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Chronic cough – different diagnostic models. Diagnostics according to the anatomical protocol versus early diagnosis of refractory chronic cough

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Abstract:

Chronic cough is one of the most common reasons for medical consultation. Its evaluation usually includes chest imaging, spirometry and selected laboratory tests. Nevertheless, even when an underlying condition is correctly identified and treated, a satisfactory reduction in cough may not be achieved. Refractory chronic cough (RCC) is a major clinical challenge because it impairs quality of life, is associated with anxiety and depressive symptoms, and increases healthcare utilization and costs. This review describes the evolution of diagnostic approaches to chronic cough, from traditional anatomy-based protocols to the contemporary concept of cough reflex hypersensitivity. Earlier recognition of RCC may reduce repeated investigations and ineffective treatment escalation, while enabling timely introduction of neuromodulatory or non-pharmacological therapy. Chronic cough should therefore also be considered within a neuropathic framework requiring a distinct diagnostic and therapeutic approach. CANVAS syndrome (cerebellar ataxia, neuropathy and vestibular areflexia syndrome) is an illustrative neurological condition in which chronic cough may result from neural injury and can precede neurological manifestations by many years.

Introduction

Cough is one of the most common reasons for consultation in primary care and frequently leads to referral to specialists. Despite its high prevalence, establishing an efficient diagnosis and selecting appropriate treatment remain challenging.

Cough is a protective airway reflex that clears bronchial secretions and irritants and helps prevent aspiration of material such as food. It is difficult to regard cough as a single uniform phenomenon, because occasional cough differs from cough occurring during infection or from a reflex that has become persistently enhanced over many years.

Cough may be classified according to duration, sputum production, awareness of the reflex, underlying cause, or response to treatment. In adults, cough is classified by duration as acute (up to 3 weeks), subacute (3-8 weeks), or chronic (>8 weeks). It may also be productive or dry. Whereas productive cough clearly serves the fundamental protective function of the reflex, the practical role of persistent dry cough is less obvious.

Diagnosis of chronic cough in current guidelines

The approach to chronic cough has changed over time, as reflected in successive guidelines. Approximately three decades ago, chronic cough was viewed primarily as a symptom of various diseases; more recent concepts emphasize cough hypersensitivity and insufficient suppression of the cough reflex [1-5]. Diagnostic algorithms have traditionally sought causes related to infection, medications, tobacco smoke exposure, upper and lower airway disease, gastrointestinal disorders - particularly gastroesophageal reflux disease - and less common conditions such as cardiac arrhythmias, obesity, or obstructive sleep apnea.

An anatomy-based diagnostic protocol can identify many disorders responsible for cough and may reveal uncommon causes. However, a subgroup of patients does not fit this model. The 2020 European Respiratory Society (ERS) guidelines acknowledge patients who, despite an appropriate diagnosis and adequate treatment, fail to improve [6]. In such cases, cough reflex hypersensitivity should be considered and refractory chronic cough (RCC) may be diagnosed. These patients may require neuromodulatory therapy and/or non-pharmacological interventions.

The 2023 British Thoracic Society clinical statement goes further by recognizing cough reflex hypersensitivity as a distinct and potentially treatable mechanism of chronic cough [7]. It emphasizes that, even at an early stage of assessment, some patients show features indicating that cough hypersensitivity itself is the predominant driver of symptoms.

Cough hypersensitivity is characterized by persistent cough triggered by low-intensity thermal, mechanical, or chemical stimuli. It is thought to reflect sensitization of neuronal sensory pathways controlling cough, including vagal afferents and central nervous system pathways [7, 8]. Defining treatment response remains challenging; a reduction of 30 mm on a cough visual analogue scale (VAS) is commonly used as a clinically relevant criterion [9].

Available data suggest that this is not a small patient group. In primary care, refractory or untreated chronic cough has been estimated to affect approximately 10% of patients with chronic cough, whereas specialist cough clinics contain a much larger proportion of difficult-to-treat cases [10]. In primary care, chronic cough is frequently associated with chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), upper airway disorders, infections, or lung malignancy. In specialist cough clinics, by contrast, clinicians often see patients in whom repeated diagnostic and therapeutic attempts have failed to reduce cough. Such patients commonly consult multiple specialties, including internal medicine, pulmonology, otorhinolaryngology, and allergology, and may undergo repeated imaging, functional testing, bronchoscopy, gastroscopy, or nasal endoscopy.

This evolution from an exclusively anatomical model toward earlier recognition of cough hypersensitivity and RCC is summarized in Figure 1. The proposed pathway retains appropriate investigation of common and treatable causes but emphasizes assessment of treatment response and earlier consideration of a neuropathic cough mechanism when symptoms persist.

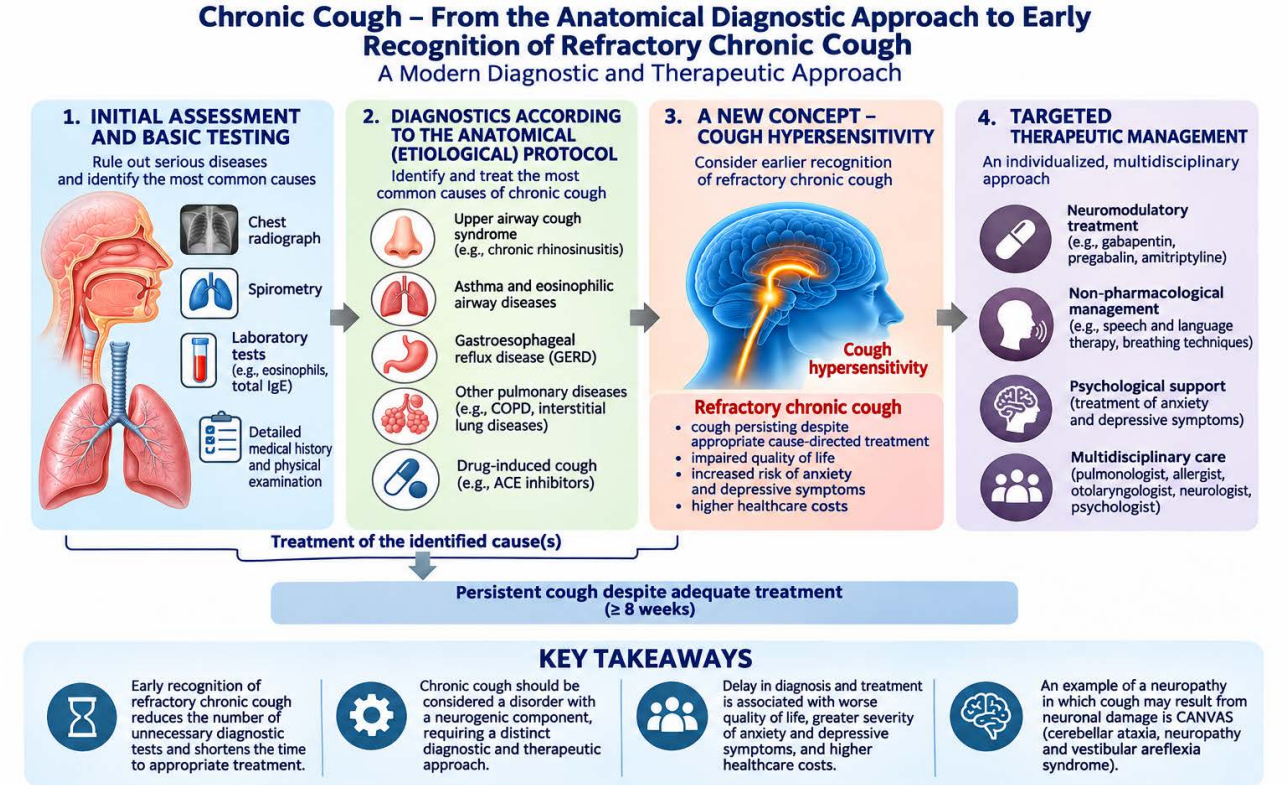


Figure 1. Evolution of the diagnostic approach to chronic cough - from an anatomical (etiological) model to earlier identification of refractory chronic cough based on the concept of cough reflex hypersensitivity.

Repeated investigations, escalation of ineffective treatment, and persistence of cough are associated with several clinically important consequences:

- substantial deterioration in quality of life;
- increased healthcare costs;
- persistent symptoms despite extensive diagnostic work-up and an established diagnosis.

Impact of chronic cough on quality of life

Chronic cough affects multiple domains of patients' lives and can substantially interfere with everyday functioning. Coughing attacks may cause sore throat, headache, chest pain, urinary incontinence, syncope, hoarseness, vomiting, hernia, and sleep disturbance. The symptoms may also intensify anxiety related to fear of serious disease, frustration, and depressive symptoms. Consequently, patients may withdraw socially, avoid public places, interrupt telephone conversations, and experience difficulties at work.

A study published in 2015 contributed substantially to the changing perception of chronic cough [11]. An online survey was made available in 12 languages on the European Lung Foundation website between January 2012 and April 2013 and was completed by 1,120 respondents from 29 European countries. Most respondents were women (67%), the mean age was approximately 51 years, and the typical duration of cough was 2-5 years. The survey demonstrated a major burden in everyday life: 93% reported an impact on quality of life, 81% reported interfer-

ence with activities they enjoyed, 91% felt fed up or depressed because of cough, and 94% reported that their cough worried or distressed family and friends. More women than men reported feeling fed up or depressed because of cough, whereas no major sex differences were found for the reported impact on quality of life or family and friends.

The same study also examined treatment experience. Seventy-two percent of respondents had seen a physician at least three times per year and 13% had attended a specialist cough clinic. Only 30% believed that their physician had addressed the cough thoroughly. Most respondents reported limited (57%) or no (36%) effectiveness of medications tried for cough; only 7% considered the medication effective. Among respondents who identified helpful treatments, over-the-counter medication was frequently considered ineffective [11].

Patients' perception of chronic cough and its treatment effectiveness may differ substantially from physicians' assessment. In a study presented at the Polish Respiratory Society congress in Wisła in 2016, 48% of physicians considered therapy effective and 38% considered it difficult but effective, whereas only 7% reported no improvement despite treatment and 7% referred the patient to another specialist [12]. This discrepancy supports earlier recognition of cough hypersensitivity and appropriate treatment rather than repeated investigations and escalation of ineffective therapy.

In a study from our center, the prevalence of refractory and unexplained chronic cough was assessed among adults referred to a cough center [13]. An underlying diagnosis could not be established in only 1.5% of patients, whereas RCC accounted for 30.6%. The low proportion of unexplained cases was notable compared with other reports.

Arinze et al. reported unexplained chronic cough (UCC) in 21.2% of adults with chronic cough in a population-based study [14]. Earlier European studies reported that 15-47% of adults with chronic cough had no identifiable treatable traits or risk factors [11, 15]. The particularly low proportion of patients without an identified cause in our study probably reflected an extensive diagnostic algorithm, including frequent second-line investigations such as computed tomography of the chest and paranasal sinuses, polysomnography, induced sputum analysis, bronchial provocation testing, nasal endoscopy and videolaryngoscopy, and bronchoscopy [13]. Treatable traits such as gastroesophageal reflux, obstructive sleep apnea, and upper airway disease were also considered potential causes rather than merely independent comorbidities. Nevertheless, recent ERS guidance supports simplification of the diagnostic process to shorten the pathway to recognition of RCC and UCC [6]. In routine practice, treatment often has to be intensified gradually and directed at coexisting causes, which is time-consuming and may impair adherence. In our practice, more than two therapeutic trials are generally performed before RCC is diagnosed.

Chronic cough, anxiety, and depressive symptoms

Psychological aspects are relevant to both diagnostic and therapeutic decisions. In a relatively small study assessing personality profiles and their relationship to the perception of chronic cough, patients did not differ in personality type, but depressive and anxiety disorders were significantly more frequent among those with chronic cough [16]. Adults with chronic cough carry a disproportionate burden of depressive symptoms and an increased risk of recurrent depression, supporting assessment for depression in this population.

A study from Toulouse estimated the prevalence of chronic cough at approximately 7.5%. Respondents with chronic cough reported substantially worse perceived health than matched controls. They also had sleep disturbances across sleep phases, greater limitations at work and in other activities, more frequent healthcare use and hospitalization, and more specialist consultations [17].

Chronic cough and healthcare costs

A UK study addressed the economic burden of chronic cough [18]. Demographic characteristics, comorbidities, investigations, prescribed treatments, and healthcare utilization were analyzed in approximately 43,000 patients. The mean age was about 64 years; 31% had no recorded comorbidity, 26% had asthma, 17% COPD, 12% rhinitis, and 15% reflux. Chronic cough was more frequent in women (57%) and was most common in those aged 65-74 years. The number of investigations increased during the 12 months before and after identification of chronic cough, particularly chest radiographs in primary care and spirometry. Pharmacotherapy use and costs were also higher, indicating increased healthcare expenditure associated with chronic cough. Importantly, approximately one-third of patients had chronic cough without a recorded comorbid disease, underscoring the importance of recognizing chronic cough as a condition in its own right.

Chronic cough as a neuropathic disorder

The cough reflex results from activation of the individual components of a reflex arc. Cough hypersensitivity or excessive activation of this reflex should be suspected when the following features are present:

- throat or upper chest irritation and laryngeal, pharyngeal, or upper-airway paresthesia;
- cough triggered by non-tussive stimuli, such as talking or laughing;
- increased cough sensitivity to inhaled stimuli and multiple triggers;
- coughing bouts that are difficult to control;
- cough after stimuli that do not provoke cough in healthy individuals;

mechanical triggers such as singing, talking, laughing, or deep inspiration; thermal triggers such as temperature change or cold air; chemical triggers such as aerosols or odors; as well as supine position, eating, and physical exertion.

Beyond clinical suspicion, there is currently no single effective tool that unequivocally establishes cough reflex hypersensitivity. The 15-item Triggers and Sensations Provoking Coughing (TOPIC) questionnaire was developed to capture sensations and triggers associated with chronic cough and to help distinguish refractory or unexplained chronic cough from other causes, but it has not yet gained widespread clinical use [19].

If chronic cough is considered a neuropathic disorder, an important question is whether a defined type of nervous system injury can cause cough and whether targeted treatment is available.

Particular attention has recently been paid to chronic cough in cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS). CANVAS is a rare neurological disorder associated with biallelic variation in the replication factor C subunit 1 (RFC1) gene, most commonly an intronic AAGGG repeat expansion. Chronic cough in patients with CANVAS resembles cough hypersensitivity syndrome.

Cough in CANVAS was first reported in 2014 by Wu et al. [20]. Two of 26 patients with clinical CANVAS had chronic cough, and in one patient cough was the first symptom, occurring five years before the onset of ataxia. Chronic cough was also described in a retrospective study published in the same year, although detailed patient numbers were not provided [21].

Published estimates of chronic cough prevalence in CANVAS associated with RFC1 repeat expansion range from 8% to 100% [22]. Reported prevalence has increased over time, probably because cough has been documented more systematically in recent cohorts. Cortese et al. noted that cough may precede gait difficulties by a decade [23]. In some patients, chronic cough has been reported up to three decades before neurological manifestations and may be the initial symptom of CANVAS.

Are neuromodulators effective in cough hypersensitivity?

A 2023 systematic review and meta-analysis assessed neuromodulators for cough associated with chronic airway hypersensitivity [24]. Three randomized controlled trials were included after screening approximately 1,000 publications. Clinical response was evaluated using several outcomes, including cough frequency, the validated Leicester Cough Questionnaire (LCQ), and cough severity on a visual analogue scale (VAS). Neuromodulatory treatment was associated with improvement in cough-related outcomes, including cough severity and quality of life.

Conclusions

Given the substantial number of patients referred to specialist clinics because of chronic cough, the available evidence supports considering cough driven by cough reflex hypersensitivity as a distinct diagnostic and therapeutic entity. It can be conceptualized as a neuropathic disorder and should be recognized early.

This approach does not replace the anatomical model or appropriate investigation of common causes of chronic cough. Rather, it complements it by emphasizing treatment response. After alarm symptoms have been excluded and common causes have been assessed, persistent cough despite adequate treatment should prompt consideration and treatment of cough reflex hypersensitivity. Repeating investigations and escalating treatments that have already proved ineffective should be avoided.

Earlier use of treatment directed at cough hypersensitivity may improve quality of life - an aspect that can be underestimated in clinical practice - and may reduce unnecessary medication, repeated diagnostic procedures, specialist consultations, and overall healthcare costs.

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