

Clinical assessment and current treatment of refractory chronic cough

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Abstract

Chronic cough is a cough that occurs for more than 2 months. Chronic cough is a health problem that can cause physical complications, psychology problem, dan impact on quality of life. The common causes of chronic cough are asthma, eosinophilic bronchitis, gastroesophageal reflux disease, angiotensin-converting enzyme inhibitor use, smoking, and upper airway cough syndrome. Refractory chronic cough is a cough that is persistent after optimal therapy of underlying diseases. Recent theory regarding the neural system contributes to the pathophysiology of refractory chronic cough known as cough hypersensitivity syndrome. Treatment of refractory chronic cough needs comprehensive evaluation of cough severity, trigger of cough, and underlying diseases. Neuromodulators can be used as pharmacology treatment of refractory chronic cough but still need more research to define standard dose and safety.

Keywords: Chronic Cough; Cough Hypersensitivity Syndrome; Cough Assessment; Neuromodulator

1. Introduction

Cough is the most common respiratory chief complained by adult patients who seek treatment at health facilities. (1) Chronic cough is a cough that lasts more than 2 months. (1,2) Several conditions that are widely known to cause chronic cough include asthma, eosinophilic bronchitis, gastroesophageal reflux disease, use of angiotensin-converting enzyme (ACE) inhibitors, smoking, and upper respiratory cough syndrome. (3) Recent evidence that a condition known as neural dysregulation plays an important role in a chronic cough that does not respond to standard treatment, which now knowing as refractory chronic cough (RCC). (1,4)

The prevalence of chronic cough is estimated at 2 – 18% worldwide. The impact of RCC includes the effect on the organ system and psychological which also affect the quality of life. The cause of the delay in diagnosis and treatment of RCC is the problem in the identification of cough triggers and recommendations for therapy.(4,5)

Refractory chronic cough is common but often difficult to diagnose and treat. (3) Clinical evidence on recommendations for the management of RCC is currently limited. Several treatment was given not based on the mechanism pathophysiology, off-label, lower efficacy, and problem side effect. (4,5) Therefore, new and alternative therapies are needed to treat RCC by targeting the underlying pathophysiological molecules or mechanisms. This literature review will discuss the risk factors, the pathophysiology of RCC, the comprehensive assessment, and current management of RCC which includes pharmacological and non-pharmacological therapy.

1.1. Definition

Cough is a reflex mediated by the vagal nerve and is part of the vegetative functions including swallowing and sound. Cough has a function to protect of the lungs from inhalation of noxious agents and also clears the secretion in the airway. (6) If the cough persists for more than 2 months it is categorized as chronic cough. (7,8)

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Previously known causes of chronic cough include cough associated with viral infections in the respiratory system, asthma, GERD, esophageal dysmotility, post nasal drip syndrome, and the use of ACE inhibitor drugs. (9–11) Not all of these disease conditions can represent the complex heterogeneity of airway disease. The sensitivity of the neural pathways plays a role in the pathophysiology of cough which is a clinical symptom consistent with chronic cough. (4,5)

Refractory chronic cough can be described as a cough of neurogenic origin, hypersensitivity in the larynx, cough hypersensitivity syndrome, laryngeal irritation, habitual cough, and also psychogenic cough. (5,12) Definition of RCC from the American College of Chest Physicians, is a cough that is persistent despite using a diagnosis and treatment approach for GERD, upper respiratory cough syndrome, inflammatory airway disease, smoking cessation, environmental exposure, and avoiding the use of ACE inhibitor. (4–6,13)

Chronic cough is called unexplained chronic cough (UCC) if the cough persists after adequate assessment, investigation, and therapy. (14) The terms RCC and UCC are commonly used in the setting of clinical trials. The Hull Airway Reflux Questionnaire (HARQ) questionnaire is used to differentiate RCC and UCC in clinical trials. (4,15)

Cough hypersensitivity syndrome (CHS) is a new paradigm in a refractory chronic cough which was introduced by the European Respiratory Society (ERS) in 2014, defined as a clinical syndrome of cough caused by exposure to thermal, mechanical, and chemical at a lower level. (16) The mechanism of cough hypersensitivity syndrome is useful for understanding the pathophysiology underlying RCC in most cases of chronic cough. (5) Cough hypersensitivity syndrome can be a target for specific therapy in RCC. (4)

1.2. Epidemiology

The differences of epidemiological data on chronic cough are caused by the study method, patient population definition, conventional treatment, and the condition of refractory cough. The prevalence of RCC will increase if the patient explains a chronic cough caused by a poor response to therapy that is not by the underlying pathology. RCC may be underreported or underestimated when the cough is considered to be a complication of another condition. Obesity and smoking can also contribute to the differences in the prevalence of chronic cough. (4,5) The global prevalence of chronic cough varies by geographic region, from the meta-analysis of 90 studies the prevalence was between 2- 18%. (4,17) In outpatient clinics, 10 – 38% of patients have a chronic cough. (4)

Aging is an important risk factor for chronic cough. A study was conducted in England, Netherlands, Sweden, South Korea, China, and America with a sample of 10,032 patients, most of whom were 60-69 years old. Chronic cough is more common in women (66-73%), according to chronic pain data more in women, suspected to be related to neural pathway factors. (4,17)

Chronic cough can persist for several years, which showed by the cross-sectional study in Europe, from 1120 patients, 20% had a cough with a duration of more than 10 years and 10% had a cough of more than 30 years based on a questionnaire survey. A longitudinal study in England over 7-10 years, not only was the cough still persistent, but also increased cough severity in 24% of patients. (4)

1.3. Etiology

Some of the characteristics associated with persistent cough include a family history of chronic cough, sensitivity to cold air, or reflux cough. (18) Chronic cough triggers can be caused by exposure to work, the environment, smoking, ACE-I drugs, exercise, and singing. (19) The following are risk factors that increase the incidence of chronic cough; (21)

1.3.1. Demographic factors

Chronic cough is more common in women and the elderly, especially those aged 60-69 years. The higher incidence of chronic cough in women can be caused by the physical impact of chronic cough which is felt to be higher, such as urinary incontinence. Another factor is that women have a more sensitive cough reflex, as indicated by a sensitivity test to cough with capsaicin inhalation. In women, there is a higher activation of the somatosensory cortex in response to inhalation of capsaicin. (1)

1.3.2. Basic disease factors

Smokers have a 3 times higher risk of developing chronic cough than non-smokers. Respiratory virus infection, which usually heals on its own, however, in post-infectious cough with viruses such as SARS CoV 2, as many as 10-20% have a chronic cough. Causes of lung disease include cough variant asthma, eosinophilic bronchitis, and cough caused by allergy. (20) Other disorders that also play a role in chronic cough include GERD, post-nasal drip, and rhinosinusitis.

Rare causes of chronic cough include OSA, diffuse panbronchiolitis, bacterial bronchitis, atypical heart failure, and tracheobronchomalacia. (8,20)

1.3.3. Environmental factors

Exposure to work-related exposure such as fumes, gases, cleaning products, dust, and air pollution which can cause irritation and trigger cough reflex.(20)

1.4. Pathophysiology

After the eosinophilic inflammatory disease of the airway was ruled out, the cause of chronic cough was considered to be a disorder in the sensory nervous system. Cough can be triggered by stimulation of afferent branches in the cough reflex of the larynx and esophagus. (10,16) Because laryngeal hypersensitivity has a role in the pathophysiology of refractory chronic cough, evaluation of disorders of the larynx and esophagus is important. (20–22)The several mechanisms of pathophysiology of refractory chronic cough are as follows :

1.4.1. Hypersensitivity of vagal afferent, brainstem, and cortical nerves.

The current pathophysiology mechanism of chronic cough is known as cough hypersensitivity syndrome. This theory is based on the finding that a large proportion of patients develop a cough after low-level temperature, chemical, or mechanical exposure. CHS is considered a neuropathological mechanism that affects the peripheral and central nervous system. (4,21) The cough reflex in humans has 2 types of afferent pathways. The first afferent pathway is induced by mechanosensory stimuli, which are transmitted via myelinated nerve fibers. The second pathway is the chemosensory pathway, formed by a group of C nerve fibers without myelin and transmitting the same as in tissue injury-induced pain which is controlled by cation channel receptors, especially transient receptor potential vanilloid 1 (TRPV1) and TRPA1 or irritant sensors. (7,21) In RCC there is an increase in nerves with TRPV-1 which causes a cough hypersensitivity reflex due to being more sensitive to exposure to certain stimuli. This is similar to hyperalgesia in chronic neuropathic pain. (3)

1.4.2. Increased activation of the peripheral nerve terminals of the airways

The cough reflex mechanism is initiated by stimulation and activation of the airway sensory nerves due to inflammatory substances such as local substance, inhalation, or aspiration which causes an increase in intracellular calcium which opens the pannexin channels and releases ATP to activate the P2X3 channels in the sensory nerves. This event causes cell depolarization which can stimulate the opening of NaV and generate action potentials that are carried via the vagal nerve to the central nervous system. (4) Inflammatory mediators in the airways play a role in TRPV1 activity, which is a sensor molecule that detects various noxious environmental stimuli. The TRPV-1 ion channel which is a chemo sensor, is upregulated in chronic cough. Capsaicin is a direct agonist of the TRPV-1 receptor, which can increase the sensation of wanting to cough. Patients with hypersensitive cough experience an increased response to the inhalation of capsaicin in the cuneiform nucleus area. In patients with chronic cough, it is easier to experience coughing along with an increase in the intensity of the stimulus. (5,23)

1.4.3. Impaired voluntary control and descending inhibitory control pathways

Current evidence on refractory chronic cough has shown interference with neurons that control descending inhibitory pathways and reduced suppression of voluntary cough, but it is still unclear which one is more dominant. (24,25)

1.5. Complication

Complications related to cough are the effects of the physiological phase of the cough. During the physiologic phase of cough, a high expiratory airflow is generated for a protective function. The physical pressure created by coughing can cause potential injury. (26) The impact of cough includes physical, psychological, and quality-of-life.

1.5.1. Physical impact

There are complications associated with cough which are related to cardiovascular, respiratory, neurology, gastrointestinal, and other organ system that can be life-threatening. (26) Failure to confirm the etiology of the cough can add a burden to the patient because of inappropriate examinations and ineffective therapy. For example, cough is a problem for patients with CHS who are accompanied by asthma or COPD. Administering corticosteroids with increased doses to treat asthma symptoms does not provide benefits for chronic coughs, instead, it can increase the risk of side effects. Giving antibiotics to treat chronic coughs is not only useless, but also can cause costs, drug side effects, and increase antibiotic resistance. (4)

1.5.2. Psychological impact

The psychological profile of chronic cough patients includes fatigue, anxiety, depression, and somatic symptoms. Psychological impacts can be in the form of fear of serious illness, changes in lifestyle, and self-confidence. Anxiety and depression occur in 33-52% and 16-91% of patients with chronic cough. One of the reasons for this anxiety is the fear of a serious illness that causes a chronic cough. (4)

1.5.3. Impact on quality of life

Qualitative research on the impact of RCC shows that there is a burden on work-related social communication, relationship, and communication, as well as a mental burden in social life due to chronic cough. The impact of coughing on the physical, psychological, and quality of life leads to a decrease in the quality of work that disrupts the economy. (27)

2. Cough Assessment

The hallmarks of chronic cough include cough symptoms, underlying disease symptoms, and laryngeal symptoms. The pathophysiological basis of chronic cough is associated with CHS, based on the symptoms described by the patient, such as the sensation of itching, irritation, discomfort, or something in the throat. (20,28) Cough is often stimulated by changes in temperature, strong aromas or perfumes, aerosols, talking, laughing, and singing. (5,24)

An assessment of a cough includes an assessment of cough frequency, an assessment of cough severity, and an assessment of the quality of life due to cough. An objective assessment of cough frequency is carried out using an electronic cough monitor. Assessment of cough severity is using a visual analog scale. The cough frequency counter is shown by the number of coughs per hour in 24 hours but does not count natural episodes of chronic cough. The highest cough frequency is found when you wake up, around 37-65 coughs per hour and 4-10 coughs per hour during sleep. (4,29)

Cough frequency monitoring is one of the methods available for cough assessment. Routine monitoring of cough frequency is more valid and reliable than information from patient memory and physician estimates. Cough frequency quantifiers can differentiate chronic cough patients and healthy individuals. Currently available systems for routinely counting coughs are the Leicester Cough Monitor and the VitaloJAK. (4,30,31) Monitoring cough frequency plays a role in evaluating changes in cough frequency to treatment and can differentiate cough frequency between diseases. (30)

Questionnaires that can be used in the assessment of chronic cough are the Leicester Cough Monitor to assess cough frequency, the Cough visual analog scale (coughVAS) to assess cough severity, and the Leicester cough questionnaire (LCQ) to assess the cough-related quality of life. (4,20,31) Leicester Cough Monitor is a validated questionnaire that objectively calculates cough frequency for 24 hours. The cough visual analogue scale is an assessment of cough severity reported by patients with a 100 mm scale. The Leicester cough questionnaire is a validated questionnaire and consists of 19 questionnaires focused on quality of life with a score of 2-21 each, higher scores indicating an improvement in quality of life. (4,29)

3. Treatment

Currently, there are no approved standard therapy guidelines for refractory chronic cough. Several treatment options have shown benefits in clinical trials, but the standard dose has not been determined and there are common side effects.

3.1. Non-pharmacological therapy

Non-pharmacological therapy consists of physiotherapy and speech therapy aimed at controlling cough. (14,16,32) Physiotherapy and speech and language therapy intervention (PSALTI) are effective methods for treating behavioral aspects of RCC. PSALTI method includes hydration and laryngeal hygiene techniques, cough control, breathing exercises, and psychoeducation. The results showed an improvement of 41% in cough frequency, reducing cough symptoms persisting for up to 3 months after therapy. (4) The use of the neuromodulator drug and speech therapy showed improvements in cough including severity and frequency, and quality of life compared to speech therapy only. (5,16,33)

3.2. Pharmacological therapy

Currently, there are several therapeutic recommendations in the management of RCC. European Respiratory Society recommended the use of neuromodulators including low-dose opioid, gabapentin, pregabalin, and tricyclic

antidepressant. The challenge in providing therapy is that the cough phenotype is still unclear so the response to therapy in each patient can vary. The recommended duration of therapy is 1-2 weeks for opioids and 2-4 weeks for other drugs. Treatment is stopped if there is no response for more than 1 month.(4)

The use of neuromodulators such as gabapentin, pregabalin, amitriptyline, and morphine in refractory chronic cough targets sensitization of the central cough reflex. (2,19)The use of neuromodulator therapy in chronic cough is based on research related to central neural sensitization which plays a role in persistent cough similar to chronic pain syndrome. (34) Administration of neuromodulators can improve cough severity but there are side effects that can limit the use of these drugs. The provision of trial therapy with neuromodulators can be given after discussing with patients regarding side effects and the benefits and risks. (14) Pharmacological treatment in refractory chronic cough includes:

3.2.1. Inhalation corticosteroid and long-acting beta 2 agonist

The level of evidence is weak because the assessment of asthma allergy, non-eosinophilic asthma, and bronchitis is often not completed. The use of inhaler salmeterol + fluticasone routine twice a day improved cough severity score. (4)

3.2.2. Opioids

This double-blind study of twice daily sustained-release morphine sulfate showed improvement in LCQ scores by 3.2 points and reduce cough severity recorded in daily cough records. Opioid side effects include constipation, drowsiness, and risk of dependence. (5,20)

3.2.3. Tricyclic antidepressants

Treatment with tricyclic antidepressants showed a good response in 72% of patients, which was determined from the doctor's subjective assessment of patient-reported cough symptoms. The side effects include drowsiness, dry mouth, and anxiety.(16,24)

3.2.4. Gabapentin

Administration of gabapentin showed significantly improved LCQ and decreased frequency and severity of the cough compared to placebo. Side effects of gabapentin include confusion, dizziness, dry mouth, fatigue, blurred vision, and cognitive changes. (4,20)

3.2.5. Pregabalin

In the RCT study, the use of pregabalin with each group receiving speech therapy showed LCQ improvement compared to placebo and improvement of cough severity. The side effects of pregabalin are similar to gabapentin. (16,20)

3.2.6. P2X3 and P2X2/3 receptor antagonists (gefapixant, eliapixant, filapixant, and sivopixant)

From RCT studies, showed that gefapixant reduced cough hypersensitivity, frequency, and severity of cough in RCC. (35) Preclinical studies and early-phase clinical trials, showed that gefapixant is more selective for homotrimeric P2X3 receptors than P2X2/3 heterotrimers, which reduce cough frequency and cough severity. (4,5)

3.2.7. Neurokinin-1 receptor (NK-1)

In phase 2 clinical trials, Orveitant, an NK-1 receptor antagonist, showed a reduction in cough frequency and cough severity.(4)

3.2.8. Transient receptor potential vanilloid receptors (TRPV) 1 and 4.

TRPV1 agonist capsaicin is still being studied to treat cough and respiratory symptoms in idiopathic chronic cough. Drugs acting as TRPV1 and 4 receptor antagonists in phase II studies have been ineffective so far. (4,24)

3.3. Algorithm for management of refractory chronic cough

Comprehensive management of chronic cough, starting from the initial assessment and diagnostic investigation of cough symptoms associated with cough triggers or stimuli, underlying disease, and cough alarm signs. (24) Initial assessment includes assessment of duration, severity, trigger, frequency of cough, and underlying disease. Other symptom assessments included cardiorespiratory, gastrointestinal, and nasal symptoms. Evaluation of the use of ACE inhibitor drugs and smoking history. The initial evaluation includes spirometry and bronchodilator tests, chest x-rays, and a complete blood count to confirm the common diagnosis of cough. Evaluation of alarm signs including hemoptysis,

weight loss, fever, and chest X-ray abnormalities. Management according to the basic disease includes treatment of asthma and COPD, smoking cessation program, stopping ACE inhibitors and replacing with ARB antagonists, treatment post nasal drip, and GERD. (5,8,24)

After initial assessment and comprehensive management of underlying disease, if the cough persists, reconfirm again for each diagnosis such as asthma by bronchial provocation test, non-asthmatic eosinophilic bronchitis by sputum or BAL examination, GERD by evaluation 24-hour pH impedance, esophageal dysmotility by manometry test, CRS by nasal endoscopy, or CT scan sinus, or laryngoscopy. Assess the severity and impact of cough using CoughVAS and LCQ, and treat according to the established diagnosis. (8,24)

If the cough persists after optimal treatment according to the underlying disease, further evaluation of the cough trigger, administration of non-pharmacological therapy for cough suppression, avoiding coughing, reducing irritation of the larynx, education and counseling, and start administration of neuromodulators such as pregabalin or gabapentin, or amitriptyline. (24)

4. Conclusion

Refractory chronic cough has heterogeneous central and peripheral nerve pathways, a variety of underlying diseases and heterogeneous clinical presentations. Assessment of chronic cough includes assessment of cough, underlying disease, triggers, and signs of cough severity. The management of RCC is ineffective with a single therapy, so a combination of non-pharmacological and pharmacological therapy is needed. The newest concept of chronic cough is related to cough triggers and cough hypersensitivity syndrome. Therefore, the management of RCC should focus on identifying and treating cough triggers, including exposure and underlying disease, as well as the management of CHS. Through this therapeutic approach, it is hoped that it can reduce cough symptoms and improve the quality of life in patients with RCC. Neuromodulators are the treatment of choice for RCC, but further research is needed to determine the duration of treatment, standard doses, safety, and drug efficacy in the management of RCC.

Compliance with ethical standards

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Disclosure of Conflict of interest

The author declares no conflicts of interest.

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