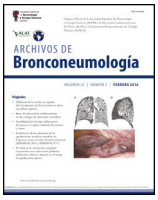
Arch Bronconeumol. 2020;56(9):545–546

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Refractory Chronic Cough at the Crossroads☆

La tos crónica refractaria en la encrucijada

Chronic cough or cough that lasts more than 8 weeks is a common problem in medical practice, accounting for about 10% of visits to respiratory medicine clinics.[1] However, even when the protocol consisting of a diagnostic-anatomical triad that has been used for more than 20 years is applied, complete resolution is not satisfactorily achieved in 40% of cases.[2] Cough of this type is described as unexplained or idiopathic chronic refractory cough (CRC). Typical symptoms are a tingling or itching in the throat followed by coughing fits that last for seconds or minutes.

Difficulties in the management of CRC derive from its complicated mechanism, which has been described as a reflex arc consisting of a peripheral component and another complex central component, partially subject to voluntary control, in the presence of hypersensitivity or an excessive tussigenic response originating in one or both of the components; this is called cough hypersensitivity syndrome (CHS).[3,4] The neurobiological basis of CHS is the dysfunction of the neurological pathways activated by the TRPV1, TRPA1 and P2X3 receptors, which causes the cough to convert from a merely defensive reflex to a hypersensitive reflex.[5] In addition, functional MRI studies have shown that patients with chronic cough show a decrease in inhibitory impulses from the brain tissues toward the cough center.[6]

As a result of this hypersensitivity, chronic cough patients experience an increase in the sensation of laryngeal irritability (paresthesia), excessive cough in response to non-tussigenic triggers such as speaking or laughing (allotussia), or disproportionate responses to cough triggers such as strong fumes or smells (hypertussia). Patients report that these symptoms occur the laryngeal area, leading Australian specialists to develop the concept of laryngeal hypersensitivity syndrome as a key factor in the analysis of CRC.[7] In laryngoscopic examination, laryngeal hypersensitivity is observed as a pathological adduction of the vocal cords as an abnormal motor response, which is very frequently combined with the sensory response mentioned above in patients with CRC. Furthermore, the timing of the inflow of stimuli from the peripheral component to the cough center located in the spinal cord will determine the appearance of central hypersensitivity. The capsaicin test that measures cough hypersensitivity in the laboratory has been shown to be useful in the clinical follow-up of CRC patients but it is not as effective in patients with predominantly central hypersensitivity.[8]

Under these premises, attempts to improve the frequency of cough in CRC have focused on decreasing both peripheral and central hypersensitivity. Leaving aside the causes, and concentrating on the altered neurobiological status, the most promising advance in the area of peripheral sensory receptors has been treatment with P2X3 receptor antagonists.[9] However, the origin of the dysfunction of these receptors remains an unresolved problem. Nevertheless, the most obvious practical clinical difficulty when faced with a patient with CRC derives from the depth of the study to be performed. Areas in which the study of a patient with CRC might need to be expanded are currently hot topics of discussion: firstly, the verification of the composition of the gastroesophageal reflux (GER) material that reaches the upper airway, which might be liquid or gaseous, acid or non-acid, and a more comprehensive study of reflux physiology in which ineffective esophageal motility can play a decisive role in chronic cough, but which are rarely analyzed in depth[10]; and secondly, the study of extrathoracic hypersensitivity that some authors agree to be the underlying cause of the so-called neurogenic cough, determined essentially by the identification and measurement of the adductor reflex of vocal cords, which if reduced contributes to the relief of CRC.[11] In the first case, antiacid therapy with high-dose proton pump inhibitors for at least 2 months is not always effective because reflux may be more closely associated with esophageal motility problems or the presence of pepsin in vocal cord tissue.[12] In the second case, laryngeal neuromuscular rehabilitation programs have shown efficacy in laryngeal dysfunction. These interventions act on the sensory and motor components of the laryngeal area and also teach the patient to consciously try to inhibit the cough, *i.e.* intervening in central hypersensitivity.[11,13] Studies of neuromodulators such as amitriptyline, gabapentin or pregabalin combined with rehabilitative therapy have already shown high rates of improvement in CRC.[14] However, 2 problems in the management of long-term CRC emerge with these procedures: 1) tolerance to neuromodulators, frequent side effects, and durability of benefit after discontinuation, and 2) poor adherence to laryngeal rehabilitation exercises.

To recap, a dual peripheral and central approach to the management of the patient with CRC is essential, but many aspects of the complexity of this syndrome at its two extremes and how they are interrelated remain unknown, so management is at a critical stage. Future research in 3 areas should shed more light on this dual issue of CRC: 1) improved reliability of tests for peripheral triggers, such as the analysis of airway reflux using Peptest (RDBiomed, Cottingham, UK), a method that detects pepsin from anti-human pepsin monoclonal antibodies either in saliva or in

☆ Please cite this article as: Pacheco A. La tos crónica refractaria en la encrucijada. Arch Bronconeumol. 2020;56:545–546.

bronchoalveolar lavage[15]; 2) the potential convergence in a single patient of inducers of peripheral inflammation of the cough reflex arc, such as allergens, respiratory virus and GER material; and 3) a more assiduous exploration of extrathoracic hypersensitivity.

Any attempt to improve the study of CRC patients necessarily involves the collaboration of the ENT, gastroenterology and pulmonology departments. A clear example in this regard is the study of the impact of extrathoracic reflux on laryngeal functioning, which is summed up in 2 parts: paradoxical vocal cord movement and loss of laryngeal mechanical sensitivity. Both events can cause 2 types of symptoms: acute dyspnea, predominantly during inspiration, consistent with laryngospasms, and chronic cough developing as a glottal opening mechanism[16] in response to aspiration. For all these reasons, a key challenge in the investigation of cough is to improve the understanding of the pathophysiology of the cough reflex, in both its peripheral, upper airway, lower airway and upper digestive tract components, and its association with the central nervous system, identifying new targets for drug therapy. However, this dimension of the problem is a difficult objective to analyze *in vivo*, so better models of cough in animals that express the mechanisms of human cough are needed.

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.
2. Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? Chest. 2005;127:1710–3.
3. Chung KF. Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. J Thorac Dis. 2014;6:S699–707.
4. Pacheco A. Chronic cough: from a complex dysfunction of the neurological circuit to the production of persistent cough. Thorax. 2014;69:881–3.
5. Chung KF. Advances in mechanisms and management of chronic cough: the Ninth London International Cough Symposium 2016. Pulm Pharmacol Ther. 2017;47:2–8.
6. Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ. Neural correlates of cough hypersensitivity in humans: evidence for central sensitization and dysfunctional inhibitory control. Thorax. 2016;71:323–9.
7. Gibson PG, Vertigan AE. Management of chronic refractory cough. BMJ. 2015;351:h5590.
8. Driessen AK, McGovern AE, Narula M, Yang SK, Keller JA, Farrell MJ, et al. Central mechanisms of airway sensation and cough hypersensitivity. Pulm Pharmacol Ther. 2017;47:9–15.
9. 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.
10. Fouad YM, Katz PO, Hatlebakk JG, Castell DO. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol. 1999;94:1464–7.
11. Murry T, Branski RC, Yu K, Cukier-Blaj S, Duflo S, Aviv JE. Laryngeal sensory deficits in patients with chronic cough and paradoxical vocal fold movement disorder. Laryngoscope. 2010;120:1576–81.
12. Johnston N, Dettmar PW, Ondrey FG Nanchal R, Lee SH, Bock JM. Pepsin: biomarker, mediator, and therapeutic target for reflux and aspiration. Ann N Y Acad Sci. 2018;1434:282–9.
13. Chamberlain Mitchell SA, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. Thorax. 2017;72:129–36.
14. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. Chest. 2016;149:639–48.
15. Hayat JO, Gabieta-Somnez S, Yazaki E Kang JY, Woodcock A, Dettmar P, et al. Pepsin in saliva for the diagnosis of gastro-oesophageal reflux disease. Gut. 2015;64:373–80.
16. Pacheco A, Domingo C. Airway reflux: an emerging topic in respiratory medicine. Lancet Respir Med. 2018;6:810–2.

Adalberto Pacheco
Centro Médico Habana 17, Madrid, Spain
E-mail address: doctorpachecogalvan@gmail.com