Cough hypersensitivity syndrome: towards a new approach to chronic cough

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The identification of cough hypersensitivity syndrome is of high importance for research on chronic cough http://ow.ly/ACr4i

Although cough is a highly frequent motive for visiting the doctor among both adults and children in primary care [1, 2], it usually resolves spontaneously within a few days or weeks. Conversely, chronic cough, broadly defined as cough persisting for more than 8 weeks, is often a more difficult clinical situation from both diagnostic and therapeutic perspectives [3]. In many patients, the anatomical diagnostic workup introduced almost 40 years ago [4] rapidly unmasks a likely underlying cause, the involvement of which is confirmed by the effectiveness of aetiological treatment. However, in some cases, the initial workup does not reveal any convincing aetiology and cough remains refractory to treatments; the proportion of patients with so-called idiopathic cough varies markedly between series (0–46%) [5], leading authors to question whether this condition exists or is only the consequence of insufficient diagnostic workup, which should include various therapeutic trials before concluding as to the idiopathic nature of cough [6]. Whatever the answer is, such situations may be worrying, as, in parallel, chronic cough is a significant cause of quality-of-life impairment [7].

It has been hypothesised that some, if not all, cases of chronic refractory/idiopathic cough may belong to a specific phenotype and share some common pathophysiological mechanism, namely hypersensitivity of the cough reflex [6]. As such hypersensitivity is not restricted to idiopathic cough, it has been proposed that, in general, chronic cough is the result of an interaction between intrinsic cough reflex abnormalities (*i.e.* hypersensitivity) and aggravating factors such as angiotensin-converting enzyme (ACE) inhibitors, gastro-oesophageal reflux disease (GORD), upper airway disorders, eosinophilic airway diseases and cigarette smoke/chronic obstructive pulmonary disease (COPD) [5]. The term ''cough hypersensitivity syndrome'' (CHS) was then proposed [8] to name the clinical entity characterised by enhanced cough reflex, comprising several phenotypes depending on which aggravating factor is involved. However, there has been some debate around the nature and definition of CHS [9], suggesting that this syndrome might remain difficult to identify, and therefore to explore and treat. For instance, although hypersensitivity to protussive agents such as capsaicin and citric acid was initially considered a prominent feature of this syndrome [8, 9], its demonstration is no longer considered specific of the diagnosis, which in turn can be present in the absence of hypersensitivity to these agents (see later).

In this context, a Task Force was established by the European Respiratory Society to assess international opinions and scientific evidence regarding CHS. This issue of the *European Respiratory Journal* contains two articles by this Task Force [10, 11]. One describes the analysis of 10 032 cases (mean age 55 years) referred to 11 cough clinics worldwide [11]. A female predominance was found (66% of cases) and most patients belonged to the 60–69-year age range. Interestingly, these characteristics did not differ markedly between

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centres and countries, suggesting that a significant proportion of patients with chronic cough might share a rather homogeneous demographic phenotype, which might be, at least in part, the consequence of some sex-related genotypic features. Accordingly, in 20 patients (10 men and 10 women), capsaicin challenge coupled with functional brain magnetic resonance imaging showed capsaicin-induced activation of cough central neural networks (involving sensory, motor and limbic cortical areas), with a higher sensitivity in women (larger responses to lower capsaicin doses) [11]. Interestingly, chronic (but not acute) cough also has more deleterious consequences on quality of life in women than in men [12].

The other article presents a 21-question survey among 44 leaders in respiratory medicine (cough experts and nonexperts) from 11 countries [10]. Altogether, participants appeared to endorse the concept of CHS, defined as ''a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure''. Interestingly, this definition of CHS is purely clinical and does not require any formal testing to demonstrate hypersensitivity of the cough reflex (which is completely distinct from bronchial hyperresponsiveness (BHR) to *e.g.* methacholine). Possible triggers include exposure to environmental tobacco smoke, spicy food, perfumes, vapours, changes in ambient temperature, *etc.* Importantly, survey participants also agreed on the possible coexistence of CHS and: 1) lower respiratory tract conditions such as asthma/eosinophilic airway disease, COPD, bronchiectasis, pulmonary fibrosis; 2) upper airway conditions (rhinosinusitis); or 3) nonrespiratory (at least primarily) conditions such as GORD or ACE inhibitor treatment. This possible overlap raises one crucial question: is CHS a unique syndrome with a given underlying pathophysiology, which can coexist with various aggravating or triggering conditions/factors or be present on its own, or is it just a clinical trait that can be found in many airway-involving diseases (in the same way troublesome dyspnoea triggered by exercise is a clinical trait common to various diseases such as COPD or pulmonary fibrosis, without being considered a syndrome)? A strong argument in favour of the first option is that not all patients with asthma, rhinosinusitis, GORD *etc.* present with chronic troublesome cough, while virtually all patients with severe COPD or pulmonary fibrosis exhibit exercise-induced dyspnoea.

In his landmark paper introducing CHS, MORICE [8] drew a parallel between this condition and COPD, considering the latter a syndrome comprising various specific phenotypes of smoking-related airway diseases, namely chronic bronchitis and emphysema. He advocated the utility of such a syndromic approach as a way to recognise the importance of a central feature (smoke-induced airway disease in COPD and cough reflex hypersensitivity in CHS) as a target for research and, potentially, treatment. A syndrome can be defined as ''a group of signs and symptoms that occur together and characterize a particular abnormality'' [13]. In the present case, the ''group of signs and symptoms'' actually comprises only one symptom, *i.e.* ''troublesome coughing'' (to which it might be worth adding the term ''chronic''). Regarding the last component of the definition, *i.e.* ''characterize a particular abnormality'', the lack of firm knowledge (for now) of what this abnormality is limits the applicability of the syndromic approach in clinical practice, as it prevents us from relying on: 1) simple and reliable tools to identify the target population; and 2) adequate, specific therapeutic strategies. But this ''practical limitation'' is also a major reason for adopting this approach, with the aim of stimulating research on the pathophysiology, diagnostic procedures and treatments of the conditions grouped under the CHS umbrella.

Indeed, currently available tests using capsaicin or citric acid explore the sensitivity of afferent pathways but results do appear to be neither specific to well-defined abnormalities/mechanisms nor useful from a diagnostic perspective at an individual level [10]. In other words, results of these tests cannot be used to distinguish patients with from those without CHS, nor CHS patients with from those without underlying diseases such as asthma, COPD and GORD.

Regarding pathophysiology, neuropathic mechanisms involving transient receptor potential (TRP) nociceptors are considered to play an important role and are probably central in the determination of CHS: for instance, TRPV1 (vanilloid receptor 1) is overexpressed in the airway nerves of patients with chronic cough and its expression correlates with the tussive response to capsaicin [14]. Interestingly, rhinoviruses upregulate TRPA1 (an ankyrin-like protein) and TRPV1 in neuronal cell cultures, which may contribute to explaining cases of CHS following airway viral infections (post-viral vagal neuropathy), independently of inflammation [15]. The role of airway inflammation in the occurrence of cough hypersensitivity is controversial. Indeed, while there is clearly an overlap between CHS and so-called eosinophilic cough, the causal nature and direction of the relationship is unclear. This concern is actually also valid for other classical causes of chronic cough such as rhinosinusitis or GORD, which are associated with various degrees and types of lower airway inflammation. In guinea pigs, allergen sensitisation induces TRVP1 overexpression in Aδ nerve fibres, which appears mediated by neurotrophic factors [16]. Mediators released by inflammatory cells including eosinophils can modulate the excitability of afferent vagal pathways in many vagal-dependent organs: in rodents, sensitisation-induced eosinophilic oesophagitis is

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accompanied by increased acid responsiveness in vagal sensory neurons [17]. Additionally, eosinophil cationic proteins, although not evoking action potentials in vagal afferent pathways, increase mechanoexcitability of some (*i.e.* Aδ) vagal nerve fibres [18]. These effects do not seem to require interactions with TRPV1 [19]. Finally, some lipoxygenase products are direct agonists of TRPV1 [20]. Following these data, it could be hypothesised that CHS can be caused by (eosinophilic) inflammation. Alternatively, eosinophilic inflammation could be an aggravating factor enhancing cough in a patient with pre-existing CHS. Interpretation of the direction of causal links, if any, is made difficult by the complexity and multiplicity of relationships between inflammation and C-fibres [21], which also appear to be involved in the development of eosinophilic inflammation through TRPV1-independent mechanisms [22]. All these findings underline the need to expand research on chronic cough and, more specifically, CHS. Underlying mechanisms and their relationships with the pathophysiology of associated diseases need to be elucidated in more detail to identify well-defined phenotypes, and develop specific diagnostic tests and appropriately targeted treatments.

At present, clinicians still face one major practical question, *i.e.* how should they classify chronic cough patients fulfilling the definition of CHS in whom underlying diseases are diagnosed? Let us take asthma and rhinitis as examples, using a real clinical scenario: a 50-year-old woman complains of chronic cough impairing her daily activities and sleep, with no other respiratory symptom such as dyspnoea or wheezing. Cough is triggered by exposure to domestic fumes (in this case, second-hand tobacco smoke). Her medical history reveals that she was treated for asthma between the ages of 12 and 18 years. She has always complained of perennial rhinitis, which has been attributed to a documented allergy to house dust mites and has long been easy to control with antihistamine agents; symptoms of rhinitis have increased in recent months. The initial diagnostic workup reveals signs of chronic sinusitis on computed tomography, BHR on methacholine testing (provocative dose causing a 20% decrease in FEV_1 400 μg) and elevated exhaled nitric oxide. All other tests are negative, including aggressive medical treatment for GORD. At this stage, what is the diagnosis? Cough-variant eosinophilic asthma associated with chronic rhinosinusitis, following the ''classical'' diagnostic classification, or asthma/(BHR+eosinophilic bronchitis) and chronic rhinosinusitis associated with CHS? Following the Task Force expert opinion document [10], the second option clearly applies. But what if cough quickly disappears with topical (inhaled and/or nasal) corticosteroids? Can the diagnosis of CHS still be put forward when a simple aetiological treatment of associated disease(s) proves undoubtedly effective? Again, following the Task Force document, the answer remains ''yes''. However, the two ''phenotypes'' (refractory or sensitive to aetiological treatment) are markedly different from a clinical perspective.

In this sense, it could be interesting to explore further what the definition of CHS comprises. From a broad perspective, three situations can be identified: 1) ''troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure'' with negative full aetiological workup; and 2) ''troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure'' with positive aetiological workup/associated respiratory disease that is a) responsive to aetiological treatment or b) refractory to aetiological treatment.

Importantly (as far as nosology is concerned), accepting the presence of CHS even if a full response of cough to simple aetiological treatment is observed implies accepting that, in some cases, CHS can be only a consequence of some well-defined diseases characterised by their own intimate (and diverse) mechanisms. This would actually not be in contradiction with the definition of a syndrome but has important conceptual implications for research. Along the same line, one might question whether troublesome chronic *productive* cough aggravated in response to nonspecific triggers should be accepted as part of CHS, even in the presence of an underlying airway disease. Indeed, it has been suggested that the anatomical diagnostic procedure developed for chronic cough as a whole is also valid for chronic cough with excessive sputum production [23], but this was long before the CHS concept was introduced. This issue is not actually addressed in the Task Force survey.

In conclusion, although many questions remain unanswered regarding virtually all aspects of CHS (definition and classification, mechanisms, diagnostic procedures, treatment, relationship with other conditions, *etc.*), the identification of this syndrome is certainly of major importance to boost research on chronic cough and progress in the care of patients whose health status is severely impaired by this symptom.

References

1 Whitburn S, Costelloe C, Montgomery AA, *et al.* The frequency distribution of presenting symptoms in children aged six months to six years to primary care. *Prim Health Care Res Dev* 2011; 12: 123–134.
2 Adekoya N. Reasons for visits to emergency departments for Medicaid and State Children's Health Insurance Program patients: United States, 2004. *NC Med J* 2010; 71: 123–130.
3 Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008; 371: 1375–1384.

4 Irwin RS, Rosen MJ, Braman SS. Cough. A comprehensive review. *Arch Intern Med* 1977; 137: 1186–1191.
5 Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet* 2008; 371: 1364–1374.
6 McGarvey LPA. Does idiopathic cough exist? *Lung* 2008; 186: Suppl. 1, S78–S81.
7 Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. *Lung* 2008; 186: Suppl. 1, S55–S58.
8 Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. *Lung* 2010; 188: Suppl. 1, S87–S90.
9 Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med* 2011; 183: 708–715.
10 Morice AH, Millqvist E, Belvisi MG, *et al.* Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014; 44: 1132–1148.
11 Morice AH, Jakes AD, Faruqi S, *et al.* A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; 44: 1149–1155.
12 French CT, Fletcher KE, Irwin RS. A comparison of gender differences in health-related quality of life in acute and chronic coughers. *Chest* 2005; 127: 1991–1998.
13 Merriam-Webster. Syndrome. www.merriam-webster.com/dictionary/syndrome Date last accessed: August 17, 2014.
14 Groneberg DA, Niimi A, Dinh QT, *et al.* Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. *Am J Respir Crit Care Med* 2004; 170: 1276–1280.
15 Abdullah H, Heaney LG, Cosby SL, *et al.* Rhinovirus upregulates transient receptor potential channels in a human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. *Thorax* 2014; 69: 46–54.
16 Lieu TM, Myers AC, Meeker S, *et al.* TRPV1 induction in airway vagal low-threshold mechanosensory neurons by allergen challenge and neurotrophic factors. *Am J Physiol Lung Cell Mol Physiol* 2012; 302: L941–L948.
17 Hu Y, Liu Z, Yu X, *et al.* Increased acid responsiveness in vagal sensory neurons in a guinea pig model of eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2014; 307: G149–G157.
18 Yu S, Ouyang A. Effect of synthetic cationic protein on mechanoexcitability of vagal afferent nerve subtypes in guinea pig esophagus. *Am J Physiol Gastrointest Liver Physiol* 2011; 301: G1052–G1058.
19 Gu Q, Lim ME, Gleich GJ, *et al.* Mechanisms of eosinophil major basic protein-induced hyperexcitability of vagal pulmonary chemosensitive neurons. *Am J Physiol Lung Cell Mol Physiol* 2009; 296: L453–L461.
20 Hwang SW, Cho H, Kwak J, *et al.* Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. *Proc Natl Acad Sci USA* 2000; 97: 6155–6160.
21 Song WJ, Chang YS, Morice AH. Changing the paradigm for cough: does ''cough hypersensitivity'' aid our understanding? *Asia Pac Allergy* 2013; 4: 3.
22 Rogerio AP, Andrade EL, Calixto JB. C-fibers, but not the transient potential receptor vanilloid 1 (TRPV1), play a role in experimental allergic airway inflammation. *Eur J Pharmacol* 2011; 662: 55–62.
23 Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995; 108: 991–997.

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