, including smoking, asthma, and allergic rhinitis.[34] Since it was reported that eosinophilic airway inflammation is common in subacute cough

following acute upper respiratory tract infection,[35] there is a possibility of overlapping diagnoses with CVA or PIC.

In conclusion, 70% of causative diseases of cough were CVA or PIC in a primary care setting. Medical histories of "recurrent episodes of prolonged cough" and "upper respiratory infections" were useful clues for predicting CVA and PIC, respectively. However, approximately one-third of patients in primary care with symptoms that are compatible with asthma and normal lung function exhibit airway hyperresponsiveness to methacholine[36]; thus, the limitations of simple spirometry for the diagnosis of asthma must be considered. In the future, the timing of a hospital consultation for cough patients, who were resistant to treatments including ICS, should be studied.

The authors declare no conflict of interest.

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