



Chronic Cough, Irritable Larynx, and Sensory Neuropathy

Chronic cough is defined by cough lasting more than 8 weeks and is most commonly caused by asthma, upper airway cough syndrome, or reflux. Irritable larynx syndrome (ILS) is described to be a hyperkinetic laryngeal dysfunction that manifests with laryngospasm, dysphonia, globus, and/or chronic cough. Neurogenic cough is a diagnosis of exclusion after negative work up for other causes and is attributed to hypersensitivity of the superior laryngeal nerve.

Anatomy and Physiology

- There is a higher concentration of cough receptors in the larynx.

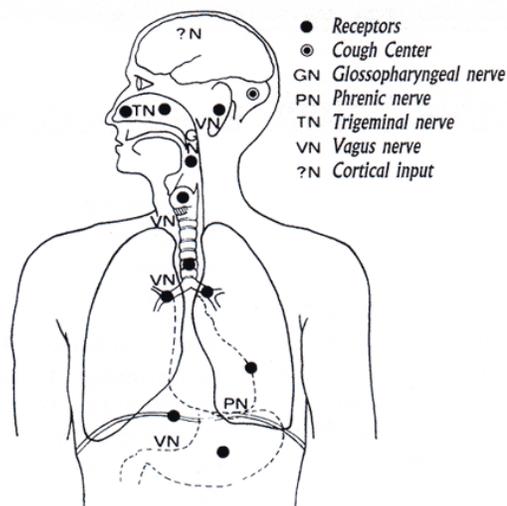


FIGURE 1. Cough Receptors involved in the normal cough mechanism. (From Irwin RS, et al., Cough: A comprehensive review. *Arch Intern Med.* 1977; 137:1186-91)

- The internal branch of the SLN, a branch of the Vagus nerve, provides general sensation (pain, touch, temperature) above the level of the true vocal folds. The SLN is divided into two branches. The upper branch supplies the inferior pharynx, epiglottis, vallecula, and laryngeal vestibule. The lower branch supplies the aryepiglottic folds and the false vocal folds
 - Paraskevas GK, Raikos A, Ioannidis O, Brand-Saberi B. Topographic anatomy of the internal laryngeal nerve: surgical considerations. *Head Neck* 2012;34:534–540.
- The laryngeal adductor reflex (LAR) is an involuntary protective response to stimuli in the larynx to protect the airway and prevent aspiration into the trachea. The reflex is activated by the nociceptive nerve endings which lay beneath and between the mucosal epithelial cells of the epiglottis, aryepiglottic folds, and interarytenoid space. The LAR is modulated by afferent limb of the superior laryngeal nerve and laryngeal adduction from the efferent limb of the recurrent laryngeal nerve. The LAR is activated in patients with neurogenic cough or irritable larynx syndrome.



- Canning B.J., Mori N., and Mazzone S.B.: Vagal afferent nerves regulating the cough reflex. *Respir Physiol Neurobiol* 2006; 152: 223-242
- Belvisi M.G.: Sensory nerves and airway inflammation: role of A δ and C-fibers. *Pulm Pharmacol Ther* 2003; 16:1-7
- Ludlow CL, Van Pelt F, Koda J. Characteristics of late responses to superior laryngeal nerve stimulation in humans. *Ann Otol Rhinol Laryngol.* 1992; 101:127–134.
- Amanda S. Domer, MS, SLP-CCC, Maggie A. Kuhn, MD, and Peter C. Belafsky, MD, PhD *Curr Otorhinolaryngol Rep.* 2013 Sep; 1(3): 178–182.

Assessment

- Patients present with a myriad of symptoms of chronic cough, throat clearing, dysphonia, globus, and laryngospasm. History taking is a significant part of the assessment and work up for these patients. Most will relay a history of symptoms that seem to be triggered by inappropriate stimuli or sensation in the throat/larynx. Components of irritable larynx may exist in addition to, or due to, other comorbidities, such as GERD, LPRD, esophageal dysmotility, UACS, allergies, and pulmonary disease.
 - 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.
- Work up should entail detailed medical history with particular attention to reflux, esophageal disorders, dysphagia, pulmonary disease, sinonasal disease and associated inciting event that precipitated the cough. Questioning on symptom should include: triggers or remitting factors, frequency and duration of cough, productivity of cough, associated symptoms, and occurrence of disordered breathing or vocal cord dysfunction. It is important to know the response of symptoms to diet changes, PPI, antihistamines, or immunotherapy. Certain medications, such as Ace inhibitors and angiotensin receptor blockers, may have cough/throat clearing as a side effect.
 - Irwin RS et al. Cough A Comprehensive Review *Arch Intern Med.* 1977;137(9):1186-1191.
- Videostroboscopy is performed to fully evaluate the biomechanics of the vocal folds. Neurologic and vibratory parameters should be assessed. Paresis may be present in the setting of post viral vagal neuropathy.
 - Sulica L. The superior laryngeal nerve: function and dysfunction. *Otolaryngol Clin North Am* 2004;37:183–201.
- In addition, evaluation by a specialized Speech Language Pathologist is important to assess inefficient coordination of vocal subsystems and disordered breathing.
 - Hess HE, Barone NA, Daniero JJ. Predicting Patient Needs for Interdisciplinary Services in a Voice and Swallowing Center.

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- Baseline evaluation of cough should include chest AP and potentially pulmonary function testing. Esophagram, modified barium swallow, EGD, capsule pH testing,



pH/impedance testing, and esophageal manometry are all used to evaluate for reflux or esophageal dysmotility disorders that can contribute to cough/ILS symptoms.

Pathophysiology

- Irritable larynx syndrome and neurogenic cough are thought to be a reaction to change in the central nervous system that causes sensorimotor pathways to be in a hyperexcitable state. This occurs through neural plasticity from injury to neurons or tissue, chronic exposure to irritant, and emotional input via the CNS to the periaqueductal gray area in the brain to place the laryngeal control center in a hyperexcitable state. Disruption or injury of the sensory fibers coming from the larynx by way of the SLN can result in hypersensitivity of the efferent motor supply to thyroarytenoid muscles.
 - Morrison M, Rammage L, Emami AJ. The Irritable Larynx Syndrome. *Journal of Voice*. Vol. 13, No. 3, pp. 447-455.
 - Ludlow CL, Nakamura K, Yamashita T. Laryngeal Sensori-Motor Response Conditioning Following Peripheral Nerve Injury. Poster session presented at the Third International Dystonia Symposium, October 1966 Miami FL
 - Lee B, Woo P. Chronic cough as a sign of laryngeal sensory neuropathy: diagnosis and treatment. *Ann Otol Rhinol Laryngol* 2005;114:253–257.

Treatment

- Disease-specific contributing factors to cough should be treated and referrals made for further work up if necessary.
- Respiratory retraining therapy is an effective treatment for irritable larynx and chronic cough.
 - Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomized placebo controlled trial of treatment efficacy. *Thorax* 2006;61:1065–1069.
 - Murry T, Tabae A, Aviv JE. Respiratory retraining of refractory cough and laryngopharyngeal reflux in patients with paradoxical vocal fold movement disorder. *Laryngoscope* 2004;114:1341–1345.
- Cough refractory to therapy or thought to have a post viral neurogenic etiology can be treated with neuromodulating medications. Multiple neuromodulating medications have been shown to be beneficial in the treatment of neurogenic cough, including amitriptyline, c-aminobutyric acid (GABA) analogs (gabapentin and pregabalin), the GABA agonist baclofen, and tramadol.
 - Dicipinigitis PV, Rauf K. Treatment of chronic refractory cough with baclofen. *Respiration*. 1998; 65(1):86-88.
- Amitriptyline is a tricyclic antidepressant that inhibits norepinephrine and serotonin reuptake. It is thought to reduce the cough reflex by reducing the sensory threshold of afferent nerve fibers.
 - 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.



- Gibson PG, Ryan NM. Cough pharmacotherapy: current and future status. *Expert Opin Pharmacother* 2011;12:1745–1755.
- GABA analogs (gabapentin and pregabalin) inhibit voltage-gated calcium channel release of excitatory neurotransmitters. These medications were traditionally used as anticonvulsants but are now typically used to treat neuropathic pain. Its mechanism of action is not fully understood but it may stimulate noradrenaline mediated descending inhibition in the supra-spinal region, which contributes to its anti-hypersensitivity action in neuropathic pain.
 - Kukkar A, Bali A, Singh N, Jaggi AS. Implications and mechanism of action of gabapentin in neuropathic pain. *Arch Pharm Res*. 2013 Mar;36(3):237-51.
 - Altman KW, Noordzij JP, Rosen CA, Cohen S, Sulica L. Neurogenic cough. *Laryngoscope* 2015;125:1675–1681.
 - Merati A, Dibildox D, Gilberto JP. Unilateral Laryngoscopic Findings Associated with Response to Gabapentin in Patients with Chronic Cough. *JAMA Otolaryngol Head Neck Surg*. 2017; 143(11):1081-1085
- Tramadol is a synthetic opioid and has been effective in improving chronic cough. The advantage of tramadol for neurogenic cough is its favorable side effect profile, easy dosing, and safety. There is a risk of dependence with tramadol, even at lower doses and patients should be followed carefully.
 - Dion GR, Teng SE, Achlatis E, Fang Y, Amin MR. Treatment of Neurogenic Cough with Tramadol: A Pilot Study. *Otolaryngol Head Neck Surg*. 2017 Jul;157(1):77-79.
- SLN block showed significant improvement in Cough Severity Index scores in patients with chronic cough. This technique involves a series of injections to instill long-acting particulate corticosteroid and a local anesthetic to block the internal branch or the superior laryngeal nerve
 - Simpson CB, Tibbetts K, Loochtan MJ, Dominguez LJ. Treatment of Chronic Neurogenic Cough With In-Office Superior Laryngeal Nerve Block *Laryngoscope*, 128:1898–1903, 2018
- Laryngeal botulinum toxin has been suggested as a treatment for chronic cough. This effect may be due to attenuation of capsaicin and C-fiber-mediated nociception (cough receptors) and also the cough-injury-cough cycle, leading to desensitization of the cough pathway.
 - Sasieta HC, Iyer VN, Orbelo DM, et al. Bilateral thyroarytenoid botulinum toxin type A injection for the treatment of refractory chronic cough. *JAMA Otolaryngol Head Neck Surg* 2016;142:881–888.
- Bilateral injection augmentation of the vocal folds in patients with chronic cough was performed by Crawley et al. They recommend injections be done in patients with chronic cough and motor paresis found on stroboscopy.
 - Crawley BK, Murry T, Sulica L. Injection augmentation for chronic cough. *J Voice* 2015;29:763–767.