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Original Research

SIGNS AND SYMPTOMS OF CHEST DISEASES

A Prospective, Multicenter Survey on Causes of Chronic Cough in China

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Background: **The causes of chronic cough in China and its relations with geography, seasonality, age, and sex are largely uncertain.**

Methods: **A prospective, multicenter survey was conducted to evaluate patients with chronic cough across five regions in China by using a modified diagnostic algorithm. The effects of geography, seasonality, age, and sex on spectrum of chronic cough were also investigated.**

Results: **The current study evaluated 704 adult patients, including 315 men (44.7%) and 389 women (55.3%). The causes of chronic cough were determined in 640 subjects (90.9%). Common causes included cough variant asthma (CVA) (32.6%), upper airway cough syndrome (UACS) (18.6%), eosinophilic bronchitis (EB) (17.2%), and atopic cough (AC) (13.2%). Collectively, these four causes accounted for 75.2% to 87.6% across five different regions without significant difference ($P > .05$), although there was variation on single causes. Gastroesophageal reflux-related cough was identified in 4.6% of causes. Seasonality, sex, and age were not associated with the spectrum of chronic cough (all $P > .05$).**

Conclusion: **CVA, UACS, EB, and AC were common causes of chronic cough in China. Geography, seasonality, age, and sex were not associated with the spectrum of chronic cough.**

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Abbreviations: AC = atopic cough; AHR = airway hyperresponsiveness; CVA = cough variant asthma; EB = eosinophilic bronchitis; GERC = gastroesophageal reflux-related cough; GERD = gastroesophageal reflux disease; IQR = interquartile range; NAEB = nonasthmatic eosinophilic bronchitis; SPT = skin prick test; UACS = upper airway cough syndrome

Chronic cough is defined as cough being the sole or predominant symptom lasting for at least 8 weeks, with no radiographic evidence of lung diseases.[1,2] Chronic cough is one of the most common symptoms for which adults seek medical care in Western countries as well as in China.[3] Irwin et al[4] first set up an anatomic diagnostic protocol for chronic cough in 1981. Since then, many investigations[5-8] have been conducted to determine the causes of chronic cough. Early studies showed that the common causes included upper airway cough syndrome (UACS) (termed postnasal drip syndrome previously), bronchial asthma, and

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gastroesophageal reflux disease (GERD). With the addition of the induced-sputum cytology test to the diagnostic protocol in later studies, nonasthmatic eosinophilic bronchitis (NAEB) was found to be an important cause of chronic cough.[9-11]

The spectrum of chronic cough varies among different countries. For example, GERD-associated cough is rare in Japan[12] and Korea.[11] Even in the surveys performed by the same group, the spectrum of chronic cough varied over time. In three articles published by Irwin et al in 1981,[4] 1990,[6] and 1996,[13] GERD-associated cough accounted for 10%, 21%, and 33% of chronic cough, respectively. In South China (Guangzhou), an early study showed that NAEB was the most common cause of chronic cough, with a proportion of 22%.[14] However, NAEB was found in far fewer (2%-5.7%) patients with chronic cough in North China (Beijing)[15] and East China (Shanghai).[16] Such a wide range in reported values seems unreasonable, and it is unclear whether such difference was due to regional variation or inconsistent diagnostic methods. The effects of seasonality, sex, and age on spectrum of chronic cough were not reported previously.

China has a large geographic area, with different climates and environments. Therefore, it is necessary to understand whether regional variation and environmental factors influence the spectrum of cause and whether discrepancies among previous studies could be attributed to differences in criteria and the diagnostic method. To address these questions, a prospective, multicenter survey was conducted on the cause of chronic cough using a standard diagnostic protocol.

Materials and Methods

Study Design

A prospective, multicenter study was conducted in nine general hospitals located in eight large cities from five geographic areas of China, including Northern China (Beijing), Northeast China (Shenyang), Eastern China (Shanghai and Hangzhou), Western China (Xi'an and Chengdu), and Southern China (Guangzhou and Foshan), from March 2009 to February 2010. The protocol was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University and the institutional review boards of each participating center. The institutional review board approval number is 2009-02.

Patients

Immunocompetent patients complaining of chronic cough were enrolled consecutively in respiratory medical clinics in nine research units over a period of 12 consecutive months between March 2009 and February 2010. Based on the climatic characteristics in China, the four seasons were defined as follows: March to May (spring), June to August (summer), September to November (autumn), and December to February (winter). The inclusion criteria included the following: (1) age $\geq$ 15 years; (2) cough as the sole or predominant symptom lasting for at least 8 weeks, with no radiographic evidence of lung diseases; (3) subjects were local residents of the surveyed geographical area; and (4) never smokers or ex-smokers with cessation of smoking for at least 6 months prior to the enrollment. All patients gave informed consent before inclusion.

Diagnostic Procedure

A validated, systematic, step-by-step diagnostic algorithm was used (Fig 1) among all the sites, with uniform diagnostic criteria and management (Table 1) according to the guideline proposed by the Chinese Medical Association.[2] In the first step, a detailed history-taking and physical examination were performed. A standardized questionnaire was used to record clinical features/characteristics (e-Appendix 1). The next step consisted of chest radiography, spirometry, bronchial provocation test, and skin prick test (SPT), and induced sputum was performed as standard investigation in all patients. Once the primary diagnosis was established, a specific etiologic treatment was initiated. During the basic diagnostic procedure, all the patients were followed up at least three times: at the end of the first, second, and fourth weeks. If cough disappeared or improved obviously, the cause of cough was identified. Upon treatment failure, alternative causes were investigated with additional tests (24-h esophageal pH monitoring, thoracic or sinus CT scan, fiber-optic bronchoscopy, and so forth). The diagnostic process was continued until a definite diagnosis was derived. The follow-up duration was increased based on the response to treatment until the final diagnosis was obtained. When more than one condition was believed to be contributing to the cough, therapy was first targeted at the most likely potential cause. Unexplained cough was identified if no abnormality was found through the entire diagnostic procedure (including standard and additional tests), and the cough persisted despite empirical treatment of potential causes. In cases with abnormal test results, if cough persisted after specific etiologic therapy, unexplained cough would be considered too.

We strictly carried out quality control to ensure the consistency among all sites. Prior to the commencement, a technical training program (including spirometry, bronchial provocation test, sputum induction, SPT, and so forth) was performed for all researchers and operators. During the study, the quality of the research across nine sites was further censured by a quality control group.

Diagnostic Methods

Spirometry and bronchial provocation test were performed as recommended by the American Thoracic Society.[17] The FEV_1,

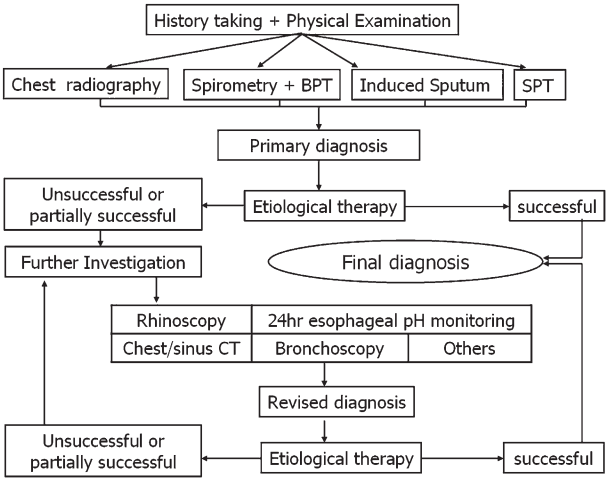

Figure 1. Diagnostic algorithm of chronic cough. BPT = bronchoprovocation test; SPT = skin prick test.