Neurogenic Cough: Overview

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1.Definition and Mechanisms

While hypersensitivity to other cough stimuli, such as in an irritable larynx, can lead to neurogenic cough (1,2), when it occurs independently, it is usually linked to sensory neuropathy (3). Although sensory neuropathy is often associated with reduced nerve sensitivity, neurogenic cough presents clinically as a hyperexcitable condition, which contradicts the common perception (1).

Since viral infections are a common cause of isolated idiopathic neurogenic cough, it is important to consider the signs and processes of laryngeal and other virus-induced nerve injuries. Several otolaryngology conditions have significant anecdotal evidence linking them to viruses, including idiopathic voice paralysis, vestibular neuronitis, facial palsy, and sudden sensorineural hearing loss. Epidemic viruses such as cytomegalovirus, herpes simplex virus, varicella-zoster, and HIV are all known to be associated with these issues. There is strong evidence connecting the 1969–1970 influenza outbreak with vocal paralysis (4). Researchers have explored how these and other injuries cause neuropathy. Viral infection may indirectly affect the nerve through its blood supply. For example, there is evidence linking varicella-zoster virus-induced optic neuropathy to vasculitis of the temporal artery (5). Similarly, systemic vasculitis-related mononeuritis multiplex has been linked to hepatitis B virus-induced Guillain–Barré syndrome (6). As shown in cases of hepatitis C virus infection in tissues and HIV peripheral neuropathy, where viral RNA has been found in the spinal cord (7), the nervous system can potentially be directly impacted by viral infection.

The pattern of impairments, pathogen location, time from infection to neuropathy development, and various causes of nerve damage all make diagnosing infection-related neuropathies challenging (8). Defining a specific injury mechanism is further complicated by the complexity and variety of cough as a symptom compared to the other disorders mentioned earlier (9). When trying to determine what might be wrong with a neurogenic cough, it helps to review the processes involved in a normal cough response (1).

Topical infectious agents of the airway, inflammatory cytokines, mucus and liquid viscosity, temperature, pH, and gene regulation leading to altered mucus in disease are all potential factors that can work together. At the sensory receptor, neuronal activity initially occurs (10). A variety of stimuli can activate different receptors, including (1):

Cough receptors are myelinated nerves with a conduction velocity of 5 m/s. RAR is rapidly adapting receptors that function as mechanoreceptors. SAR are slowly adapting receptors that sense stretch. TRPV1 is a transient receptor/ion channel, a potential vanilloid receptor stimulated by acids, protons, and capsaicin. TRPA1 is transient receptor potential ankyrin receptors stimulated by cigarette smoke and toluene diisocyanate.

• Afferent C-fiber nerves: narrow in diameter, slow conduction, and a velocity of less than 1 m/s. Those that end in the brainstem jugular ganglia start coughing, and those that end in the nodose ganglia stop coughing.

Similar changes in sensory receptor excitability can occur due to submucosal activity, which includes dilated blood vessels and contracted smooth muscles. Human studies on the effects of neurokinin and substance P on C-fiber and cough receptor excitability are in their infancy (11). The nucleus solitarii are a site of convergence for subpopulations of relay neurons, and sensory afferent axons project to these nuclei (10). The respiratory motor drive is reconfigured in anticipation of the efferent cough mechanism due to excitatory stimulation. The cortices also show excitatory and inhibitory activity, which can be used to control the coughing reflex voluntarily. Behavioral adaptations, such as compensating improperly (as demonstrated with laryngeal guarding during a laryngoscope examination) or even a lack of inhibition of the cough, could cause or contribute to the cough (1).

2.Evaluation for persistent cough

A comprehensive history and physical examination should be part of the evaluation process for every patient presenting with a persistent cough. Obtaining a chest radiograph is also recommended for all patients (12). What happens next when a chest X-ray returns abnormal depends on the particular finding. If a pulmonary lesion is detected, further investigations, such as chest computed tomography (CT) scanning, bronchoscopy, needle biopsy, and sputum testing, may be necessary.

In addition, the following are included in the workup:

• Upper airway cough syndrome (UACS) — When necessary, a workup may involve sinus CT scanning or allergy tests to rule out sinusitis or allergic rhinitis. In asthma cases, a spirometry and bronchoprovocation challenge with methacholine should be performed on the patient to identify reversible airflow blockage.

The preferred diagnostic technique for non-allergic eosinophilic bronchitis (NAEB) is an induced sputum test that shows increased eosinophils (13)

The gold standard for diagnosing gastroesophageal reflux disease (GERD) is dual-channel 24-hour pH probe monitoring. Flexible nasopharyngoscopy, which can show glottic reflux-related changes, is another option. However, this test is only used for cases that do not respond to the first two methods.

• Induced sputum testing for acid-fast bacilli, high-resolution CT scanning of the chest, and bronchoscopy may be necessary in cases of refractory persistent cough after the most frequent causes have been addressed without success.

Medical Care

Efficacy in alleviating neurogenic cough symptoms is the primary goal of treatment. However, the possibility of a long-term impact on the underlying pathophysiology of the condition is still up for debate. Some symptoms shared by individuals with neurogenic cough and other neuralgias include a trigger phenomenon in which a stimulus causes the patient to cough in the case of neurogenic cough and pain episodes in the case of trigeminal or postherpetic neuralgia (3, 14-16), For the treatment of certain types of neuropathic pain, the tricyclic antidepressants, gabapentin, and pregabalin are the drugs of choice

The medicine amitriptyline

The study by Jeyakumar et al. compared amitriptyline with codeine/guaifenesin in a randomized controlled trial. The results showed that 86.7% of the amitriptyline group saw a cough improvement of 50% or more and an increase in cough-specific quality of life (QOL). In comparison, only 7.7% of the codeine/guaifenesin group had these effects (18). In a similar vein, amitriptyline was found to alleviate cough symptoms in three separate studies. For example, Bastian et al. discovered that six out of eight patients showed sustained improvement of 50% or more in 20 days following the discontinuation of treatment (16, 19, 20). Laryngeal examination evidence of motor neuropathy was associated with a better treatment response in patients studied by Norris and Schweinfurth (19). The amitriptyline cough reflex may be improved because it inhibits norepinephrine and serotonin reuptake, which lowers the sensory threshold of the afferent nerve terminals (16,21).

Analogs of GABA

When it comes to treating people with chronic cough, gabapentin and pregabalin have been studied for their ability to suppress the release of neurotransmitters by voltage-gated calcium channels. In a randomized, double-masked, placebo-controlled study, participants who used gabapentin for coughing had better cough-specific quality of life and less coughing overall. Still, these benefits did not last when the participants stopped taking the medication (22). According to uncontrolled studies, gabapentin and pregabalin can be helpful for patients with neurogenic cough. Lee and Woo also found that patients with motor neuropathy of the recurrent or superior laryngeal nerve responded better to treatment, which lends credence to the neuropathic model of chronic cough (1,3,23,24).

Additional Medications

The management of patients with neurogenic cough has shown promise with other pharmacologic drugs with neuromodulating potential. In healthy individuals, the γ-aminobutyric acid agonist baclofen raised the threshold for coughing up irritants like capsaicin (25). After trying baclofen, two people with chronic cough reported less coughing and a higher cough threshold (26). Botulinum toxin has the potential to dampen glottal trauma and cough intensity via changes in sensory and motor pathways, as it blocks acetylcholine release at presynaptic neuromuscular junctions and inhibits neurogenic inflammation by lowering neuropeptide release from C-fiber receptors (27,28). Nonpharmacologic Interventions Two case studies showed that botulinum toxin effectively treated persistent cough in children and adults who had tried other methods without success (29,30).

Among patients whose cough continued despite proton pump inhibitor treatment, Murry et al. found that respiratory muscle retraining, which aims to increase the abdominal musculature during inspiration while reducing the force of the oropharyngeal muscles, improved cough symptoms after at least two sessions (31,32). In research that involved medically refractory chronic cough patients, 88% of those who received therapy (patient education, cough control techniques, vocal hygiene, counseling) reported an improvement in their cough. Still, 13% of those who received a placebo (healthy lifestyle education) reported the same improvement (33). In addition, individuals who were medically refractory to cough medication showed improvements in cough-specific quality of life, reduced cough frequency as determined by an objective cough monitor, reduced sensitivity to cough reflexes, and higher threshold to capsaicin exposure after four therapy visits (34).

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