

## Chronic cough: clinical characteristics and etiologies of 510 cases

Guiyuan JIANG\*, Xinying HUANG, Tianlin LI, Dongping XU  
Respiratory Department, Xiamen Chang Gung Hospital, Xiamen, P.R. China

Received: 27.08.2015 • Accepted/Published Online: 09.03.2016 • Final Version: 20.12.2016

**Background/aim:** To investigate the clinical features and underlying etiologies of chronic cough (CC).

**Materials and methods:** Five hundred and ten CC patients were enrolled. The phases, characteristics and associated clinical manifestations of CC among the gastroesophageal reflux cough (GERC), cough-variant asthma (CVA), and upper airway cough syndrome (UACS) groups were compared, and the diagnostic values of each group were evaluated by multiple regression analysis.

**Results:** In the 510 patients, 404 had CC with single etiology—GERC (n = 175), CVA (n = 134), and UACS (n = 95). The characteristic features of GERC included gastric acid backflow symptoms such as sour-tasting regurgitation, heartburn, endoscopic esophagitis, poststimulation cough, frequent throat clearing, daytime mono-cough, and feelings of heaviness and pain in the chest. Patients with CVA typically exhibited sensitivity to smog and other irritants; the cough occurred mostly at night, and was associated with positive bronchodilator and provocation test results. The typical features of UACS included a history and/or symptoms of rhinitis, retropharyngeal postnasal drip, and wet cough occurring mostly during the daytime. The diagnostic specificities of above factors were >70%.

**Conclusion:** The most common causes of CC include GERC, CVA, and UACS, and their diagnosis is based on the characteristics of the underlying disease.

**Key words:** Chronic cough, single cause, symptomatic characteristic, diagnosis

### 1. Introduction

Cough is among the most common complaints for which individuals worldwide seek medical attention (1). As many as 40% of the patients treated in cough clinics present with unexplained chronic cough (uCC). Patients with uCC show increased rates of decline of the forced expiratory volume (FEV) (1), and a significant minority of the patients develop fixed airflow obstruction (2). Clinically, uCC is defined as the condition in which cough, persistent for more than 8 weeks, is the only or main clinical sign, and chest radiography reveals no obvious abnormalities (3). The manner of assessment of cough has undergone radical changes in the last decade, and hypersensitivity is no longer the only reason for chronic cough (CC) (4). There is sparse evidence to indicate that appropriate strategies have been employed hitherto for the diagnosis and management of CC in adults (5). Moreover, a meta-analytical study revealed that opioids and dextromethorphan are often chosen for symptom control (6). Therefore, accurate diagnosis of CC is of great importance.

In children with uCC, asymptomatic acid and nonacid gastroesophageal reflux (GER) is a potential etiology (7). Cough-variant asthma (CVA) or nonasthmatic

eosinophilic bronchitis (EB) (8) are other possible etiologies; iron and vitamin B-12 deficiencies are rare causes of CC (9,10).

The present study investigated the etiologies and associated symptoms of uCC in 510 patients, with the aim of identifying the clinical features associated with the diagnosis of CC.

### 2. Materials and methods

#### 2.1. Clinical data and patient grouping

This study included 510 patients with CC who visited the Respiratory Medicine Department of our hospital between August 2012 and August 2014; the inclusion criteria were 1) main symptom of cough, persistent for longer than 8 weeks, and no obvious lesions on the chest radiographs or computed tomography (CT) images; 2) age greater than 18 years with no smoking habits; 3) no history of respiratory infections in the 8 weeks before infection or on-going cough 8 weeks after respiratory infection; 4) no history of treatment with angiotensin converting enzyme inhibitors (ACEI); and 5) willingness to complete the etiological examination and cooperate with treatment and follow-up.

\* Correspondence: gyxycn@126.com

Each of the patients underwent the following procedures for the investigation of the cause of cough: 1) recording of medical history including symptoms and history of ear, nose, throat, respiratory tract, and digestive tract problems; 2) detailed physical examination with the targeted evaluation of throat congestion, follicular hyperplasia, and retropharyngeal postnasal drip; and 3) chest X-ray examination, bronchodilator test, methacholine-challenge test, CT imaging of the sinuses, or endoscopy in patients with suspicious symptoms or signs. A total of 404 patients were diagnosed with CC with single etiology including GER cough (GERC,  $n = 175$ ), CVA ( $n = 134$ ), and upper airway cough syndrome (UACS;  $n = 95$ ). The remaining 106 cases of CC included 4 cases caused by CVA, GERC, and UACS; 20 by GERC and UACS; 18 by CVA and UACS; 11 by CVA and GERC; and 53 of unclear etiology.

## 2.2. Research methods

The causes, duration, characteristics, phases, and associated symptoms and signs of cough were recorded for each patient (Table 1). We assessed the relationships between the symptoms and laboratory results of the specificities, sensitivities, and positive and negative predictive values of each of the three groups.

## 2.3. Statistical analysis

SPSS 16.0 was used to calculate the incidence rates of the clinical characteristics and associated symptoms of each group as well as the sensitivities, specificities, and positive and negative predictive values of the variables associated with the symptoms and diagnoses. The percentage of distribution of causes was expressed by the percentage of ascertained causes to the total number of causes. The chi-square ( $X^2$ ) test was used to evaluate the variables.

## 3. Results

### 3.1. General information

The 510 study subjects included 286 male (56.1%) and 224 female (43.9%) patients, with an average age of  $36.45 \pm 13$  years (15–68 years of age). The patients reported CC durations of 2–360 months (median duration, 11 months). The 404 patients with single-etiology CC were divided into three groups based on the etiology (GERC, CVA, and UACS). There were no statistically significant differences between the groups in terms of age, sex, or duration of cough (Table 1).

### 3.2. Clinical features

The clinical signs of the patients in the GERD group included cough after talking or eating, daytime mono-cough, frequent throat clearing, hoarseness after talking, sour-tasting regurgitation, heartburn, and a feeling of heaviness in the chest. The patients in the CVA group presented with nighttime cough as the most characteristic feature. The patients in the UACS group reported history and associated symptoms of rhinitis, including nasal congestion, runny nose, and postnasal drip. The patients in the UACS group typically exhibited wet daytime cough (Table 2).

### 3.3. Diagnostic values of clinical signs

Multivariate regression analysis revealed that hoarseness after talking, cough associated with eating, chest pain, mono-cough, sour-tasting regurgitation, and heartburn were the main clinical signs of GERC; cough after talking, chest pain, and daytime cough were the dominant factors. The patients with CAV presented with frequent nocturnal coughing and rarely coughed during the daytime. The specificities of a history of rhinitis, nasal congestion, and runny nose with postnasal drip in diagnosing UACS were 70.6%, 72.5%, and 89.6%, respectively (Table 3).

## 4. Discussion

Cough is among the most common complaints for which patients worldwide seek medical attention (11) and the quality of life of the affected patients is significantly impaired (12). The evaluation and treatment of cough entails tremendous financial expenditures and consumption of health care resources (13). The etiologies of uCC in patients with normal chest radiographic findings are complex. Over 70% of the CC cases reported by Chinese and foreign researchers are caused by CVA, UACS, EB, GERD, and other underlying causes. Although GERC accounts for 21%–41% of CC cases in Western countries, early studies reported it to be a very rare cause of CC in Japan (0.5%) (14). In adults, asthma, GERD, and postnasal drip have been reported to cause 72%–90% of CC cases (15); however, currently, UACS and CVA are also considered to be among the common causes of CC (16). In China, the percentage distribution of the CC etiologies varies from that in foreign countries, possibly since

**Table 1.** General conditions of each group.

Group	Age ( $\bar{x} \pm s$ , year)	Male (n, %)	Duration ( $\bar{x} \pm s$ , min)
GERD (n = 175)	$36 \pm 15$	98 (56.0)	$63 (2 \pm 360)$
CVA (n = 134)	$34 \pm 14$	67 (50.0)	$24 (2 \pm 48)$
UACS (n = 95)	$36 \pm 12$	55 (57.9)	$16 (2 \pm 120)$

**Table 2.** Incidence rates of clinical features of different causes.

History, symptoms and signs		GERD (n = 175)	CVA (n = 134)	UACS (n = 95)
Previous history	Chronic rhinitis or sinusitis	47 (26.8%)	44 (32.8%)	72 (75.8%)
	Chronic stomach disease or stomach discomfort	55 (31.4%)	25 (18.7%)	24 (25.3%)
Characteristic	Dry cough	159 (90.8%)	116 (86.6%)	69 (72.6%)
	Wet cough	16 (9.1%)	18 (13.4%)	22 (23.3%)
Talking-related cough	Cough after talking	40 (22.9%)	3 (2.2%)	4 (4.2%)
Eating-related cough	Cough after eating	58 (33.1%)	8 (6.0%)	8 (8.4%)
Frequent throat clearing	Frequent throat clearing cough	59 (33.7%)	5 (3.7%)	16 (16.8%)
Associated symptoms	Hoarseness after talking	21 (12%)	0 (0%)	3 (3.2%)
Continuity	Single cough	85 (48.6%)	34 (25.3%)	28 (29.5%)
	Paroxysmal coughs	90 (51.4%)	100 (74.6%)	67 (70.5%)
Cough characteristic	Irritated cough	108 (61.7%)	68 (50.8%)	30 (31.6%)
	Nonirritated cough	67 (38.3%)	66 (49.2%)	65 (68.4%)
Time characteristic of cough	Daytime cough	128 (73.1%)	49 (36.7%)	81 (85.3%)
	Nighttime cough	16 (9.1%)	55 (41%)	3 (3.2%)
	Both daytime and nighttime cough	31 (17.8%)	30 (22.4%)	10 (10.5%)
Provocative factors	Pungent odor such as smog	56 (32%)	94 (70.2%)	54 (56.8%)
	Cold air	76 (43.4%)	63 (47%)	35 (36.8%)
Associated symptoms	Feeling of foreign mass in pharyngeal portion	98 (56%)	21 (15.7%)	37 (38.9%)
	Itchy throat	86 (49.1%)	36 (26.9%)	44 (46.3%)
	Nasal congestion and (or) discharge	37 (21.1%)	48 (35.8%)	67 (70.5%)
	Feeling of postnasal drip	16 (9.1%)	16 (12%)	50 (53%)
	Sour regurgitation	64 (36.7%)	5 (3.7%)	3 (3.2%)
	Heartburn	44 (25.1%)	2 (1.5%)	1 (1.1%)
	Chest distress	47 (26.9%)	31 (23.1%)	8 (8.4%)
	Chest pain	23 (13.1%)	2 (1.5%)	3 (3.2%)
Physical examination	Retropharyngeal postnasal drip	0 (0%)	0 (0%)	19 (20%)
Other laboratory tests	Positive in bronchodilator test	0/175	51/134	0/95
	Positive bronchial provocation test	0/175	134/134	0/95
	Sinusitis shown in sinus CT	0/96	0/0	86/95
	Esophagitis shown in endoscopy	82/175	0/0	0/0
	Esophagitis not shown in gastroscopy	93/175	0/0	0/0

misdiagnosis and mistreatment of cough are common in China. The common causes of CC are UACS (previously called PNDS), CVA, GERD, and EB; the most common cause of CC in China is CVA, which accounts for 33% of the CC cases, followed by UACS, EB, and atopic cough (AC) (17,18); EB is also a common cause, accounting for 13.2%–24% of CC cases (19). However, GERD is not as common in China as it is in Western countries. Differences in the inclusion criteria (foreign studies excluded patients with upper respiratory tract infections within 8 weeks of treatment as well as those who had received treatment with ACEI), case selection, regions, ethnicity, diet, and sample

sizes might account for the discrepancies in the etiology distributions between Chinese and foreign studies. All the patients included in our study had previously been treated in other clinics or hospitals, and 80% of the 456 patients with CC had been misdiagnosed as having chronic bronchitis or chronic laryngitis, possibly because an irritable larynx is common in patients with CC (20). Another reason might be the limited knowledge of the basic-level medical staff, who often treat CC in the same manner as chronic bronchitis or chronic laryngitis. The misdiagnosis of GER-related cough was also common in tertiary hospitals. Together with the UACS (formerly

**Table 3.** Diagnostic values of clinical features of different causes.

Causes	Clinical features	Sensitivity	Specificity	Positive predictive value	Negative predictive value
GERC	Cough after talking	22.9	97	85.1	62.2
	Hoarseness after talking	12	98.7	87.5	59.5
	Eating-related cough	33.1	93	78.4	64.5
	Oppression in chest	26.9	83	54.7	59.7
	Chest pain	13.1	97.8	82.1	59.6
	Mono-cough	48.6	73.0	57.8	65.0
	Sour regurgitation	36.7	96.5	88.9	66.7
	Heartburn	25.1	96.7	93.6	63.3
CVA	Mainly nighttime cough	41.0	93	74.3	76.1
	Mainly daytime cough	36.7	23.3	19.0	42.6
UACS	History of rhinitis	75.8	70.6	44.2	90.5
	Rhinitis symptoms	70.5	72.5	44.1	88.9
	Postnasal drip	53	89.6	61.0	86.0
	Wet cough	23.3	89.0	39.3	79.0

PNDS) and eosinophilic airway inflammation (asthma and nonasthmatic EB), GERD is generally considered among the most common etiologies of CC (21). Chinese experts have found that inflammation in nonasthmatic EB has some similarities with that in CVA, and recent evidence has also suggested a mechanistic link between airway neurogenic inflammation and GERC (22). In the present study, there might have been discrepancies in the identification of the CC etiologies because nonspecialized and even specialized physicians in tertiary hospitals lack the knowledge to recognize GERD-related respiratory manifestations. Physicians at all levels should improve their knowledge within different disciplines in order to improve the accuracy of diagnosis of patients with GER-related respiratory symptoms. The results of this study revealed that CC caused by GERC occurred more frequently than CC due to other causes. There were some differences in the distribution of the etiologies compared to those reported in studies in China and abroad. Possible explanations for these discrepancies include the following: 1) Our city is newly developed and has a large population of immigrants from other cities, who have huge pressures of life and irregular dietary habits, both of which are conducive to GER-related diseases. 2) Xiamen is a coastal city, and sweet potatoes are the main crop produced in the adjacent rural areas. The local residents like eating sweet potatoes, and this might predispose them to GER. 3) Our hospital has previously conducted research on GER-related diseases

under the guidance of Taiwanese doctors; therefore, our local hospitals have relatively better diagnostic awareness and experience in treating GER-related diseases. Our hospital specializes in the diagnosis of cough, which encourages larger numbers of patients with CC to seek medical attention at our hospital. 4) There are differences between China and other countries in the diagnosis of GER in patients who mainly exhibit external esophageal signs. Some scholars think that there is a small possibility that, in the absence of the typical symptoms including reflux and heartburn, external esophageal symptoms including cough, asthma, and laryngitis might be due to a single underlying condition such as GER; therefore, reflux cough might be easily misdiagnosed.

It has been reported that the three main causes of chronic cough—airway cough syndrome, cough-variant asthma, and gastroesophageal reflux cough—accounted for 79% of the CC cases in Chongqing and for 86.8% of the CC cases in the Beijing China-Japan friendship hospital. In the Xinjiang region, acidophilic granulocyte bronchitis has been reported to be the cause of CC in a greater proportion of cases (72.8%) than airway cough syndrome and cough-variant asthma. The main causes of CC in different regions vary; this variation might be related to the differences in the environment, climate, lifestyle, dietary habits, etc. We also found in our clinical practice that, although many patients with GER-induced cough do not experience the typical sour-tasting regurgitation

and heartburn symptoms, they clearly exhibit esophagitis upon endoscopy and respond to PPI treatment. This indicates that partially affected patients might exhibit atypical sour-tasting regurgitation and heartburn, but exhibit cough as the only sign of CC (23). The diagnosis of GER-related cough often requires 24-h esophageal pH monitoring, which is time consuming and labor intensive. Most patients find the procedure uncomfortable, and it is more difficult to perform than endoscopy (24). Based on the experience of our respiratory department, the rate of incidence of endoscopic reflux esophagitis caused by suspected GERD-related respiratory symptoms might be greater than 40%. We think that endoscopy should be used to assist in the diagnosis of GER-related CC.

CC caused by two or more complex factors has also attracted great concern from Chinese and foreign scholars. It has been reported in foreign literature that complex causes account for 18%–61.5% of CC cases (25–27), and usually involve two or three forms of UACS, CVA, and GERC that might be related to the pathogenesis of CC.

For example, allergic rhinitis has a certain relationship to the pathogenesis of CVA—CVA- or UACS-induced cough might secondarily induce GERD because of increased abdominal pressure, and GERD, in turn, might induce CVA because of reflux-directly-damaged-nasopharynx-caused sinusitis or esophagus-trachea reflection-caused secondary airway hyper-responsiveness. In the present study, 52 patients (11.4% of the cases with known etiologies) had two or more etiologies of CC. In our experience, if the patients show no obvious improvement or only a partial response after treatment for one or two known causes, the possibility of a combination of causes should be considered. The results of the present study showed that, in addition to nighttime cough being an indicator for CVA-related cough, cough after talking and eating, hoarseness after talking, mono-cough, chest pain, and the feeling of heaviness in the chest were also important indicators for GERC, and the diagnosis and treatment of CC on the basis of these clinical features could be more targeted.

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