

Chronic Cough: Etiology, Management and Challenges

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Summary

Cough is one of the commonest symptoms of lung disease and is a frequent problem encountered in general practice as well as in hospital patients. It is a common symptom of most respiratory disorders and is a most common reason for patients of all ages to consult their doctor

Chronic cough in general adult populations global prevalence of 9.6% was found compared to India that was less than 5%.^[1] Chronic cough poses a great diagnostic and management challenge due to various etiologies and is commonly considered to be caused by gastroesophageal reflux, post-nasal drip or asthma. This article covers the etiology and mechanism of cough with recent advances in the field of cough and showing some of the diagnostic and management challenges.

Introduction

Cough is an important natural defence mechanism of the respiratory tract a warning sign of several respiratory and non-respiratory diseases for which patients are taking medical advice and treatment.^[2] However, chronic cough (persisting greater than eight weeks) can lead to considerable morbidity, exhaustion, cough syncope, disturbance of sleep, urinary stress incontinence, and work absenteeism. Chronic cough can also be associated with significant distress and impairment in quality of life.^[3] Chronic cough, in more severe cases, can also cause pneumothorax, rib fractures, pneumomediastinum (PM), and subcutaneous emphysema. Chronic cough is reported in about 10-20% of the population.^[4]

This article presents a systematic approach to the evaluation of chronic cough, mechanism and etiology of the cough, based on the results of prospective studies and an evidence-based practice guideline and highlighting some of the diagnostic and management challenges.

Mechanisms of Chronic Cough: Pathophysiology

Cough is a defensive reflex mechanism that clears secretions from the upper airways of the respiratory tract; it is triggered by the stimulation of a complex reflex arc. Cough is caused by a reflex-evoked modification of the normal breathing pattern, can also be initiated and suppressed voluntarily and caused by the stimulation of the peripheral sensory nerves. A cough centre in the medulla of the brain receives signals from the activated cough receptors via afferent fibers in the vagus nerve. Voluntary inhibition or production of cough is possible because of the influence of higher cortical centres on this cough centre. Then efferent signals are sent to the muscles that produce the forced expiratory effort.^[5] The transmission in these neurons occurs through myelinated nerve fibers and both these sensory afferent pathways

terminate at the brainstem, at the nucleus of the solitary tract and the spinal trigeminal tract. Second-order neurons from the solitary nucleus and the trigeminal nucleus are connected to neurons of the brainstem and the spinal respiratory circuit, which coordinate the efferent cough response.^[6]

Etiology of cough

Cough in adults is classified as acute, subacute, or chronic based on duration. Acute cough lasts up to three weeks, subacute cough lasts three to eight weeks, and chronic cough lasts longer than eight weeks.^[7] Chronic cough can be caused by a respiratory or non-respiratory conditions. The common causes of chronic cough include viral infections of the upper respiratory tract, upper airway cough syndrome (UACS; postnasal drip syndrome), cough-variant asthma, gastroesophageal reflux disease (GERD), eosinophilic bronchitis, mediastinal tumors, pleural diseases, early interstitial fibrosis, use of an angiotensin converting enzyme-inhibitor (ACE), and psychogenic and idiopathic cough.^[4] Most episodes of chronic cough in adults are caused by UACS, asthma, or GERD, alone or in combination, comprising two-thirds of all diagnoses.^[8]

The evaluation of chronic cough can be done with a thorough history which includes smoking status, environmental exposures, and medication use. Chest radiography should be obtained if the patient does not smoke or take an angiotensin-converting enzyme (ACE) inhibitor, or if the cough persists after withdrawal of the medication.^[9]

Upper airway cough syndrome

UACS is caused by a variety of upper respiratory conditions. It is the most common cause of chronic cough in non smoking, immune competent adults who have normal

chest radiography. The common clinical signs and symptoms associated with UACS include a feeling of drainage in the posterior pharynx, frequent throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, and mucopurulent secretions in the oropharynx. Although these clinical findings are sensitive, but are generally nonspecific.^[10] Some patients with cough will have no upper respiratory signs or symptoms that suggest UACS, but they will respond to the therapy.^[11]

In patients with an atypical clinical presentation, the diagnosis is established after the response to empirical treatment with first-generation antihistamines/decongestants, which are preferred over newer agents.^[12] The nonsedating antihistamines are not as effective if the postnasal drip is not mediated by histamine.^[13] Use of intranasal corticosteroids for two to eight weeks or oral antihistamines or nasal ipratropium bromide is also recommended in selected patients with rhinitis.^[10] Plain radiography may be used as a screening modality; computed tomography is used to confirm and stage chronic inflammatory diseases of sinonasal cavities.^[14]

Asthma

Asthma is the next most common cause of chronic cough in adults. Chronic dry cough may be the only symptom in asthma and in majority of the cases with cough variant asthma, dry cough generally occurs at night.^[10]

There are two Mechanisms to explain the pathophysiology of asthma. It is due to Sensitization of cough receptors by increased levels of inflammatory mediators, such as, bradykinin, tachykinin, or prostaglandins and Stimulation of cough receptors through constriction of the bronchial smooth muscle.^[2]

Spirometry is usually done to diagnose asthma and can be used to demonstrate airflow obstruction and assess reversibility of the condition in patients older than four years.^[15] Bronchoprovocation tests can be done in patients who may not have demonstrable airflow obstruction on spirometry which is commonly done by methacholine or histamine. A negative methacholine challenge test excludes the diagnosis of cough-variant asthma.^[16] Raised sputum eosinophil count or increased exhaled nitric oxide (NO) concentration are considered important for diagnosis of cough-variant asthma.^[2] Non-asthmatic eosinophilic bronchitis (NAEB) also presents in a similar manner. Patients with NAEB present with cough and sputum eosinophilia. However, the major characteristic to differentiate between asthma and NAEB is the absence of variable airflow obstruction and bronchial hyperresponsiveness.^[12]

Atrial of inhaled corticosteroids should be considered in patients with unexplained chronic cough in order to rule out asthma and NAEB. Other options for patients with cough-variant asthma include long-acting bronchodilators, antileukotrienes, and/or low-dose theophylline. Oral corticosteroids for 14 day may be an option for selected patients with severe and/or refractory asthmatic cough.^[12]

Gastroesophageal reflux disease

GERD is the third leading cause of chronic cough in adults.^[17] Heartburn and regurgitation suggest a GERD-induced chronic cough. These symptoms may be absent in "silent" GERD.

Mechanisms of Gastroesophageal reflux disease-associated cough are Intraesophageal reflux (stimulation of the esophageal-tracheobronchial cough reflex), laryngopharyngeal reflux, and microaspiration. All these mechanism act by triggering cough events or indirectly by sensitization of the cough reflex.^[18] The major mechanism responsible for GERD-associated cough is vagally-mediated esophageal-tracheobronchial cough reflex. Classical reflux symptoms such as heartburn, acid regurgitation, water brash may not be common in chronic cough patients and cough may be the only presenting manifestation of GERD.^[19] This makes GERD more difficult to diagnose.

For management an empiric trial of a proton pump inhibitor is recommended.^[20] Also management includes anti-reflux diet and lifestyle changes, a prokinetic agent (e.g. metoclopramide), and an acid suppressant.^[12] PPI can be still considered for patients with evidence of pathological esophageal acid exposure and/or reflux esophagitis.^[21]

Angiotensin-converting enzyme (ACE) inhibitors

5 to 20 percent of patients suffer from nonproductive cough by ACE inhibitors affecting women more often than men.^[22] Cough may begin one week to six months after therapy is initiated and it is not dose related. After discontinuation of ACE inhibitor cough should spontaneously resolve within few days to several weeks, a four-week trial of withdrawal is usually sufficient to determine the cause of cough by medication.^[23]

Other causes

Nonasthmatic eosinophilic bronchitis

It is defined as a chronic cough in patients with normal airway hyperresponsiveness, sputum eosinophilia, and no symptoms or objective evidence of variable airflow obstruction. The diffrenciating points between classic chronic bronchitis and nonasthmatic eosinophilic bronchitis is the presence and activation of eosinophils and metachromatic cells in the sputum. This condition can be

ruled out if induced sputum contains insufficient eosinophils (< 3 %) or if corticosteroid therapy does not cause improvement in the cough. This condition may be episodic, transient, or persistent unless it is treated.^[24]

Chemical irritants

Cigarette smoke or other irritants is an important cause of chronic cough by chronic bronchitis. The most common risk factor for chronic obstructive pulmonary disease is cigarette smoking.^[25] The initial treatment is eliminating the patient's exposure to irritants.

Psychogenic cough

Many patients with this condition do not cough during sleep, are not awakened by cough, and generally do not cough during enjoyable distractions. Triggers for psychogenic cough include changes in ambient temperature; taking a deep breath; laughing; talking on the telephone for more than a few minutes; exposure to cigarette smoke, aerosol sprays, or perfumes; or eating crumbly, dry food.^[26]

Sleep apnoea and chronic cough

Obstructive sleep apnea (OSA) is being increasingly recognized as a cause of chronic cough.^[27] Two mechanisms are proposed for sleep apnea. An increase in trans-diaphragmatic pressure during apnea episodes causes lower esophageal sphincter insufficiency which leads to GERD. Another mechanism for cough is that results from upper airway inflammation secondary to epithelial injury, associated with snoring and apnea. To reduce or resolve the cough in patients with OSA continuous positive airway pressure therapy is reported.^[28]

Bronchiectasis

Bronchiectasis can be associated with UACS, asthma, GERD, and chronic bronchitis, chest radiography shows increased thickening of the bronchial wall. Etiologies include postinfectious and idiopathic causes; genetic disease like cystic fibrosis, primary ciliary dyskinesia etc. aspiration or GERD; immune deficiency; rheumatoid arthritis; ulcerative colitis; and allergic bronchopulmonary aspergillosis.^[29]

Tuberculosis

patients with chronic cough having sputum production, fever, hemoptysis, or weight loss and who live in endemic areas with a high prevalence of the disease, also in those at high risk (e.g., human immunodeficiency virus-seropositive persons). These patients may have normal physical examination and chest radiography findings, so additional testing (e.g., skin testing, sputum culture) may be needed to make the diagnosis.^[30]

Sarcoidosis

Sarcoidosis is less common cause of chronic cough. Patients with sarcoidosis will have chest radiography findings suggestive of the diagnosis. Chest radiography shows mediastinal widening caused by bilateral hilar adenopathy and reticular opacities.^[31] Other more common disorders such as UACS and GERD should be excluded as primary or contributing causes before diagnosing sarcoidosis.

Cough hypersensitivity syndrome

Chronic cough is considered as a single syndrome with a common intrinsic mechanism of cough hypersensitivity, diseases such as rhinitis, eosinophilic bronchitis, asthma or GERD are believed to be triggers.^[32] In this syndrome there is increased expression of cough receptors in the airways of patients with cough.^[28]

Cough monitoring devices

Cough monitoring devices, which include, Leicester Cough Monitor (LCM) and the VitaloJak and coughcount.^[28] The Leicester Cough Monitor comprises of an MP3 recorder and a microphone. It measures the 24-hour cough frequency in the patients' own environment.^[33] Coughcount an automated, sound-based cough monitoring system is introduced. But it has not been validated in patients with chronic cough. To assess outcomes with drug therapy several clinical trials have shown the feasibility of using this technology and it is believed that positive cough monitoring data may provide strong support for the efficacy of antitussive drugs in future.^[28]

Conclusion

Chronic cough has been considered to be caused by gastroesophageal reflux, postnasal drip or asthma. However recent studies suggests that with these conditions patients may not have cough. Also there are many causes recognised for chronic cough and treatment for these conditions are unpredictable. Many chronic cough patients do not have an identifiable cause or cannot be identified due to wrong history or lack of investigations. In recent years significant progress has been made to find out the conditions associated with chronic cough. Development of objective ambulatory cough monitoring systems and cough diary scores and visual analog scales have improved the assessment of chronic cough.

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