Chronic Cough

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Introduction

Cough is a normal protective mechanism of the respiratory tract, as well as a common symptom of respiratory disease. Chronic cough is defined as cough lasting for more than 8 weeks. This definition is based on fact that a cough lasting longer than 8 weeks is unlikely to be due to post infectious cough. Chronic cough is a common symptom of almost all chronic respiratory and some non-respiratory illnesses with an estimated prevalence of 11% to 20% of the population. It can be associated with significant distress and impairment in quality of life. Effective management requires accurate etiologic diagnosis. Several recognisable causes of chronic cough, such as chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, sarcoidosis, interstitial lung disease, lung cancer, an inhaled foreign body, and heart failure will be obvious after clinical examination, chest radiography, and spirometry. However despite extensive investigation and treatment trials, up to 46% of patients with chronic cough have an unexplained etiology.

Pathophysiology

Cough is a defensive reflex mechanism that clears secretions from the upper airways of the respiratory tract; which is triggered by the stimulation of a complex reflex arc. Cough receptors are located in the respiratory tract from the hypopharynx and larynx to the segmental bronchi. Several different types of sensory nerve receptors respond to chemical, mechanical, inflammatory or thermal stimuli activating cough receptors connected to vagal afferent nerves. A cough centre in the medulla receives signals from these activated cough receptors via afferent fibres in the vagus nerve. Voluntary inhibition or production of cough is possible because of the influence of higher cortical centres on this cough centre. Efferent signals are then sent to the muscles that produce the forced expiratory effort.

Differential Diagnosis

The common causes of chronic cough in an immunocompetent non-smoking adult with normal chest radiograph are angiotensin-converting enzyme (ACE) inhibitor medication, upper airway cough syndrome (UACS, also known as postnasal drip syndrome), asthma, or gastroesophageal reflux disease (GERD), alone or in combination. Chronic cough has two or more causes in 18 to 62 percent of patients, and three causes in up to 42 percent of patients. Empiric treatment should be initiated sequentially for the three most common causes of chronic cough until symptoms are resolved.

UACS

Rhinitis, often associated with sinusitis and post-nasal drip, is frequently identified as a common cause of chronic cough. Mechanical stimulation of cough receptors in the hypopharynx and larynx either directly or indirectly through inflammatory mediators has been proposed as a mechanism of cough in patients with UACS.

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GERD

Gastro-esophageal reflux (GERD) is an important cause of chronic cough that may be the sole clinical manifestation. LPR refers to extraesophageal manifestations of GERD, when gastric contents reach the larynx and pharynx. A number of symptoms are reported with LPR, including chronic cough, throat clearing, hoarseness, globus sensation, and vocal cord dysfunction. Up to 75% of patients who were found to have GERD-induced cough do not have symptoms of heartburn or acid indigestion. Endoscopy is typically not helpful, and most patients with chronic cough and GERD do not have evidence of esophagitis.

Asthma Syndrome

Asthma is characterized by chronic or recurrent respiratory symptoms associated with airway inflammation and variable airflow obstruction. Symptoms include wheeze, dyspnea, and/or cough. Because of possible pathophysiologic differences, patients with cough variant asthma are thought to represent a different phenotype from those with classic asthma. A third cough-predominant eosinophilic airway disorder is nonasthmatic eosinophilic bronchitis (NAEB). These are non-smoker with eosinophilic airway inflammation, normal chest radiographic and spirometric results, and no evidence of variable airflow obstruction.

Usually most coughs related to upper respiratory tract infections resolve within 3 weeks however, cough may persist in a small number of patients. Infection in most cases remains unidentified; Mycoplasma pneumoniae, Chlamydia pneumoniae, and Bordetella pertussis have been among the organisms implicated in adults. Persistent cough due to infection might be more likely in patients with pre-existing airway problems.

Obstructive sleep apnea (OSA) at times can cause chronic cough. Possible mechanisms of OSA-associated cough include apnea causing increased transdiaphragmatic pressure leading to lower esophageal sphincter insufficiency, GERD, and cough. Airway inflammation from epithelial injury associated with OSA can also be operative.

Psychogenic or Habitual Cough

A habitual cough is a diagnosis of exclusion. Many patients with this condition do not cough during sleep, are not awakened by cough, and generally do not cough during enjoyable distractions.

Some investigators have suggested that up to 20% of patients with chronic cough have more than one potential aggravating factor, and all factors need to be addressed before satisfactory control can be achieved.

Chronic Cough in Children

In children, a cough lasting longer than four weeks is considered chronic. The most common causes of chronic cough in children are asthma, respiratory tract infections, and GERD. The differential diagnosis for chronic isolated cough without associated wheezing in an otherwise healthy child includes recurrent viral bronchitis, postinfectious cough, pertussis-like
illness, cough variant asthma, UACS, psychogenic cough, and GERD. Signs suggestive of serious underlying lung disease include neonatal onset of cough, chronic moist or purulent cough, cough starting with and persisting after a choking episode, cough occurring during or after feedings, or associated failure to thrive. Foreign body aspiration should be considered in young children. Congenital conditions, cystic fibrosis, and immune disorders are possible diagnoses in children with chronic cough and recurrent infections. Congenital abnormalities, although rare, can include vascular rings, tracheoesophageal fistulas, and primary ciliary dyskinesia.

**Evaluation of the Patient with Chronic Cough**

The evaluation of chronic cough includes a detail history, including smoking status, environmental exposures, and medication use. History of the onset of cough is important: an abrupt onset of coughing when eating raise the possibility of foreign body aspiration and the onset of cough shortly after introduction of ACE-inhibitor therapy raise the possibility of ACE-inhibitor associated cough. The presence of hemoptysis, sputum production, systemic symptoms, breathlessness, wheeze, or abnormal physical signs increases the probability of lung disease requiring appropriate investigations, which could include high-resolution CT scan of the chest and bronchoscopy. Onset of cough with symptoms suggestive of an upper or lower respiratory tract infection raises the possibility of a post infectious cough: prominent whoops, a very troublesome nocturnal cough, and cough associated with vomiting are all associated with pertussis. An important next step is to assess objectively cough severity, frequency, intensity and sensitivity. Cough that worsens when supine suggests postnasal drip, esophageal reflux, bronchiectasis, chronic bronchitis or heart failure. Production of clear sputum suggests a hypersensitivity mechanism, while purulent sputum implies chronic infection (sinusitis, bronchiectasis, tuberculosis), and blood-tinged sputum points to cancer, tuberculosis, or bronchiectasis. A non-productive cough is commonly due to ACE inhibitors. Sour taste or heartburn is reported by 60% of patients with a reflux etiology. Smoking history, ACE inhibitor use, presence of systemic symptoms (fever, anorexia/weight loss, night sweats, and progressive fatigue), geographic and environmental exposure to infectious or toxic agents, and previous diagnoses of cancer, tuberculosis, or human immunodeficiency virus are also key historical points.

Physical examination focuses on the upper and lower respiratory tract and cardiovascular system. Examining the nose (polyps, discharge, and obstruction), sinuses (tenderness), oropharynx (secretions, mucosal edema and tonsillar enlargement), ears (tympanic membrane or external canal inflammation), and neck (adenopathy) can provide important confirmatory information. Diffuse wheezing implies asthma, COPD or heart failure, while localized wheezing may be found when a tumor is present. Evidence of heart failure should also be sought. Epigastric tenderness, or reflux symptoms is suggestive of esophageal reflux. Chest radiograph is important in the diagnostic algorithm. HRCT should be considered in patients with abnormal chest radiographs. Sputum for Gram stain, culture, and acid-fast staining are indicated when purulent or blood-tinged sputum is noted, or suggestive radiograph findings are present. Sputum cytology and examination for eosinophils may also be helpful when history and physical examination suggest a neoplastic or allergic etiology or NAEB. Bronchoscopy is indicated in patients with abnormal chest radiograph, hemoptysis, obstructing lesions and infiltrates that
otherwise elude diagnosis. Spirometry with bronchoprovocation should be considered when asthma is suspected (Figure 1).

Management

Smoking should be stopped and exposure to passive smoke eliminated in all patients. ACE inhibitors should be stopped if possible, or dose reduced; if causative, this will result in symptom relief in 2-4 weeks. Persistence of cough after withdrawal of ACE inhibitors raises the possibility of another cause of cough, such as asthma, the onset of which has been linked to the use of ACE inhibitors. Therapeutic trials are appropriate. Upper airway cough syndrome may respond to removal of inhaled irritants or offending antigens, treatment of chronic sinusitis with a course of antibiotics, and weaning off topical decongestants. Empiric therapy may also include a first-generation antihistamine with or without oral pseudoephedrine; improvement may be seen within 2 weeks, while some patients will require several months to respond.17 Asthma (highly suspected or proven by spirometry) should be treated with inhaled corticosteroids and beta-2 agonists; a clear improvement within 1 week. Sedating antihistamines may also ease associated insomnia. 2-week trial of oral prednisolone should be given in cases of NAEB.18 Treatment for GERD includes conservative measures (diet manipulation), drug therapy (e.g., motility or prokinetic agents, H2 antagonists, proton pump inhibitors (PPIs)).19 A trial of treatment with acid-suppression therapy with a PPI for 2–3 months would be reasonable in patients with otherwise unexplained cough, even when there are no suggestive upper gastrointestinal symptoms (Table).

Antitussive Treatment

In many patients, the cause of increased cough reflex will probably remain at least partly unexplained, and treatments directed against potential aggravating factors will not achieve complete results. In many such patients, antitussive therapies are needed.20 Narcotic antitussives (codeine 8-15 mg every 4 hours) are preferred when chronic cough interferes with sleeping or eating. Opioids, mainly acts centrally on the cough network in the brainstem, but might also inhibit peripheral activation of cough receptors. Such therapies are ineffective against acute cough of the common cold and against cough in patients with COPD. A non-narcotic antitussive, dextromethorphan, has proved to have some effect on cough associated with upper respiratory tract infections, although the effect on cough frequency was small and of uncertain clinical relevance. The use of morphine and diamorphine has been restricted to severe distressing cough in malignant disease, in which cough is often associated with pain and distress. There is evidence of the effectiveness of as low-release formulation of morphine in a population with distressing, unexplained cough. Expectorants and mucolytics (guaifenesin) will improve symptoms by mobilizing sputum in patients with inflammatory etiologies. Sedating antihistamines may also ease associated insomnia.

Summary

Chronic cough is often viewed as a difficult clinical problem. It can be physically and psychologically debilitating, occasionally leading to serious complications. Although there are many etiologies, an organized approach including focused history and physical examination, directed testing in select cases, and treatment trials lead to accurate, safe, and cost-effective diagnoses in most patients. Additional symptomatic treatment is frequently beneficial. Occasionally, diagnostic dilemmas, treatment failures, or more serious causative disorders necessitate referral for further testing and management.

References

17. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 suppl):63S-71S.