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The Role of the Methacholine Inhalation Challenge in Adult Patients Presenting with Chronic Cough

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SUMMARY **One hundred and twenty two patients who were presenting with chronic persistent cough for more than 3-4 weeks were studied. Using anatomical and stepwise approach, we could identify the cause of chronic cough in 96% of the patients. The most common causes were due to postnasal drip syndrome (PND) (45%) and bronchial asthma (26%). We also demonstrated the important role of methacholine inhalation challenge in the diagnostic work up. The procedure could identify the patients who had bronchial hyperresponsiveness (BHR) in 52% of the cases. The severity degree of the BHR was classified into three levels. Mild or nonspecific BHR was defined as PC_{20} 16-25 mg/ml. This could be found in many diseases such as PND and bronchiectasis. Moderate degree of BHR (PC_{20} 8-16 mg/ml) was found in patients with PND and asthma. PC_{20} of less than 8 mg /ml was considered to be the most severe degree and it seemed to be specific for the diagnosis of asthma (positive predictive value 100%). Other conditions that caused chronic cough were drug-induced, especially angiotensin-converting enzyme inhibitors, gastroesophageal reflux disease (GERD), idiopathic pumonary fibrosis, subgottic cancer and idiopathic cough. These conditions may require invasive diagnostic work up, such as fiberoptic bronchoscopy and tissue biopsy. The treatment of chronic cough was according to the etiology. Thus, the patients presenting with chronic cough should be investigated to identify the cause, and it was not just only the administration of cough suppressant drugs in these patients.**

Cough is a complex physiological mechanism of the pulmonary defense that protects the lungs from injuries.[1] It is a normal reflex and it can also be a manifestation of pulmonary diseases.[2] Chronic persistent cough is a common medical problem. It is defined as a cough in a nonsmoker for at least 3-4 weeks without an obvious cause.[3] In the previous studies, Irwin and colleagues [4,5] proposed an approach to patients with chronic cough based on the anatomical location of the receptors and afferent pathways involved in the cough reflex. They found that the most common causes of chronic cough in adults were postnasal drip syndrome, mainly from chronic sinusitis, followed by bronchial asthma. Both diseases, either alone or in combination accounted for cough in 75% of the patients. Gastroesophageal reflux was the third most common cause. In Thailand, chronic cough is also common in medical practice. However, there was no such a study about this matter in this country. Thus, the purpose of our study was to evaluate the anatomical and stepwise approach to identify the causes and the management of chronic cough in Thai subjects. We also determined the value of methacholine inhalation challenge (MIC) in the evaluation of chronic cough.

MATERIALS AND METHODS

Subjects

All patients who were con-

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sulted to the Chest Unit, Chulalongkorn University, with a complaint of chronic cough were considered for study. Inclusion criterias were: (1) persistent cough was the only presenting symptom; (2) it had been presented for at least 3 weeks; (3) there was no prior history of chronic respiratory disease to account for the cough; and (4) chest roentgenogram did not contribute to the diagnosis. The followings were exclusion criteria: (1) immunocompromise; (2) cigarette use within 12 months; (3) pregnancy; (4) contraindication to bronchial challenge including FEV_1 less than 70% of predicted value.

Diagnostic work up and management protocol

Initial evaluation

The initial evaluation included a history taking and physical examination, stressed mainly on the duration, frequency, time preference and severity of cough, including postnasal drip symptoms, dyspnea, wheezing, and symptoms of gastroesophageal reflux.

Roentgenogram of the paranasal sinuses was done if there was clinical suspicion of sinusitis. Skin prick tests for common aeroallergens were performed if there was a history of allergic condition.

Then spirometry was performed. At least three satisfactory and two reproducible spirometric results were required before making an appointment to perform the MIC, usually within one week after initial evaluation. Mist tussis was given for the symptomatic treatment. The patients were also asked to refrain the drugs or food that may interfere to the test for at least 24 hours.

Methacholine inhalation challenge

MIC was performed at 9.00 am by using the procedure as previously described.[6] Briefly, stock solutions of methacholine in a buffer (pH 7.0) were prepared under sterile condition for each concentration; 0 (diluent), 0.5, 1, 5, 10, and 25 mg/ml. Six ml of the solution were filled in nebulizer (Provocation Test 1, Pari-Starnberg, Germany). It has been calculated that about 0.4 ml of the solution was used to produce a 10 liter reservoir bag of methacholine aerosol.

Before methacholine inhalation, baseline spirometry was performed with subjects standing using the Autospiror Discom-21 (Chest Corporation, Tokyo, Japan). At least three satisfactory and two reproducible spirometric maneuvers were required according to ATS recommendation.[7] The largest FEV_1 value from acceptable maneuver was used for the baseline FEV_1. Then each subject inhaled methacholine aerosol (each concentration-0, 0.5, 1, 5, 10, and 25 mg/ml, respectively) from the reservoir bag via slow inspiratory vital capacity maneuver until the bag was empty. Three minutes after inhalation of each concentration of methacholine, spirometry was repeated. The largest FEV_1 form an acceptable maneuver was selected for analysis. The test was terminated when post-inhalation FEV_1 decreased more than 20% of baseline. Then, PC_{20} (the concentration of methacholine that caused a decrease of FEV_1 more than 20% from baseline) was calculated by the extrapolation of the last two points on the dose-response curve. At the end of the test, the subjects who had a decline of FEV_1 more than 15% were given bronchodilator and spirometry was repeated 10 minutes later and they were discharged from the unit after their FEV_1 had returned to within 10% of their baseline values.

Steps of management and follow-up

Step 1

An antihistamine-decongestant preparation was prescribed to be taken twice daily as an empyric therapy for possible post nasal drip syndrome. If the cough improved after one week of therapy, the drug was continued until it resolved. If the cough did not improve, paranasal sinus X-ray was obtained, and in the cases of normal sinuses, topical nasal corticosteroids were prescribed.

Patients with sinus roentgenogram consistent with sinusitis were consulted to the ENT specialist for evaluation and they were treated with antibiotics, topical nasal decongestant for one week, also antihistamine-decongestant for as long as 4-6 weeks until they were cured.

Step 2

Patients who had PC_{20} of less than 2 mg/ml or patients who still had coughing after step 1 were administered oral bronchodilator and prednisolone 20-30 mg/day for one week. If their cough improved after the treatment, the patients were considered to have asthma. Then, they were treated with long-termed inhaled corticosteroids.

Step 3

Patients who continued to have persistent cough were evaluated for gastroesophageal reflux disease (GERD), and were treated with ranitidine and metoclopramide as well as an avoidance of caffeine, al-

cohol, chocolate and others that known to exacerbate GERD.

Step 4

Patients who had persistent coughing underwent fiberoptic bronchoscopy. If the bronchoscopic result was nondiagnostic, they were considered to have an idiopathic cause of chronic cough. Psychogenic cough was considered by exclusion and response to an anxiolytic drug.

Diagnostic criteria

Postnasal drip syndrome (PND) was considered when (1) patients described secretion drip into their throats need to frequently clear their throats, or (2) the examinations of oropharynx revealed mucoid or purulent secretion or a cobblestone appearance of the mucosa, and (3) having cough disappear with antihistamine-decongestant and/or topical corticosteroids.

Asthma was diagnosed when (1) patients experienced episodic shortness of breath and wheezing heard on examination, or (2) reversible airflow obstruction was demonstrated by spirometry (FEV_1 increased at least 15% from baseline after inhaled bronchodilator), or (3) MIC was positive at PC_{20} < 2 mg/ml and (4) having response to bronchodilator and corticosteroids treatment.

Gastroesophageal reflux (GER) was considered when (1) patients complained of heartburn and a sour taste, or (2) upper gastrointestinal contrast X-ray showed reflux of barium, and (3) having a response to antireflux therapy.

Angiotensin converting enzyme inhibitor (ACEI)- induced cough was considered when patients developed cough during taking ACEI and having cough disappear with discontinuation of the drug.

The diagnosis of other diseases were based on pathologic findings and/or cough resolution in response to the specific therapy.

Data analysis

Subjects were categorized as having BHR (positive test) if they showed more than 20% decrease in FEV_1 (PC_{20}) from baseline after inhalation of any concentration of methacholine up to and including 25 mg/ml (PC_{20}< 25mg/ml). The degree of responsiveness was classified to 3 categories:-

Cat. 1 PC_{20} < 8 mg/ml was considered to be severe BHR.

Cat. 2 PC_{20} > 8-16 mg/ml was considered to be moderate BHR

Cat. 3 PC_{20} > 16-25 mg/ml was considered to be mild BHR.

Data was analyzed by computer using program Exel 5.0. Results were presented as the mean ± standard deviation (SD). For comparison of the mean value, the *t*-test was used. A *p* value of less than 0.05 was considered statistical significant.

RESULTS

One hundred and thirty patients with chronic persistent cough consulted at the Chest Unit between 1993 to 1995. However, eight patients were excluded from the study because their spirometric performance was not acceptable. Two had an initial FEV_1 less than 70% of predicted and they were considered to have chronic bronchitis from previous smoking. One had severe headache during MIC performance, and he had a good response to antihistamine-decongestant. Finally, one patient refused to comply with the management protocol because she lived outside Bangkok.

Of 122 patients, there were 37 men and 85 women, 19 to 65 years of age with a mean of 36.7 ± 12.5 years. The mean duration of cough was 24.5 ±15.2 weeks (range 3 to 60 weeks). Most of the patients had been treated with antihistamine, cough-suppressant, bronchodilator and corticosteroids. Many had some improvement with these treatments, however, when they stopped the medication, the cough appeared again.

Table 1. Dermographic characteristics and lung function parameters of the patients with chronic cough.

	Group 1 (64) (MIC +ve)	Group 2 (58) (MIC -ve)	P-value
1. Age (yr)	38.1 ± 11.5	35.2 ± 12.2	NS
2. Sex (M:F)	1:2	1:2.5	NS
3. Height (cm)	165.7 ± 14.3	164.5 ± 12.1	NS
4. Duration (wk)	23.2 ± 16.1	25.5 ± 13.5	NS
5. FVC (l)	3.37 ± 0.7	3.31 ± 0.6	NS
6. FEV_1 (l)	2.95 ± 0.4	2.89 ± 0.4	NS
7. %FEV_1/FVC	85 ± 8.2	84.2 ± 4.6	NS
8. Mean PC_{20}	11.2	>25	<0.05

Table 2. Severity level of bronchial responsiveness and the causes of cough.

1. Mild nonspecific BHR (PC_{20} >16-25 mg/ml) :	13	cases
- Postnasal drip syndrome (PND)	9	
- Asthma	1	
- ACEI-induced cough	1	
- Bronchiectasis	1	
- Gastroesophageal reflux (GER)	1	
2. Moderate BHR (possible asthma; PC_{20} 8-16) :	27	cases
- PND and asthma	12	
- Asthma	12	
- PND	2	
- ACEI-induced	1	
3. Severe BHR (asthmatic range; PC_{20} < 8) :	24	cases
- Asthma	19	
- PND and asthma	4	
- PND and asthma and GERD	1	

Table 3. The causes of chronic cough (122 cases).

Cause	Cases	Percent
Postnasal drip syndrome (PND)	56	45
Asthma	32	26
PND and asthma	16	13
ACEI-induced	5	4
Bronchiectasis	4	3
Gastroesophageal reflux (GER)	2	1.6
Idiopathic pulmonary fibrosis	1	0.8
Subglottic cancer	1	0.8
PND+asthma+GERD	1	0.8
Idiopathic cough	4	3

The subjects were divided into 2 groups on the basis of MIC response. There was no significant difference in cinical data and spirometric parameters between the two groups except for the PC_{20} (Table1). The results of MIC were positive in 64 patients (52%). Classification of the severity of airway responsiveness to methacholine is shown in Table 2. Non-specific BHR was found in 13 cases: PND (9), asthma (1), bronchiectasis (1), ACEI-induced (1), and GERD (1 case). A severe degree of BHR was found in 24 cases and all were asthma (asthma alone 19, asthma in combination with PND 4, and asthma in combination with PND and GERD 1 case).

We could identify the definite cause of chronic cough in 118 (96%) cases. The most common causes were PND (45%), asthma (26%), and the combination of both diseases (13%). If the ACEI-induced cough was excluded, bronchiectasis was the next most common. The diagnosis of bronchiectasis was made by fiberoptic bronchoscopy and bronchography. Two patients were considered to have GERD which was diagnosed from the response of the anti-reflux therapy. Each case of idiopathic pulmonary fibrosis (IPF) and subglottic cancer was diagnosed by transbronchoscopic tissue biopsy. Four patients were considered to have idiopathic cough because their cough did not resolved in spite of their being managed with aggressive treatment.

DISCUSSION

Our results demonstrated that we could make a definite diagnosis of patients who presenting with chronic cough in 118 (96%) of 122 cases. The cough was most commonly due to a single cause. The most common causes were postnasal drip syndrome (45%), bronchial asthma (26%), and both of them (13%). These findings were consistent with previous reports in the literature.[4,5,8,9] As in the first report of Irwin and his colleagues[4] in 1981, the cause of cough could be diagnosed and treated with the specific therapy with a sucess rate of 97%. The most common causes of cough in their study were PND, asthma, chronic bronchitis and GERD.

We also demonstrated that MIC was useful in the investigation of the patients. It could help to the

diagnosis of cough variant asthma. Concerning the cut-off point that indicated a positive test for the MIC, it varied among the reports. Irwin defined a positive response as a decrease in FEV_1 from baseline of 20% or more after the inhalation of 195 or less cummulative dose unit of methacholine according to the standard procedure of Chai *et al.*[10] Pratter [9] used a modified method of Hargreave *et al.*[11] and BHR was defined as a 20% decrease in the FEV_1 (PC_{20}) at a methacholine concentration of 8 mg/ml or more. Galvez *et al.*[12] used the standard method of Chai *et al.* and $PC_{20} < 25$ mg/ml was considered to be positive. Others also used $PC_{20} < 25$ mg/ml as a cut-off point.[13,14] Our study used this point to indicate the positive BHR test and we also classified the degree of severity of BHR into 3 levels; mild, moderate and severe.

If the $PC_{20} < 8$ mg/ml was used as a cut-off point in the diagnosis of cough variant asthma, the positive predictive value was 100% but the negative predictive value was only 74%. If we used $PC_{20} < 16$ mg/ml, the positive predictive value was 94% and the negative predictive value was 99%. And, if the point of $PC_{20} < 25$ mg/ml was used to diagnosed asthma, it would be too sensitive but not specific. Pratter *et al.*[9] used $PC_{20} < 8$ mg/ml and they found that the positive predictive value was only 74% and negative predictive value was 100%. However, some patients in their report who were better with the PND treatment had $PC_{20} < 8$ mg/ml. These patients may also have asthma in combination with PND.

Multiple logistic regression was done to identify covariates that predicted the need for antiasthma therapy for cough resolution. Only nocturnal cough and previous wheezing were found to have significant association, with odds ratios of 3.7 and 3.3, respectively. These findings were consistent with the fact that asthmatic patients usually had cough during the night and some may have only nocturnal attacks which labelled them as nocturnal asthma.

Though the association between cough and asthma has been known for long time, it was not understandable until Mc Fadden[15] reported that cough may be the only presenting symptom of asthma. Some asthmatic patient would present with cough and normal spirometry, but they had obstruction on the provocation test.[16] They were labelled as cough-variant asthma.[17] Burrow *et al.*[18] demonstrated that many elderly subjects had chronic cough for many years before the diagnosis of asthma was made.

PND syndrome was the most common cause of chronic cough. It had been postulated that cough from PND was due to draining secretions that stimulate cough receptors in posterior pharynx and larynx. Irwin *et al.*[19] found the evidence of upper airway obstruction shown by flow-volume loop in these patients and it improved after treatment. PND could be caused by postviral, allergic, and nonallergic chronic rhinosinusitis. The patients usually had the sensation of nasal discharge back into their throat and frequent throat clearing. The typical pattern of cobble-stone appearance or presence of the secretion on the mucosa of posterior pharyngeal wall were uncommon. It was found that 40% of these patients also had mild or moderate degree of BHR.

Chronic cough has been found as a side effect of ACEI therapy. We found five patients who had cough associated with ACEI. Two cases had mild BHR. This has been reported in the previous study.[20]

Bronchiectasis, especially dry type, was common in Thai subjects. It may be the sequele pathology after the treatment of pulmonary tuberculosis. The patients usually had dry cough, except during acute bacterial infection. The diagnosis of bronchiectasis was confirmed by bronchography. However, in the present time, it may be diagnosed by the resolution CT scan.

We found three cases with GERD who presented with chronic cough. GERD was not common in Thai subjects, whereas Irwin *et al.*[5] found that GERD was the third most common cause. It may be due to the cultural difference in food habits between Western and Asian countries such as high fat diet in the Western and high carbohydrate diet in Thailand. The mechanism of GERD-induced cough may be due to the repeated aspiration and the impaired clearance of reflux acid.[21]

Idiopathic pulmonary fibrosis was the cause of cough in one patient. Firstly, the patient was considered to have asthma because his chest reontgenogram was normal and the cough improved with the corticosteroids therapy. Six months later, he developed breathlessness and the chest X-ray revealed interstitial infiltrations. Then the diagnosis was made by transbronchial lung biopsy.

One patient with subglottic cancer was misdiagnosed for six months. The first time of bronchoscopic finding was negative. Later,

he had blood streak sputum and the cancer was found at the second time of bronchoscopy. Fiberoptic bronchoscopy still had an important role in the evaluation of the patients with refractory cough.[22]

The treatment of cough was done according to the etiology. However, some patients still had cough in spite of aggressive management, even with a cough suppressant such as codeine preparation. In the case of unknown intractable cough nebulized lidocaine may palliate the symptom.[23]

In conclusion, we reported 122 pationts with chronic cough. By using the anatomical and stepwise approach, we could identify the cause of cough in 96% of the patients. The most common causes were postnasal drip syndrome and asthma. We also demonstrated the usefulness of methacholine inhalation challenge in the diagnostic work-up and also described the severity degree of BHR into three groups according to the range of PC_{20} which may be helpful in the diagnosis of cough variant asthma.

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