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LITERATURE REVIEW

The chronic cough syndrome

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ABSTRACT

Cough is a common symptom encountered in medical practice and can occur throughout the life of a person. From a physiological point of view, it represents a mechanism responsible for the elimination of secretions from the airways. At the same time, cough may be the first symptom of an illness. There are many causes that may lead to the emergence of a chronic cough syndrome, the most frequent being pulmonary diseases. Besides the bronchopulmonary pathology, there are a number of extrapulmonary disorders that may manifest with coughing. The first step in evaluating the patient with chronic cough is performing a correct and complete anamnesis, followed by the physical examination of the patient. The treatment of the chronic cough syndrome must address mainly the underlying disease but, in case of failure of the established treatment, the antitussive therapy is used.

KEYWORDS: chronic cough, pulmonary disease, posterior rhinorrhea, asthma, antitussives

INTRODUCTION

Cough is a common symptom encountered in medical practice and can occur throughout the life of a person. From a physiological point of view, it represents a mechanism responsible for the elimination of secretions from the airways. At the same time, cough may be the first symptom of an illness.

The cough syndrome may have an acute character, presenting itself as a self-limiting disorder and is associated with an acute condition of the upper respiratory tract[1,2], or a chronic character, lasting more than 3 weeks. Most of the times, chronic cough is the sign of a chronic lung disease, but it may also appear in the context of an extrapulmonary pathology[2-5].

Regarding the epidemiology of the chronic cough syndrome, there are various studies that have tried to establish its incidence in the general population[6-9]. Studies have shown that chronic cough is one of the most frequent causes for presentation to the doctor, with prevalence between 40 and 60 %[10]. An extensive study conducted in 16 countries on 18.277 subjects aged between 20 and 48 years showed the presence of the productive cough in 10% of cases, of the dry one in 10% and of the nocturnal cough in 40% of the subjects included in the study[10].

THE MECHANISM OF CHRONIC COUGH

The cough reflex has an afferent component, a central one and an efferent one.

The afferent pathways of the cough syndrome are represented by the trigeminal, glossopharyngeal and vagus nerves, which take over the impulses from the receptors located in the upper airways. There are three types of receptors[11-14]:

1. nociceptors – activated by chemical stimuli, inflammatory and immunological mediators (histamine, bradykinin, prostaglandins, capsaicin, substance P);
2. slowly-adapting receptors (SARs);
3. rapidly-adapting receptors (RARs) – activated by mechanical stimuli, cigarette smoke, acidic and alkaline solutions, pulmonary congestion, atelectasis, etc.

The information taken over by receptors is transmitted through the afferent pathways to the cough center located at the level of the solitary tract nucleus in the brainstem. From this level, efferent impulses are transmitted through the vagus nerve towards the larynx and the tracheobronchial tree, as well as towards the intercostal muscles, the abdominal wall, the diaphragm and the pelvis, via the phrenic nerve and the C3 and S2 spinal motor nerves.

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CAUSES OF CHRONIC COUGH

There are many causes that may lead to the emergence of a chronic cough syndrome, the most frequent being pulmonary diseases (cancer, COPD, chronic bronchitis, bronchiectasis, asthma, pulmonary tuberculosis, pulmonary fibrosis, etc). Of a special importance is the bronchopulmonary cancer, disease with a high incidence and mortality. In the European Union, an incidence of 52,5/100,000/year and a mortality of 48,7/100,000 inhabitants/year (77,0/100,000 men/year and 23,9/100,000 women/year) are reported, while in Romania, a mortality of approximately 59,29/100,000 men/year and 12,4/100,000 inhabitants/year among females is reported[15]. Currently in Romania, the bronchopulmonary cancer represents the main cause of mortality in men and it occupies the third place in women[16,17].

Besides the bronchopulmonary pathology, there are a number of extrapulmonary disorders that may manifest with coughing[18,19] (Table 1). From the extrapulmonary causes, the three etiologies most frequently incriminated in the emergence of chronic coughing are[20-23]:

1. *the posterior rhinorrhea syndrome* occurred in the context of chronic rhinosinusitis or of a rhinitis (allergic or non-allergic);
2. *asthma*;
3. *gastroesophageal reflux disease* (in approximately 75% of cases, cough may be the only symptom[24]).

The posterior rhinorrhea syndrome seems to be incriminated in the occurrence of chronic cough, according to the literature, in 2 – 57% of cases[25,26]. The existence of this syndrome is directly related to an antecedent diagnosis of rhinosinusal pathology, represented by rhinitis or rhinosinusitis. The trigger mechanism is considered to be the stimulation of vagal receptors in the pharynx or the larynx by posterior nasal secretions[27-30].

Table 1
Extrapulmonary causes of chronic cough

Upper airway diseases	Post nasal drip syndrome Vocal cord dysfunction Obstructive sleep apnea
Esophageal causes	Gastroesophageal reflux disease Laryngopharyngeal reflux Tracheoesophageal fistula
Cardiac disease	Chronic heart failure Pulmonary congestion Endocarditis, etc.
Drugs	Angiotensin-converting enzyme inhibitor B-blockers
Neurological or psychological causes	Psychogenic cough

Asthma is a condition characterized especially by dyspnea, wheezing, coughing. Although it is a symptom often associated with asthma, the cough syndrome is not always found in the same clinical picture with the other symptoms. In asthma, the main trigger mechanism of the symptomatology is airway inflammation, cough being triggered by the obstructive phenomenon and the accumulation of secretions.

Regarding **GERD**, it can trigger the cough reflex through two different mechanisms: a direct mechanism and an indirect one[31]. The direct mechanism occurs by stimulating nerve endings either in the larynx through the emergence of an extraesophageal reflux (laryngeal esophageal reflux), or in the bronchi determined by intratracheal microaspiration of the gastric juice. The indirect mechanism can be explained by the esophagobronchial vagal reflex, which occurs by irritation of the vagus nerve and secondary activation of the cough center[31,32].

Paresis and paralysis of vocal cords may also be associated with the existence of a chronic cough syndrome[33-35], as well as the sleep apnea syndrome[18].

The literature reports the existence of over 350 *drugs* which may cause cough as a side effect[22]. Cough is most frequently associated with treatment with angiotensin-converting-enzyme inhibitors. 5 to 35 % of patients undergoing chronic treatment with these compounds present cough as a side effect. The trigger mechanism would be bradykinin release by the angiotensin-converting-enzyme inhibitors[23].

Beta-blockers may be associated, in their turn, with a cough syndrome because of their bronchoconstrictor effect. The same mechanism seems to be incriminated also in the case of nonsteroidal anti-inflammatory drugs, especially in patients with asthma[23].

Cardiac pathology (e.g. chronic heart failure, endocarditis, pulmonary congestion, etc.) is, as well, quite frequently associated with a chronic cough syndrome.

Moreover, certain *neurological* or *psychiatric disorders* can present cough in their clinical picture (e.g. psychogenic cough).

There are many studies in the literature that demonstrate that, in approximately 94% of patients with chronic cough, the main cause is represented by the posterior rhinorrhea syndrome, asthma, chronic bronchitis, gastroesophageal reflux disease, or pulmonary tuberculosis[36-40]. Unfortunately, the latter has a very high incidence in Romania, representing probably the main pulmonary cause of cough along with lung cancer.

In 82% of the cases, the chronic tusigen syndrome seems to have a single cause, while multiple etiology

has been described in approximately 18% of the patients[36,38,40].

Another very common cause in the etiology of chronic cough is *smoking*.

Among the rarer causes that may be associated with chronic cough is the exposure to noxes or various irritating substances.

Given the multitude of factors that can cause a chronic cough syndrome, identifying the real cause or causes is particularly important.

THE POSITIVE DIAGNOSIS OF CHRONIC COUGH

The first step in evaluating the patient with chronic cough is performing a correct and complete anamnesis, followed by the physical examination of the patient.

The anamnesis must determine the time and circumstances of the occurrence of cough, the factors that aggravate or limit the excess of cough, the character of the syndrome (productive or non-productive). Also, it is important to know if cough is associated with other symptoms, such as: hemoptyses, weight loss, dyspnea, orthopnea, fever or chills.

Nasal obstruction can be an important symptom associates with a chronic cough syndrome, as well as posterior rhinorrhea.

The discussion with the patient must clarify the doctor about the existence of certain diseases associated (e.g. gastric, cardiovascular, pulmonary diseases, etc.), the chronic medication for these disorders, and the existence of surgical interventions in antecedents.

The carefully conducted *clinical examination* should include, from the point of view of the otorhinolaryngologist:

- anterior and posterior rhinoscopy with identification of certain rhinosinusal disorders that determine the appearance of posterior rhinorrhea;
- bucopharyngoscopy;
- indirect laryngoscopy.

Thorax examination must identify the existence of a lung disease to be associated with the cough syndrome. The doctor should monitor the existence or absence of intercostal circulation, stridor, crackles.

The paraclinical examination must complete the clinical examination:

- nasal endoscopic exam – may reveal the existence of a rhinosinusal disease associated with the posterior rhinorrhea syndrome; it also allows the assessment of the nasopharynx;
- laryngofibroscopic examination – allows viewing the hypopharynx (diagnosing a hypertrophy of the tongue base, the existence of a contract between the tongue base and the epiglottis, the larynx, the upper esophageal sphincter with identification of an arytenoid edema or an interarytenoid sign of the existence of an extraesophageal reflux;
- bacteriological examination of the nasal secretion;
- bacteriological and mycological pharyngeal exudate;
- lingual scraping;
- bacteriological and mycological examination of sputum;
- heart-lung imaging - radioscopy should be part of the standard investigation protocol of all patients with a chronic cough syndrome;
- cranio-facial CT or MRI exam for identifying the rhinosinusal damage;
- radiography of the anterior facial sinuses or the posterior sinuses.

The gastroenterological evaluation must be part of the investigation protocol of a patient with chronic cough syndrome. This should compulsorily include a pharyngo-eso-gastric barium examination for objectifying the gastroesophageal reflux disease, an upper gastrointestinal endoscopy in order to detect lesions in the esophageal or gastric mucosa, or a hiatal hernia. In patients with chronic cough being assessed for GERD, the esophageal manometry and a 24-hour pH monitoring may be the most sensitive and specific tests.

Nevertheless, in patients in whom there is direct causality between chronic cough and GERD, with changes in the results of the esophageal pH test, we cannot say that there is a direct relationship between the tusigen syndrome severity and the reflux frequency and duration[41,42].

Allergy evaluation is important for identifying the allergic component of the cough syndrome.

From the battery of investigations of the patient with a chronic cough syndrome, the pulmonary evaluation should not be missing. It is well known that the main cause incriminated in the occurrence of such a syndrome is the lung pathology. Therefore, functional respiratory tests, the pulmonary radioscopy, the lung CT exam or the bronchoscopy with bronchopulmonary lavage must be part of the examination of these patients.

TREATMENT OF THE CHRONIC COUGH SYNDROME

The main objective in the therapy of chronic cough syndrome is treating the cause that has led to its occurrence. There are numerous studies in the literature showing that the treatment of the etiology of chronic cough has a positive result in most cases[3,43,44] (Table 2).

However, there are cases when, although the etiology is known and treated properly, symptomatology

Table 2
Treatment of the cough etiology

Asthma	Bronchodilators and inhaled corticosteroids
Eosinophilic bronchitis	Inhaled corticosteriods Leukotriene inhibitors
Bronchiectasis	Postural drainage Treatment of disease exacerbations
Chronic obstructive pulmonary disease	Smoking cessation Treatment for the pulmonary disease
Allergic rhinitis Postnasal drip	Topical nasal steroids, antihistamines Topical nasal anticholinergics
Gastroesophageal reflux	Proton pomp inhibitors, histamine H2-antagonist Conservative measurements
Angiotensin-converting enzyme inhibitor	Use an alternative drug, like angiotensin II receptor antagonist

does not disappear. In this situation, the symptomatic treatment of the cough syndrome should be sought by using *antitussive medication*[45]. These compounds may have a peripheral action, by acting on the receptors located at the level of the airways, or a central one, by inhibiting the cough center in the central nervous system[44,46]. Antitussives may be classified in opioid and non-opioid.

Opioids (e.g. morphine, codeine, methadone, etc.) are the most effective antitussive agents, their action being exerted on the central nervous system. Codeine is perhaps the most common antitussive prescribed in medical practice, its effectiveness having been proven in the chronic cough syndrome[47-49]. Compounds such as morphine or methadone are only recommended in cases of terminal illness or in those cases when the previous treatment did not result in the reduction or disappearance of symptoms, due to their particularly important side effects (sedation, respiratory distress, constipation, addiction).

Non-opioid antitussives (e.g. oxeladin, butamirate, clofedanol, glaucine, etc.) are effective in the suppression of chronic cough, without exercising a sedative and analgesic effect[48,50,51]. Their action is aimed at cough receptors located at the level of the airways[52-54].

Expectorant and mucolytic agents may be used on the premise of the existence of secretions and their irritative role on the cough reflex receptors.

CONCLUSIONS

The chronic cough syndrome is one of the most frequent symptoms for which patients present at the specialist. They affect patient's life quality and can interfere with their social and professional life.

Cough represents the main symptom of a pulmonary disease, but may be the first warning sign of an extrapulmonary disease. For this reason, multidisciplinary assessment of a patient with chronic cough is compulsory.

The treatment of the chronic cough syndrome must address mainly the underlying disease but, in case of failure of the established treatment, the antitussive therapy is used.

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