

# Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome

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**Abstract:** Chronic cough is a common symptom that can be difficult to manage because associated causes may remain elusive and treatment of any associated cause may not provide relief. Current antitussives have limited efficacy and undesirable side-effects. Patients with chronic cough describe sensory symptoms suggestive of upper airway and laryngeal neural dysfunction, and report cough triggered by low-level physical and chemical stimuli supporting the concept of cough reflex hypersensitivity. Mechanisms underlying peripheral and central augmentation of the afferent cough pathways have been identified. Chronic cough is a neuropathic condition that could be secondary to sensory nerve damage caused by inflammatory, infective and allergic factors. Recent success in the treatment of chronic cough with agents used for treating neuropathic pain such as gabapentin and amitriptyline would also support this concept. Research into neuropathic cough may lead to the discovery of more effective antitussives.

**Keywords:** Chronic cough; cough hypersensitivity syndrome; gastroesophageal reflux

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## Introduction

Cough is a chronic symptom not only found in patients with a range of respiratory and non-respiratory conditions but also in apparently “normal” individuals. Chronic cough is very prevalent in the community (9-33% according to various studies) and may be increasing in association with increasing environmental pollution to which we are increasingly exposed to (1-3). An acute cough is a cough that lasts for less than 3 weeks and is usually caused by an upper respiratory tract virus infection such as the common cold. A cough that persists for more than 8 weeks is termed “chronic” although it may have been persistent for much longer periods before presentation to the doctor. Chronic cough can persist for months and years and remains a difficult problem to manage because of our poor understanding of why a cough can be so persistent and also by the lack of effective antitussive therapies. However, there has been recent progress both in our diagnostic approach

and in our general understanding of the process of chronic cough over the recent years.

## Approach to the cough patient in the clinic

The recognition of chronic cough as being an important increasing problem has led to the publication of national guidelines for the diagnosis and management of cough in many countries in the world (4-7). These guidelines correctly propose an anatomico-diagnostic approach to the potential causes of the chronic cough, and treating the cause. The most common conditions associated with causing chronic cough, with a normal chest radiograph, include the corticosteroid-responsive eosinophilic airway diseases (asthma, cough variant asthma and eosinophilic bronchitis), and a range of conditions typically associated with an inhaled corticosteroid-resistant cough including gastro-oesophageal reflux disease (GORD) and the post-nasal drip syndrome or rhinosinusitis (*Table 1*). There are

**Table 1** Types of chronic cough

1. Chronic cough associated with conditions that are treated leads to resolution of cough, e.g., asthma, gastroesophageal reflux disease (GORD), upper airway syndrome
2. Chronic cough associated with conditions that are treated does not lead to resolution of cough, e.g., asthma, chronic obstructive pulmonary disease (COPD), GORD
3. Chronic cough not associated with any conditions and unresponsive to any treatments of conditions, such as asthma, GORD, COPD, upper airway syndrome
4. Chronic cough associated with an increased cough reflex
5. Chronic "cough hypersensitivity syndrome" encompasses patients with an increased cough reflex that could be in any of the examples above

some geographical variants. In China, a recent survey of chronic cough patients presenting to a hospital respiratory clinic showed a distribution of associated diagnoses as described in Europe or USA (8). However, in Japan, atopic cough and sinobronchial disease are more commonly diagnosed, while GORD is much less so (9,10).

### Asthma and eosinophilic conditions

Chronic cough in asthma is not always associated with airflow obstruction, wheezing or dyspnoea. Asthma can predominantly present with cough, which is often nocturnal; the diagnosis is supported by the presence of bronchial hyper-responsiveness (11). Cough is often the symptom most reported by patients with chronic asthma, despite achieving good asthma control with inhaled corticosteroids. Other related conditions have been described: cough-variant asthma, atopic cough, and eosinophilic bronchitis. Cough-variant asthma presents with a dry cough, often nocturnal, without other symptoms of asthma; it is characterised by bronchial hyper-responsiveness, and eosinophilic inflammation in sputum, bronchoalveolar lavage fluid, or airway submucosa (12). Atopic cough is an isolated chronic cough characterised by an atopic background, eosinophilia in sputum, cough hypersensitivity, normal pulmonary function and airway responsiveness (13). The clinical condition of eosinophilic bronchitis is characterised by a troublesome cough without other symptoms of asthma or bronchial hyper-responsiveness, but with increased numbers of eosinophils in the sputum (14,15). Pathological features of the airway submucosa are similar to those of asthma (16).

Eosinophilic-associated cough is usually controlled by inhaled corticosteroids, implying a role for inflammatory factors. Although patients with classic asthma do not usually have an enhanced cough reflex, patients with cough-variant

asthma might do so (17), as do patients with eosinophilic bronchitis and atopic cough. Inflammatory cells, such as eosinophils, have been implicated, since corticosteroids reduce eosinophilic inflammation and also inhibit cough. A case-report of hypereosinophilic syndrome also supports a direct effect of eosinophils on the cough reflex (18). Sensitivity to capsaicin in asthmatic patients who are allergic to birch pollen, increases during the birch pollen season (19), suggesting that allergic inflammation can trigger neurogenic mechanisms of sensitisation.

Chronic cough is now being considered as an important symptom of chronic obstructive pulmonary disease (COPD) that has been relatively undervalued so far. It is associated with an augmented capsaicin cough reflex (17,20). Cough can be the earliest sign of an impending exacerbation and can be the worst symptom experienced by the COPD patient. More importantly, cough impacts adversely on patients' health status and forms an important component of recently validated quality of life instruments (21).

### Gastro-oesophageal reflux disease

GORD encompasses symptoms or complications such as heart burn, chest pain, sour taste or regurgitation, and also a chronic persistent cough. Direct aspiration of gastric contents into the larynx and upper airways that could directly stimulate cough receptors and increases in tracheal acidity have been recorded during episodes of reflux (22), but the majority of coughs in GORD does not coincide with an acid reflux episode (23). In fact, episodes of reflux could precede or occur after a cough (24). The fact that very effective pharmacological control of gastric acid with proton pump inhibitors are not usually effective in controlling cough associated with GORD would suggest that acid reflux alone does not cause the cough (25). The role of non-

**Table 2** Symptoms associated with cough hypersensitivity syndrome

Irritation in the throat or chest
Clearing the throat
Hoarse voice
Dysphonia
Vocal cord dysfunction
Chest irritation
Chest tightness
Globus
Gastro-oesophageal reflux symptoms

acid reflux mechanisms still need to be excluded and the potential use of fundoplasty for GORD-associated cough is unclear. It is possible that that gastric reflux contents may be related to the cough hypersensitivity syndrome in that there is a greater sensitivity of ‘cough’ receptors caused by mucosal damage at the level of the oesophagus. Laryngopharyngeal reflux is an extraesophageal variant of GORD recognised by otorhinolaryngologists, and the symptoms often include hoarseness, chronic cough, sore throat, globus pharyngeus, and throat-clearing (26).

### Post-nasal drip

Post-nasal drip (“nasal catarrh”) is characterised by a sensation of nasal secretions or of a “drip” at the back of the throat, accompanied very often by a frequent need to clear the throat (“throat-clearing”) associated with nasal discharge or nasal stuffiness. This symptom of throat clearing could also be considered as a symptom of “hypersensitivity”. The term upper airway cough syndrome is proposed as an alternative to stress the association of upper airways disease with cough (27). The pathogenesis of cough in the post-nasal drip syndrome may be related to the direct pharyngeal, laryngeal or sublaryngeal stimulation by the mucoid secretions from the rhinosinuses which contain inflammatory mediators that could induce cough. Specific treatment of rhinosinusitis with an antihistamine, an anticholinergic and topical corticosteroids provided only partial relief of the accompanying cough (28).

### “Idiopathic” cough or cough of unknown cause

*Table 1* summarises the various types of chronic cough. Out of those mentioned, the chronic cough associated with conditions that are treated that does not lead to resolution

of cough and the chronic cough not associated with any conditions and unresponsive to any treatments remain the most difficult to manage. These patients are often labelled as “idiopathic” cough and constitute a significant proportion of any cough clinic (1). Therefore, such a label is usually applied to a chronic cough that is not apparently associated with known causes of cough, established either through intensive investigation to exclude these causes or through trial of therapy of these causes. The initiating cause of the cough may have disappeared, but its effect on enhancing the cough reflex may be more prolonged. An example could be the transient appearance of an upper respiratory tract virus infection or an exposure to toxic fumes that causes prolonged damage of the airways mucosa. These insults may have induced inflammatory neuropathic changes in the sensory nerves. The repetitive mechanical and physical effects of coughing bouts on airway cells could activate the release of various chemical mediators that could enhance chronic cough through inflammatory mechanisms (29), providing a positive feed-forward system for cough persistence. Changes in the upper airways of inflammation and tissue remodelling may be induced by various causes associated with cough or by the act of coughing itself that could lead to an enhanced cough reflex, that in turn is responsible for maintaining cough. The cough becomes “idiopathic” when the primary inciting cause has resolved while cough remains persistent.

### Symptoms associated with chronic cough

Patients with chronic cough often complain of a persistent tickling or irritating sensation in the throat (feeling of an itch) or a choking sensation, and it is sometimes felt in the chest, often leading to paroxysms of coughing. Other symptoms associated with chronic cough patients include an irritation in the throat or chest, with clearing of the throat, an irritation in the chest associated with chest tightness, hoarse voice and dysphonia, vocal cord dysfunction symptoms, a feeling of globus, dysphagia and acid reflux symptoms (*Table 2*). Coughing induced by reflex mechanisms, as distinct from voluntary or habit coughing, is often associated with unpleasant sensation in the chest or throat; however this is not always present, especially with conditions in the lower airways involving, for example, excessive mucus. The terms used to describe the sensations are multiple, and include irritation, rawness, even pain (30). Unpleasant sensations related to cough may be localized in the throat or in the chest. Other respiratory sensations, such

**Table 3** Characteristics of cough hypersensitivity syndrome

1. Irritation in the throat or upper chest: laryngeal/pharyngeal/upper airway paresthesiae
2. Cough triggered by non-tussive stimulus eg talking, laughing: allotussia
3. Increased cough sensitivity to inhaled stimuli and number of triggers: hypertussia
4. Cough paroxysms that are difficult to control
5. Triggers:
Singing, talking, laughing, deep breath: mechanical activation
Changes in temperature, cold air: thermoactivation
Aerosols, scents, odors: chemoactivation
Lying supine
Eating
Exercise

as air-hunger, sense of effort and sense of lung volume are not usually associated with cough. Triggers such as changes in ambient temperature, taking a deep breath, laughing, talking over the phone for more than a few minutes, cigarette smoke, aerosol sprays, perfumes or eating crumbly dry food are common.

Urge-to-cough is a distinct sensation that, with increasing levels of cough stimulation, has a lower threshold and occurs before the cough itself (31). While urge-to-cough has no particular anatomical location, unpleasant sensations related to cough may also be felt in the chest or the throat. The urge-to-cough has been shown to be a sensory measure of this sensation of tickling or irritation that is induced at lower concentrations of inhaled capsaicin than those that will elicit a cough reflex (32).

### Cough hypersensitivity syndrome

The combination of irritation in the throat or upper chest representative of laryngeal or pharyngeal or upper airway paresthesiae, of cough triggered by non-tussive stimulus such as talking, laughing termed allotussia, and of increased cough sensitivity to inhaled stimuli and number of triggers termed hypertussia (*Table 3*) suggest a disorder of airway sensory neural function that has led to the introduction of the term chronic “*cough hypersensitivity syndrome*” to describe chronic cough (33). This term proposes that this disordered sensory neural function (and hence the cough hypersensitivity which underlies

chronic cough in general) reflects an underlying sensory neuropathy. Recently, a Task Force of the European Respiratory Society has defined the cough hypersensitivity syndrome as “a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure” (34). The Laryngeal Hypersensitivity Questionnaire has been developed recently as a simple, non-invasive tool to measure laryngeal paresthesia in patients with laryngeal conditions such as chronic cough, paradoxical vocal fold movement (vocal cord dysfunction), muscle tension dysphonia, and globus pharyngeus (35), conditions which can be considered to be part of the cough hypersensitivity syndrome (36).

### Mechanisms of cough hypersensitivity

These potential mechanisms have recently been reviewed (37). Sensory afferent nerves are susceptible to sensitization by neuroactive molecules such as nerve growth factor through changing the activation profiles of cough afferent nerves, and facilitating afferent encoding signals in response to irritant stimuli (38-40). Furthermore, sensitization may be related to altered expression of ion channels and other receptor molecules, including TRPV1 which regulates afferent nerve excitability to many chemical stimuli (41). Cough hypersensitivity can also be induced when normal afferent signals are augmented by central events through the interaction of different subsets of afferent neurons in the brainstem (42). Neuropeptide expressed in airway nociceptors and airway mechanosensors can reduce the cough reflex threshold through the convergence onto common second order neurons in the brainstem (43). This process may lead to the amplification of the incoming signals that are received by the brainstem cough network. For example, cigarette smoke exposure in primates can lead to increased excitability of second order neurons in the brainstem receiving inputs from the airways, an effect prevented by blocking the neuropeptide, substance P (44). Induction of neuropeptide expression by airway mechanosensors following antigen or viral exposure (39,40) may negate the need for these convergent inputs to cause central sensitization. Neurons in the medulla receiving inputs from airway afferents also project to many subcortical nuclei in the pons, thalamus, hypothalamus, midbrain and amygdala. Using functional brain imaging, neural activation pathways have been shown during voluntary cough and the urge-to-cough (45,46).

### Inflammatory factors and neurogenic mechanisms

Chronic cough has been associated with airway inflammation and remodelling. Damaged bronchial epithelial, basement membrane thickening and a chronic inflammatory infiltrate have been described in airway biopsies from patients with unexplained chronic cough (47-49). In bronchial biopsy studies of chronic cough, an increase in the number of mast cells together with features of airway wall remodelling characterised by an increase in vascular profiles, subepithelial fibrosis and hyperplasia of goblet cells has been reported (47). Other studies have reported increased mast cells and neutrophils in bronchoalveolar lavage fluid, with increased levels of various inflammatory biomarkers including histamine, prostaglandin D<sub>2</sub> and E<sub>2</sub>, TNF $\alpha$  and IL-8 in induced sputum samples (50-53). The expression of the growth factor, TGF $\beta$ , was increased in the airways of patients with chronic cough in relation to the degree of airway fibrosis as measured by the thickness of the subbasement membrane (53), and that could in turn lead to activation of the cough reflex.

Chronic eosinophilic conditions such as asthma, cough variant asthma and eosinophilic bronchitis frequently present as chronic cough and suppression of the eosinophilic inflammation improves cough, indicating a pathogenic role for eosinophils. Eosinophils co-localise with sensory airway nerves (54), which may lead to the release of mediators including eosinophil peroxidase and leukotrienes (55). The neuroinflammatory effects of these eosinophil derived mediators may provide a mechanism whereby cough reflex hypersensitivity may be maintained during airway inflammation (56). Inhalation of inflammatory mediators such as bradykinin and PGE<sub>2</sub> by healthy volunteers upregulated the capsaicin cough response (57). Both mediators are known to indirectly sensitize airway neuronal responses to capsaicin presumably via activation of the TRPV1 channel by intracellular (protein kinase) pathways (58). Increased H<sup>+</sup> ions in exhaled breath condensates from chronic cough patients has been reported, which together with the increase in TRPV1 receptors reported in the epithelial nerves of chronic cough patients (41,59) could form the basis for the increased cough.

There is evidence of airway neuronal activation reflected in the detection of elevated levels of substance P and neurokinin A in induced sputum samples obtained from asthmatic coughers (60). Furthermore, levels of the neuropeptide calcitonin-gene-related peptide (CGRP) measured in airway lavage samples from paediatric patients

with chronic cough were positively correlated with capsaicin cough reflex sensitivity (61). CGRP expression is also reported to be increased in airway nerves from patients with chronic cough (62). Nerve growth factor (NGF) is released from a variety of airway cells including the bronchial epithelium and has important neuroinflammatory consequences which may be important in chronic cough. In diseases such as cryptogenic fibrosing alveolitis where cough is often an intractable problem airway levels of NGF are elevated (63). NGF may exert its action on airway sensory nerves via sensitization of the TRPV1 receptor. In primary cultured rat dorsal root ganglion neurones, NGF potentiated basal and capsaicin-induced expression of substance P and TRPV1 suggesting a mechanism for chronic nerve sensitization (64). In patients troubled with airway sensory hyperreactivity to scents and chemicals, typically manifest by bouts of coughing, higher levels of NGF have been detected in nasal secretions compared to healthy controls (65), although in bronchoalveolar lavage fluid obtained from chronic cough patients, the levels of NGF were not increased (53).

### Respiratory viruses and cough: a neuropathic link?

Respiratory viral infections such as rhinoviruses or influenza viruses are typically accompanied by an acute cough, but this cough may persist for weeks or months in some patients. Experimental models of rhinovirus infection have demonstrated cough reflex hypersensitivity to chemical (66,67) and mechanical stimulation (68). The mechanisms by which these respiratory viruses can induce neuropathic changes are unknown but could certainly contribute to the cough hypersensitivity syndrome.

### Evidence from recent antitussive therapies of a neuropathic cough

The recent use of drugs such as amitriptyline and gabapentin used to treat chronic pain as an antitussive also lends support to the concept of chronic cough being a neuropathic condition. In 12 patients treated with the antidepressant amitriptyline, 11 had prompt significant reduction of their cough (69). A prospective, randomized, controlled open trial comparing the effectiveness of amitriptyline versus codeine/guaifenesin for chronic cough with suspected post-viral vagal neuropathy showed that most subjects in the amitriptyline arm achieved a complete

response while none of the codeine/guaifenesin group had a complete response (70). Indeed, ear-nose-throat specialists have long recognised chronic cough as a vagal neuropathic condition and have taken such an approach for a while. Gabapentin is another agent that has been used to treat neuropathic pain and has been shown to be effective in reducing cough in chronic cough patients in a randomised double-blind trial, suggesting that there is a central reflex sensitisation in refractory chronic cough (71). Gabapentin was also beneficial in chronic cough patients with laryngeal sensory neuropathy (72).

There is evidence that amitriptyline and gabapentin have central anti-nociceptive actions. Thus, relief from rectal pain by amitriptyline is associated with a reduction in pain-related responses in the anterior cingulate cortex in irritable bowel syndrome (73). Gabapentin reduces pain via an action on GABAergic neurotransmission or voltage gated ion channels in the spinal cord, midbrain, thalamus and/or sensory and insula cortices in the brain (74,75). Although gabapentin was effective in reducing cough in the chronic cough patients, it had no effect on capsaicin sensitivity arguing against a suppressive effect on cough reflex pathways. It is not excluded that amitriptyline and gabapentin may also have actions outside of the central nervous system, primarily by blocking the activation of peripheral afferent terminals.

## Conclusions

The approach to management of chronic cough will still focus on diagnosing associated conditions and their treatments. The concept of cough hypersensitivity syndrome will help us understand the mechanisms underlying cough and will provide better antitussives to treat chronic cough.

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