

Laryngeal Dysfunction in Chronic Cough: A Sign for Specific Cough Endotype?



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The recent recognition of cough hypersensitivity as the key pathophysiologic mechanism underlying chronic cough¹ has contributed to the opening of a new window of opportunity in the treatment of chronic persistent cough. Recent clinical trials have demonstrated that targeting specific receptors in the neural pathways regulating the cough reflex may be highly effective.^{2,3} However, there is still an unmet need for developing further precise modalities to evaluate and control cough. It is becoming more likely that the pathways of cough hypersensitivity syndrome are heterogeneous.^{4,5} Thus, further identification of specific endotypes and therapeutic targets may be crucial to gaining complete control of cough.

Cough is a vital reflex to protect the lower airways against aspiration, and the larynx is a principal organ for the protection.⁶ The larynx is highly innervated and contributes to airway protection through its delicate sensitivity to mechanical stimulation.⁷ Thus, it is not surprising that laryngeal sensitivity is associated with cough. Indeed, abnormal laryngeal sensation is commonly found in patients with chronic cough. Most patients with chronic cough localize their cough to the larynx and complain of trivial triggers, such as cold air, perfume, or smoke.⁸ Phonation, which is an intrinsic function of the larynx in humans, is another frequent trigger for the urge-to-cough sensation.⁹ The degree of laryngeal sensory dysfunction in chronic refractory cough (CRC) is comparable to that in well-recognized laryngeal disorders, such as vocal cord dysfunction (VCD) or muscle tension dysphonia (MTD).¹⁰ These observations suggest that laryngeal dysfunction is highly relevant to cough hypersensitivity. However, subjective outcomes alone may offer only indirect evidence on the nature of laryngeal problems in cough. In the literature, laryngoscopy studies have provided some evidence of the presence of laryngeal motor dysfunction in patients with chronic cough¹¹⁻¹⁴; however, the evidence is not yet robust enough to draw definitive conclusions.

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Vertigan et al¹⁵ examine the nature and extent of

laryngeal dysfunction in chronic cough. This study has important relevance in providing comprehensive and objective evidence that laryngeal motor dysfunction is prevalent in patients with CRC and possibly those with cough hypersensitivity syndrome. They recruited several groups of participants, including those with CRC, VCD, and MTD, along with healthy controls. Here, CRC was defined as a cough that remained problematic after at least 8 weeks of medical treatment based on anatomic diagnostic protocols.¹⁶ They used several tools to characterize cough and laryngeal functions and movements, including objective cough frequency, cough-specific quality-of-life questionnaires (the Leicester Cough Questionnaire), laryngeal hypersensitivity questionnaires, voice assessment tools, electroglottography, timed swallow test, and functional laryngoscopy based on standardized scoring systems. They measured laryngeal motor dysfunction during quiet respiration and phonation, and after an odor challenge with perfume in patients with chronic cough and compared these findings with those of patients with laryngeal disorders, such as VCD or MTD. Importantly, laryngeal motor dysfunction was common in patients with CRC (47% during quiet respiration and 45% during phonation), which was comparable to that in patients with VCD or MTD. Furthermore, laryngeal motor dysfunction became more evident and prevalent (67%) after the odor challenge in the patients with CRC, which underscores the hypersensitive nature. The odor challenge is usually used to identify VCD, but its utility has not been previously reported in patients with chronic cough. This may lead us to imagine that these perfume-induced abnormal vocal fold *movements* are the visual analog to the urge-to-cough *sensation*. The authors only used moderate to severe ratings to define dysfunction, so including mild dysfunction in the definition might have increased laryngeal motor dysfunction prevalence.

Another interesting finding was the similar profiles in voice function and laryngeal motor dysfunction in CRC and VCD, leading to the hypotheses that chronic cough and VCD are within a spectrum of laryngeal dysfunction syndrome⁶ or cough hypersensitivity syndrome.^{1,15} However, because the presence of abnormal cough (defined by a Leicester Cough Questionnaire score of <17 and cough frequency of >2 coughs/h) was not significantly associated with laryngeal motor dysfunction among all patients together as a group, it is likely that cough hypersensitivity is indeed related to laryngeal sensory dysfunction rather than motor dysfunction. The patients with MTD had a high degree of laryngeal motor dysfunction, but most of them did not have abnormal cough. Therefore, it remains to be elucidated which laryngeal investigation is essential to the management of chronic cough.

These findings give rise to several possibilities and questions, including the possibility that laryngeal dysfunction indicates a specific cough phenotype or endotype (such as *larynx-cough*

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syndrome or *neuropathic cough*); otherwise, it could be a common finding across different cough phenotypes. In a recent retrospective cohort study of 27 patients with chronic cough who received gabapentin,¹⁴ clinical response to gabapentin was significantly associated with vocal fold motion asymmetry on laryngoscopy. Motion asymmetry was present in 94% of overall gabapentin responders ($n = 16$) but in 56% of nonresponders ($n = 9$) (odds ratio, 12; 95% CI, 1.07-134.0). Similarly, Lee and Woo¹² found that laryngeal motor neuropathy (documented by laryngeal electromyography or videostroboscopy) was significantly associated with a good response to gabapentin in their 28 patients with chronic cough or laryngeal irritability. As Vertigan et al¹⁵ suggest, laryngeal dysfunction may also be possibly related to better treatment response to speech pathology therapy. However, Bucca et al¹¹ previously reported that laryngeal hyperresponsiveness (defined as paradoxical inspiratory vocal cord adduction upon histamine inhalation challenge) was highly common among 372 patients with chronic cough across different comorbidities (overall prevalence, 77%), whereas it was found in only 11% of patients with mild persistent asthma without cough. Of note, laryngeal hyperresponsiveness resolved in 63% and improved in 11% of patients with chronic cough after specific treatment for their cough-triggering conditions (such as perennial rhinitis, chronic rhinosinusitis, reflux, or asthma). Thus, it is tempting to hypothesize that laryngeal dysfunction is characteristic to cough hypersensitivity syndrome and may not indicate a specific endotype. However, this hypothesis warrants further prospective longitudinal investigation in a larger group involving different patient phenotypes and controls.

Major challenges in further expanding the clinical evidence are a consensus definition of laryngeal dysfunction and standardization in the measurements. It is also necessary to identify essential components of laryngeal sensory and motor dysfunction that have relevance and practicability in the management of patients with cough hypersensitivity syndrome. These efforts will bring further advances to our clinical practice, and the current work by Vertigan et al¹⁵ is a welcome encouragement for us all in this journey.

REFERENCES

1. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014;44:1132-48.
2. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015;385:1198-205.
3. Smith JA, Allman D, Badri H, Miller R, Morris J, Satia I, et al. The neurokinin-1 receptor antagonist orvepitant is a novel anti-tussive therapy for chronic refractory cough: results from a phase 2 study (VOLCANO-1). *Am J Respir Crit Care Med* 2017;195:A2672.
4. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JW, Stone H, Maher TM, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *Lancet Respir Med* 2017;5:806-15.
5. Mazzone SB. A cough is a cough, is it not? Neurophenotypes define patients with chronic cough. *Am J Respir Crit Care Med* 2016;193:1324-6.
6. Hull JH, Backer V, Gibson PG, Fowler SJ. Laryngeal dysfunction: assessment and management for the clinician. *Am J Respir Crit Care Med* 2016;194:1062-72.
7. Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest* 2014;146:1633-48.
8. Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. *Allergy Asthma Immunol Res* 2017;9:394-402.
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.
10. Vertigan AE, Bone SL, Gibson PG. Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. *Respirology* 2013;18:948-56.
11. Bucca CB, Bugiani M, Culla B, Guida G, Heffler E, Mietta S, et al. Chronic cough and irritable larynx. *J Allergy Clin Immunol* 2011;127:412-9.
12. Lee B, Woo P. Chronic cough as a sign of laryngeal sensory neuropathy: diagnosis and treatment. *Ann Otol Rhinol Laryngol* 2005;114:253-7.
13. Ryan NM, Vertigan AE, Gibson PG. Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement. *Cough* 2009;5:4.
14. Giliberto JP, Dibildox D, Merati A. Unilateral laryngoscopic findings associated with response to gabapentin in patients with chronic cough. *JAMA Otolaryngol Head Neck Surg* 2017;143:1081-5.
15. Vertigan AE, Kapela SM, Kearney EK, Gibson PG. Laryngeal dysfunction in cough hypersensitivity syndrome: a cross sectional observational study. *J Allergy Clin Immunol Pract* 2018;6:2087-95.
16. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:1S-23S.

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