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Editorial

How to Apply the Concept of Cough Hypersensitivity in Clinical Practice?

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Cough is a defensive respiratory response of the human body. However, cough is one of the most frequent causes of seeking medical services. Moreover, about 10% of the general population globally suffers from chronic cough.[1] Chronic cough is becoming an important social problem because it is associated with not only a significant loss of quality of life but also the cost of medical care.[2] Chronic cough is defined as a cough lasting for more than 8 weeks in adults.[3] Chronic cough was initially thought to be caused by chronic conditions that stimulate the afferent sensory limb of the airway.[2] Through this anatomical approach, asthma, gastroesophageal reflux disease and upper airway cough syndrome were identified as the most common causes of chronic cough. Diagnostic and therapeutic trials focused on this triad was very effective in managing chronic cough.[4] However, despite this success in managing chronic cough, substantial numbers of patients still suffer from chronic cough.

Chronic cough persisting with extensive evaluation and therapeutic trials is called unexplained chronic cough (UCC).[5] UCC has raised the concept of cough hypersensitivity syndrome. The definition of cough hypersensitivity syndrome is a clinical entity characterized by a cough as the most important component, which is often triggered by low levels of thermal, mechanical or chemical exposure.[2] It is an umbrella term including various cough-related conditions or unexplained cough.[3] The main mechanism of cough hypersensitivity syndrome has been suggested as dysregulated sensory neural pathways and central processing in cough reflex regulation. Although cough hypersensitivity syndrome is still a conceptual entity, some guidelines for the treatment of chronic cough have already accepted this concept at least partially.[3,6] They recommend investigation and treatment of chronic cough patients focused on possible causative diseases first. When this conventional approach fails to treat such a patient, the patient is diagnosed with UCC. The guidelines recommend giving a therapeutic trial with neuromodulatory agents to the patient with UCC because it is thought that cough hypersensitivity plays a more important role in coughing than underlying conditions in some patients with UCC. However, with this approach, patients who need to use neuromodulatory agents require much time to get proper treatment. Moreover, although the neuromodulatory agents could be used for the treatment of UCC, their potential adverse effects can be significant and become an obstacle to using these agents.[6] Thus, it would be desirable that we select a patient with chronic cough who will benefit from neuromodulatory drugs at an earlier stage of the disease.

In this issue of the *Allergy, Asthma & Immunology Research* journal, Won *et al*,[7] addressed this practical issue using simple questionnaires on cough hypersensitivity. Some characteristics of cough hypersensitivity revealing in the previous studies were an abnormal sensation in the laryngeal area, such as irritation and tickling, and sensitive responses to unusual causes of cough such as talking, physical exercise and eating (non-tussive triggers) as well as usual causes (tussive triggers).[8,9] However, these reports did not compare the characteristics found with control groups, which limits the clinical relevance of their results. In the study, they compared the various aspect of cough hypersensitivity between UCC and the control (newly referred to chronic cough) groups using the cough hypersensitivity questionnaire (CHQ). The CHQ consists of 7 items on cough-associated laryngeal sensations and 16 items on cough triggers. The subjects with UCC complained about more laryngeal symptoms and cough triggers than the control group. Interestingly, there were significant differences not only in the total score but also in the responses to specific items in the questionnaire between the 2 groups when they asked accompanying laryngeal symptoms. The subjects with UCC more frequently had dry throat and irritation in the throat. On the other hand, there was no difference in tickle in the throat, throat clearing, urge to cough, sensation in the chest or itchy throat. Similarly, in the subjects with UCC, dry air, talking, postnasal drip, perfumes, eating, heartburn, indigestion, and hot air were reported more frequently as a cough trigger than in the control group. On the other hand, there was no difference between the 2 groups in the frequency of sputum or smoking, which was included in the questionnaire trigger. The relationship between cough hypersensitivity assessed by CHQ and UCC did not change after adjusting for various factors. These results confirm that cough hypersensitivity is one of the main characteristics of UCC and provided simple and practical way to detect patients with UCC in clinical practice.

Yet, the design and methodology of this study have several problems as the authors described in the limitation. The control group of this study was newly referred chronic cough patients to 1 of the 6 tertiary centers in Korea. The control groups were not fully evaluated, so that patients with UCC would be included in the control groups. In fact, although the UCC group showed significantly more positive responses to individual questionnaire items than the control group, many subjects in the control group also showed positive responses to some questions. For example, subjects who complain of dry throat and irritation in the throat in the control group were significantly fewer than those in the UCC group, but more than a half of the subjects in the control group responded positively to these symptoms (64.9% and 50.9%, respectively). The higher positive response in the control group may underestimate the clinical significance of the result of this study. Then, what would be the appropriate control group in this study? For an ideal comparison, the patient and control groups should be mutually exclusive for the factor to be compared—that is the diagnosis of UCC in this study. Therefore, a good control group in this study may be the subjects with explained chronic cough. In this context, it is uncertain whether UCC and explained chronic cough differ in terms of pathophysiological and etiological aspects. There is difficulty in answering this question. Some researchers raise suspicion whether the so-called triad really causes chronic cough directly or it only acts as a trigger of cough.[2] Moreover, there is evidence that respiratory viral infection, allergen or air pollutant exposure can lead to phenotypic changes in the sensory neurons of the airway and these changes may, in turn, provoke neurogenic inflammation. Such neuro-immune interactions would lead to a vicious cycle of hypersensitive responses.[6] This raises the question as to whether UCC is a distinct phenotype of explained chronic cough or whether UCC and explained chronic cough are in the same spectrum of disease? Thus, the selection of a mutually exclusive control group in

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the study on UCC is not easy. Although they might thoroughly phenotype UCC, there could be some overlaps between the experimental and control groups. To solve this problem, more information on the natural courses and on the pathophysiology of cough is urgently needed. Although the work of Won *et al.*[7] is worthy of attention, the following studies will help set up the control group appropriately.

Recently, the concept of treatable traits has been suggested in chronic airway diseases rather than previously existing rigid clinical definition.[10] Cough has been proposed as one of the treatable traits, but if this approach is to be adopted, there must be available treatment with a relevant biomarker.[5] For example, the presence of eosinophilic inflammation is associated with a positive response to inhaled corticosteroid in patients with chronic cough.[5] Although there would be complex disease-specific endotypes in UCC, some of them were reported to respond to neuromodulatory agents as discussed above. However, these agents usually affect the central portion of the cough reflex pathway, which results in many adverse effects. More effective treatments based on the mechanism of specific endotypes of UCC are needed. In that sense, the recent success of gefapixant, a P2X3 antagonist, provides a promising future management of UCC.[11] In addition to the mechanism-based agents, research on UCC treatment through multiple approaches such as environmental control, lifestyle modification and speech-language therapy should be pursued. It would be necessary to manage chronic cough through multimodal approaches because the cough is a very complex problem, which also needs proper biomarkers. A symptom-based biomarker might be easier to use than other ones as shown by Won *et al.*[7,8] However, since the characteristics of many types of cough may considerably overlap, efforts to develop biomarkers from all possible sources should made. The sources could include various human biologic materials, such as sputum, blood or exhaled breath condensate, as well as images such as quantitative computed tomography of the chest as well as symptom-based biomarkers. These biomarkers and their combinations would help identify individual subtypes of chronic cough more accurately.

Precise phenotyping of chronic cough by a combination of specific biomarkers and proper management through multimodal approaches, including mechanism-based agents, would be the key to the successful management of UCC and cough hypersensitivity syndrome.

REFERENCES

1. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J 2015;45:1479-81.
PUBMED | CROSSREF
2. Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. Allergy Asthma Immunol Res 2017;9:394-402.
PUBMED | CROSSREF
3. Song DJ, Song WJ, Kwon JW, Kim GW, Kim MA, Kim MY, et al. KAAACI evidence-based clinical practice guidelines for chronic cough in adults and children in Korea. Allergy Asthma Immunol Res 2018;10:591-613.
PUBMED | CROSSREF
4. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008;371:1364-74.
PUBMED | CROSSREF
5. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. Lancet Respir Med 2018;6:636-46.
PUBMED | CROSSREF
6. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. Chest 2016;149:27-44.
PUBMED | CROSSREF

https://doi.org/10.4168/aair.2019.11.5.589

7. Won HK, Kang SY, Kang Y, An J, Lee J, Lee SM, et al. Cough-related laryngeal sensations and triggers in adults with chronic cough: symptom profile and impact. Allergy Asthma Immunol Res 2019;11:622-31.
CROSSREF

8. Ryan NM, Vertigan AE, Bone S, Gibson PG. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough. Cough 2010;6:5.
PUBMED | CROSSREF

9. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. Respir Med 2015;109:701-7.
PUBMED | CROSSREF

10. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016;47:410-9.
PUBMED | CROSSREF

11. Morice AH, Kitt MM, Ford AP, Tershakovec AM, Wu WC, Brindle K, et al. The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. Eur Respir J 2019;54:1900439.
PUBMED | CROSSREF