

Challenges in the treatment of chronic cough as observed by a laryngologist and a pulmonologist

Trudności w leczeniu przewlekłego kaszlu okiem laryngologa i pulmonologa

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ABSTRACT:

Chronic cough affects about 4–10% of adults and has a negative impact on the patients' quality of life. Chronic cough may be a symptom of many different diseases and its management should be based on treating the underlying cause. The most common cough cause in adults is chronic bronchitis due to smoking. Next, in non-smoking adults upper airway cough syndrome, gastroesophageal reflux and asthma account for the majority of cough reasons. Despite thorough diagnostics and management in 5–10% adults management of chronic cough is unsuccessful. In difficult-to-treat cough neuromodulators and speech therapy may be effective.

KEYWORDS:

asthma, chronic cough, difficult to treat chronic cough, gastroesophageal reflux, laryngopharyngeal reflux, upper airway cough syndrome

STRESZCZENIE:

Przewlekły kaszel występuje u 4–10% dorosłych, wpływając negatywnie na ich jakość życia. Może on być objawem wielu chorób, a w większości przypadków jego leczenie powinno mieć charakter przyczynowy. Najczęstszym powodem przewlekłego kaszlu jest przewlekłe zapalenie oskrzeli związane z paleniem papierosów, natomiast wśród osób niepalących są to: choroby górnych dróg oddechowych, choroba refluksowa i astma. Pomimo starannej diagnostyki i prób terapii, u 5–10% chorych z przewlekłym kaszlem nie udaje się uzyskać zmniejszenia jego nasilenia. W takiej sytuacji rozpoznaje się kaszel trudny do leczenia, a jego zmniejszenie można uzyskać stosując rehabilitację logopedyczną lub leki neuromodulujące.

SŁOWA KLUCZOWE:

astma, kaszel trudny do leczenia, kaszel związany z chorobami górnych dróg oddechowych, przewlekły kaszel, refluks krtańowo-gardłowy, refluks żołądkowo-przełykowy

ABBREVIATIONS

ACE – angiotensin-converting-enzyme
CHS – cough hypersensitivity syndrome
COPD – chronic obstructive pulmonary disease
CT – computed tomography
CVA – cough variant asthma
EAHR – extrathoracic airway hyperresponsiveness
ERS – European Respiratory Society
GERD – gastro-esophageal reflux disease
GER – gastroesophageal reflux
H₂ – histamine receptor 2
ICS – inhaled glucocorticosteroids
IPP – proton pump inhibitors
L-EMG – laryngeal electromyographic examination
LPR – laryngo-pharyngeal reflux

NAEB – nonasthmatic eosinophilic bronchitis
PND – post nasal drip syndrome
PP – drug to reduce stomach acidity
RSI – reflux symptom index
RTG – X-ray
SCUAD – severe chronic upper airway disease
SNOT-20 – sino-nasal outcome test 20
TRP – transient receptor potential
UACS – upper airway cough syndrome

INTRODUCTION

Cough (the Latin *tussis*) is the most common symptom of respiratory diseases. Concurrently it is mainly a defensive reflex, the purpose of which is to clean the respiratory system from excess secre-

tions or foreign bodies. It occurs most often secondary to irritation by substances aspirated with air into the respiratory system. It can also appear as a result of diseases of the upper and lower respiratory tract, diseases of the lungs or circulatory system. Sometimes coughing is an idiopathic or psychogenic symptom unrelated to somatic changes. Chronic cough, especially refractory to treatment, significantly impairs patients' quality of life. Intensive chronic cough can lead to voice disorders, headache, urinary incontinence, vomiting, muscle pain, chronic fatigue and depression [1–5].

The cough reflex consists of three phases:

1. inspiration phase,
2. phase of rise in chest pressure after glottis closure,
3. phase of increased exhalation at sudden opening of the glottis, which leads to a rapid pushing out of air with a characteristic sound.

As a result of violent coughing, which is a deliberate defensive reflex, the air leaves the lungs at a speed at times exceeding 100 km/h, with an accelerated movement reaching its maximum at the laryngeal level, which is preceded by a large increase in pressure in the lower respiratory tract [6].

On account of the duration, cough can be divided into:

1. acute cough – it persists less than 3 weeks and is most often caused by upper respiratory tract infection (mainly viral), less often by allergies; it may also appear as a sign of pulmonary embolism, pulmonary edema or bronchitis or pneumonia;
2. subacute cough – it persists 3–8 weeks and is most often caused by past respiratory viral infections or atypical infections;
3. chronic cough – above 8 weeks (causes are specified below) [1–5].

Chronic cough often poses a considerable diagnostic and therapeutic challenge. Basing on research conducted in Europe and the USA involving large groups of patients, the incidence of chronic cough is estimated at 4–10% of the adult population [7–8].

One of the most common causes of chronic cough is undoubtedly smoking. It also intensifies the symptoms of most diseases, which may have a shared responsibility for this condition in patients. Chronic cough diagnostics should always take into account both common and rare diseases.

In non-smokers, a chronic cough can be caused by many diseases, including:

1. upper airway cough syndrome (UACS);
2. asthma;
3. gastroesophageal reflux, or GER and laryngopharyngeal reflux, or LER;

4. past infection (post-infectious cough) – mainly of viral etiology or caused by atypical pathogens;
5. non-asthmatic eosinophilic bronchitis, or NAEB;
6. chronic bronchitis or chronic obstructive pulmonary disease (COPD);
7. use of medicines, primarily ACE inhibitors;
8. bronchiectasis;
9. other chronic respiratory diseases – interstitial lung diseases, tuberculosis, lung cancer, cystic fibrosis;
10. cardiovascular diseases – heart failure, heart defects (most often mitral valve disorders), cardiomyopathies;
11. nervous system diseases – in adults: neuropathy, Parkinson's disease; in children: Tourette syndrome, Hallervorden-Spatz disease, autism, Asperger's syndrome;
12. long-term exposure to irritants – e.g. passive smoking, air pollution, air-conditioned rooms, contact (e.g. professional) with harmful substances.

In the vast majority of cases it is possible to establish the cause of chronic cough, and thus offer the patients appropriate causal treatment. However, in some patients, despite careful diagnostics, the cause cannot be found – in such case we diagnose unexplained chronic cough (idiopathic) [1–6]. Much more often, specifically in up to 80% of patients with chronic cough we find two or more of causes for the condition. Three or more reasons are responsible for the occurrence of cough in a dozen or so percent of patients [9]. Certainly, this group of patients poses the greatest diagnostic and therapeutic challenge.

DIAGNOSIS AND TREATMENT OF CHRONIC COUGH ASSOCIATED WITH UPPER RESPIRATORY TRACT DISEASES

Upper respiratory tract disorders are the most common cause of chronic cough in adults. Hence, patients with chronic cough often report to the otolaryngologist as the first specialist to help solve their problems, but it is more common that otolaryngological consultation is a component of the complex diagnostic process conducted by many doctors [2–4, 10]. Upper airway cough syndrome (UACS) is a name introduced in place of the previously used term of post nasal drip (PND) syndrome [10–11]. Among non-smoking patients with a normal chest radiograph, not treated with ACE, UACS inhibitors were the main cause of cough, diagnosed in 20–40% of coughing patients [1–5]. The feeling of secretions moving down the back of the throat (post-nasal drip, or PND) is one of the leading symptoms of chronic sinusitis and rhinitis, but not all PND patients declare cough [12–15]. Upper respiratory tract infections as well as the coexistence of reflux symptoms, which clearly intensifies ailments [12–14], appear to be a major additional factor causing cough. The mechanisms responsible for the occurrence of cough in the course of UACS include:

- direct irritation of pharyngeal and laryngeal structures by flowing secretions,
- airway inflammation (joint inflammation of the upper and lower respiratory tract),
- upper respiratory tract hyperactivity (EAHR), manifested as an increased response to stimuli in the form of a cough reflex [16–18].

Postinfectious cough is a common diagnosis, but infectious etiology is unfrequently confirmed. With the exception of pertussis, little is known about the role of other infectious factors. It can be observed that past infections of the upper respiratory tract (especially of viral and atypical pathogen origin) constitute a trigger factor for the occurrence of cough against the background of other chronic diseases, e.g. asthma, rhinitis, chronic sinusitis or GERD. A typical feature is the occurrence of extrathoracic airway hyperresponsiveness (EAHR), which is diagnosed by inhalation challenge tests with histamine, hypertonic salt or exercise tests. A positive result of a provocation challenge test is considered as the appearance of obstruction at the level of the upper respiratory tract (primarily the larynx – inhalation tests), most often with symptoms of cough.

EAHR is a typical feature of cough in the course of ACE-inhibitor therapy, in chronic sinusitis or GER, and probably also in asthma, where it occurs alongside bronchial hyperresponsiveness. Unlike infectious, transient bronchial hyperreactivity, whose mechanisms are well understood, EAHR still requires further investigation [16–20].

Chronic cough is one of the basic symptoms of a group of conditions known under the name SCUAD – severe chronic upper airway disease. SCUAD defines those diseases which, despite applied treatment carried out in line with the applicable standards, do not respond to therapy in a satisfactory manner [21]. In-house and other authors' research indicate that chronic cough is often a symptom accompanying chronic rhinitis, both allergic and non-allergic, and less often chronic sinusitis [9, 11].

Otorhinolaryngological diagnostics of patients with chronic cough includes the following elements:

1. medical history including otorhinolaryngological symptoms,
2. physical examination with complete otorhinolaryngological examination,
3. phoniatic assessment,
4. video-laryngoscopy with reflux assessment,
5. computed tomography of the paranasal sinuses (if symptoms occur, it is appropriate to perform after initial pharmacological treatment),
6. endoscopy of nasal cavities and paranasal sinuses,
7. cytology of the nasal mucosa (should be performed before entering treatment),
8. acoustic rhinometry and anterior rhinomanometry (to be performed before entering treatment),

Tab. I. Treatment of chronic cough in the course of upper respiratory tract diseases.

CAUSE		TREATMENT: BASIC PRINCIPLES
Chronic rhinitis	Allergic	Intranasal glucocorticosteroids Aze-Flu (combination drug) Antihistamines: oral, nasal Alternatively montelukast
	non-allergic	Intranasal glucocorticosteroids Ipratropium bromide (not available in Poland) Other supportive methods
Rhinopathies		Intranasal glucocorticosteroids Ipratropium bromide Azelastine with fluticasone propionate (Aze-Flu)
Chronic rhinosinusitis	With nasal polyps	Intranasal glucocorticosteroids (Alternatively for a short period of time – oral glucocorticosteroids) In justified cases – surgery
	Without nasal polyps	Intranasal glucocorticosteroids In justified cases – surgery
	In exacerbations	Antibiotic therapy

9. SNOT-20 test (sino-nasal outcome test 20), assessing the severity of symptoms associated with the pathology of the nose and paranasal sinuses along with the basic parameters of quality of life.

Laryngeal endoscopy permits the identification of patients with clinical changes suggestive of GERD. Phoniatic evaluation allows the diagnosis of pathological changes in the larynx and the exclusion of swallowing disorders. Computed tomography of the paranasal sinuses along with an endoscopic examination of the nose and sinuses enables recognition of chronic sinusitis or structural changes in the lateral wall of the nose and/or nasal septum. Acoustic rhinometry and anterior rhinomanometry – objective research of intranasal spaces are helpful in differentiating inflammatory, edematous and structural changes in the nasal cavities. A valuable complement is nasal cytology (exfoliative cytology with the application of quantitative techniques – the percentage assessment of the presence of individual cells in smears), which permits diagnosis of the inflammatory response of the nasal mucosa and differentiation of the type of ongoing inflammation [5, 16, 18].

Such a way of proceeding is the basis for use of appropriate treatment in the management of chronic cough. Depending on the pathology found: anti-inflammatory treatment – in chronic inflammation of the nose and paranasal sinuses, anti-reflux treatment, or in justified cases referring patients for surgical treatment of the nose and/or paranasal sinuses.

Depending on the diagnosed cause of chronic cough, it is recommended to begin appropriate treatment [Tab. I].

DIAGNOSIS AND TREATMENT OF CHRONIC COUGH ASSOCIATED WITH GASTROESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX DISEASE

The occurrence of a cough in a reflux patient appears to be due to two reasons:

1. microaspiration of the receding gastric contents into the respiratory tract – the larynx and throat, and sometimes even the trachea and bronchi;
2. the esophageal-tracheobronchial reflex transmitted by the vagus nerve, resulting from stimulation of the X nerve receptors by acidic gastric contents [2, 3, 22, 23].

Due to the coverage by reflux disease of not only the esophageal structures, but also those of the larynx and throat, some authors suggest replacement of the name gastroesophageal reflux with gastroesophageolaryngeal reflux. Moreover, some authors postulate to distinguish between gastroesophageal reflux (GER) and laryngopharyngeal reflux (LPR).

It is noteworthy, that cough can be provoked not only by acidic content from the stomach retreating backwards, but also by neutral or alkaline content [23, 24]. Symptoms in gastroesophageal reflux disease can be grouped into three categories [25]:

1. typical esophageal symptoms: regurgitation (regurgitation of sour-tasting foods) and heartburn; clearly intensifying when lying down and when bending down, especially after a generous meal,
2. alarming symptoms (caused by disease complications) – painful swallowing, swallowing disorders, weight loss, gastrointestinal bleeding,
3. atypical, non-esophageal symptoms:
 - chronic cough, sometimes wheezing in the chest (imitating asthma), hoarseness, grunting, sore throat and burning (increased especially in the morning),
 - chest pain (behind the sternum, imitating coronary pain).

Often, gastroesophageal reflux disease does not give typical symptoms, except for coughing or hoarseness, in which case diagnosis based on the symptoms themselves is much more difficult. It is estimated that up to 75% of patients with chronic cough in the course of GER do not report typical esophageal reflux symptoms [22].

Although gastroesophageal reflux disease and laryngopharyngeal reflux disease are similar conditions, there are certain differences between them [26]. The most common symptoms of LPR are hoarseness, a lump in the throat, expectoration, secretions being produced in the back of the throat, chronic cough, difficulty in swallowing, and less often episodes of choking or laryngospasm.

Assessment of the intensification of these symptoms in the form of reflux symptom index, or RSI, could be helpful in diagnosing LPR (a score of > 5 speaks in favor of LPR) [27]. Diagnosis of cough in the course of gastroesophageal reflux or pharyngolaryngeal reflux can be based on:

1. symptoms (both typical and atypical) and visible improvement under influence of treatment;
2. confirmation of reflux in 24-hour pH-metrology, impedance or esophageal manometry;
3. imaging tests: X-ray with barite or scintigraphy of esophageal motor activity;
4. gastroscopy, if esophagitis or other gastroesophageal reflux disease complications are found;
5. suspected reflux in laryngeal endoscopy and marked improvement under influence of treatment.

Due to the occurrence of LPR in a significant group of patients with chronic cough, it is proposed to use ENT probes during pH metrology or esophageal impedance (with pH or impedance sensors at the level of the lower part of the pharynx), however this method requires further research and standardization of results [22, 23]. Until quite recently, the best diagnostic test was considered to be 24-hour esophageal impedance, often paired with esophageal pH test, while the latest recommendations by the European Respiratory Society for the diagnosis and treatment of patients with chronic cough question the relevance of this test. They indicate that esophageal pH test is not appropriate for the diagnosis of cough associated with reflux, while esophageal manometry could be useful for assessing cough-related motility disorders [24].

A vital element in the diagnosis of gastroesophageal reflux disease is the evaluation of laryngeal structures [26]. Belafsky et al. developed a scale for the intensification of reflux changes known as the Reflux Finding Score extremely useful in clinical practice, which assesses the following parameters: subglottic edema, atrial obliteration, hyperemia, swelling of the vocal folds, diffuse laryngeal edema, changes in grading of posterior commissure hypertrophy, formation of granulation, and thick secretions. A score of above 7 points on this scale supports the suspicion of LPR [28]. Effective treatment of reflux cough is difficult [23, 24] and encompasses several components:

- modification of diet,
- reduction of weight in the case of overweight,
- medications for reduction of stomach acid (PPIs, H2 antagonists),
- prokinetic drugs.

As recently as a dozen or so years ago, gastric acid suppression therapy, and primarily proton pump inhibitors (IPP), were considered the basis of treatment. In contrast, results of randomized trials and meta-analyses did not confirm the efficacy of PPIs in

reducing the severity of chronic cough [29–30]. Only patients with cough associated with common reflux symptoms (heartburn, regurgitation) are more likely to improve under the influence of PPIs. Hence, the latest recommendations of the European Respiratory Society suggest against routine and long-term use of PPIs in the treatment of chronic cough [24]. Currently, experts emphasize the role of esophageal motility disorders as one of the pathomechanism of chronic cough, rather than irritating the esophagus by acidic stomach contents.

DIFFICULTIES IN DIAGNOSTICS AND TREATMENTS OF COUGH VARIANT ASTHMA

Asthma is the cause of chronic cough in 20–25% of patients [1–5]. Most frequently, coughing is among the three main symptoms of asthma along with shortness of breath and wheezing, but sometimes it may be the only symptom – then cough variant asthma (CVA) is diagnosed. In the classic form of asthma, in addition to paroxysmal breathlessness, wheezing and coughing, it is important to confirm time-varying bronchial obstruction by spirometry [31]. On the other hand, the diagnosis of cough asthma variant may be more difficult, and the criteria for diagnosis vary depending across authors (Tab. II.) [31–34]. Together, the elements that determine CVA, regardless of the author, include:

- occurrence of chronic paroxysmal cough,
- absence of other asthma symptoms, i.e. paroxysmal breathlessness with wheezing,
- normal spirometry results,
- confirmation of bronchial hyperresponsiveness in bronchial provocation test,
- reduction of severity of coughing under influence of treatment, most commonly with inhaled glucocorticoids (ICS).

The effectiveness of treatment for chronic asthma associated with cough is usually good, but it is not always very high. Similarly to all forms of asthma, the basis for treatment of cough variant asthma is ICS, although some authors suggest treatment with combination drugs (ICS and bronchodilators) [1–5, 24]. Leukotriene receptor antagonists are also effective (in Poland only montelukast is available). The recent recommendations for the management of chronic cough suggest treatment only with ICS [24]. In situations of incomplete response, it is recommended to try treatment with prednisone 30 mg for 10–14 days [1–5].

It is, however, noteworthy that despite careful diagnosis and treatment in some patients with CVA, it is impossible to achieve a reduction in the severity of cough – this is often due to the coexistence of other causes of cough or hypersensitivity of the cough reflex [24]. Recent years have brought a marked improvement in the effectiveness of treatment of severe asthma due to the availability of biological medicines, among others omalizumab, mepolizumab or benralizumab. It is also worth stressing that chronic persistent cough is an underestimated symptom of asthma that is not considered a symptom of the severity of this disease; thus, it is not a criterion that could be included in the qualification for biological treatment.

Tab. II. Differences in the criteria for diagnosis of cough variant asthma.

	CORRAO W.M. ET AL. 1979	GUIDELINES OF THE JAPANESE RESPIRATORY SOCIETY 2017	RECOMMENDATIONS OF GINA 2019
Cough > 8 weeks	X	x	x
Absence of asthma symptoms, i.e. shortness of breath, wheezing	X	x	x
Absence of symptoms from the upper respiratory tract (post nasal drip)		x	
Spirometry unremarkable	X	x	+/-
Documented bronchial hyperresponsiveness	x	x	x
Eosinophilic airway inflammation		x	
Reduction of cough under influence of bronchodilators	x	x	
Recurrence of cough after treatment discontinuation	x		
Reduction of cough under influence of glucocorticosteroids		x	

DIFFICULT TO TREAT COUGH

Despite careful diagnostics and new options, the effectiveness of chronic cough treatment is limited, and difficult to treat cough now poses a significant clinical challenge [35]. It is estimated that 5–10% of adults with chronic cough fail to obtain reduction of cough intensity despite careful diagnosis and attempts at treatment. From the perspective of cough clinics dealing with chronic cough, the percentage of treatment failures is higher – it is estimated that it could reach up to 40% [24, 35]. Difficult to treat cough most often affects women in the peri- or post-menopausal age, which is probably associated with greater sensitivity of the cough reflex in women [36].

The reason for therapeutic failure may be limited effectiveness of treatment in individual cause of cough or coexistence of several. On the other hand, failure in management of chronic cough may result from cough hypersensitivity syndrome, or CHS (other names for this syndrome also include: laryngeal hyperresponsiveness, reactive airways dysfunction syndrome, irritable larynx syndrome). Laryngeal dysfunction is increasingly recognized as a component of chronic cough syndrome [16]. Beside chronic cough, the clinical picture mainly reveals dysphonia and hoarseness. An increased motor response of the larynx to non-specific stimuli with various disorders of air flow is observed. Those consist in: decreasing the inspiratory airflow (obturation), excessive glottal closure reflex and disturbances in mobility of the vocal folds, up to paradoxical movements of the vocal folds (including paradoxical adduction of the vocal folds during inspiration, with closure of the true glottis). The literature also lists that chronic cough could be a symptom of laryngeal sensory neuropathy of the superior laryngeal nerve or recurrent laryngeal nerve. In case of suspicion of this pathology, diagnosis should be supplemented with laryngeal electromyography (L-EMG) and stroboscopy [37, 38].

Cough in patients with cough hypersensitivity syndrome occurs in response to variety of nonspecific stimuli that do not induce

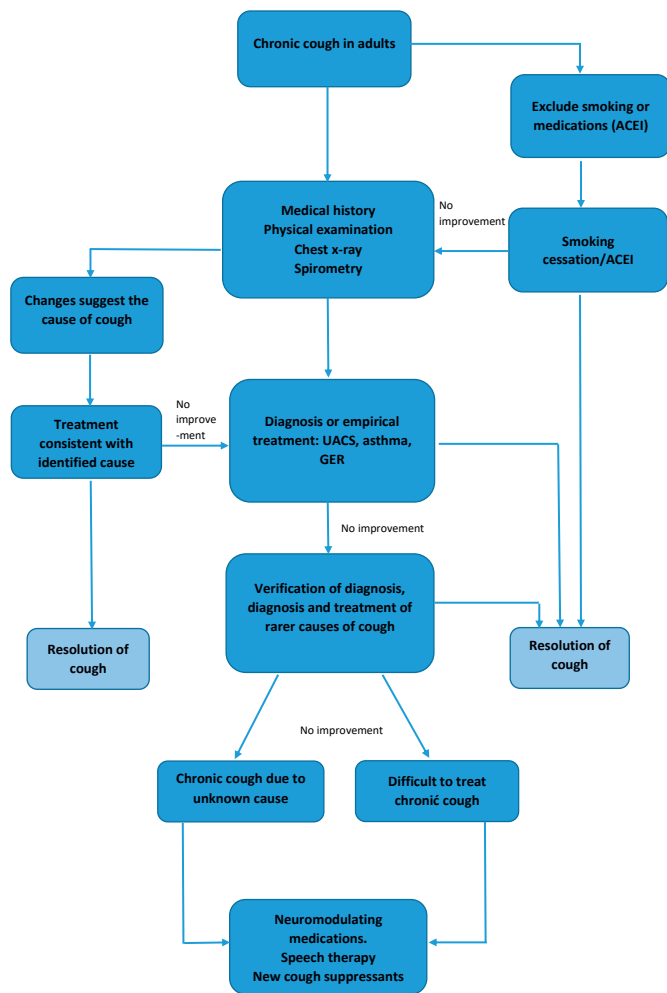


Fig. 1. Algorithm for diagnosis of chronic cough (short version).

coughing in most individuals. It is often accompanied by a feeling of irritation in the pharynx/larynx/upper chest, dry throat, urge to cough, pharyngeal or laryngeal paresthesia, grunting, hoarseness, dysphonia, up to vocal fold dysfunction. Coughing attacks occur during phonation, laughter (allotussia), breathing cold or dry air (hypertussia) [35, 36, 37]. The factors often entailing coughing attacks in this group of patients include:

- phonation, laughter, singing, deep breathing,
- air temperature changes (mainly cold air),
- aerosols, irritating odors,
- supine position,
- food,
- physical effort.

It is worth stressing that the quality of life of patients with difficult to treat cough is significantly impaired due to its frequency, intensity, chronic nature and lack of improvement. During the last years there has been a search for new treatment methods dedicated to patients with difficult to treat or idiopathic cough. Among them are phoniatic rehabilitation (speech therapy), neuromodulation or new cough receptor antagonists, medicines, including P2X3 receptor antagonist, gefapixant [1, 24, 35].

Phoniatic rehabilitation (speech therapy)

Due to the frequently observed laryngeal dysfunction in cough hypersensitivity syndrome, Vertigan et al. suggested the use of phoniatic or speech therapy rehabilitation [39]. This rehabilitation not only enables improvement in the mobility of the vocal folds, but also relaxation of the laryngeal muscles, and often also other muscles of the neck, as well as correction of voice emission, thereby reducing excessive laryngeal reactivity to non-specific stimuli and decreasing attacks of uncontrolled cough [33, 34]. This therapy encompasses the following procedures:

- education about the nature of coughing, and pharyngeal and vocal hygiene,
- correct voice emission,
- training in diaphragmatic breathing,
- techniques for reducing laryngeal muscle tension.

Methods aiding the treatment of cough hypersensitivity syndrome should also include sufficient supply of oral fluids, control of environmental conditions (adequate air humidity, avoidance of air-conditioned rooms, exposure to air pollution), use of agents reducing irritation and dryness of the upper respiratory tract (e.g. appropriate compositions of natural oily substances in the form of spray with applicators adapted for administration to the back of the throat) and psychological support [24, 35, 38, 39].

Neuromodulators and new cough suppressants

The persistent nature of cough may be largely due to disturbances in neuronal regulatory mechanisms, therefore in cases of difficult to treat cough, neuromodulators such as amitriptyline, gabapentin or pregabalin are proposed. The effectiveness of these drugs has been confirmed in randomized trials [41]. Recent ERS recommendations also suggest that slow-release morphine (ERS) could be used in low doses (5–10 mg, 2 x day) for difficult to treat coughs, although this treatment has been reserved only for cancer patients until now [24].

Medicines which are antagonists of TRP receptors could become a therapeutic option directly dedicated to neurogenic mechanisms. One of them is gefapixant, a P2X3 receptor antagonist. So far, it has been proven to be effective in reducing cough (phase III studies are currently underway), although its use has been associated with common side effects, most often taste disorders. Numerous clinical trials are ongoing with other new cough suppressants, which gives hope for more effective help for patients with persistent cough in the near future [42].

SHORT VERSION OF DIAGNOSTIC ALGORITHM

The detection scheme for chronic cough in adults is shown in Fig. 1. This diagnosis should encompass:

1. in-depth interview, with particular emphasis on smoking cigarettes, taken medications and chronic diseases;
2. physical examination with particular regard to the upper and lower respiratory tract;

3. chest X-ray, in justified cases CT of the chest;
4. spirometry;
5. otorhinolaryngological consultation and diagnostics, in justified cases CT of the sinuses;
6. bronchial provocation test;
7. induced sputum analysis;
8. allergy diagnostics;
9. diagnostics toward gastroesophageal reflux disease (GERD).

References

1. Irwin R.S., French C.L., Chang A.B. et al.: Classification of cough as a symptom in adults and management algorithms. *Chest Guideline and Expert Panel Report*. *Chest*, 2018; 153: 196–209.
2. Irwin R.S., Baumann M.H., Bolser D.C. et al.: Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*, 2006; 129: 1–23.
3. Morice A.H., McGarvey L., Pavord I.: Recommendations for the management of cough in adults. *Thorax*, 2006; 61(supl. 1): i1–24.
4. Morice A.H., Fontana G.A., Sovijari A.R.A. et al.: The diagnosis and management of chronic cough. *Eur. Respir. J.*, 2004; 24: 481–492.
5. Arcimowicz M., Dąbrowska M., Tarchalska-Kryńska B., Domeracka-Kołodziej A., Grabczak E.M.: Diagnostyka otorynolaryngologiczna w przewlekłym kaszlu. *Postępy Dermatologii i Alergologii*, 2009; 26: 487–488.
6. Chung K.F., Widdicombe J.G.: Cough as a symptom. *Pulm. Pharmacol. Ther.*, 2004; 17: 329–332.
7. Song W.J., Chang Y.S., Faruqi S., Kim J.Y., Kang M.G. et al.: The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur. Respir. J.*, 2015; 45: 1479–1481.
8. Çolak Y., Nordestgaard B.G., Laursen L.C., Afzal S., Lange P. et al.: Risk factors for chronic cough among 14,669 individuals from the general population. *Chest*, 2017; 152: 563–573.
9. Dąbrowska M., Grabczak E.M., Arcimowicz M., Domeracka-Kołodziej A., Domagała-Kulawik J. et al.: Causes of chronic cough in non-smoking patients. *Adv. Exp. Med. Biol.*, 2015; 873: 25–33.
10. Pratter M.R.: Chronic upper airway cough syndrome secondary to rhinosinus diseases. ACCP evidence-based clinical practice guidelines. *Chest*, 2006; 129: 63S–71S.
11. Watelet J.B., Van Zele T., Brusselle G.: Chronic cough in upper airway diseases. *Respir. Med.*, 2010; 104: 652–657.
12. Millqvist E., Bende M.: Role of the upper airways in patients with chronic cough. *Curr Opin Allergy Clin Immunol*, 2006; 6: 7–11.
13. Macedo P., Saleh H., Torrego A., Arbery J., MacKay I. et al.: Postnasal drip and chronic cough: An open interventional study. *Respir. Med.*, 2009; 103: 1700–1705.
14. Tatar M., Plevkova J., Brozmanova M., Pecova R., Kollarik M.: Mechanism of the cough associated with rhinosinusitis. *Pulm. Pharmacol. Ther.*, 2009; 22: 121–126.
15. Yu L., Xu X., LvH., Qiu Z.: Advances in upper airway cough syndrome. *Kaohsiung J. Med. Science*, 2015; 5: 223–228.
16. Ryan N.M., Gibson P.G.: Characterization of laryngeal dysfunction in chronic persistent cough. *Laryngoscope*, 2009; 119: 640–645.
17. Saleh H.: Rhinosinusitis, laryngopharyngeal reflux and cough: An ENT viewpoint. *Pulm. Pharmacol. Ther.*, 2009; 22: 127–129.
18. Sherrill D.L., Guerra S., Minervini M.C., Wright A.L., Martinez F.D.: The relation of rhinitis to recurrent cough and wheezing: A longitudinal study. *Respir. Med.*, 2005; 99: 1377–1385.
19. Simpson C.B., Amin M.R.: Chronic cough: State-of-the-art review. *Otolaryngol. Head Neck Surg.*, 2006; 134: 693–700.
20. Vertigan A.E., Bone S.I., Gibson P.G.: Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. *Respirology*, 2013; 18: 948–956.
21. Bousquet J., Bachert C., Canonica G.W., Casale T.B., Cruz A.A. et al.: Unmet needs in severe chronic upper airway disease (SCUAD). *J. Allergy Clin. Immunol.*, 2009; 124: 428–433.
22. Irwin R.S.: Chronic cough due to gastroesophageal reflux disease. ACCP Evidence-Based Clinical Practice Guidelines. *Chest*, 2006; 129: 80S–94S.
23. Kahrilas P.J., Altman K.W., Chang A.B. et al.: Chronic cough due to gastroesophageal reflux in adults. *Chest Guideline and Expert Panel Report*. *Chest*, 2016; 156: 1341–1360.
24. Morice A.H., Millqvist E., Bieksiene K., Birring S.S. et al.: ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur. Respir. J.*, 2020 2; 55: pii: 1901136.
25. Talar-Wojnarowska R.: Choroba refluksowa przełyku w: *Interna Szczeklika 2019*, red. Gajewski P., Medycyna Praktyczna, Kraków 2019.
26. Ford C.N.: Evaluation and management of laryngopharyngeal reflux. *JAMA*, 2005; 294: 1534–1540.
27. Belafsky P.C., Postma G.N., Koufman J.A.: The validity and reliability of the reflux symptom index (RSI). *J. Voice*, 2002; 16: 274–277.
28. Belafsky P.C., Postma G.N., Koufman J.A.: The validity and reliability of the reflux findings score (RFS). *Laryngoscope*, 2001; 111: 1313–1317.
29. Chang A.B., Lasserson T.J., Kiljander T.O., Connor F.L., Gaffney J.T. et al.: Systematic review and meta-analysis of RCT of gastroesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *B.M.J.*, 2006; 7(332): 11–17.
30. Chang A.B., Lasserson T.J., Gaffney J., Connor F.L., Garske L.A.: Gastro-esophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database of Systemic Reviews*, 2011; CD 004823.
31. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*, 2019 (dostęp: www.ginasthma.org).
32. Corrao W.M., Braman S.S., Irwin R.S.: Chronic cough as the sole presenting manifestation of bronchial asthma. *N. Engl. J. Med.*, 1979; 22(300): 633–637.
33. Ichinose M., Sugiura H., Nagase H. et al.: Japanese guidelines for adult asthma 2017. *Inter. Allergy*, 2017; 66: 163–189.
34. Nimii A., Matsumoto H., Mishima M.: Eosinophilic airway disorders associated with chronic cough. *Pulm. Pharmacol. and Therap.*, 2009; 22: 114–120.
35. Gibson P., Wang G., McGarvey L.: Treatment of unexplained chronic cough: Chest guideline and expert panel report. *Chest*, 2016; 149: 27–44.
36. Morice A.H., Millqvist E., Belvisi M.G.: Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur. Respir. J.*, 2014; 44: 1132–1148.
37. Ryan N.M., Gibson P.G.: Characterization of laryngeal dysfunction in chronic persistent cough. *Laryngoscope*, 2009; 119: 640–645.

CONCLUSION

Chronic cough affects about 4–10% of adults and is a frequent clinical challenge which significantly impairs patients' quality of life. The most common cause is chronic bronchitis linked to smoking, but paradoxically this specific group of patients rarely reports to the doctor due to cough. Diagnostics of the causes of chronic cough in non-smokers consists of several steps, and the most common causes of cough include upper respiratory tract disease, gastroesophageal reflux disease, and asthma. The effectiveness of treatment of causal cough is limited which may be due to an incomplete response to treatment, the coexistence of several reasons for cough or hypersensitivity of the cough reflex. Difficult to treat cough is now better recognized entity for many specialists; apart from pharmacological treatment, speech therapy should also be part of treatment.

38. Vertigan A.E., Theodoros D.G., Gibson P.G., Winkworth A.L.: The relationship between chronic cough and paradoxical vocal fold movement: A review of the literature. *J. Voice*, 2006; 20: 466–480.
39. Vertigan A.E.: An update on speech pathology management of chronic refractory cough. *J. Allergy Clin. Immunol. Pract.*, 2019; 7: 1756–1761.
40. Slinger C., Mehdi S.B., Milan S.J., Dodd S., Matthews J. et al.: Speech and language therapy for management of chronic cough (Review). *Cochrane Database of Systematic Reviews*, 2019, 7. CD013067.
41. Ryan N., Vertigan A.E., Birring S.S.: An update and systematic review on drug therapies on refractory chronic cough. *Exp Opin Pharmacotherapy*, 2018; 19: 687–671.
42. Smith J., Badri H.: Cough: new pharmacology. *J. Allergy Clin. Immunol. Pract.*, 2019; 7: 1731–1738.

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