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► **To cite this version:**

| K F Chung. : a more precise label for chronic cough. Pulmonary Pharmacology & Therapeutics, 2011, 24 (3), pp.267. 10.1016/j.pupt.2011.01.012 . hal-00750475

HAL Id: hal-00750475

<https://hal.science/hal-00750475>

Submitted on 10 Nov 2012

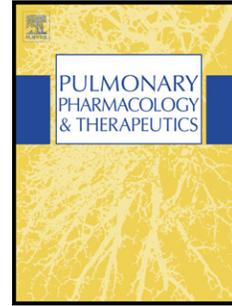
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Accepted Manuscript

Title: Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough

Authors: K F Chung



PII: S1094-5539(11)00017-4

DOI: [10.1016/j.pupt.2011.01.012](https://doi.org/10.1016/j.pupt.2011.01.012)

Reference: YPUPT 1081

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 23 November 2010

Revised Date: 11 January 2011

Accepted Date: 24 January 2011

Please cite this article as: Chung KF. Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough, *Pulmonary Pharmacology & Therapeutics* (2011), doi: 10.1016/j.pupt.2011.01.012

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Chronic 'cough hypersensitivity syndrome': a more precise label for chronic cough

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Summary

Chronic cough remains a challenge to many clinicians because there is often no diagnostic link to causation, and because indirect antitussives are largely ineffective. Chronic cough can also be a predominant symptom associated with many chronic respiratory diseases such as COPD, asthma and pulmonary fibrosis. Chronic cough itself does impair quality of life and is associated with psychological impairment. The symptoms associated with chronic cough include persistent tickling or irritating sensation in the chest or throat, hoarse voice, dysphonia or vocal cord dysfunction. Currently, the clinical diagnosis of cough is associated with chronic cough caused by airway eosinophilic conditions such as asthma, gastro-oesophageal reflux disease or postnasal drip (or upper airway syndrome) , which implies cause and effect, or with chronic cough associated with other diseases such as COPD, cancer or heart failure, that does not necessarily imply cause and effect. A recently-recognised category is idiopathic cough with no associated or causative diagnosis. We suggest that there is a better label needed for chronic cough, that includes the common association with a hypersensitive cough response to tussive stimuli such as capsaicin or citric acid. This would invoke a hypersensitive syndrome, and there are good reasons to use a new label that would encompass the problem of chronic cough: the chronic 'cough hypersensitivity syndrome'. This would focus the problem on the cough symptomatology and lead to greater focus on understanding the mechanisms of cough sensitisation, with the ultimate aim of obtaining more effective antitussives.

Introduction

Cough is a common symptom of many diseases including non-respiratory diseases and cough that persists for more than 8 weeks, termed chronic cough, is a common problem often encountered by most doctors. Epidemiologic studies indicate that chronic cough is very prevalent in the community (up to 20% of the population) and could be increasing in relation to rising environmental pollution(1). Many patients seek medical advice specifically about their cough symptoms because chronic cough is an important cause of impaired quality of life. Some patients may have a chronic illness or disease associated with the cough while others may turn out to have 'idiopathic' or unexplained cough. Commonly, no treatments, either indirect or direct antitussives would appear to work(2), and therefore the problem of chronic cough remains important in the clinic. In some diseases such as idiopathic pulmonary fibrosis or COPD, cough may be the symptom of major importance for the patient, in contrast to other frequent accompanying symptoms such as dyspnea. In idiopathic cough, no 'causative factor is found or treatment of potential causative factors are not effective in controlling cough. Patients with chronic cough invariably have an enhanced cough reflex, which could be the basis of the chronic cough, but the mechanism(s) underlying this hypersensitivity deserves further understanding in order to obtain better treatments for the cough. On the basis of these recent observations and of the continuing burden of chronic cough, it is sensible to propose that chronic cough be labelled more precisely as a condition of *chronic 'cough hypersensitivity syndrome'* that will allow us to focus both at the clinical and mechanistic levels on this increasing problem of chronic cough. While the name 'cough hypersensitivity syndrome' has been proposed before (3), it is more

accurate to use the term *chronic 'cough hypersensitivity syndrome'* for a very specific group of chronic cough patients that I will define later.

Conditions associated with chronic cough (Table)

These have been the focus of many reviews and series from around the world in the last 40 years. Chronic cough is not uncommon and its prevalence varies from 9 to 33% of the population, and there is an association with cigarette smoking (4-6), with asthma or respiratory wheeze, or with symptoms of gastroesophageal reflux (5;7), and with exposure to environmental pollutants particularly PM₁₀ particulates (8;9).

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 gastroesophageal reflux disease (GORD) and the post-nasal drip syndrome or rhinosinusitis. There may be 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 (10). However, in Japan, atopic cough and sinobronchial disease are more commonly diagnosed, while GORD is much less so (11;12). The related conditions, cough variant asthma, atopic cough and eosinophilic bronchitis, are related to classic asthma, are all associated with an eosinophilic airway inflammation and the cough usually responds well to inhaled corticosteroid therapy.

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 (13), but the majority of coughs in GORD does not coincide with an acid reflux episode (14;15). In fact, episodes of reflux could precede or occur after a cough (16). 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. Rather one could argue that reflux of gastric contents may be related to cough hypersensitivity syndrome and to complicate the issue further the strain of coughing could cause or worsen the reflux.

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 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 (17). The pathogenesis of cough in the postnasal 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.

In summary, the clinical diagnosis of cough is associated with chronic cough caused by airway eosinophilic conditions such as asthma, gastro-oesophageal reflux disease or postnasal drip (or upper airway cough syndrome) , which implies cause and effect, or with chronic cough associated with other diseases such as COPD, cancer or heart failure, that does not necessarily imply cause and effect.

Idiopathic cough or cough of unknown cause

Recent series have identified a significant proportion of patients labelled as 'idiopathic' cough, ranging from 7 to 46%, despite thorough diagnostic workup (1). It may be interesting to determine whether this represents a genuine change from the situation 30 years ago or whether different methodologies were being used regarding diagnostic approaches. 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 results in prolonged damage of the airways mucosa. An example of this is the 'World Trade Centre cough syndrome' that occurred in patients exposed to the toxic fumes resulting from the collapse of the World Trade Centre on September 11, 2001(18). While the exposure was transient, it caused persistent coughing that has persisted to this day in many subjects.

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 (19), providing a positive feed-forward system for cough persistence. It seems possible that there is an induction of changes in the upper airways of inflammation and tissue remodelling 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 is 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, that often leads 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 and acid reflux symptoms. Reflex coughing, 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 various, and include irritation, rawness, even pain (20). Unpleasant sensation related to cough may be localized vertically, in the throat or in the chest, but not usually more precisely or laterally. Other respiratory sensations, such 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 (21;22). The parts of the cerebral cortex and upper brain that are activated by these sensations have also been mapped out (23). Urge-to-cough can occur with stimuli, such as aerosols of capsaicin, citric acid and distilled water, and intravenous injections of lobeline and capsaicin, that are too weak to cause cough, a sensation that can occur in the presence or absence of unpleasant sensations(20). While urge-to-cough has no particular location in the body, unpleasant sensation related to cough may also be felt in the chest or the throat (24). The urge-to-cough has been shown to be a sensory measure of this sensation of tickling or irritation that is induced at concentrations of inhaled capsaicin that are lower than those necessary to

elicit a cough reflex, that is a motor cough behaviour (25); it may also be present in patients with chronic cough but this has not been investigated systematically.

Quality of life in chronic cough and treatment effects

Quality of life cough questionnaire have helped to define the impact of chronic cough on the patient(26;27). Physical symptoms related to the direct effect of coughing such as syncope, urinary incontinence, vomiting, sleep deprivation and depression are some of the more severe symptoms associated with chronic cough. More than 50% of patients with chronic cough may have signs of depressive illness(28;29). Other generalised symptoms such as lethargy and tiredness, associated with chest muscular pains can also contribute to a reduction in quality of life, interfering with work and social life. The Leicester quality of Life questionnaire (LCQ) is a useful tool to assess cough and successful therapy of cough has resulted in clinically significant improvement in health-related quality of life as measured by LCQ(30;31).

A publication from a centre in Shanghai, China in the English literature reported findings in 110 patients with chronic cough, with nearly half of the patients been diagnosed with cough variant asthma, and the rest comprising of upper airway cough syndrome, gastroesophageal reflux, nonasthmatic eosinophilic bronchitis and post viral cough(10). They report 6.4% percent as being idiopathic, a figure smaller than that reported from other centres in UK. This report also presented data as to the effect of treatment on the cough with an improvement of total scores on a Leicester cough questionnaire (translated in Chinese) from 14.2 to 19.5, with improvements reflected in all the 3 domains, physical, psychological and social, although these effects while clinically significant may not be large improvements.

Concept of enhanced cough reflex and of cough sensitisation

The mechanisms of idiopathic cough are unclear but we assume that the initiating cause of the cough has disappeared, leaving an enhancement of the cough reflex which can be measured by the tussive response to inhalation of citric acid or capsaicin, as compared with non-coughers (32;33). The increase in cough sensitivity to capsaicin is related to the presence of a tickling or irritating sensation localised to the throat or lower chest area that often leads to a paroxysm of coughing which patients with chronic cough find most distressing because it cannot be controlled. This sensation may be a 'referred' sensation since very often there are no visible abnormalities of the pharynx and larynx that are associated. The cough paroxysm can be triggered in some patients by inhaling cold air, by a deep breath, by the act of laughing and by breathing irritants such as cigarette smoke, aerosol sprays or perfumes.

This enhanced cough reflex may result from an increased sensitivity of cough receptors with plasticity of the afferent innervation such as changes in nerve densities or in ion channels (peripheral sensitisation) (34;35). The presence of increased expression of the transient receptor potential vanilloid receptor, TRPV-1, in epithelial nerves of patients with non-asthmatic chronic cough indicates a potential mechanism of peripheral sensitisation(36). Indeed, TRPV-1 and other related channels such as TRPA1, are considered potential targets for new antitussives acting at the primary afferents(37). Inflammation and remodeling of the airway submucosa with an increase in submucosal mast cells and airway wall remodelling with goblet cell hyperplasia, subepithelial fibrosis and increased vascularity is reported in chronic cough patients (38). Increased mast cells have also been observed in bronchoalveolar lavage fluid (39), with increased neutrophils (40), and higher histamine,

prostaglandins PGD₂ and PGE₂, TNF α and IL-8 concentrations in induced sputum (41). These inflammatory changes could certainly contribute to peripheral sensitisation of the cough reflex. In addition, the physical damage to the airways from the coughing act could also contribute to the chronicity of the cough, a possibility worth exploring. The role of these inflammatory changes in enhancing cough sensitivity is unclear.

Peripheral cough sensors can be 'sensitized' in animals (35;42) with lowering of the threshold and increase the cough response to tussigenic agents such as citric acid or capsaicin, and increase the action potential response in fibres thought to originate from cough sensors. Atmospheric exposure to pollutants or experimental exposure to ozone lowers the cough threshold to agents such as citric acid and capsaicin (43). The disease process could cause a greater stimulus to cough sensors otherwise of 'normal' sensitivity; for example the presence of excess mucus, oedema in the mucosa, greater release of tussigenic agents such as bradykinin or neuropeptides, could move the cough sensor response up the stimulus/response curve and give the impression of sensitization while in reality it is the stimulus that is increased (44).

Central nervous sensitization of the cough reflex has also been shown in animals including primates. In particular, the role of substance P (SP) released from first-order neurones and acting on second-order neurones in the nucleus tractus solitarius (NTS) has been established, and the membrane receptor mechanisms on the second-order neurones has been analysed (45). With an upregulated cough reflex, due for example to inhaled pollutants, the SP levels in the NTS are increased, just as they are in the first-order neurones. Injections of SP into the NTS enhance coughing due to a peripheral stimulus, and NK1 receptor antagonists depress cough in animals (46;47). Disease processes in the airways

will sensitize the sensors there, which in turn will cause sensitization at the first- second-order neurones in the brainstem.

A new label for chronic cough: Chronic 'cough hypersensitivity syndrome'

Chronic 'Cough Hypersensitivity Syndrome' (CCHS) can be defined as a syndrome presenting with a chronic persistent cough that has lasted for more than 8 weeks, that is associated with characteristic trigger symptoms and sensations that indicate the presence of an enhanced cough reflex. This condition is usually unexplained by any associated medical conditions, or usually by lack of or poor response to treatments targeted at any medically-associated condition, but not exclusively.

Setting the name for this syndrome is not creating a new disease entity but in the case of CCHS, only culminating into the delineation of a distinct set of symptoms that has implications with regards to the underlying mechanism and to its management. Focusing on the cough means that we will need to define a semantic nomenclature and also study whether there are different types of cough from a study of cough patterns, acoustics and strength (48;49). We already have tools to diagnose and evaluate this new syndrome (50). These include: measurement of cough frequency in an ambulatory setting, quality of life (e.g. Leicester quality of life cough questionnaire), scale for measuring the severity of cough and the cough sensitivity using citric acid or capsaicin as tussive agent. How good are these measures of cough sensitivity in picking up hypersensitivity has not been worked out properly, and more work would be needed to define an abnormal response from a 'normal' response. Perhaps, other tussive stimuli may be more discriminatory. However, it should also be possible to develop a patient-based questionnaire to come to a diagnosis of CCHS. This would need further research into the symptoms and sensations of CCHS as related to

capsaicin cough challenge. There appear to be a good correlation between citric acid challenge and the cough frequency in chronic coughers and between citric acid cough challenge and the time spent coughing (51;52).

Implications of a CCHS label

This condition of CCHS will not be exclusively the province of the cough expert but can be used by other clinicians since this is a common condition. New guidelines for cough should recognise chronic cough as CCHS and provide guidance as to its diagnosis and management. The advantages of having the CCHS label are many-fold. First, from the clinical perspective, it will focus the mind on the cough problem as being an important issue for the physician to treat despite the lack of very effective antitussive therapies. There are some approaches that can be taken and these should probably be used in 'specialised' cough centres. Secondly, it will mean that such labels carry with it the knowledge that these patients have been investigated or had followed a pathway where the diagnosis of idiopathic cough has been reached. From the translational perspective, this group of patients called CCHS could be considered as a uniform population for testing novel agents to control chronic cough.

Having a new entity such as CCHS would signal to physicians and service providers a new category of specific patients where there is clearly an unmet need. It could also be the springboard for a global recognition of chronic cough through inclusion in the WHO International Classification of disease. For the translational researchers looking for new antitussive drugs, renewed impetus and encouragement to find pathways of cough hypersensitivity and new treatments for this syndrome.

CCHS and other hypersensitivity syndromes

The term airway sensory hyperreactivity (SHR) has been defined by Millqvist and colleagues as a syndrome of self-reported odour intolerance combined with heightened sensitivity of inhaled capsaicin (53). This syndrome has also been loosely referred to as airway symptoms due to chemicals, multiple chemical sensitivity syndrome and sick-building syndrome attributed to low level exposure to chemical and physical hazards in indoor environments.

In a specialist cough clinic of 135 patients, SHR was identified in 85 (63%) of cough patients using the a positive response to the question as to whether there is aggravation or triggering of cough in the presence of one or more triggers such as a change in air temperature, exposure to aerosols, scents and odours and/or talking, laughing and singing (54). Thus, there is a large overlap between CCHS and SHR, with CCHS being a form of SHR because the term SHR encompasses other symptoms arising from the airways apart from the cough sensations, in addition to lower airways hyperreactivity.

However, CCHS would potentially encompass other hyperreactive conditions such as the irritable larynx syndrome, or the upper airway reactive syndrome associated with rhinosinusitis. It is also interesting to discuss the potential link of CCHS with other conditions that are presumed to be associated with central sensitivity, including chronic fatigue syndrome or fibromyalgia, irritable bowel syndrome and irritable bladder syndrome. There is little data in terms of the prevalence of cough in these conditions, but there is anecdotal evidence for increased cough symptoms in patients with fibromyalgia (55). Interestingly, the treatments used or proposed for these conditions bear similar resemblance to approaches for chronic cough, since they target central pathways such as opioid-like agents, tricyclic antidepressants, and gabapentin. In terms of potential new approaches, TRPV1 antagonists

are being considered in many of these hypersensitivity syndromes including cough (56). Exchanging notes across these hypersensitive conditions will be beneficial.

Conclusion

The time has come to label chronic cough as the chronic 'cough hypersensitivity syndrome'. Not all patients with chronic cough would fall into this category, and use of this label should not change the clinical approach to diagnosing chronic cough as recommended in most cough guidelines (57;58). However, this will bring enormous advantages to the field of chronic cough both to patient, medical attendants and researcher. We should delay no more.

Acknowledgements:

I thank my friend and teacher, John Widdicombe, for his wise comments and advice.

Table:*Summary of types of chronic cough*

1. Chronic cough associated with conditions which when treated abolishes the cough e.g. asthma, gastro-oesophageal reflux disease (GORD), upper airway syndrome
2. Chronic cough associated with conditions which when treated does not resolve the 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 first 3 categories.

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