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WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation – Updates in COVID-19

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ABSTRACT

Background: Chronic cough can be triggered by respiratory and non-respiratory tract illnesses originating mainly from the upper and lower airways, and the GI tract (ie, reflux). Recent findings suggest it can also be a prominent feature in obstructive sleep apnea (OSA), laryngeal hyper-responsiveness, and COVID-19. The classification of chronic cough is constantly updated but lacks clear definition. Epidemiological data on the prevalence of chronic cough are informative but highly variable. The underlying mechanism of chronic cough is a neurogenic inflammation of the cough reflex which becomes hypersensitive, thus the term hypersensitive cough reflex (HCR). A current challenge is to decipher how various infectious and inflammatory airway diseases and esophageal reflux, among others, modulate HCR.

Objectives: The World Allergy Organization/Allergic Rhinitis and its Impact on Asthma (WAO/ARIA) Joint Committee on Chronic Cough reviewed the current literature on classification, epidemiology, presenting features, and mechanistic pathways of chronic cough in airway- and reflux-related cough phenotypes, OSA, and COVID-19. The interplay of cough reflex sensitivity

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with other pathogenic mechanisms inherent to airway and reflux-related inflammatory conditions was also analyzed.

Outcomes: Currently, it is difficult to clearly ascertain true prevalence rates in epidemiological studies of chronic cough phenotypes. This is likely due to lack of standardized objective measures needed for cough classification and frequent coexistence of multi-organ cough origins. Notwithstanding, we emphasize the important role of HCR as a mechanistic trigger in airway- and reflux-related cough phenotypes. Other concomitant mechanisms can also modulate HCR, including type2/Th1/Th2 inflammation, presence or absence of deep inspiration-bronchoprotective reflex (lower airways), tissue remodeling, and likely cough plasticity, among others.

Keywords: Multifactorial cough, Cough phenotypes, Type 2 inflammation, COVID 19, Reflux-cough, Upper airway cough syndrome, Lower airway disease, Obstructive sleep apnea

INTRODUCTION

Epidemiological studies suggest the prevalence of cough ranges from 2.5% to 18%¹⁻⁴ with significant impact on quality of life (QoL),^{4,5} especially in the elderly.⁶ Acute cough is defined as lasting up to 3 or 4 weeks in adults,⁷ and is usually self-limited.^{8,9} Cough persisting for ≥ 8 weeks in adults¹⁰ or $4 \geq$ weeks in children^{7,11,12} can be defined as chronic cough. In this arbitrary classification, adult patients presenting for an interim period (ie, 4-8 weeks) may be either recovering from an acute cough-associated illness or in the pre-chronic cough stage and can be labelled as having “probable” chronic cough.¹ Chronic cough affects all ages and genders, although the typical chronic cough patient is a female in her sixth decade.¹³ Chronic cough is more prevalent in western countries compared to Asia and Africa.² A variety of respiratory and non-respiratory tract illnesses can trigger the condition, and the illnesses are listed in Fig. 1. Upper and lower airway etiologies of chronic cough are collectively termed upper airway cough syndrome (UACS) and lower airway cough syndrome (LACS), respectively. Other important etiologies include gastroesophageal reflux disease (GERD)-related cough and laryngeal hyperresponsiveness (LHR), obstructive sleep apnea (OSA), and COVID-19, tumors, and drugs (ie, ACE inhibitors, opioids), among others. However, chronic cough can occur in the absence of known triggers. While cough has been considered traditionally a symptomatic byproduct of these illnesses, the majority of patients do not report

cough, although if asked, most patients describe it to be aggravating. Also, cough severity correlates poorly with severity of cough-associated illnesses.¹⁴ This suggests chronic cough is a distinct clinical entity. Based on clinical models, it is speculated that the underlying mechanism of chronic cough is a neurogenic inflammation of the cough reflex which becomes hypersensitive, thus the term hypersensitive cough reflex (HCR).¹⁵ Still, the physician struggles to decipher how various infectious and inflammatory airway diseases and esophageal reflux, among others, modulate HCR. In a previous part of the consensus (Part I),¹⁵ we reported on the role of transient receptor potential (TRP) ion channels in pathogenesis of chronic cough by mediating a crosstalk between neurogenic and inflammatory pathways in cough associated airways diseases. The current part II of the consensus (see Appendix) examines the presenting features, and mechanistic tussive pathways, in addition to the role of TRP ion channels, in airway- and reflux-related cough phenotypes, OSA, and COVID-19. Cough management in primary and cough specialty care will be further reported in part III of the consensus.

UPPER AIRWAY COUGH SYNDROME

Classification and epidemiology

The term UACS, previously called postnasal drip syndrome (PNDS), is used to describe protracted cough triggered by common infectious, inflammatory, or neurogenic diseases involving the

upper airways (Fig. 1). These can encompass several rhinitis and rhinosinusitis phenotypes, anatomic abnormalities, or chemically induced rhinitis, as well as pharyngeal diseases, among others.¹⁶⁻¹⁸ Also, diseases of the upper digestive tract can trigger cough. Mechanical manipulation of the external auditory canal can stimulate the auricular branch of the vagus nerve (Arnold's nerve) resulting in chronic dry cough.^{19,20} A uniform definition of UACS/PNDS is lacking across the United States, Europe, and Asia. The discrepancy lies in considering postnasal drip (PND) as a symptom or a separate disease entity.¹⁶ Furthermore, patients with PND do not account for a homogeneous group with respect to etiology. Other considerations, such as lack of standardized objective measures for clinical assessment of chronic cough, co-existence of more than one upper airway cough-associated disease, and absence of a uniform management protocol for chronic cough pose a great challenge to a clear definition of UACS. The characterization of UACS is even more complex in children. Challenges include age-related changes in etiologic frequencies of chronic cough in nursery, preschool, and school-age children,²¹ possibly related to differential maturation and modulation of cough reflex postnatally.²² Also, inability to perform invasive or noninvasive diagnostic modalities in young children, such as induced sputum analysis, bronchial provocation testing, and computed tomography (CT) scans requiring sedation, poses additional challenges to the classification and consequently to the management of chronic cough in this age group.²³

Epidemiological data on prevalence of upper airway-related cough among chronic cough

patients is highly variable.²⁴ This is partly due to poor awareness amongst physicians of upper airway cough phenotypes leading to chronic cough. Enhanced diagnostic accuracy of cough etiological factors can also affect prevalence data. Other confounding variables can be type of patient population, whether studied in primary or cough-specialty care; this can overestimate or underestimate the true prevalence, respectively. In a 10-year longitudinal study (N = 1311), the reported etiological frequency for chronic cough dramatically changed as UACS and cough variant asthma (CVA) decreased by 50%, while GERD increased by 50%. Moreover, in a series of chronic cough patients, allergic rhinitis (AR), classic asthma (CA), chronic rhinosinusitis (CRS), and nasal polypsis (NP) were found in 46.5%, 31%, 12%, and 8.6% of patients with chronic cough, respectively. The high predictive value for concomitant asthma in UACS warrants a careful search for a lower airway pathology in patients presenting with chronic cough of upper airway origin.²⁵ Cough quality that is either dry or productive cannot predict cough phenotype in adults; however, it can prove useful in determining etiological diagnosis in children.²⁶ For example, in children with bacterial bronchitis a persistent wet cough warrants urgent attention whereas its value in adults remains questionable.²⁷ In conclusion, the characterization of UACS in epidemiological studies lacks objective measures. This is partly due to presence of confounding variables, more so in the pediatric population.

Pathogenesis

It is speculated that upper airway cough-associated diseases can induce mechanical, systemic, or neurogenic stimulation of the afferent limb

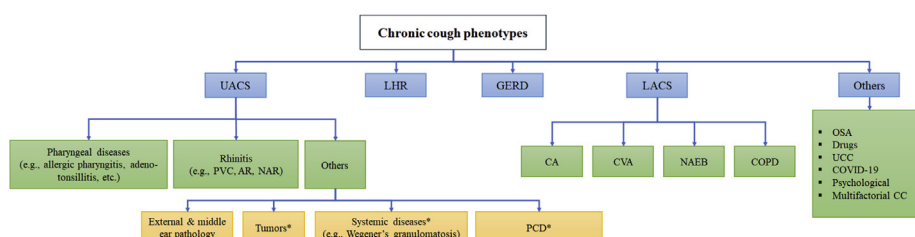


Fig. 1 Classification of chronic cough phenotypes. Abbreviations: AR (Allergic rhinitis), CA (Classic asthma), CC (Chronic cough), CVA (Cough variant asthma), COPD (Chronic obstructive pulmonary disease), GERD (gastroesophageal reflux disease), LACS (Lower airway cough syndrome), LHR (Laryngeal hyperresponsiveness), NAEB (Non-asthmatic eosinophilic bronchitis), NAR (Non allergic rhinitis), OSA (Obstructive sleep apnea), PCD (Primary ciliary dyskinesia), PND (Post-nasal drip), PVC (Post-viral cough), UACS (Upper airway cough syndrome), UCC (Unexplained chronic cough), *disease of rare occurrence.

of cough reflex.²⁸ This includes sensory fibers of the trigeminal nerve^{16,29} and superior laryngeal and pharyngolaryngeal branch of the vagus nerve. Pathogenic mechanisms can be mechanical or chemical stimulation of the vagal afferent nerve by postnasal drip,^{17,30} hematogenous spread of inflammatory mediators,¹⁶ or cough reflex hypersensitivity.¹⁶ As a mechanistic trigger, PND, whether subjectively reported or noted on physical examination, is not a consistent complaint/finding in patients with chronic cough.³¹ Furthermore, the united airway theory speculates a hematogenous or neural spread of inflammatory mediators between upper and lower airways. This is evidenced by bidirectional involvements of both nose/sinuses and lungs in airway inflammatory diseases, such as atopy, and CRS with or without NP.^{32,33} Although evidence of a hypersensitive cough reflex involving vagus central and peripheral neuronal pathways is abundant, data supporting a hypersensitive cough reflex involvement of trigeminal nerve are relatively scarce. Notwithstanding, direct stimulation of trigeminal afferents in the nose can promote the cough reflex. In support of this, mechanical, thermal, and chemo-sensitive polymodal afferent receptors of the trigeminal nerve can be activated by capsaicin through its selective receptor TRPV1.³⁴ Clinical models involving tussigen inhalation and nasal challenges have provided great insight into the mechanism involved in UACS. It is important to note that tussive challenges reflect only a predisposition to cough under controlled conditions since experimental tussigen concentrations demonstrate only a moderate correlation with cough frequency.³⁵ Capsaicin, a TRPV1 agonist, is an important tussigen used in animal and human models of cough inhalation challenges, where capsaicin-mediated activation of TRPV1 results in bronchospasm.³⁶ In healthy subjects, nasal challenge with histamine which lowers activation threshold of TRPV1 triggered sneezing and itching but no cough. One explanation for the absence of cough reflex can be insufficient lowering of the cough receptor threshold by histamine.³⁷ At the peak of nasal itching ensuing from intranasal histamine challenge, subjects who were sequentially challenged with capsaicin inhalation reported more coughs when compared to a concomitant challenge with intranasal saline and

inhaled capsaicin. This suggests nasal triggers can potentiate the cough reflex arc in the lower airways.^{29,38} It also supports existence of a central crossover between trigeminal and vagus neuronal pathways referred to as cough plasticity or the modulation of the cough reflex by other afferent inputs within the vagal neuronal pathway and out of it.³⁹ Hypothetically, "convergence" centers among nasal putative sensory afferents along the paratrigeminal nucleus and afferent cough fibers along the vagal second order neurons in tractus solitarius, can feature interactive activity of both afferent nerves.⁴⁰ This can modulate cough response by increasing cough sensitivity to capsaicin.⁴¹ In support of the convergence theory, capsaicin challenge in guinea pigs increased neuronal activity simultaneously in the brainstem and the trigeminal nerve, as suggested by increased expression of C-fos (proto-oncogene),^{16,38} the gene group of second and higher order neurons.

In conclusion, UACS lack a uniform definition of trigger diseases, such as PND, rhinitis, or rhinosinusitis in children or adults. Additionally, mechanistic triggers of chronic cough in UACS can involve a neurogenic or systemic communication between upper and lower airways, and likely cough reflex sensitivity. Because rhinitis or rhinosinusitis are frequent comorbidities of reactive airways and reflux disease, it is sometimes difficult to discern if chronic cough reflects HCR involving the vagus nerve, trigeminal nerve, or both.

Infectious rhinitis

Infectious rhinitis or common cold has been traditionally linked to chronic cough, the so-called post-viral cough (PVC). Mechanical stimulation of the chest by high frequency chest percussion in non-coughing patients with upper respiratory tract infection (URTI) increased cough when compared to healthy volunteers. This suggests airway mechanical and rapidly adapting receptors can trigger cough reflex sensitivity in patients with URTI.⁴² Previous reports demonstrated patients with URTI have increased cough sensitivity to capsaicin but no change in airway responsiveness to methacholine challenge, when compared to healthy volunteers.⁴³ This suggests respiratory infections can induce a hypersensitive cough reflex without airway hyperresponsiveness. Also,

lipopolysaccharide can activate TRPA1, independently of their activation of Toll-like receptor 4 (TLR4),⁴⁴ and viral mRNA is capable of stimulating purinergic receptors via TLR7.⁴⁵

Allergic and non-allergic rhinitis

A longitudinal cohort study demonstrated non-infectious rhinitis is a significant and independent risk factor for development of chronic cough in adults.⁴⁶ In AR, many patients have cough, wheezing, and shortness of breath, and during the pollen season, cough is often severe with no major change in forced expiratory volume during the first second (FEV1), thereby suggesting an upper airway origin.⁴⁷ Bronchial hyperresponsiveness is more frequent in AR patients in cross-sectional studies,⁴⁸⁻⁵⁰ and compared to seasonal rhinitis, perennial rhinitis is much more important as a risk factor for developing nonspecific bronchial hyperresponsiveness.⁵¹ Experimental data suggest that AR is a risk factor for chronic cough. Tussigen challenges in AR indicate that capsaicin-sensitive TRPV1 receptors and capsaicin-insensitive A- δ stretch receptors modulate cough sensitivity.³⁹ Cough reflex sensitivity in the upper airways is heightened in atopic patients^{52,53} when compared to healthy controls. By comparing adults³⁹ or children⁵⁴ with seasonal AR outside their pollen season to healthy controls, a standardized (inhaled) capsaicin challenge model demonstrated significantly increased cough in atopic patients. Using the same model, allergic patients in-season reported significantly more coughs than those out-of-season.⁵² These findings are also in accordance with the "priming effect" reported in the upper airways, that is, reduced activation threshold of sensory nerves in response to IgE and non-IgE related stimuli following allergen exposure.^{55,56} As stated previously, combined challenge with inhaled capsaicin and nasal topical histamine enhanced capsaicin induced cough reflex hypersensitivity in seasonal AR.^{29,41} Conversely, treatment of atopic inflammation with inhaled corticosteroids or antileukotrienes in an animal model of ovalbumin-sensitive guinea pigs restored the cough sensitivity reflex to its pre-treatment values.^{57,58} In conclusion, these results are in line with a speculated increased reactivity

of cough afferent nerve endings in patients with clinical or subclinical AR.

Non-allergic rhinitis is a collective term used to describe non-allergic non-infectious rhinitis phenotypes characterized by nonspecific nasal hyper-reactivity. The latter denotes induction of rhinitis symptoms (rhinorrhea, nasal congestion) in response to nonspecific irritants such as tobacco smoke, changes in temperature and humidity, and air pollutants, among others.^{18,59} Idiopathic (vasomotor) rhinitis constitutes the majority of nonallergic rhinitis⁶⁰ and features many characteristics relevant to UACS. Clinically, this is exemplified by triggering of rhinitis symptoms following nonspecific thermal, mechanical, and endogenous inflammatory triggers. In vasomotor rhinitis there is also over expression of TRPV1 and TRPM8 channels along the C-fiber sensory distribution of the trigeminal nerve endings in the nose.^{61,62} Along the same line, data suggest presence of neuroimmune modulation in vasomotor rhinitis as manifested by neuropeptides (substance P and calcitonin gene-related peptide [CGRP]) mediated-inflammatory response.⁶³ Interestingly allergic, infectious, and nonallergic rhinitis can all have components of nasal hyperactivity, to a varying degree.⁶⁴ Yet, chronic cough is infrequently reported in idiopathic rhinitis,⁵⁹ and to our best knowledge no capsaicin inhaled challenge studies addressing chronic cough have been performed in this rhinitis phenotype.

Chronic rhinosinusitis

Although rhinosinusitis can constitute up to 20% of adult patients with chronic cough,⁴ coughing is not a major feature of chronic rhinosinusitis (CRS),⁶⁵ and cough aggravation has been associated with presence of bacterial biofilms.⁶⁶ In one study of adult patients with rhinosinusitis presenting with chronic cough, pharmacotherapy improved lung function parameters but not subjective cough scores, probably related to the small size of the study.⁶⁷ In contrast to adults, the majority of children with CRS present with chronic cough.⁶⁵ Several studies reported improvement of pediatric CRS-associated (chronic) cough with medical^{68,69} or surgical⁷⁰ treatment modalities. Mechanistic analysis of cough triggers in CRS is hampered by the

frequent coexistence of other cough-associated illnesses such as lower airway pathology⁷¹ or gastroesophageal reflux disease,⁷² which can act as confounding variables.

Obstructive sleep apnea syndrome (OSAS)

OSAS is an increasingly recognized important risk factor for cough in children⁷³ and adults.⁷⁴ OSAS can present solely with cough⁷⁵ and absence of daytime somnolence (normal Epworth sleepiness score).⁷⁶ Other associated symptoms in patients with OSA and cough include rhinitis and GERD.^{75,77,78} The prevalence of chronic cough in OSA patients and general population is estimated at 33–39%^{74,78,79} and 2.5–18%, respectively, which suggests a strong association between cough and OSA. This has been linked to increased production of inflammatory mediators (IL-6, IL-8, INF- γ),⁷⁶ exhaled nitric oxide, and sputum neutrophilia⁸⁰ in OSA. Compared to normal subjects, OSA patients reported a higher incidence of chronic cough, reportedly secondary to nocturnal GERD.⁷⁸ Also, patients with OSA manifest frequent nocturnal arousal and awakening episodes concomitant with the obstructive respiratory events which can cause a dysfunctional central inhibition of cough.⁷⁶ Continuous positive airway pressure (CPAP) therapy in patients with OSA and cough improves cough reflex sensitivity as measured by citric acid challenge,⁸¹ cough-related QoL (Leicester cough questionnaire)^{75,81,82} and cough scores.^{75,78,81} Taken together, these data suggest OSA is implicated in the pathogenesis of chronic cough. The role of CPAP titration in cough improvement requires further elucidation with large scale randomized trials.

LARYNGEAL HYPERRESPONSIVENESS

Anatomical and pathophysiological considerations

Laryngeal hyperresponsiveness (LHR) denotes inspiratory movement of vocal cords towards each other (adduction) in response to noxious chemical stimuli or inhaled histamine challenge.⁸³ LHR encompasses a range of laryngeal pathologies, including vocal cord dysfunction, muscle tension dysphonia, and globus, among others.⁸⁴ LHR is present in up to 50% of patients with chronic

cough.⁸⁵ The laryngo-constriction chemoreflex is mediated by the afferent superior laryngeal branch of the vagus nerve and the efferent recurrent laryngeal nerve. It forms a basic defense mechanism in newborns against aspirated liquids, and is phylogenetically complemented in adults by reflex cough and bronchoconstriction.⁸⁶ LHR can be measured by a decrease in extrathoracic (maximal) mid- inspiratory and expiratory airflow rates and a reduction in the size of the laryngeal inlet, as noted on endoscopic exam. Most patients with upper inflammatory airway diseases and cough displayed LHR as revealed by histamine inhalation protocol.⁸⁷ Using glottic airflow rates as index of extrathoracic hyperresponsiveness and subsequent laryngeal adduction,⁸⁸ LHR was significantly associated with sinusitis, postnasal drip, female gender, and dysphonia.⁸⁷ Also, LHR was prevalent in chronic cough patients with rhinitis/rhinosinusitis (76%), gastroesophageal reflux disease (77%), and asthma (93%); however, it was absent in non-coughing asthmatic patients.⁸³ Taken together, these data suggest LHR is associated with UACS, GERD-associated chronic cough, and cough associated with asthma. However, presence of asthma seems independent of the association of LHR and chronic cough of different etiologies.

Clinical aspects

Cough localized primarily to the larynx, commonly referred to as “throat” cough, is one manifestation of a hyperfunctional larynx along with episodic laryngospasm, muscle tension dysphonia, stridor, wheezes, and globus.⁸⁹ These phenotypes of laryngeal dysfunction have overlapping symptomatology and can be induced by nonspecific triggers such as scents, emotional stress, exertion, and reflux.⁸⁸ The underlying sensory nature of these triggers is suggestive of a neural plasticity of the central laryngeal neuronal pathways,^{89,90} similar to chronic cough and chronic neuropathic pain. Laryngeal provocation models consist of incremental endoscopic insufflation of gases directly into laryngeal inlet and measuring laryngeal adductor reflex as expressed by the air pressure required to achieve glottic closure. A challenge with inhaled air⁹¹ or diluted acid⁹² can reflect mechanical and sensory laryngeal

	Airway eosinophilia ^{113,143,154}	Deep inspiration cough broncho-protective reflex ^{113,143}	PGE2 (bronchodilator) expression ^{98,134,220-222}	Bronchial hyperresponsiveness (methacholine) ^{113,143,152}	HCR mechanism in CC/tussigen challenge studies ^{107,108,124,145,161,162}	Innate/adaptive immune system ^{223,224}
CA	Normal or increased	Absent or impaired	Decreased (Vs NAEB)	Present	Confirmed/conclusive data	Innate (ILC ₂) & adaptive (Th ₂) response
NAEB	Increased	Likely preserved	Increased (Vs CA)	Absent	Unconfirmed/Insufficient data	Innate (ILC ₂) response
CVA	Normal or increased	Preserved or impaired	Increased (Vs CA)	Present or Borderline	Confirmed/Preliminary data	Innate (ILC ₂) response
COPD	Normal or increased	Attenuated	Increased (Vs CA)	Present	Confirmed/Preliminary data	Innate (ILC ₁ /ILC ₂) & adaptive (Th ₁) response

Table 1. Comparative analysis of immunological and clinical properties of cough-phenotypic traits originating from lower airways. Abbreviations: CA (classic asthma), CC (Chronic cough), COPD (chronic obstructive pulmonary disease), CVA (cough variant asthma), HCR (hypersensitive cough reflex), ILC (innate lymphoid cell), NAEB (non-asthmatic eosinophilic bronchitis), PGE2 (prostaglandin E2), Th2 (T helper 2). ^aIn comparison with healthy individuals

hypersensitivity, respectively. These models revealed diminished laryngeal sensitivity in patients with chronic cough-associated reflux disease and paradoxical vocal fold motion.⁹³ Therefore, an exaggerated laryngeal adduction reflex was proposed as a compensatory motor response to LHR.⁹³ A recent review on methods of laryngeal sensory provocation confirms that endoscopic visualization of vocal fold motion, in different laryngeal pathologies and during exposure to multiple sensory triggers, is clinically appropriate to objectively assess vocal cord dysfunction;⁸⁸ it can be also assisted by computational algorithms. Comprehensive immunological and physiological data on neurogenic inflammatory pathways involved in LHR are currently lacking. Nevertheless, earlier data suggest efficacy of neuromodulators in treating chronic cough patients with laryngospasm and throat clearing.⁹⁴ Thus, laryngeal cough reflex sensitivity is an evolving concept.

LOWER AIRWAY COUGH SYNDROME

Reactive lower airway diseases can be associated with chronic cough, most commonly classic asthma, cough variant asthma, non-asthmatic eosinophilic bronchitis and chronic obstructive pulmonary disease.¹⁰ Immunological and clinical highlights of these closely related cough phenotypes are shown in Table 1.

Pathogenesis

As stated earlier, HCR involves neurogenic and inflammatory dysfunction of vagus nerve cough neuronal pathways. Neurogenic dysfunction involves neuromediators, such as neurokinins (bradykinins) and neuropeptides (substance P), leukotrienes and prostaglandins (PGs) (E2 and D2), nerve growth factor (NGF), and CGRP, among others.^{95,96} These powerful tussigens are associated with TRP channels and can increase cough sensitivity to bronchoconstrictor agents used in human and animal cough models, such as capsaicin, citric acid, and histamine. The inflammatory component of HCR in lower airways is characterized mainly by type 2 inflammation and airway eosinophilia reportedly noted in 50-60% of asthmatics.^{96,97} Type 2

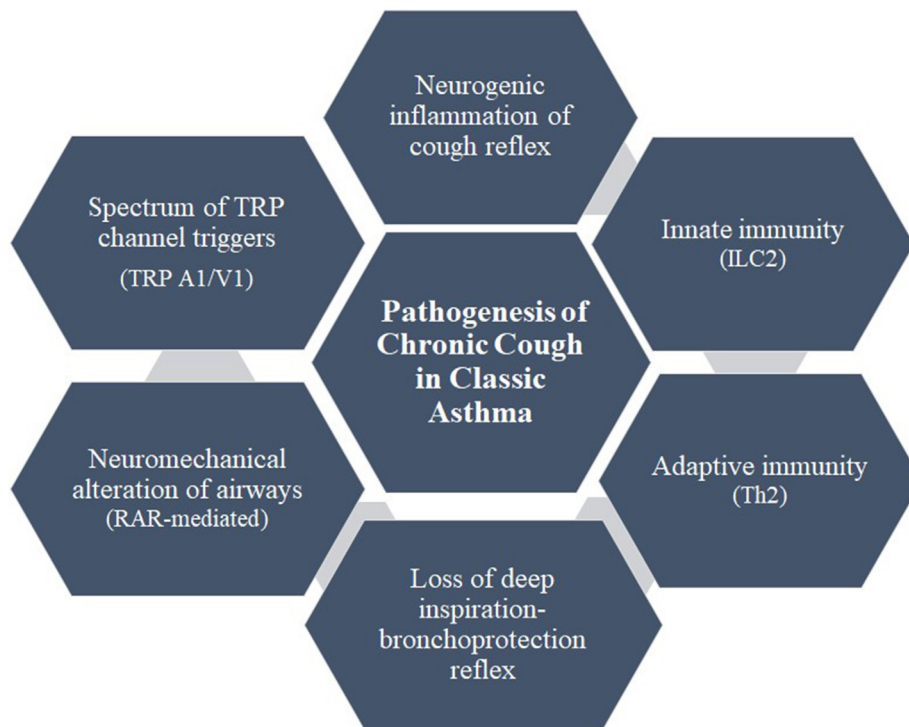


Fig. 2 Classic asthma: suggested mechanisms in pathogenesis of chronic cough, Abbreviations: ILC2 (group 2 innate lymphoid cells), RAR (Rapidly adapting receptors), Th2 (T helper cell type 2), TRPA1 (transient receptor potential ankyrin 1), TRPV1 (transient receptor potential cation channel subfamily V member 1).

cytokines such as IL-4, IL-5, and IL-13 may be expressed following stimulation of the innate immune response orchestrated by mast cells and innate lymphoid cells type 2, among others.^{98,99} The resultant signal cascade can give rise to cough phenotypes such as cough variant asthma (CVA), non-asthmatic eosinophilic bronchitis (NAEB), and nonatopic asthma.^{100,101} Atopic asthma displays activation of innate and adaptive immunity where inflammatory mediators such as histamine, prostaglandins, leukotrienes and platelet activation factor can cause bronchoconstriction and cough secondary to allergen exposure.⁹⁶ Recent evidence supports that neuromechanical properties of the lungs, which are related to a change in airway caliber as occurs during bronchoconstriction, can also contribute to chronic cough in asthmatics¹⁰² (see below). However, the relationship between neurogenic and inflammatory components of cough hypersensitive reflex and their impact on inherent mechanical properties of lower airways through bronchoconstriction is still unclear. Components of neurogenic inflammation are discussed in different cough phenotypic traits of the lower airways highlighting important clinical

symptomatology, tussive challenge testing, and response to medical therapy.

Classic asthma

Asthma is a clinical diagnosis marked by cough, variable airflow obstruction, and airway remodeling. It is one of the most common etiologies of chronic cough and accounts for up to 29% of cases.¹⁰³ Cough is a decisive symptom of asthma. Chronic cough is associated with poor asthma control;^{104,105} conversely, cough control predicts prognosis of asthma.¹⁰⁴ Other factors associated with more severe disease phenotype include objective increase in cough frequency¹⁰⁶ and heightened cough response to tussigen challenges.^{107,108} Cough in asthma is typically dry or minimally productive. Mucus-secreting cough may be potentially associated with steeper decline of pulmonary functions¹⁰⁹ and severe asthma, bronchiectasis, or chronic bronchitis.¹¹⁰ The mechanism of chronic cough in asthma is complex and features intertwined components of a hypersensitive cough reflex, IgE or non-IgE mediated eosinophilic airway inflammation, abnormal neuromechanical properties of the

lungs, and presence or absence of deep inspiration reflex (Fig. 2). In healthy individuals deep-inspiration causes bronchodilation.¹¹¹ During methacholine challenge studies, deep inspiration can also protect against induced bronchoconstriction.¹¹² It is generally agreed that the deep inspiration bronchoprotective reflex is absent or impaired in asthma.¹¹³ Hence, testing airway hyperresponsiveness can assist in the differential diagnosis of asthma (Table 1). Evidence for neuroinflammation of cough-sensitive neurons in asthma is not fully established but supported in several reports. An increased expression of bradykinin and its effector molecules prostaglandin-E2 and leukotrienes can trigger cough in the asthmatic airways¹¹⁴⁻¹¹⁶ by activation of TRP channels (A1 and V1).⁹⁵ Also, compared to healthy subjects or patients with mild intermittent asthma, moderate asthma was associated with increased airway innervation, substance P expression, in addition to airway and serum eosinophilia.⁹⁷ Along the same line, other data suggest asthmatics, compared to healthy subjects, have heightened cough response to capsaicin challenge, independent of inhaled corticosteroids (ICS) dose,¹¹⁷ airway inflammation,¹⁰⁷ FEV1 and airway hyperresponsiveness. Similarly, the observation of a heightened capsaicin-evoked cough response in asthmatics with mild airflow obstruction was independent of fractional exhaled nitric oxide (FeNO), lung function testing or airway hyperresponsiveness.¹⁰⁷ These data suggest presence of a hypersensitive cough reflex in asthmatics independently of airway inflammation or reduction of airway caliber through induced bronchoconstriction. Furthermore, the role of atopy in the etiology of chronic cough in asthma is also revealed from capsaicin challenge models. Patients with mild to moderate stable atopic asthma have unexpectedly lower cough response to capsaicin challenge when compared to nonatopic asthmatics; although both asthmatic groups, in single or combination, had worse cough scores when compared to healthy controls.¹⁰⁷ To note, these observations ensued using a capsaicin challenge which consisted of monitoring maximal cough response following any capsaicin challenge concentration (E_{max})¹¹⁸ as opposed to a model which determines the lowest capsaicin concentration triggering 2 or 5

coughs (C_2 , C_5).¹¹⁹ Reportedly, the former model (E_{max}) can discriminate better chronic cough patients from healthy controls compared to the conventional model (C_2, C_5).¹¹⁸ In addition, the role of airway neuromechanical properties or change in airway caliber, length, and pressure in inducing cough through capsaicin-sensitive nerves is highlighted in both atopic and non-atopic asthmatics. In one report, asthmatics had higher cough response to capsaicin-induced cough (E_{max}) independently of markers of eosinophilic airway inflammation. More importantly, a decrease in FEV1 resulted in doubling of cough responses in these asthmatics.¹²⁰ This was also confirmed by a recent study involving combined allergen, capsaicin, and methacholine challenges in steroid-naïve stable and atopic asthmatics. These challenges also suggested cough reflex sensitivity is linked to bronchoconstriction and mechanical decrease in airway caliber in addition to type 2 inflammation.¹⁰² In summary, these data highlight the role of altered neurobiology of the afferent cough reflex in addition to atopic or nonatopic inflammatory status as modulators of cough mechanism in asthmatics. Presence of a hypersensitive cough reflex seems independent of airway eosinophilia or hyperresponsiveness. Also, both methacholine and allergen-induced bronchoconstriction or reduction in airway caliber correlates well with capsaicin-provoked cough sensitivity in asthmatics.

Non-asthmatic eosinophilic bronchitis

Epidemiological data suggest that non-asthmatic eosinophilic bronchitis (NAEB) represents up to 35% of chronic cough patients in Asia^{121,122} and can involve children according to a large series.¹²³ Clinically, NAEB is a cough phenotype which lacks bronchoconstriction and bronchial hyperresponsiveness^{124,125} (Table 1). Similar to asthma, it is characterized by airway eosinophilia in induced sputum and responds well to anti-inflammatory therapy.^{126,127} NAEB can include patients with or without atopy. In Japan, atopic patients with a dry cough who lack airway hyperresponsiveness and are resistant to bronchodilator therapy, have been designated to have an atopic cough or eosinophilic tracheobronchitis.¹²⁸⁻¹³⁰

In patients with NAEB, presence of a heightened cough response is studied in relation to anti-asthma medications using capsaicin challenge models. In one report evaluating the cough response in NAEB patients following anti-asthma therapy,¹³¹ an initial increase in HCR at baseline was improved to near normal levels following inhaled corticosteroid therapy. Changes in sputum eosinophil count also correlated with improvement in cough sensitivity following therapy. In NAEB, the role of IL-17A, a Th17-pathway cytokine involved in asthma development, remains obscure.¹³² Comparative analysis of immunopathological profiles of NAEB and asthma has been reviewed elsewhere and highlights mechanisms underlying the absence of airway hyperresponsiveness in NAEB.¹³³ Patients with NAEB have increased mast cells in bronchial brushings, whereas asthmatics have increased mast cells in airway smooth muscle cells, a finding reported to be inversely related to airway hyperresponsiveness in asthma.^{84,134} In addition, patients with NAEB have decreased IL-13 in bronchial submucosa and sputum¹³⁵ and less narrowing of the airway lumen compared to asthma, although both asthma and NAEB express airway remodeling.¹³⁶ Unlike asthma, there is marked expression of the endogenous bronchodilator PGE-2^{134,137} in NAEB, which may account for preservation of deep inspiration-induced bronchoprotective effect from cough,^{113,134} and an antiproliferative effect of bronchial smooth muscle.⁸⁴ In conclusion, NAEB represents a cough trait with distinct immunopathological profile in LACS. Yet, scarcity of tussigen challenge data makes it difficult to ascertain a clear role of HCR as a mechanistic trigger for cough in NAEB.

Cough variant asthma

Cough variant asthma (CVA) is a cough phenotypic trait which lacks wheezing or dyspnea and is associated with airway hyperresponsiveness (Table 1) and a favorable response to anti-asthma medications.¹³⁸ Patients with CVA can account for around 30% of chronic cough referrals¹³⁹ and can present solely or predominantly with cough^{129,140} in response to innocuous triggers such as talking and laughing, allergens and cold air.^{141,142} Currently there is insufficient data to

speculate if CVA is a precursor of classic asthma or a separate cough phenotype.¹²⁹ The discrepancy lies partly in the presence or absence of airway hyperresponsiveness which, as stated earlier, has been linked to the deep inspiration cough bronchoprotective effect.^{113,143} Data suggest the absence of airway hyperresponsiveness in a subset of patients with CVA is due to preservation of cough bronchoprotective reflex.¹⁴³ Conversely methacholine challenge data demonstrated presence of “borderline” airway hyperresponsiveness in patients with CVA compared to moderate-severe airway hyperresponsiveness in asthmatics.¹¹³ This suggests that patients with CVA can manifest mild airway hyperresponsiveness on methacholine challenge with preservation of deep inspiration bronchoprotective reflex.¹⁴³ In support, prospective epidemiological studies demonstrated up to one third of CVA patients can eventually develop wheezing.¹²⁹ Suggested mechanisms of airway hyperresponsiveness in CVA can relate to hypersensitivity of vagal neuronal pathway,¹⁴³ although understanding the nature of the involved mediators requires further evaluation.¹²⁰ Other possible mechanisms to explain CVA airway hyperresponsiveness include variable cough^{144,145} thresholds, or structural changes in respiratory smooth muscle cells secondary to small airway remodeling.^{113,143} The latter has been suggested as a positive feedback mechanism for cough persistence in animal studies.¹⁴⁶

CVA patients can feature an eosinophilic airway inflammation as reflected by increased eosinophil count in induced sputum, biopsied bronchial mucosa, and bronchoalveolar lavage fluid.¹⁴⁷ Eosinophilia in CVA patients has been linked to more severe disease, yet when comparing eosinophilic to non-eosinophilic patients with CVA, no significant difference in spirometry findings was noted and the bronchial hyperresponsiveness (BHR) difference was not dramatic.¹⁴¹ Reportedly, patients with CVA express increased cough sensitivity when compared to healthy controls, but not asthmatics. To note, these observations ensued using a continuous sequential dilutions of capsaicin challenge for 1 min and determining the

concentration at which the total number of coughs per minute was 10 or more (C10min).¹⁴⁵ One explanation for presence of comparable HCR among patients with CVA and asthma can be an insufficient observation period (1 year) of CVA patients prior to their enrollment in the study in order to exclude patients who transitioned to bronchial asthma. In patients with CVA, HCR is also studied in relation to anti-asthma medications using capsaicin challenge models.⁹⁶ Data indicate cough reflex sensitivity measured in terms of the lowest capsaicin concentration triggering 2 or 5 coughs (C₂ or C₅) responds well to leukotriene receptor antagonists (LTRAs) with variable effects on airway hyperresponsiveness.^{148,149} This effect is likely attributed to the anti-inflammatory properties rather than the bronchodilator effects of LTRAs. Conversely, in CVA, bronchodilators or ICS have demonstrated insignificant improvement in capsaicin-induced cough thresholds and variable improvement in airway hyperresponsiveness.¹⁵⁰ Taken together, these data suggest CVA can be a precursor of asthma, and both cough phenotypes can manifest overlapping clinical symptomatology, airway inflammation and hyperresponsiveness. This may act as confounding variable in research studies comparing HCR among both cough phenotypes, despite presence of increased cough sensitivity in both CVA and classic asthma (CA) patients when compared to healthy individuals.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) manifests predominantly as productive cough associated with airflow limitation¹⁵¹ and occasionally bronchial hyperreactivity.¹⁵² Several COPD phenotypes exist, including frequent and non-frequent exacerbators, in addition to the asthma COPD overlap (ACO). The frequent exacerbator phenotype is characterized by airway (and serum) eosinophilia. The ACO phenotype represents asthmatics who later on develop COPD secondary to smoking.¹⁵¹ According to a large Korean survey, COPD constitutes 26.4% of patients with chronic cough.³ Severity of airflow restriction is linked to increased epithelial Th2 signature gene expression¹⁵³ in addition to blood and sputum¹⁵⁴ eosinophilia; the latter

being also a biomarker for frequency of exacerbations¹⁵⁴ and corticosteroid responsiveness.^{155,156} In COPD patients, the presence of chronic cough is associated with lower FEV₁,¹⁵⁷ more severe dyspnea, and worse QoL compared to COPD patients without chronic cough. Chronic cough is also associated with more severe airflow limitation and higher levels of inflammatory biomarkers in blood. These include high-sensitivity C-reactive protein, fibrinogen, leukocytes, neutrophils, and eosinophils.¹⁵⁸ Data also suggest chronic cough is an independent risk factor for acute exacerbation of COPD.¹⁵⁷ It is speculated that this property is linked to activation of TRPV1 by oxidative stress, inflammation, hypoxia, and mechanical stress.¹⁵⁹ In fact, TRPV4 may be implicated in the pathogenesis of COPD as revealed by data on genetic polymorphism in TRPV4-encoding genes.¹⁶⁰ Capsaicin challenge data in COPD patients reveal HCR improves in the recovery period (6 weeks) following an acute exacerbation of COPD. This correlated with cough frequency, severity (VAS), but not cough-related QoL questionnaire. Furthermore, improvement of HCR in the recovery period was inversely correlated with frequency of future acute exacerbations monitored over 1 year.¹⁶¹ Despite the small size of the studied patient population, this suggests HCR is heightened in acute exacerbation of COPD and can potentially predict future ones. In another report, chronic cough, or its suppression, was studied in COPD patients and compared to patients with chronic refractory cough (CRC), or to healthy subjects.¹⁶² All subjects with chronic cough, being COPD or CRC patients, had increased HCR when compared to subjects without chronic cough, being COPD patients or healthy individuals. Also, non-coughing COPD patients had comparable cough reflex sensitivity to healthy subjects. This suggests HCR has an important role in COPD patients with cough but is not a general feature of COPD per se. In addition, the ability of all COPD participants, but not those with CRC, to suppress cough suggests different cough mechanisms in both diseases. In conclusion, chronic cough in COPD patients is associated with worse clinical outcomes and manifests as a heightened HCR on tussigen challenge. Yet, underlying cough mechanisms need further elucidation.

REFLUX-RELATED COUGH SYNDROME

Epidemiology

In GERD, gastric regurgitation results in troublesome esophageal and extra-esophageal symptoms, including cough.¹⁶³ Extraesophageal symptoms can manifest in the mouth, lungs, and upper airways, and can lead to asthma (9.3-14%), laryngitis (7-14%), chronic cough (13%), dental erosions, and non-cardiac chest pain (23.1%).¹⁶⁴ Epidemiological data suggest GERD-related cough comprises 7%-85% of chronic cough cases with higher prevalence in western compared to Asian countries.^{10,122,165-167} The high variability in reported prevalence data may be related to different geographical population studies, lack of uniform criteria for diagnosis of chronic cough, and type of patient referral, among other factors.

Pathogenesis

Gastric or esophageal refluxate can be acidic or non-acidic, liquid or gaseous, and proximal or distal in location. Gastric refluxate can trigger cough or be induced by the act of coughing. Cough-induced reflux can be detected by the temporal association of a coughing episode followed by a reflux event on impedance/pH monitoring,^{168,169} which is subsequently computed as a symptom association probability (SAP).¹⁷⁰ The degree and duration of acid or non-acid exposure in esophageal and extraesophageal sites can determine the extent of mucosal injury and the presence or absence of heartburn, ie, silent reflux.¹⁷¹ Reflux events can induce coughing despite natural esophageal and laryngeal mucosal protective structures and mechanisms, such as upper/lower esophageal sphincters and esophago-glottic reflex, respectively.¹⁷² Patients with gastroesophageal and laryngopharyngeal reflux have invariably non-acid and gas reflux which is more likely located in the proximal esophagus as compared to the distal part. This suggests an overlap between laryngopharyngeal and gastroesophageal reflux-related cough.¹⁷³ One mechanism of GERD-related cough speculates a central crosstalk between airway and esophageal afferents (esophageal-bronchial reflex) at their site of convergence in the brainstem, the so-called "reflex theory".¹⁷⁴ Another mechanism of GERD-related cough suggests direct triggering of

the chemo/stretch receptors located on the afferent limb of the laryngopharyngeal reflex by refluxate in the upper esophagus, and/or micro-aspiration into the lungs, the so-called "reflux theory".¹⁷⁴ Several reports investigated the role of HCR and neurogenic inflammation in GERD-related cough.^{175,176} Compared to healthy subjects or patients with GERD but no cough, chronic cough patients with acid or non-acid reflux had lower cough threshold and higher levels of substance P and mast cell tryptase in induced sputum. However, the latter tested parameters were comparable among chronic cough patients with acid and non-acid reflux.¹⁷⁷ This underlines an important role of HCR in coughing patients with GERD but also suggests the acidity of the refluxate may not be of major importance in the mechanistic pathways linking reflux and cough. Discordant data on mechanisms involved in GERD-related cough also exist. Compared to healthy subjects, unselected patients with chronic cough have comparable frequency of proximal esophageal reflux events and extent of acidity. Likewise, the comparison of healthy subjects to chronic cough patients, where extraesophageal causes of chronic cough have been excluded, revealed similar findings.^{169,174} More importantly, no correlation was noted between the number of proximally occurring reflux events and the frequency of coughing. This implies that frequency of proximal reflux events may not be important for provocation of cough.^{174,178} However, in the same studies, a significant temporal association between cough and proximal reflux events (ie, SAP) was observed, reminiscent of hypersensitivity of esophageal-bronchial reflex, ie, reflex theory.¹⁷⁴ Other comorbid conditions need be considered in coughing patients with GERD, such as ineffective esophageal peristalsis.¹⁷⁹ Data revealed that esophageal dysmotility is twice more prevalent in chronic cough compared with heartburn patients, irrespective of the refluxate acidity (ie, acid or non-acid).¹⁷⁹ This adds to the complexity of chronic cough in patients with GERD. In conclusion, pathogenic mechanisms linking chronic cough and GERD are yet unclear. Direct triggering of cough by proximal reflux events (reflex theory) in patients with chronic cough and GERD lacks clear evidence. There is seemingly an

important role of HCR in GERD-related cough (reflex theory) which requires further elucidation.

COVID-19 COUGH

Epidemiology

Three stages of COVID-19 have been described: (i) a viral infection lasting for 1 to 2 weeks; (ii) a second phase characterized by an intertwined cytokine and oxidative stress storm, independent of infection; and (iii) a recovery phase that may last for months during which cough may be persistent.¹⁸⁰⁻¹⁸³ Cough is a major COVID-19 symptom¹⁸⁴ but is not necessarily associated with severity.¹⁸⁵ To date, epidemiological data suggest that prevalence of persistent cough, beyond 2 months from COVID-19 recovery, ranges from 7% to 34%;¹⁸⁶⁻¹⁸⁸ it is infrequently severe or troublesome and associated with symptoms of residual fatigue, breathlessness, and dyspnea, among others.¹⁸⁹ Whether COVID-19 is a risk factor for chronic cough remains to be elucidated. Prevalence data of chronic/persistent cough in general population and in COVID-19, being 2.5-18%¹⁻⁴ and 7-34%¹⁸⁶⁻¹⁸⁸ respectively, are highly variable. Confounding variables may include the spatiotemporal variation in prevalence data of chronic cough in general population studies^{10,190} and likely in COVID-19; also, prevalence data in COVID-19 cough are preliminary¹⁸⁷ and need be constantly updated until after the pandemic is controlled.

Pathogenesis

Mechanistic data on cough in COVID-19 are slowly unveiling and likely involve different immune pathways. TRP channels are involved in lung injury, COVID-19 morbidity, and severity of disease. The underlying pathological events leading also to mortality may be closely linked to the TRPV1-expressing neuronal system (afferent/efferent neurons) in the lungs¹⁹¹ with TRPV1 and TRPV4 also involved in pulmonary chemical injuries.¹⁹² Recent proof-of-concept clinical data in COVID-19 suggest that TRP channels may play a role in cough during all 3 stages of the disease as defined above. Specifically, spices (see below), which are TRPA1 and/or TRPV1 agonists, reduce COVID-19 cough within 1 to 2 min suggesting a channel desensitization. Furthermore, there may be a crosstalk between TRP channels and the

antioxidant transcription nuclear factor erythroid 2-related factor 2 (Nrf2).¹⁹³⁻¹⁹⁷ Activation of TRPA1 and TRPV1 channels augment sensory or vagal nerve discharges to evoke several symptoms of COVID-19, including cough, nasal obstruction, pain, vomiting, diarrhea and, at least partly, sudden and severe loss of smell and taste.¹⁹⁸ Considering another mechanism for cough, the mucosal angiotensin converting enzyme-2 receptor for COVID-19 regulates metabolism of the proinflammatory bradykinin,¹⁹⁹ an important tussigen of the bronchopulmonary C fiber population of the vagus nerve. Increased expression of bradykinin in COVID-19 can induce cough, reminiscent of drug (ACE inhibitors)-induced cough.²⁰⁰ The "two pathways" animal model speculates that chemoreceptors have both a stimulatory and an inhibitory role on cough in proximal and distal airways, respectively.^{201,202} It has been suggested that COVID-19 can curtail cough by stimulating distal cough chemoreceptors and concomitantly induce peripheral lung damage resulting in breathlessness and dyspnea.²⁰³ In summary, clear evidence on immune pathways involved in COVID-19 cough is currently lacking. Current data suggest multiple mechanistic triggers and likely an important role of TRP channels are involved in COVID-19 cough.

Comparison with post-viral cough

COVID-19 cough and post-viral cough (PVC) may have different characteristics in terms of clinical course, immune pathways, and pharmacological response pattern. PVC has a benign clinical symptomatology and frequently manifests solely with cough.²⁰⁴ COVID-19 often requires hospitalization, and residual cough is frequently associated with breathlessness and other symptoms as stated above. Immune pathways in PVC, as inferred from *in vitro* infectious models (human rhinovirus), reveal enhanced expression of TRP channels (A₁/V₁/M₈) mediated by increase in infected cell supernatants of IL-6 and IL-8,²⁰⁵ among others. Similar effects have been described in COVID-19²⁰⁶⁻²¹¹ which, additionally, can also manifest as hemophagocytic lymphohistiocytosis²⁰⁷ and persistent inflammatory interstitial lung disease.²¹² In PVC, a combination of anticholinergic (ipratropium bromide) and a beta-2 agonist (salbutamol) significantly reduced

cough severity,²¹³ but this treatment has not been studied yet in COVID-19.

UNEXPLAINED CHRONIC COUGH

Cough-associated illnesses can frequently point to the origin of cough as upper and lower airway or as reflux-related. In some patients, diagnostic testing and empirical therapies fail to treat cough-associated common and uncommon conditions, hence the name "chronic refractory cough". Its prevalence ranges from 2%²¹⁴ to 42%²¹⁵ of chronic cough patients seen by specialists and reportedly is more prevalent in middle-aged females.

MULTIFACTORIAL CHRONIC COUGH

Chronic cough is multi-morbid with rhinosinusitis, asthma, and GERD and thus can represent a syndrome with multifactorial etiologies. Data on multifactorial chronic cough in terms of prevalence, symptomatology, and response to therapy are being published but they may relate to the most severe patients. A Korean survey revealed that the majority (80%) of chronic cough patients in referral clinics have 1 or multiple etiological diagnoses, including rhinosinusitis, asthma, and bronchitis.²¹⁶ Extracted data from systematic analysis of chronic cough patients revealed prevalence of multifactorial cough is highly variable (7-72%), hence a recommendation to maintain all partially effective treatments during cough management.¹⁰ Reportedly, the most common combinations of cough etiologies are CVA + UACS in school-aged children,²⁴ and atopic cough (atopy and absence of airway hyperresponsiveness) + GERD in adults.¹⁹⁰ Although rarely reported, chronic cough with 3 concomitant etiologies encompassed atopic cough + GERD + UACS.¹⁹⁰ However, these data require careful interpretation due to lack of standardized objective measures for clinical diagnosis of chronic cough (International Classification of Diseases-ICD). In a recent large (N > 11 000) cohort specialty registry, chronic cough patients with both GERD and (upper/lower airway) respiratory diseases were compared to 3 subgroups of chronic cough patients. The comparative subgroups were either GERD (+ve)/Respiratory (-ve), GERD (-ve)/Respiratory (+ve), or GERD (-ve)/Respiratory (-ve) patients, at both

baseline and follow up year.²¹⁷ Specifically, GERD (+ve)/Respiratory (+ve) patients exhibited more cough potential comorbidities, health care resource utilization, use of antitussive medications and psychotherapeutics, when compared to the remaining 3 subgroups, in both baseline and follow up year. Also, the subgroup with GERD (-ve)/Respiratory (-ve) patients scored the lowest frequency of psychological disorders, cough complications and emergency department visits, hospitalizations and use of antitussive medications. In conclusion, multifactorial chronic cough is poorly defined in terms of impact on QoL,²¹⁸ cough severity, and cough control.²¹⁹ This indicates that all causes of cough should be considered in patients who are not responding to classical treatment of asthma or GERD.

SUMMARY

Epidemiological studies in conjunction with tus-sigen challenge protocols and expression studies of neuroinflammatory biomarkers are helpful in assessing the impact of HCR on the clinical presentation and severity of cough-associated illnesses. These tools also enable us to better understand how inflammation in various cough phenotypic traits can modulate the HCR. Type 2/Th1/Th2 inflammation, tissue remodeling, and cough plasticity, among others, can modulate HCR in cough-related phenotypes, yet exact mechanisms of such interaction need further elucidation. Exploring the mechanistic pathways involved in various chronic cough phenotypes is helpful in designing a better-targeted anti-tussive pharmacotherapy including anti-inflammatory agents, antibiotics, proton pump inhibitors (PPIs), or neuromodulators, among others.

In UACS, HCR is heightened in AR and nasal triggers can potentiate the cough reflex in the lower airways. HCR involving the trigeminal nerve afferents and/or their speculated central convergence centers with vagal neuronal pathway remains to be elucidated. Histamine inhalation protocols reveal laryngeal hyperresponsiveness is a multi-morbid condition with chronic cough irrespective of cough etiology and independently of asthma. Yet, evidence of HCR involving the laryngo-constrictive reflex in LHR is currently lacking. In the lower airways, cough phenotypic traits express considerable

similarity in biocellular profile marked by an important role of mast cells and innate immune system. In asthma, current data suggest chronic cough is a complex interplay between a hypersensitive cough reflex, an IgE or non-IgE mediated airway inflammation, absence of deep inspiration cough bronchoprotective reflex, and the recently recognized abnormal neuromechanical properties of the lungs. HCR in asthma seems independent of airway eosinophilia or hyperresponsiveness and preliminary data suggest atopy in asthma is not a risk factor for chronic cough. In NAEB, the role of HCR as a mechanistic trigger of cough is not clearly evidenced due to scarcity of tussigen challenge data. In CVA and COPD, preliminary data suggest HCR is important in the pathogenesis of chronic cough. The role of esophageal-bronchial reflex hyperreactivity as a mechanism of GERD-related cough awaits further research. Notwithstanding, impedance and pH monitoring can assist in diagnosis of GERD-related cough. TRP channels are involved in COVID-19 cough, but clear description of mechanistic pathways is currently lacking. Prospectively, cough-related QoL questionnaires need be standardized for a better definition and classification of chronic cough in epidemiology surveys. Cough challenge tests are difficult to perform in daily practice, lack a uniform administration protocol and assessment methods, and cannot reliably differentiate patients with HCR from healthy subjects. They also need be validated for reproducibility and correlation with other cough assessment tools.

Abbreviations

ACO: (Asthma COPD overlap), AR: (Allergic rhinitis), CA: (Classic asthma), CGRP: (Calcitonin gene-related peptide), COPD: (Chronic obstructive pulmonary disease), CPAP: (Continuous positive airway pressure), CRS: (Chronic rhinosinusitis), CVA: (Cough variant asthma), FeNO: (Fractional exhaled nitric oxide), FEV1: (Forced expiratory volume during the first second), GERD: (Gastro-esophageal reflux disease), ICS: (Inhaled corticosteroids), HCR: (Hypersensitivity cough reflex), LACS: (Lower airway cough syndrome), LHR: (Laryngeal hyperresponsiveness), LTRA: (Leukotriene receptor antagonist), NAEB: (Non-asthmatic eosinophilic bronchitis), NGF: (Nerve growth factor), NP: (Nasal polyps), Nrf2: (Nuclear factor erythroid 2-related factor 2), OSA: (Obstructive sleep apnea), OSAS: (Obstructive sleep apnea syndrome), PG: (Prostaglandin), PND: (Postnasal drip), PNDS: (Postnasal drip syndrome), PVC: (Post-viral cough), P2X: (Purinoreceptor), QoL: (Quality of life), SAP: (Symptom association probability), TLR: (Toll like receptor), TRP: (Transient receptor potential),

UACS: (Upper airway cough syndrome), URTI: (Upper respiratory tract infection).

Authors' consent

All authors reviewed the final version and agreed to publication of the work.

Authors' contributions

Philip Rouadi designed the plan of the article and contributed to the data collection. He wrote the manuscript draft, conceived and designed the tables/figures, and reviewed all parts of the article. Samar Idriss contributed to data collection, tables/figures, and manuscript draft. Jean Bousquet participated to the manuscript draft and reviewed the whole article. Tanya Laidlaw, Cecilio Azar, Mona Al-Ahmad, Anahi Yanez, Maryam Al-Nesf, Talal Nsouli, Sami Bahna, Eliane Abou Jaoude, Fares Zaitoun, Usamah Hadi, Georges Juvelekian and Moussa Riachy contributed the manuscript draft each according to his/her specialty and domain of interest. The rest of authors reviewed closely the whole article and added their remarks.

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