

Review Article

Upper Airway Cough Syndrome

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Abstract:

Introduction: Chronic cough is a challenge to both the patient and the treating physician. Most common cause of chronic cough in adult nonsmokers is UACS, followed by GERD and asthma. The spectrum of diseases causing UACS includes various rhino sinus conditions.

Pathophysiology: The mechanisms causing cough are post nasal drip, cough hypersensitivity, micro aspiration and rhino bronchial reflex. The altered sensitivity to the cough receptors seems to be the predominant mechanism of cough.

Clinical features and diagnosis: Chronic cough with or without sputum, nasal congestion and discharge, frequent throat clearing and sensation of fluid dripping through posterior pharyngeal wall are the symptoms. In addition to the above symptoms, findings of mucus or secretions in the posterior pharyngeal wall and cobble stone appearance of pharyngeal mucosa on examination suggest a diagnosis of UACS.

Treatment: First generation antihistamines with decongestants are the treatment found to be effective in UACS. Other treatments directed towards the specific causes and non-pharmacologic measures are generally advisable.

Key Words: chronic cough, upper airway cough syndrome, cough hypersensitivity, rhinitis, sinusitis, antihistamines

Introduction

Cough is one of the most common symptoms leading to medical consultations worldwide¹. Acute cough, lasting up to three weeks is generally curable with initial appropriate therapy or even without treatment sometimes, whereas chronic cough frequently cause discomfort and lead to considerable medical expenditure. The importance of cough as a clinical problem is evident from the number of practice guidelines published by various pulmonary societies over recent years. In spite of these guidelines, chronic cough still remains a challenge for the practicing physician. There are several reasons for this: a lot of diseases cause cough, but many of these do not have any characteristic signs or specific treatment. Many underlying mechanisms related to the pathophysiology and hence treatment options of chronic cough are still not clear. Chronic cough is defined

as cough lasting for more than eight weeks. Most common causes of chronic cough are Asthma, Gastro Esophageal Reflux Disease and Upper Airway Cough Syndrome (previously known as Post Nasal Drip syndrome), collectively known as 'diagnostic triad of cough'. In children also upper airway cough syndrome constitutes a major cause of chronic cough, but not the commonest⁴. There are several pulmonary as well as extra pulmonary conditions associated with chronic cough. Studies among different populations have shown that UACS is the commonest cause for chronic cough for which people seek specialist help.

The name 'Upper airway cough syndrome' was coined to encompass diseases affecting upper airways, like rhinitis and sinusitis, which results in chronic cough¹. Rhinitis is usually associated with nasal discharge and cough. Sinusitis causes secretions dripping down on to pharynx and larynx

from the sinuses. This drainage of secretion was thought to be the mechanism responsible for the cough in UACS. However this could not explain the occurrence of cough in many other situations, which do not produce secretions. A minority of patients with sinusitis who did not have any obvious dripping of secretions were found to have cough. New theories have been brought forward to explain the mechanisms of cough in such situations. Post nasal drip as a mechanism could not explain the cough seen in all the conditions associated with UACS and hence 'post nasal drip syndrome' has been replaced with 'upper airway cough syndrome'.

Pathogenesis

Cough is a protective reflex which helps clearance of secretions and inhaled particles from airways and protects lower airways from aspirations. The afferent limb of cough reflex consists predominantly of Vagus nerve fibers- situated in the airways and upper respiratory tract, Trigeminal and Glossopharyngeal nerves. Cough receptors are present throughout pharynx to terminal bronchioles and comprises two types, rapidly adapting receptors that respond to mechanical stimuli, and nociceptors on C fibers, responding to chemical, immunological as well as inflammatory mediators³. The sensory inputs are processed at medulla where the central cough center is situated; which then sends off efferent signals through Vagus, to larynx and tracheobronchial tree, and through Phrenic and various spinal motor neurons, to diaphragm, intercostal, abdominal and perineal muscles to bring about cough. Cough reflex is a polysynaptic reflex and it is modulated by many other sensory inputs in the vagal neurons and out of it. This modulation of reflex is called cough plasticity⁶. In addition to this, a cortical component is also involved in the regulation of cough, as evidenced by the presence of voluntary cough.

In disease states different mechanisms cause cough. Stimulation of sensory receptors by secretions, foreign bodies and mass lesions etc. represents one. Another mechanism is the change occurring in cough receptors, leading to increased sensitivity to cough receptors resulting in either persistent cough or decreased threshold for cough. This abnormal regulation of the cough receptors can either be an up regulation, manifested as enhanced cough reflex and too long cough, as seen in many upper airway diseases

like sinusitis and rhinitis. It is believed that this 'cough hyper sensitivity' is the underlying mechanism in many of the cases of chronic cough, in spite of their different aetiology and clinical presentations.

Post nasal drip syndrome has been used to denote conditions associated with upper airway pathology and chronic cough. It was believed that, the draining of secretions from the upper airway caused generation of cough, through direct stimulation of cough receptors situated in the oropharynx and larynx or by inflammatory cells and mediators stimulating cough receptors. However this could not be the reason in all cases of chronic cough associated with upper airway diseases, as there were conditions without secretions being produced. Rhinitis is not always associated with cough, even though it is considered to be the commonest cause of acute cough. Also, in a minority of patients with sinusitis, there were no evidence of secretions draining from sinuses, called silent sinusitis, but were associated with cough. In view of this findings and with the emergence of new hypotheses, the name, post nasal drip syndrome has been replaced with 'upper airway cough syndrome'. The recent concepts regarding the pathogenesis of UACS comprise different mechanisms, instead of one as in PNDS. Along with post nasal drip, unified airway concept and cough hypersensitivity may be helpful in explaining the underlying mechanisms in UACS.

Cough hypersensitivity: Increased sensitivity to cough reflex is seen during upper respiratory infections and allergies. This hyper sensitivity has been experimentally proven using challenge tests using capsaicin. The enhanced reactivity is found to be resolving, once the infection is controlled. Morice et al⁵ were of the opinion that cough hypersensitivity could be a universal phenomenon in chronic cough, so that, it may be prudent to consider all the causes of chronic cough as part of a separate syndrome with cough as common presentation and cough hypersensitivity as unifying mechanism among them - 'Chronic cough hypersensitivity syndrome'. Studies have shown that there is a gender difference in the occurrence of cough hypersensitivity. Adult females were manifesting more of this phenomenon, compared to males⁵.

Recently, Jana Plevkova, and Woo-Jung Song also studied the pathophysiology of UACS more thoroughly⁶.

The possible mechanisms suggested were post nasal drip, micro aspiration, nasobronchial reflex, propagation of inflammation via systemic circulation and loss of nasal function while inhaling cold air through mouth breathing during rhinitis. Their speculation was that, this cough hypersensitivity during infections was a protective strategy to prevent spread of diseases from upper respiratory tract to other parts. There was also a cortical component to this, in the form of an 'urge to cough' which is considered to be a specific sensation of airway irritation leading on to cough; it represents cortical conscious contribution to the airway defense. Their hypothesis was that, nasal inflammation was a strong trigger for cough in persons with either inherited or acquired cough hypersensitivity or upper airway diseases itself could be the cause of cough hypersensitivity.

Unified airway hypothesis states that there are structural and functional similarities between upper and lower airways, so that insults in the form of infections or allergy occurring in one part may cause changes in the other part. This is brought about by systemic effect of inflammation, through trafficking of inflammatory mediators. According to this model, pathology in one part of respiratory mucosa can evoke a system wide response which can cause pathophysiological changes in other parts of respiratory mucosa, distal to the initial site of insult. This could explain enhanced cough reflex in rhino sinusitis⁷.

Thus, the current evidence suggests that, apart from post nasal drip, hypersensitivity to cough receptors in upper airways may be the predominant mechanism leading on to chronic cough in UACS. Other mechanisms like micro aspiration, nasobronchial reflex or systemic propagation of inflammation are likely, but there is lack of evidence to support these mechanisms at present.

Clinical Features and Diagnostic Evaluation

Finding out etiology in chronic cough is often not easy. History as well as patient described symptoms may be useful in some situations, where suggestive symptoms are available, as in the case of Asthma and GERD. In the evaluation of UACS as a cause of chronic cough, symptoms and signs lack specificity. Presence of chronic cough, with or without expectoration, frequent throat clearing, nasal

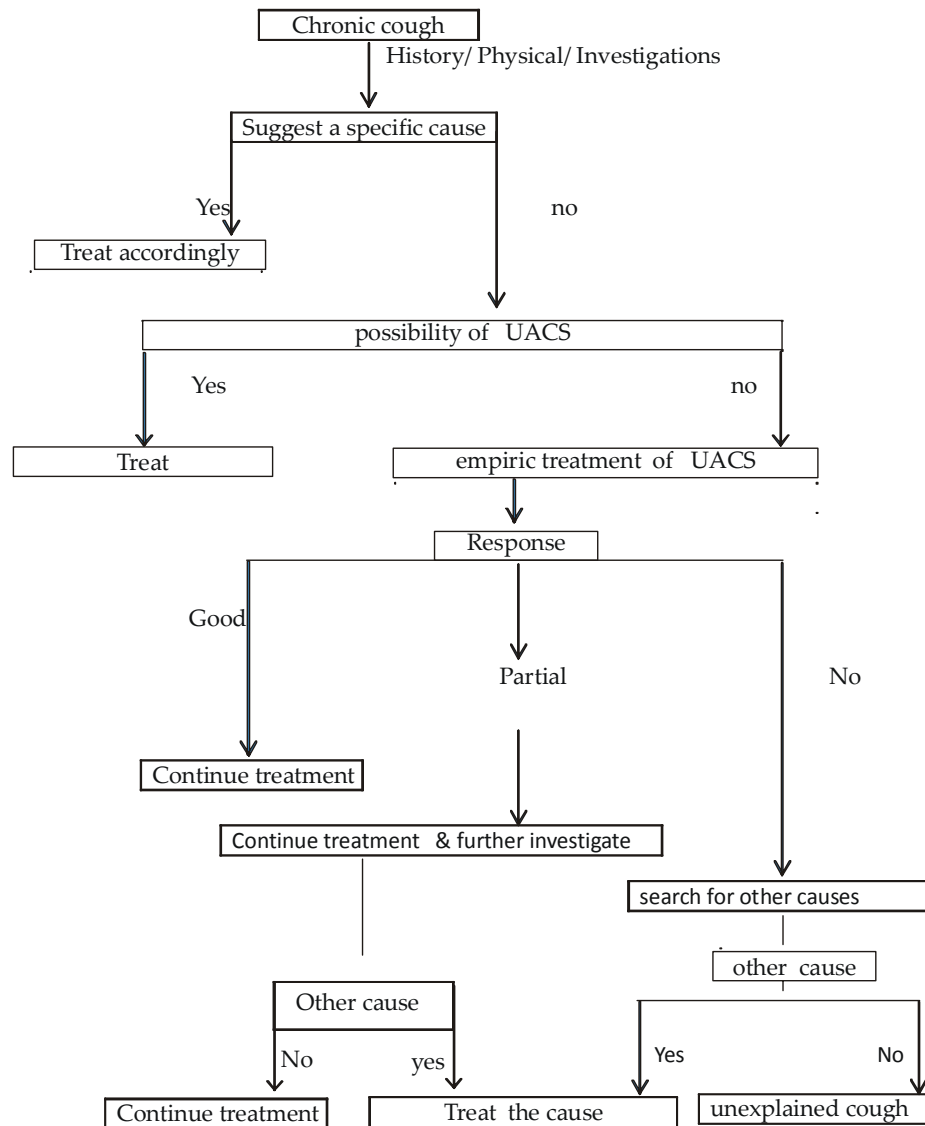
discharge, a sensation of secretions dripping down the throat, and on examination, presence of secretions in posterior pharyngeal wall or cobble stone appearance of the pharyngeal wall mucosa may suggest a diagnosis of Upper Airway Cough Syndrome. However, these symptoms are largely based on patient's subjective sensations. It was reported that nearly 20% patients were unaware of the sensation in the throat, when actually they had sinusitis. Thus, the hallmark of UACS is that, it does not have any pathognomonic finding. Hence response to treatment directed to UACS may also be taken as evidence of diagnosis in UACS. The ACCP guideline suggest a diagnostic approach based on a combination of criteria, including symptoms, physical examination findings, imaging and response to therapy¹. If symptoms specific to any particular disease is forthcoming, treatment should be directed to that. If the patient does not respond to treatment, further diagnostic evaluations like sinus imaging and nasal endoscopy should be done. It should be remembered that, other conditions like silent GERD or Cough variant Asthma, may occur simultaneously with UACS and when there is only partial or no response at all to treatment, patient should be further evaluated.

Conditions associated with UACS

- Rhinitis** Allergic rhinitis
- Perennial non-allergic rhinitis
- Vasomotor rhinitis
- Nonallergic rhinitis with eosinophilia (NARES)
- Post-infectious rhinitis
- Rhinitis due to anatomic abnormalities
- Rhinitis due to physical or chemical irritants
- Occupational rhinitis
- Rhinitis medicamentosa
- Rhinitis of pregnancy
- Sinusitis** Bacterial sinusitis
- Allergic fungal sinusitis

Adapted from PratterMR ,Chest 2006, 129:635-71S1

DIAGNOSTIC ALGORITHM



Treatment

Management of chronic cough is often difficult; though some studies have shown that a guideline based approach may be helpful¹⁰. Treatment of UACS include treatment of specific causes, with pharmacologic and non-pharmacological approach. Avoidance of allergens, antibiotics, methods to reduce inflammation and obstruction are generally advised. When a specific cause is obvious, treatment should be directed to that, and the response to treatment will be good. But many a times a specific cause will not be apparent. In such situations, an empiric therapy

initiated before starting further investigations has found to be effective. A first generation anti histamine or decongestant is usually recommended as empiric therapy⁸. Studies have shown that compared to non-sedating second generation antihistamines, first generation antihistamines are effective in relieving cough associated with UACS. The mechanisms of older generation antihistamines in controlling cough in UACS seems to be due to its anticholinergic action, however, other possible explanations being, actions of these drugs on histaminergic and nonhistaminergic receptors in central nervous system⁹.

Mechanisms by which antihistamines cause suppression of cough in UAC

Mechanism	Mode of Action
Peripheral action	<p>Antihistamines suppress cough by directly acting on histaminic receptors and modulating peripheral sensory afferents that promote cough.</p> <p>Indirectly antihistamines suppress cough by decreasing mucous secretion induced by histamine receptors and through cholinergic mechanisms.</p>
Central action	<p>H1 receptor blocking drugs act directly on histamine receptors that promote cough and on nonhistaminergic receptors in central nervous system that control cough excitability.</p> <p>Indirectly these drugs act on histaminergic and nonhistaminergic receptors that regulate secretion of mucous, thereby decreasing cough.</p> <p>Another mechanism is the sedative effect that reduces cough excitability</p>

First generation antihistamines and decongestants are the preferred pharmacologic treatment in UACS, because of their cough suppressant effect. Second and third generation antihistamines do not have any effect on cough, hence, are generally not advised. However, second generation, non-sedating antihistamines have a role through reduction in nasal congestion when allergic rhinitis is the causative factor in UACS. In patients with rhinitis prolonged treatment with intranasal corticosteroids may be useful. When empiric therapy is given, patient has to be evaluated for possible causes while continuing treatment. If cough improves in 2-3 weeks, it is suggestive of possible UACS. If response is only partial, possibility of multiple causes for cough has to be considered and should be further investigated. When the patient is not responding to initial therapy, look for other etiologies like sinusitis, for which sinus imaging and prolonged antibiotics may be required. Still the patient continues to be symptomatic further evaluations to rule out other unrelated causes has to be done; since simultaneous occurrence of multiple causes is not uncommon in patients with chronic cough. In children first generation oral antihistaminic drugs are generally not advisable. Antihistamines as nasal preparations and chromolins may be useful.

Treatment of allergic rhinitis include avoidance of

allergens wherever possible, antihistaminic drugs, decongestants, topical steroids and allergen immunotherapy. Antihistaminic drugs available are chlorpheniramine, cetirizine, fexofenadine, loratidine etc. Topical antihistamines are azelastine and olopatadine. Second generation antihistamines are preferred as first line therapy for their non-sedating advantage. Pseudoephedrine had been the most commonly used oral decongestant, but now it has been replaced by phenylephrine. Leukotriene antagonist, montelukast, inhaled anticholinergic ipratropium, and chromolin sodium are useful in selected cases.

Intranasal steroid sprays are considered to be the first line therapy in Perennial non-allergic rhinitis. Azelastine and olopatadine are topical antihistamines useful in perennial non allergic rhinitis. Ipratropium spray help to control rhinorrhea. Oral antihistamines and decongestants are also useful. But in children, because of safety concerns, many oral antihistaminic drugs are not advised. Surgical removal of allergic mucin, corticosteroids, antifungal treatment and immunotherapy are the usual treatment adopted in allergic fungal sinusitis. Avoidance of offending substances is the mainstay in rhinitis caused by environmental agents and occupational rhinitis. Steroid nasal sprays, cromolyn sodium and antihistamins like chlorpheniramine, loratidine and cetirizine are found to

be safe and effective for treating rhinitis of pregnancy.

There are still unresolved issues in the management of UACS. There is dearth of studies on UACS, so that, the optimum combination of drugs and duration of treatment are not well established.

Conclusion

Chronic cough is caused by a variety of conditions and when initial evaluations do not point to a specific etiology, possibility of UACS has to be considered. Many rhino sinus conditions cause cough through excessive secretions and altered cough reflex mechanisms. Post nasal drip as a possible single mechanism is no longer tenable because, it cannot explain the occurrence of cough due to various causes in UACS. Rhinitis and sinusitis produced

by allergens and infective agents play a major role in UACS. Often identification of the underlying cause is unsuccessful and occurrences of multiple underlying conditions are not uncommon. Initial empirical therapy with first generation antihistamines and decongestants are generally effective. However exact duration and treatment responses are still not clear. Emerging scientific evidences point to the role of cough hypersensitivity and other possible underlying mechanisms in the causation of cough in UACS. There is need for the development of newer drugs effective in controlling cough, like transient receptor potential vanilloid receptor (TRPV1) inhibitors.

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