Editorial
Allergy Asthma Immunol Res. 2014 September;6(5):373-375.
http://dx.doi.org/10.4168/aair.2014.6.5.373
pISSN 2092-7355 • eISSN 2092-7363

Now is the Right Time to Establish a New Strategy for Managing Chronic Cough as a Neuropathic Disorder

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No clinician would disagree with the fact that chronic cough is a very common and annoying clinical condition and is not so easy to treat as anticipated. Chronic cough is considerably heterogeneous in terms of clinical features and many possible underlying causative disorders. Indeed, managing chronic cough patients can be very tricky at times, especially when they show neither symptoms suggestive of certain disorders nor definite abnormalities in physical examination or chest X-rays. In consideration of its high prevalence and heterogeneity, several algorithmic approaches have been proposed for the diagnosis and management of chronic cough,[1] though there have been no widely accepted guidelines, such as GINA for asthma.[2] The proposed algorithms mostly focus on diagnosing underlying causative diseases, such as asthma, rhinosinusitis, gastroesophageal reflux disease (GERD), and laryngopharyneal reflux , which are the common causes of chronic cough. The question is: Do most coughing patients get better when clinicians mainly focus on identification of culprit disorders with the guidelines? Unfortunately, the answer would not be affirmative. A substantial proportion of patients continue to suffer from chronic cough despite proper treatment of underlying diseases, and a significant number of patients are regarded as so-called idiopathic chronic cough.[3] Although chronic cough is an umbrella term encompassing various underlying diseases and the importance of searching for the specific diagnosis for each patient should not be ignored, diagnosing the underlying disease is definitely not sufficient to solve this bothersome problem.

What is interesting in the article on this issue by Song *et al.*[4] is that almost all chronic cough patients show symptoms strongly suggestive of neuropathy, namely hypertussivity to capsaicin and allotussivity to cold air regardless of underlying diseases, which are consistent with those of other previous studies.[5,6] Those observations lead to a reasonable assumption that the same pathophysiologic mechanism may function to generate the symptom 'chronic cough' in a variety of underlying disorders. Moreover, it would be further speculated that the level of contribution of enhanced cough sensitivity to the development of chronic cough can be even greater than that of the causative disease itself. In fact, only a small proportion of patients with each of the representative diseases, such as asthma, postnasal drip, and GERD, suffer from chronic cough symptom.[7] The so-called cough hypersensitivity syndrome is not a new concept anymore, and the results of the article on this issue support current understanding of the pathogenesis of chronic cough. A series of recent research has strongly indicated that increased cough sensitivity is closely linked to neuropathy of the cough reflex.[8-10] The concept that chronic cough should be considered as a neuropathic disorder just like neuropathic chronic pain begins to be widely accepted.

Both pain and cough are primarily initiated by exciting specialized peripheral sensory fibers, named 'nociceptors.'[9] Various irritating or potentially noxious stimuli are detected by these nociceptors and then induce cough or pain responses as a principal protective action through modulation of signals in the central nerve system.[9] Neuropathy related to peripheral or central sensitization of the cough or pain reflex is expected to cause abnormally enhanced responses, which can result in both neuropathic chronic cough and pain.[11,12] Presumably, sensory hypersensitivity induced by damage to the afferent nerve fibers in the airway or the esophagus may underlie mechanisms of cough, and peripheral nerve injury can be associated

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Received: August 4, 2014; Accepted: August 5, 2014
• There are no financial or other issues that might lead to conflict of interest.

with airway inflammation or refluxed acidic gastric contents. Interestingly, peripheral sensitization in the cough reflex circuit has been strongly suggested to be linked to central sensitization, which also contributes to the development of chronic cough.[13] Recently, a few clinical studies have been published, supporting the idea that neuropathy of the cough reflex critically leads to the development of chronic cough through generating exaggerated cough responses to low-level tussigenic or nontussigenic stimuli. In line with these ideas, amitriptyline and gabapentin, which are frequently used to treat chronic pain with neuropathy, successfully reduce cough symptoms in chronic cough patients.[14,15] These results not only prove the efficacy of such drugs as antitussives but also demonstrate involvement of central neural pathway sensitization in refractory chronic cough.

Now, many investigators are curious about molecular mechanisms involved in the induction of cough hypersensitivity. The expression of transient receptor potential vanilloid 1 (TRPVI), which is a capsaicin-sensitive sensor on nerves, has been reported to be significantly increased in chronic cough patients.[16] Currently, TRPV1 is known to play an important role in the regulation of afferent nerve excitability to various chemical stimuli and is also considered a potential target molecule for modulating cough sensitivity. Several other molecules, such as N-methyl-D-aspartate receptors on second neurons,[17] nerve growth factor,[18] substance P,[19] and calcitonin gene-related peptide,[20] have been shown to have increased expression in neuronal cells and airway epithelium of chronic cough patients and to be critically related to increased cough sensitivity. The precise molecular mechanism underlying cough hypersensitivity, however, has not yet been clearly elucidated, so there is an urgent need to clarify the mechanism through further studies.

Acknowledging chronic cough as a neuropathic disorder would greatly affect future strategies for the diagnosis and management of chronic cough. Specific treatment to correct altered cough sensitivity will become an independent therapeutic approach, while current practice mainly focuses on treating underlying disorders. In order to correct enhanced cough sensitivity, treatment of the neuropathy in the cough neural reflex pathway would be essential. Accordingly, research into precise pathogenetic mechanisms underlying increased cough sensitivity will be actively carried out. Given that much research into neuropathic chronic pain has already been performed, studies on chronic neuropathic cough seem to be rather too late. Also, standardization of methods of assessing the level of cough sensitivity will be necessary. For instance, the capsaicin inhalation test has most frequently been used to determine if the cough reflex response is altered. However, interpretation of test results is often difficult because there is neither the reliable reference range of tussive response nor the standardized operating protocol. Still, experts have not agreed upon the ideal method to determine the level of cough hypersensitivity: for instance counting the total number of induced coughs *versus* determining the provocation concentration of capsaicin that induces a certain number of coughs. Moreover, there are neither solid diagnostic tests nor biomarkers to detect neuropathic status in chronic cough patients. Another problem that we are faced with is that there is no standardized questionnaire to evaluate symptoms or signs suggestive of enhanced cough sensitivity. Above all, standardization of tests to diagnose neuropathy and enhanced cough sensitivity is an urgent problem to solve.

Meanwhile, what should be ready in the clinical area to prepare for future strategic changes in the management of chronic cough? The study on this issue has suggested some answers.[4] In that study, clinical features related to responses to the capsaicin cough provocation test were presented and summarized in chronic cough patients. They also tried to evaluate the value in questionnaires to detect allotussivity or hypertussivity. Clinical characteristics of chronic cough patients as a whole should be defined and analyzed by using various clinical data obtained from a large number of patients because chronic cough, as a neuropathic disorder, has not been considered one disease entity. With a more precise definition of clinical characteristics of chronic cough patients, we will be able to come up with better designed clinical studies to prove the efficacy of novel therapeutics and to investigate useful biomarkers in the future. Taken together, in order to improve the management of chronic cough, it is fundamental to standardize various diagnostic tests for measuring cough sensitivity and to characterize clinical features of chronic neuropathic cough patients regardless of underlying causative diseases.

Approaches to chronic cough are now focusing on one common critical pathophysiology, namely cough reflex neuropathy despite the diversity of underlying disorders. Thus, antitussive agents specifically targeting enhanced nociceptor responsiveness are expected to be ideal drugs for treating chronic cough patients besides treatment of underlying diseases. Interestingly enough, it contrasts with recent changes in asthma, which has long been treated as one disease entity, but is now recognized as a heterogeneous disease syndrome[2] and many attempts to classify the disease into various pheno-endotypes are under process in pursuit of personalized medicine. Hopefully, all of the chronic cough patients can return to their normal daily lives with novel antitussive agents that can effectively correct abnormal cough responses by modulating the cough reflex neuronal circuit in the near future.

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REFERENCES

1. Pratter MR, Brightling CE, Boulet LP, Irwin RS. An empiric integra-

tive approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:222S-231S.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention 2014 [Internet]. [place unknown]: Global Initiative for Asthma; 2014 [cited 2014 Jul 31]. Available from http://www.ginasthma.org/.
3. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008;371:1364-74.
4. Song WJ, Kim JY, Jo EJ, Lee SE, Kim MH, Yang MS, et al. Capsaicin cough sensitivity is related to the older female predominant feature in chronic cough patients. Allergy Asthma Immunol Res 2014;6:401-8.
5. O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med 1994;150:374-80.
6. Choudry NB, Fuller RW. Sensitivity of the cough reflex in patients with chronic cough. Eur Respir J 1992;5:296-300.
7. Tatar M, Plevkova J, Brozmanova M, Pecova R, Kollarik M. Mechanisms of the cough associated with rhinosinusitis. Pulm Pharmacol Ther 2009;22:121-6.
8. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med 2013;1:414-22.
9. O'Neill J, McMahon SB, Undem BJ. Chronic cough and pain: Janus faces in sensory neurobiology? Pulm Pharmacol Ther 2013;26:476-85.
10. Bastian RW, Vaidya AM, Delsupehe KG. Sensory neuropathic cough: a common and treatable cause of chronic cough. Otolaryngol Head Neck Surg 2006;135:17-21.
11. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:S2-15.
12. Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. J Voice 2011;25:596-601.
13. Chen CY, Bonham AC, Schelegle ES, Gershwin LJ, Plopper CG, Joad JP. Extended allergen exposure in asthmatic monkeys induces neuroplasticity in nucleus tractus solitarius. J Allergy Clin Immunol 2001;108:557-62.
14. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. Laryngoscope 2006;116:2108-12.
15. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet 2012;380:1583-9.
16. Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A, et al. Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. Am J Respir Crit Care Med 2004;170:1276-80.
17. Canning BJ, Mori N. Encoding of the cough reflex in anesthetized guinea pigs. Am J Physiol Regul Integr Comp Physiol 2011;300:R369-77.
18. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:995-1002.
19. Yang XD, Liu Z, Liu HX, Wang LH, Ma CH, Li ZZ. Regulatory effect of nerve growth factor on release of substance P in cultured dorsal root ganglion neurons of rat. Neurosci Bull 2007;23:215-20.
20. O'Connell F, Springall DR, Moradoghli-Haftvani A, Krausz T, Price D, Fuller RW, et al. Abnormal intraepithelial airway nerves in persistent unexplained cough? Am J Respir Crit Care Med 1995;152:2068-75.