

Classic symptoms revisited

Diagnosis and management of chronic persistent dry cough

KF Chung, UG Laloo

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 practice. A wide range of disease processes may present with cough and definitive treatment depends on making an accurate diagnosis of the cause. A diagnostic work-up for patients with persistent dry cough is presented. The most common associated conditions are post-viral cough, asthma, rhinosinusitis (post-nasal drip or 'nasal catarrh') and gastro-oesophageal reflux. Treatment with angiotensin-converting enzyme inhibitors can also lead to a persistent dry cough. Specific treatment of the cause should control the cough, but this may not occur in all cases and in a sizeable proportion of patients, no associated cause can be found. An increased sensitivity of the cough reflex can be observed in patients with persistent dry cough. Symptomatic relief must be considered when the cough interferes with the patient's health and sleep but the most effective antitussive opiates cause sedation and may be addictive. Treatment of persistent dry cough remains a challenge in some patients and there is still scope for improvement in its diagnosis and effective therapy.

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Department of Thoracic Medicine,
Royal Brompton Hospital, National
Heart & Lung Institute, London
SW3 6LY, UK
KF Chung
UG Laloo

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Cough is a common symptom of most respiratory disorders and is a frequent reason for patients of all ages to consult their doctor. Chronic cough has been estimated to occur in 14–23% of nonsmoking adults in the US,^{1,2} where it appears to be the fifth most common symptom to be seen in outpatient clinics.³ One of the recognised functions of cough is to clear excessive secretions from the respiratory tract and, as such, it is a useful protective reflex. Persistent cough also occurs in the absence of excessive mucus production and could be triggered by the presence of a tumour or foreign body. Often, there is no visible trigger but the presence of a heightened cough sensitivity. In the latter category, one can include viral upper respiratory tract infections, some patients with asthma, post-nasal drip and gastro-oesophageal reflux. The differential diagnosis of chronic cough is extensive and includes infections, inflammatory and neoplastic conditions, and many pulmonary conditions may present solely as a troublesome cough. In a handful of patients, there is no cause found despite thorough investigation or intensive treatment of suspected causes. Persistent cough interferes with quality of life with social embarrassment and deranged sleep and not rarely, patients experience respiratory muscle cramp and ache, with fractured ribs, urinary incontinence and rarely syncopal attacks. A rational approach to the diagnosis and management of chronic persistent cough has been made possible by recent developments in our understanding of the pathophysiology of the cough reflex.

Physiology and pathology of cough

The cough reflex is subserved by vagal efferent pathways arising from the trachea and intrapulmonary airways, and also by the larynx whose afferent nerves pass into the superior laryngeal nerves. Cough-sensitive nerves in the lower airways extend to the division of segmental bronchi⁴ and possibly beyond. The most important tussigenic zones are at the level of the larynx and trachea, especially in the region around the carina. Sensory nerve fibres presumed to mediate cough are present in the airway epithelium and have been observed under the electron microscope.^{5,6} Cough receptors have also been described in the auditory canal which are subserved by the auricular branch of the vagus nerve. The afferent pathways are carried to the medulla in the brainstem. Neurotransmitters such as 5-hydroxytryptamine and γ -aminobutyric acid have been implicated, and the antitussive effects of opiates may be mediated through an effect on these neurotransmitters. An abnormality of these central pathways in chronic persistent dry cough is a possibility.

Afferent nerve endings of the tracheobronchial tree can be divided into four types: slow-adapting pulmonary stretch receptors, rapidly adapting pulmonary stretch or irritant receptors, pulmonary C-fibres or J-receptors, and bronchial C-fibres.⁷ It is likely that all the known categories of airway afferent receptors participate in the cough reflex, with the primary mechanism being activation of irritant receptors and of bronchial C-fibres. Various tussive agents such as citric acid, capsaicin and low-chloride content solutions are used to assess the cough reflex, and although some of the stimuli have been used as specific stimulants of certain afferent nerve endings, the evidence that they are selective for one type of receptor (eg, irritant receptors versus bronchial C-fibres) in man is circumstantial at best. Nevertheless, these stimuli can be used to provide an index of the state of the cough reflex in persistent cough.

Of relevance to the evaluation and treatment strategies for persistent dry cough is the fact that the cough response can be augmented by various mediators of inflammation such as the prostaglandins PGE₂ and PGF_{2 α} through a process of sensitisation.⁸ Hence, although cough can be induced directly by airway secretions and irritants, persistent cough may also result from an increase in the sensitivity of the cough receptor. Patients with a nonproductive persistent cough due to a range of causes possess an enhanced cough reflex to

capsaicin when compared to healthy noncoughing subjects.⁹ Successful treatment of the primary condition underlying the chronic cough often leads to a normalisation of the cough reflex.¹⁰ In contrast, patients with a productive cough such as bronchiectasis and chronic bronchitis do not demonstrate an enhanced cough reflex.

Cough can be stimulated by bronchoconstriction but it appears that these phenomena are subserved by different neural pathways. Cough very often occurs independently of bronchoconstriction and cough often occurs in asthmatics without evidence of bronchoconstriction.

Common causes of persistent dry cough

Several common causes of persistent dry cough have been identified and are usefully considered separately. Smoking is a common independent determinant of cough, with or without mucus hypersecretion. There are several explanations for the 'smoker's cough', including bronchitis and airflow limitation, that will not be considered here. However, a smoker may also develop a chronic cough due to other causes not directly related to cigarette smoke.

UPPER RESPIRATORY TRACT INFECTION

This is perhaps the most common cause of acute cough, that may persist for months or years.^{11,12} Some patients with a long history of dry cough describe the onset of their cough following an upper respiratory tract infection. An increased cough reflex to capsaicin is usually present and disappears as the spontaneous cough recedes.¹³ Bronchial epithelial inflammation and damage has been demonstrated in children with chronic cough following lower respiratory tract illness. Irritants may penetrate more readily through the damaged epithelium, and endogenous peptidases may be reduced allowing a greater concentration of endogenous tachykinins to stimulate hypersensitive cough receptors. However, the basis for the persistence of cough after the infection remains to be elucidated. Inhaled corticosteroid therapy is usually effective in controlling the cough.

POST-NASAL DRIP

The strong association between post-nasal drip (rhinosinusitis) and chronic persistent cough is based on epidemiologic evidence and on a prospective study in adults.^{2,14} Post-nasal drip, or nasal catarrh, is characterised by a sensation of nasal secretions or of a 'drip' at the back of the throat, often accompanied by frequent throat clearing. With sufficient nasal blockage and congestion, there may be a nasal quality to the voice. Physical examination of the pharynx is often unremarkable although infrequently, a 'cobblestoning' appearance of the mucosa and draining secretions are observed. Computed tomography (CT) of the sinuses may reveal mucosal thickening or sinus opacification and air-fluid levels. An extrathoracic variable upper airway obstruction has been described presumably arising from upper airway inflammation.¹⁵ Excitation of laryngeal cough receptors by secretions emanating from the nasal cavity or sinus is the most likely mechanism for cough associated with the post-nasal drip.

Topical administration of corticosteroid drops in the head-down position is probably the best treatment, sometimes with the concomitant use of antihistamines. A response is usually observed with two or three weeks of treatment. Topical decongestant vasoconstrictor sprays may be useful adjunct therapy for a few days, but rebound nasal obstruction may occur after prolonged use. This is useful to relieve nasal obstruction, therefore increasing the penetration of topical steroids into the sinuses. Antibiotic therapy is advisable when mucopurulent secretions are present. Post-nasal drip is a very common cause of cough and empirical therapy is justified in the presence of suggestive symptoms.

ASTHMA

Chronic dry cough may occur in asthma in different clinical settings. Asthma may present predominantly with cough, often nocturnal, and the diagnosis is supported by reversible airflow limitation and bronchial hyperresponsiveness.¹⁶ This condition is often referred to as 'cough-variant' asthma which is a common type of asthma in children. Elderly asthmatics may give a history of cough prior to a diagnosis of asthma made on the basis of episodic wheeze.¹⁷ Cough may also occur as a sign of worsening of asthma usually presenting first at night, associated with other symptoms such as wheeze and shortness of breath with falls in early morning peak flows.¹⁸ On the other hand, some patients with asthma develop a persistent dry cough despite good control of their asthma with anti-asthma therapy. There may be another associated cause for the cough such

as post-nasal drip or gastro-oesophageal reflux. Twenty-four hour ambulatory monitoring of cough in such patients reveals a wide range of cough counts (45 to 1577 coughs), with very few coughs occurring during the sleeping hours.¹⁹

Patients with asthma do not usually have an enhanced cough reflex, apart from a subgroup with a persistent cough.^{9,19} In these patients, cough receptors may be sensitised by inflammatory mediators such as bradykinin, tachykinins and prostaglandins. Induction of sputum by inhalation of hypertonic saline often reveals a predominance of eosinophils, and bronchial hyperresponsiveness is invariably present. A condition of eosinophilic bronchitis in patients with chronic cough associated with eosinophils in sputum but without bronchial hyperresponsiveness has been described.²⁰ However, the cough and sputum production is responsive to steroids. It is not clear whether this condition is associated with an enhanced cough reflex.

Treatment of cough occurring with asthma is similar to that for 'typical' asthma, with maintenance inhaled corticosteroid therapy and bronchodilators such as β -adrenergic agonists. Often, a trial of oral corticosteroids (eg, prednisolone 40 mg daily for two weeks) is recommended. Treatment with nedocromil sodium can be a useful addition.²¹

GASTRO-OESOPHAGEAL REFLUX

Patients with symptoms of reflux such as heartburn and chest pain may also complain of a chronic persistent dry cough. Not infrequently, there may be no symptoms of gastro-oesophageal reflux^{22,23} or impaired clearance of oesophageal acid.²⁴ Treatment of acid reflux with agents that suppress acid production or with other anti-reflux measures is usually effective in the treatment of cough.^{25,26} An oesophageal-tracheobronchial cough reflex mechanism has been proposed on the basis of studies in which distal oesophageal acid perfusion induced coughing episodes in such patients, while saline alone induced a lesser number of episodes. Local distal oesophageal perfusion of lignocaine suppressed the acid-induced cough in the patients with chronic cough, and the inhaled anticholinergic agent, ipratropium bromide, was also effective. Thus, the afferent limb was antagonised by lignocaine while the efferent limb by ipratropium bromide. Over 90% of the cough episodes are temporally related to reflux episodes. Significant reflux occurs in both supine and upright positions. A high proportion of patients with gastro-oesophageal reflux also appear to have gastrohypopharyngeal reflux, and there may be a direct effect of acid reflux on cough receptors in the larynx and trachea. Continuous monitoring of tracheal and oesophageal pH in patients with symptomatic gastro-oesophageal reflux has demonstrated significant falls in tracheal pH (down to 4.10) during these episodes of reflux.²⁷ This direct effect may explain the occurrence of hoarseness and upper airway symptoms in these patients.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR COUGH

Angiotensin-converting enzyme (ACE) inhibitors are often prescribed for the treatment of hypertension and heart failure and cough has been observed in up to 2–8% of treated patients. The effect disappears rapidly following withdrawal of drug. Patients with ACE inhibitor cough demonstrate an enhanced response to capsaicin inhalation challenge²⁸ and ACE inhibitor ingestion by normal volunteers increased the capsaicin cough response.²⁹ The mechanisms underlying ACE inhibitor cough are not clear. Cyclo-oxygenase inhibitors inhibit the cough, suggesting that prostaglandins are important. One hypothesis is that ACE inhibitors prevent the degradation of endogenous kinins such as bradykinin, and allows bradykinin to sensitise the cough receptors directly or through the release of prostaglandins. The cough response to bradykinin has been shown to be increased in such patients.³⁰ ACE inhibitor cough has been successfully prevented by sodium cromoglycate.³¹

CHRONIC PERSISTENT COUGH OF UNKNOWN CAUSE

Identification of a potential cause has been reported in 78–99% of patients attending a specialised cough clinic.^{10,14} Treatment of identifiable causes may also not be successful. Such patients remain a difficult group to treat because most available antitussive agents are not very effective. These patients present in a similar way as others where an identifiable cause has been found. An enhanced cough reflex is found. Patients often complain of a persistent tickling sensation in the throat that often leads to paroxysms of coughing. This sensation can be triggered by factors such as changes in ambient temperature, taking a deep breath, cigarette smoke or other irritants such as aerosol sprays. These symptoms are the hallmark of a sensitised cough reflex. Attempts have been made to identify abnormalities of the neural sensory system in the airways. An increase in calcitonin-gene-related-peptide-immunoreactive nerves has been

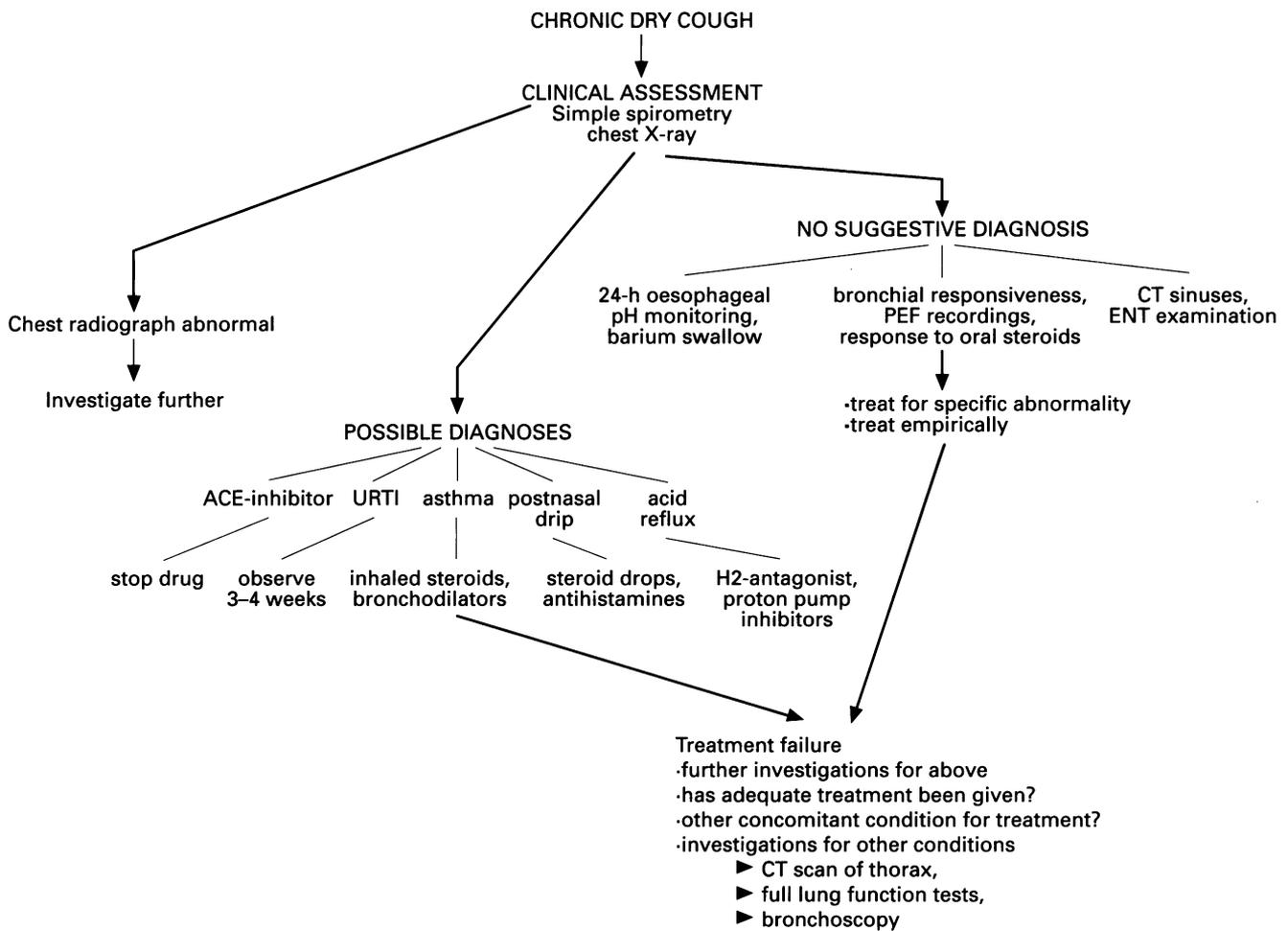


Figure Some approaches to the investigation of persistent dry cough. Abbreviations: ACE: angiotensin-converting enzyme; URTI: upper respiratory tract infection; PEF: peak expiratory flow; CT: computed tomography; ENT: ear, nose, and throat

observed in such patients.¹³ In a group of nonasthmatic patients with chronic dry cough, increased epithelial desquamation and inflammatory cells, particularly mononuclear cells, has been observed.³² It is not known whether or not these features represent the sequellae of chronic trauma to the airway wall following intractable cough.

Because no clear effective and safe antitussives are available, the control of persistent cough without associated cause remains difficult. Opiates are the best antitussives that work centrally but they must be given at high doses that usually induce drowsiness, nausea and vomiting. Inhalation of local anaesthetics may provide temporary relief but at the expense of suppressing upper airway defensive reflexes. Better antitussives may be found when mediators involved in the enhanced cough reflex and when the neurotransmitters involved in the central control of cough are better defined.

A practical approach to chronic persistent cough (figure)

The clinical approach to cough is to identify and treat the cause(s). One approach is illustrated in the figure and is based on our experience of running a cough clinic at the Royal Brompton Hospital (box 1). The history and examination will often indicate likely associated diagnoses, and the timing of various investigations may be variable from patient to patient. Initial investigation may be limited to a chest X-ray if there is a high suspicion of a tumour, particularly in a smoker. A period of observation of three to four weeks in a patient who provides a good history of an upper respiratory tract infection prior to further investigation or therapeutic trial is adequate, although inhaled corticosteroids may be useful in controlling this type of cough.

Post-nasal drip, asthma and gastro-oesophageal reflux, the three most common conditions associated with chronic dry cough, should be considered at this stage.³³ It would be sensible in the diagnostic approach to exclude these conditions first. Direct inspection of the nasal passages and throat, together

Common causes of cough
● acute infections (eg, tracheobronchitis, bronchopneumonia, viral pneumonia and acute-on-chronic bronchitis)
● chronic infections (eg, bronchiectasis, tuberculosis and cystic fibrosis)
● airway disease (eg, asthma, chronic bronchitis and chronic post-nasal drip)
● parenchymal disease (eg, interstitial fibrosis, emphysema)
● tumours (eg, bronchogenic and alveolar cell carcinomas, and benign airway and mediastinal tumours)
● foreign body
● cardiovascular (eg, left ventricular failure, pulmonary infarction and aortic aneurysm)
● other disease (eg, reflux oesophagitis, recurrent aspiration)
● drugs (eg, ACE inhibitors)

Box 1

Proposed treatments for specific causes of dry cough

- asthma: β -adrenergic agonist bronchodilator and inhaled corticosteroids
- allergic rhinitis: topical nasal steroids and antihistamines
- oesophageal reflux: proton pump inhibitor/H₂-histamine receptor antagonist
- ACE-inhibitor (for systemic hypertension): alternative therapy for hypertension
- post-viral cough: trial of inhaled corticosteroids; symptomatic relief (eg, simple linctus)

Box 2

with a CT scan of the sinuses, may be indicated, and ambulatory pH monitoring, with possible gastroscopy. The diagnosis of asthma is supported by the presence of significant diurnal variation in peak flow measurements, bronchial hyperresponsiveness to histamine or methacholine challenge and eosinophils in induced sputum. However, a therapeutic trial may be the best initial approach particularly when the history and examination provide supportive clues. It is important that effective doses of medication are given for sufficient time. It has been stated that a longer-than-usual period of treatment is sometimes necessary to control the cough. Post-nasal drip is a most often overlooked condition and aggressive treatment should consist of steroid nasal drops with an antihistamine, with the possibility of adding antibiotic therapy and a short period of a nasal decongestant. Inhaled steroid therapy or acid suppression with H₂-histamine blockers or a proton pump inhibitor would be indicated for asthma and gastro-oesophageal reflux. It ought to be stressed that more than one of these conditions may coexist and cough may only respond with concomitant treatment of both (eg, asthma with post-nasal drip).^{33,34} Often, symptoms of reflux, post-nasal drip or asthma are absent, and a 'blind' therapeutic trial of medication specific for these conditions may be indicated. However, it would be preferable to proceed to investigations first.

Assessment of the cough reflex with capsaicin or low chloride content solutions is at present only a research tool but the presence of an enhanced cough reflex does support the presence of an abnormal cough response. Measurement of the cough reflex may be used to assess the therapeutic efficacy of a particular treatment. Bearing in mind that there are a myriad of other less common causes of a chronic cough, investigations must proceed further if the above causes are excluded. Full lung function tests to include lung volumes and gas transfer factor, and CT of the lungs should be considered in case of bronchiolar or parenchymal disease or unsuspected bronchiectasis. Fibre-optic bronchoscopy may be considered; apart from excluding small central tumours, it may also provide mucosal biopsies for histological examination.

Whether or not cough may entirely arise from psychogenic causes is unclear but it is conceivable that an enhanced cough reflex is made worse by psychogenic factors. In a minority of cases, a psychiatric assessment with appropriate treatment is useful.

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