Editorial

Management of chronic unexplained cough

Mohamed S. Al-Hajjaj

Department of Medicine, College of Medicine, University of Sharjah, Sharjah, UAE

Address for correspondence:
Dr. Mohamed Al-Hajjaj, 12 Alkuday Street, Alhamra District, P.O. Box 106911, Riyadh 11676, Saudi Arabia.
E-mail: msalhajjaj@yahoo.com

Submission: 19-11-2016
Accepted: 27-11-2016

Cough is a natural defense mechanism that allows the clearance of bronchial tree secretions and elimination of inhaled foreign particles.[1] It is a common respiratory symptom for diseases that are either apparent or covert and can produce significant suffering for patients and a diagnostic dilemma for physicians.[2-4] Acute cough that is caused by a known cause is dealt with by managing the underlying cause. Here, discussion will focus only on cough as the only symptom without clear presence of an etiology. This could be either a subacute (4–8 weeks) or a chronic cough (>8 weeks). For sub-acute cough, if it is an extension of a known cause, then it needs to be dealt with accordingly. If the cause is not apparent, then it is managed as in chronic cough.

There are three phases of cough: An inhalation phase which generates enough volume for an effective cough, a compression phase with pressure against a closed larynx by the contraction of chest wall, diaphragm and abdominal muscles, and an expiratory phase when the glottis opens resulting in high air flow.[5] Cough could be a voluntary or an involuntary act. Voluntary cough is manifested by cough inhibition or initiation. Involuntary cough is regulated by the vagal afferent nerves. By stimulating cough receptors that present in the airways and other areas in the upper body, impulses travel thru the vagus nerve to the cough center in the medulla which is controlled by the higher cortical centers. Afferent signals move down through the phrenic and spinal motor nerves to the expiratory muscles producing the cough.[6] Chronic cough may also be brought about by abnormalities of the cough reflex and sensitization of its afferent and central components with exaggerated cough reflex sensitivity to stimuli that normally do not cause cough (cough hypersensitivity syndrome [CHS]).[7]

Upper airway cough syndrome (UACS) includes all nasopharyngeal conditions (including allergic rhinitis [AR], rhinosinusitis and laryngopharyngitis) that may be associated with postnasal drip and subtle sensation of irritation of secretions in the back of the throat and the upper airways that present with cough as the only symptom. Throat examination may reveal sings of pharyngitis and cobble-stone appearance. These conditions can be silent (no symptoms besides cough) in up to 20% of cases.[8] Because of disease chronicity, it is likely that, over time, patients will become tolerant to other symptoms, which are not as bothersome as cough. The diagnosis of silent UACS can reliably be made only after patients show a significant improvement with prescribed treatment directed to suggestive features in history, physical examination, or laboratory testing.

Cough can be the only manifestation of asthma or what is known as cough-variant asthma (C-VA). Unlike silent UACS, the diagnosis of C-VA can be confirmed in most cases with pre- and post-bronchodilator spirometry with or without methacholine challenge test (MCT).[8]

Nonasthmatic eosinophilic bronchitis (NAEB) shares eosinophilic airway inflammation with asthma, but there is no demonstrable airflow limitation on spirometry and MCT is negative. Chest X-ray (CXR) is usually normal. Missing this diagnosis is possible because sputum examination and/or bronchoalveolar lavage to detect airway eosinophilia are not routinely performed during the diagnostic work-up, and NAEB tends to respond to corticosteroids in the same way as asthma.[9]

Gastroesophageal reflux disease (GERD) triggers cough by direct effect of acid on the proximal part of the esophagus and the laryngopharyngeal areas or by indirect vagal stimulation through the effect of gastric contents on the distal part of the esophagus. Other symptoms of acid reflux, such as heartburn, may be absent (silent reflux) in as many as 75% of cases of reflux-induced

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.197761

How to cite this article: Al-Hajjaj MS. Management of chronic unexplained cough. Ann Thorac Med 2017;12:1-2.

cough. pH esophageal monitoring may confirm the presence of silent reflux; although, anti-reflux therapy does not always resolve the cough.[10]

CHS is defined as "troublesome coughing triggered by low level of thermal, mechanical, or chemical exposure." It is characterized by enhancement of the cough reflex through sensitization of afferent neuronal pathways of cough, both at the peripheral and central levels. Patients with CHS develop cough in an exaggerated response to stimuli that would not otherwise elicit cough. It is thought that this nerve hypersensitivity is a result of various recurrent triggers, such as URTI, AR, or dust.[11] Chronic cough seen with UACS, asthma, and reflux may be induced by the development of cough hypersensitivity.[12] Pharyngeal and/or laryngeal sensations (irritation, tickle, tightness, throat clearing), which are frequently associated with UACS and reflux-induced cough, may represent a sensory neuronal dysfunction of vagal afferents in the upper airways and a phenotype of CHS. Symptoms such as dysphonia, dysphagia, dyspnea, and abnormalities of vocal fold motion on laryngoscopy may also be present along with cough as the part of the pharyngeal/laryngeal nerve dysfunction seen with CHS.[13]

Initial evaluation of the patient with chronic cough should include a detailed history, a focused physical examination, and CXR.[11,14] Patients who smoke are advised to quit smoking and those who are taking an angiotensin-converting enzyme inhibitor should switch to a medication from another drug class. Sequential empirical therapy is advised before embarking on extensive work-up. The most common causes of chronic cough in adults are UACS, asthma, and GERD, alone or in combination. If UACS is suspected, a trial of nasal saline rinses, a decongestant, a first-generation antihistamine and nasal steroids is recommended. Further tests such as sinus computed tomography (CT) scanning and nasopharyngoscopy are spared for nonresponders. The diagnosis of asthma should be confirmed based on clinical response to inhaled bronchodilators and/or corticosteroids. Empiric treatment for GERD with diet, lifestyle modification, and proton-pump inhibitors for 3 months should be prescribed before considering 24-h esophageal pH monitoring. NAEP is treated with inhaled steroids if sputum or bronchoalvelar lavage testing is showing >3% eosinophils. After a period of targeted treatment, patients with persistent cough are subjected to further investigations such as chest high-resolution CT scanning, bronchoscopy, and echocardiography. For cases with no clear etiology after extensive work up, CHS is the most likely explanation. A trial of antitussive drugs that can down-regulate cough reflex sensitivity (like dextromethorphan or gabapentin) can be used.[15,16] Another less common possibility is psychogenic cough and it is also a diagnosis of exclusion.

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