

REVIEW ARTICLE

The Role of the Larynx in Chronic Cough[☆]

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Abstract Cough lasting more than 8 weeks is considered chronic. If the classic causes of chronic cough have been discarded, vagus nerve sensory disturbances are currently considered the most important etiological cause. Patients with chronic cough of laryngeal origin have associated symptoms such as globus, dysphagia, dysphonia, dyspnoea and/or stridor. These patients are more likely to have paradoxical vocal fold movement. There is a higher cough reflex sensibility and neuropathic laryngeal response, mainly caused by viral infection or reflux. The cough associated with reflux has 2 mechanisms: Exposure to acid in the distal oesophagus (gastroesophageal reflux) and microaspiration of oesophageal contents into the larynx and tracheo-bronchial tree (pharyngo-laryngeal reflux). Laryngeal neuropathy hypersensitivity responds well to speech therapy as a treatment for refractory chronic cough. Because chronic cough is a sign of laryngeal sensory, neuropathy can improve with neuroleptic drugs such as amitriptyline and gabapentin. © 2012 Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE

Tos crónica;
Reflujo
gastroesofágico;
Reflujo
faringolaríngeo;
Movimiento vocal
paradójico

Participación laríngea en la tos crónica

Resumen La tos crónica es la que dura más de 8 semanas. Una vez descartadas las causas clásicas de tos crónica, actualmente se considera que la etiología más probable está constituida por los trastornos sensoriales del nervio vago. Los pacientes con tos crónica de origen laríngeo presentan síntomas asociados como globo, disfagia, disfonía, disnea y/o estridor. Estos pacientes tienen mayor tendencia a sufrir movimiento vocal paradójico. Existe una sensibilización al reflejo de la tos y una respuesta neuropática laríngea causada principalmente por infección viral o por reflujo. La tos asociada a reflujo tiene 2 mecanismos: exposición al ácido en el esófago distal (reflujo gastroesofágico) y microaspiración del contenido esofágico en la laringe y en el árbol traqueobronquial (reflujo faringolaríngeo). La neuropatía laríngea crea hipersensibilidad que respondería bien a la readaptación (rehabilitación) logopédica como forma de tratamiento a tos crónica refractaria. Por ser la tos crónica un signo de neuropatía sensorial de la laringe puede mejorar con medicamentos neurolépticos como amitriptilina y gabapentina. © 2012 Elsevier España, S.L. Todos los derechos reservados.

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Introduction

Chronic cough (CC) is a cough that lasts for more than 8 weeks. It constitutes a complex symptom in which at least 4 specialties intervene: pneumology, otorhinolaryngology, allergy and gastroenterology. Chronic cough provokes a lowering in quality of life from the psychological and physical point of view, given that it can lead to patients abandoning social activities or thinking that it is a serious disease and can even provoke urinary incontinence. The cough itself is the final result of a reflex mediated by the vagus nerve, in which the larynx plays a very important physiopathological role.

Once the most frequent causes of CC have been ruled out¹ (Table 1), there is growing evidence for considering sensory disorders of the vagus nerve as the most significant aetiology, leading to what is called chronic laryngeal cough (CLC). We use the term CLC or that of laryngeal sensory neuropathic cough to indicate a cough that has its origin in an alteration of the vagus nerve with action on the larynx, given the greater amount of cough receptors it contains. Patients with larynx-origin CC, in contrast to patients with pulmonary-origin CC, almost always present associated symptoms such as globus, dysphagia, dysphonia, dyspnoea and/or stridor. However, even the appearance of CC associated to eosinophilic inflammation of the airway can be related with concomitant gastroesophageal reflux (GER).² Clinical guidelines on CC rarely consider CLC^{3,4} because the symptoms of the cough of this origin are confused with cough from extra-esophageal reflux.^{5,6}

Prevalence of unexplained CC varies, but publications indicate that it could reach as high as 42%.⁷ In this circumstance, the larynx plays an important role as the origin of the cough reflex due to its position between the oesophagus and the tracheobronchial tree. Patients with CC frequently describe symptoms that suggest a sensitisation of the cough reflex and a neuropathic response mainly caused by viral infection of laryngopharyngeal reflux (LPR). It has been demonstrated in animal models that exposing the larynx to acid can trigger laryngeal spasm, which contributes to thinking about the possibility that reflux might be a potential factor.⁸

The 3 terms most frequently found in the literature to designate entities having cough of laryngeal origin are paradoxical vocal fold movement (PVFM), laryngeal spasm and vocal fold dysfunction. All of these have a permanent or intermittent closure of the glottis in common. The term PVFM is generally the designation preferred by the ear, nose

and throat specialists. In contrast, vocal fold dysfunction is the term generally used more by pneumologists and allergists. Do these terms represent exactly the same disorder, with a common origin? Many recent studies identify the population at risk, the common symptoms presented, the possible physiopathology of the vagal neuropathy, and several very promising treatments.⁹⁻¹²

Patients with reactive airway disease currently present in 2 groups. On the one hand, there are the patients with asthma (reactive disease in the lower airway); and, on the other, the patients with reactive disease in the upper airway with possible obstruction of the larynx or with a certain degree of vocal fold abduction. The distinctive feature of the first group is wheezing and that of the second, stridor. Many patients with laryngeal spasm or PVFM are erroneously diagnosed as having asthma, although with a thorough history it is almost always possible to reveal that these patients have inspiratory stridor and not wheezing.¹³

The protocols for diagnosis and treatment of CC, generally speaking, come from the field of pneumology.³ However, we otolaryngologists now demonstrate new perspectives in management and treatment¹⁰ with the idea that a sensory or motor neuropathy of the larynx can be responsible for many of the CC cases unresponsive to treatment. With this review, we hope to update the panorama of CC with origin in the ear, nose and throat territory, and present its aetiopathogenic mechanisms and current tendencies in therapy.

Chronic Cough Mechanisms

Disorders of cough and breathing have afferent sensory stimuli from the aerodigestive tract in common.¹⁴ The cough reflex (Fig. 1) is initiated by the stimulus from the upper aerodigestive tract, which excites the sensory receptors and sends information to the brain stem. It is now known that a single stimulus is incapable of provoking the cough reflex, so integration among various branches of the vagus nerve is required.¹⁵ There are 5 types of intraepithelial sensory receptors involved in the cough reflex, of which the most important are the rapidly adapting stretch receptors and the bronchial C-fibre receptors.¹⁶

In general, the receptors in the area of the larynx are distributed in a mechanosensitive fashion, while the distribution in the distal airway is of a more chemosensitive type.¹⁴ The afferent branch of the vagus nerve innervates wide areas where the cough reflex arises: ears, pharynx, larynx, lungs and areas innervated by gastric, cardiac, esophageal and intestinal vagus branches. The sensory and respiratory afferent pathways end at the brainstem nucleus of the solitary tract.¹⁷ The cough centre may be influenced by the voluntary movement area of the cortex, as the cough reflex decreases when the state of consciousness is depressed. Neurogenic inflammation may be a mechanism that establishes a relationship between coughing, acid reflux and lower airways.¹⁸ This would make it possible that the same element that triggers hyper-reactivity of the airways produces the release of neuropeptides to initiate the cough, so both cough and wheezing can coexist in the same patient.

The presence of CC has been associated with states of hypersensitivity or hyposensitivity of the laryngeal mucosa. In 1999 Morrison et al.¹⁹ presented the concept of

Table 1 Most Frequent Causes of Chronic Cough.

Pneumonology	ORL	Others
Asthmatic bronchitis	Rhinosinusitis	Tobacco
ACE inhibitors	Pharyngo-laryngeal reflux	Cardiac insufficiency
Nonasthmatic eosinophilic bronchitis		
COPD		
Tumour		

Afferent neurological pathways of the COUGH reflex

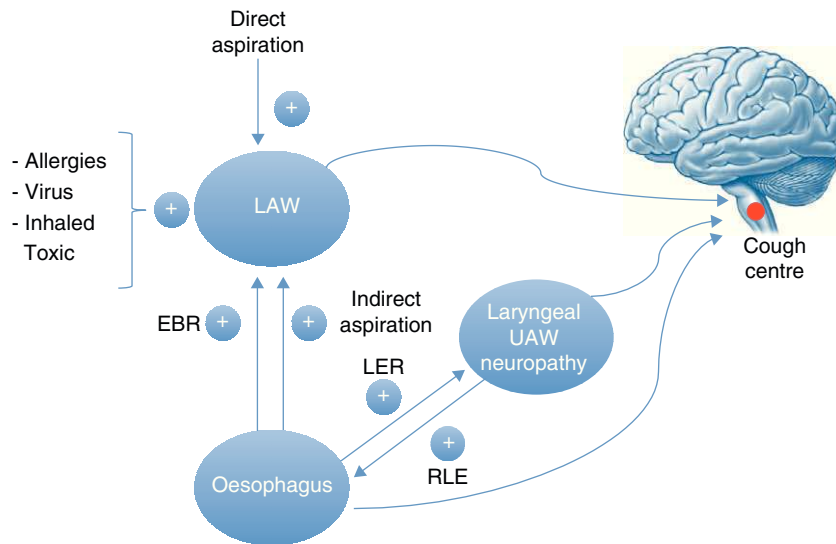


Figure 1 Efferent neurological pathways of the cough reflex. EBR, esophago-bronchial reflex; LAW, lower airway; LER, laryngeal esophageal reflex; LPR, laryngopharyngeal reflux; UAW, upper airway.

irritable larynx for the first time. This concept has gradually been defined in greater detail over the years and has received various names, such as postviral vagal neuropathy, sensory neuropathic cough and laryngeal sensory neuropathy. Vagal neuropathy can affect the motor branches of the vagus nerve, with a paralysis or paresis of the vocal folds; and it can also affect the sensory branches, which would lead not only to CC but also to paresthesias of the pharynx, sensation of *globus pharyngis*, excessive pharyngeal mucous, odynophonia or laryngeal spasms.²⁰ These symptoms can be intensified by vocal efforts (prolonged phonation) and by irritating stimuli, which we can check by triggering the discomforts by lightly palpating the cricoid cartilage.

There are many studies that confirm that the stimulus that produces gastric reflux in the larynx and pharynx causes the lack of laryngopharyngeal sensitivity in patients with CC and GER in comparison with the controls.^{9,21,22} Likewise, we have seen in our series of 170 patients with GER that 34% presented a positive endoscopy index of laryngeal reflux²³ considering the following parameters in the larynx: subglottic oedema, ventricular oedema, erythema/hyperaemia, vocal fold oedema, diffuse laryngeal oedema, hypertrophy of the posterior commissure, granuloma and thick laryngeal mucosity. In turn, Rees et al.¹² reported that a third of the patients with postviral vagal CC had LPR; while Murry et al.,⁹ in an interesting study on the relationship between CC and PVFM, found a decrease in the mechanical sensitivity of the laryngeal mucosa in patients with LPR. Based on all of this, we can postulate that there is an association between neuropathic cough, LPR and CC. The mechanism of cough in larynxes with reduced mechanosensitivity, paradoxically, can lead to a state of sensory irritant alteration that leads to irritating cough as the main symptom, along with other symptoms such as itchy throat, sensation of *globus pharyngis*, excessive pharyngeal mucus and even laryngeal spasm.

Chronic Cough Associated With Laryngeal Neuropathy and Laryngopharyngeal Reflux

The idea of neuropathy after a viral infection has been studied in various diseases such as Bell paralysis, Guillain-Barré syndrome and post-herpetic neuralgias. In this respect, otolaryngologists would be interested in a small but significant group of patients with CC resistant to treatment and having a history and clinical signs and symptoms suggestive of vagal neuropathy after viral infection.²⁴ An important feature of neuralgia is the presence of the triggering phenomenon (decrease in the provocation threshold). It is thought that neuralgia of the upper laryngeal nerve might present as a sudden and exaggerated sensation that would provoke uncontrollable cough. Lee and Woo²⁵ suggested that untreatable CC might also be a manifestation of laryngeal sensory neuropathy revealed through electromyography of the cricoid muscles and/or stroboscope. In 2001, Amin and Koufman⁸ described for the first time the association between cough from laryngeal neuropathy and viral infection of the respiratory tract, presenting through laryngeal paresis, dysphagia and neuropathological pain.

In addition, CC is a symptom that has been connected to reflux. However, this relationship is still not complexly proven even in spite of the fact that a characteristic clinical history and gastro-esophageal disease can be identified in patients with CC.⁵ If the allergy tests, tomography of paranasal sinuses and lung function are normal in patients with CC, the cause is almost always GER.²⁶ In fact, Irwin indicated that CC can be the only symptom in patients with GER, given that CC can be clinically silent, without pyrosis. Patterson et al.²⁷ reported that up to 75% of the patients studied to discover the cause of a CC had silent GER.

The physiopathology of CC associated with reflux has 2 mechanisms. In the first, exposition to acid in the distal oesophagus stimulates the oesophageal-tracheal-bronchial reflex; and in the second, microaspiration of the

oesophageal content penetrates into the larynx and the tracheobronchial tree. The first mechanism takes place in the distal GER and the second in the proximal GER or LPR (reflux of gastric content in the larynx). However, it is not only the liquid acidity that can be relevant in LPR pathogenesis; the gas-liquid composition of the reflux can also have an effect. Regurgitation and cough are the symptoms most often associated with non-liquid acid reflux.^{28,29} And although the diagnosis of LPR can be achieved reliably using the laryngeal reflux index²³ or double probe, Wo et al.³⁰ suggest that it is a good idea to control the pharynx more reliably for non-liquid reflux.

The original methods for measuring pharyngeal pH were not completely correct due to technical problems such catheter dryness, mucous accumulation and the presence of food residues. The Dx-pH measurement system (Dx-pH; Restech Corporation, San Diego, CA, USA) is a very sensitive, minimally invasive device used for detecting acid reflux in the posterior pharyngeal wall, in both liquid and spray form. Wiener³¹ compared the traditional 24-h pharyngoesophageal pH test with Dx-pH in 15 patients with extra-oesophageal symptoms. All the events measured with the Dx-pH method were preceded by, and associated with, drops in distal oesophageal pH. The oropharynx generally presents a pH that is slightly acid, although rarely lower than 4. This could explain the reason why the results were not reliable in the previous attempts to distinguish normal subjects in the subgroup of patients with atypical symptoms, with the quantitative cut-off values of pH<4.

In the larynx, a state of acute hypersensitivity is probably secondary to the vagal nerve lesion. However, when a chronic disease has developed, the cause could be an anomalous regeneration of the nerve, or some alteration in the nuclei of the central nervous system. A case of CC of laryngeal origin in patients in which larynx paresthesia caused by a state of hypersensitivity predominate might be provoked by a postviral infection; this idea could justify the recently-published success of readaptation (rehabilitation) of the airways in patients with CC that did not improve completely.^{10,11} There is also evidence that the cough associated with PVFM could be attributed to a decrease in the sensitivity of the receptors located in oedematous mucosa. It is interesting to see that the decrease in mechanical sensitivity and the increase in chemosensitivity of the laryngeal mucosa from the acid irritation could produce an accumulation of particles or irritants in the mucosa; consequently, the CC reflex could be a simple and adaptive mechanism to clear the larynx.⁹

Murry et al.⁹ quantified the sensory laryngeal response in a series of patients with PVFM and CC that had not improved by taking proton pump inhibitors (PPI) twice a day for 3 months, but had done so after combining vocal and respiratory rehabilitation with PPI treatment. Cukier-Blaj et al.³² reported that reflux-caused laryngeal irritation reduces laryngeal sensitivity, which in turn yields a compensatory motor response with hyperadduction of the vocal folds during inspiration, with cough and dysphonia. Another theory proposes that the chronic irritation of the larynx by GER (once allergic processes or inhaled irritants are ruled out, with evident laryngeal clearing) predisposes the larynx to be more sensitive to various external stimuli, creating a vicious circle.¹⁹ According to this theory, after the initial

exposure many patients report having developed "sensitivity" to various triggering factors such as tobacco smoke, cold air, soaps, perfumes, other smells, exercise and emotional stress. The fact that this pathology continues leads to the patients being unsuccessfully treated for asthma or other comorbidities. Of course, there are patients with concomitant LPR and asthma; but there are others in which the CC presents associated with LPR-produced symptoms, the respiratory symptoms beginning at the same time. In these cases, LPR seems to be the cause of or decisive factor in the respiratory problems.

Treating Chronic Cough When it is Associated With Vagal Neuropathy

The majority of patients with CC can have rhinosinusitis, eosinophilic inflammation of the airways, allergies or reflux and respond to specific therapies for these pathologies, but those who fail to respond to empiric treatment should receive a series of tests to search for a CLC¹¹ (Fig. 2). In a study on long-term follow-up of patients with unexplained chronic cough, the cough was seen to last in most patients, although its intensity dropped in more than 50% of the subjects.³³ Speech therapy (vocal rehabilitation for cough control and easier breathing) can be useful, with long-lasting results, for CC refractory to normal treatment. Ryan et al.³⁴ showed that speech therapy (learning strategies to suppress the cough using swallowing or to reverse the PVFM by slow breathing techniques) is an effective treatment modality for refractive CC based on decreasing laryngeal irritation (less urge to cough) and increasing (normalising) the cough threshold. Another study carried out by Vertigan et al.¹⁰ showed that CC persisting despite medical treatment may respond to speech therapy, with a success rate of 88% as against 14% in the placebo group. The intervention received by these patients consisted in teaching them about the nature of their cough, about strategies to control cough through breathing and swallowing, in psychological suggestions and vocal health. Other authors, such as Murry et al.,⁹ found improved laryngeal sensation and reduced cough after a rehabilitation programme with continuance of the medication. The rehabilitation consisted of breathing exercises that included slow, rhythmic breathing, breathing with vocal resistance, pulsed exhalation and abdominal movement while lying face down with resistance from weights.

Lee et al.^{25,35} feel that CC may be a sign of sensory neuropathy of the larynx and consequently, as in the case of neuropathic pain, can improve with neuroleptic drugs. Open studies³⁶ using drugs used for treating neuropathic pain that act on the peripheral nerves, such as amitriptyline and gabapentin, have shown that they reduce the severity of the cough; however, more studies based on controlled clinical trials are needed. Gabapentin belongs to a new group of drugs for epilepsy. The initial dose is 100 mg/day, increasing until the ideal dose of 300 mg/8 h is reached at the end of a month. Possible side effects include dizziness and drowsiness. Amitriptyline is a tricyclic antidepressant that is administered in a dose of 10 mg, 2 h before bedtime; this can be increased up to 40 mg. It can produce anticholinergic effects as well as less frequent side effect such as A-V conduction disorders and diffuse liver disease; it should

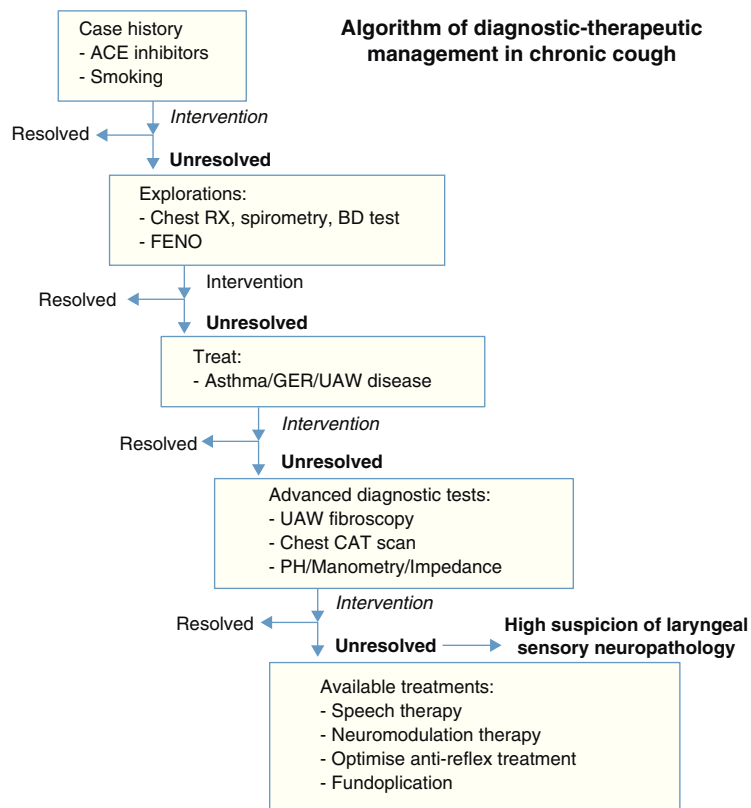


Figure 2 Algorithm of diagnostic-therapeutic management of chronic cough. BD, bronchodilators; ACE inhibitor, inhibitor of angiotensin converting enzyme; FENO, fraction of exhaled nitric oxide (normal <30 ppb – parts per billion); GER, gastroesophageal reflux; UAW, upper airway.

be used with caution in pregnant women and patients with hypertension or diabetes.

At present, the dose of amitriptyline that can interfere in the cough reflex is not clear. Amitriptyline acts very quickly and is long-lasting, making it superior to the classic local anaesthetic; its effectiveness stems from blocking cholinergic muscarinic receptors or histamine H1 receptors, instead of blocking fibres of transmission of neuropathic pain.³⁷ In cases of LPR it may be necessary to double the PPI dose (40 mg/12 h) and add a bedtime dose of H2 inhibitors (ranitidine 300mg) to cover the excess of nocturnal acid secretion³⁸; this treatment should continue until the symptoms are resolved or under control, and should then be continued for an additional period of 3 months.³⁹

In conclusion, clinical judgement and symptom staging back the hypothesis that speech therapy rehabilitation treatment to control cough is effective in treating CC and could be considered a valid alternative for individuals whose cough persists in spite of medical treatment, bearing in mind the fact that the appearance of CLC and LPR frequently coincide, so a double treatment regimen is advisable from the start. All these treatment objectives can lead to having the coordinated efforts of pneumologists, otolaryngologists, gastroenterologists and speech therapists for a single patient.

Conflict of Interests

The authors have no conflicts of interests to declare.

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