Mini-review

Chronic and unexplained cough

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Summary

Cough is a frequent symptom reported in general practice consults. Even though most of the cases concern acute and self limiting episodes, if cough persists a comprehensive diagnostic evaluation should be started. Patients that scarcely respond to empiric therapy or whose symptoms are not clearly referable to one of the most common causes of cough may receive the diagnosis of unexplained cough. These patients frequently develop depression or social retirement. Recent studies have suggested that hypersensitivity of the cough reflex could be the pathogenic mechanism underlying unexplained cough. However hypersensitivity syndrome should not be used as an easy way out for patients with a complicated history of cough. Through our paper we will briefly review the most common causes of cough and how they could be involved in the development of hypersensitivity cough syndrome.

KEY WORDS: chronic cough; hypersensitivity syndrome; idiopathic cough; unexplained cough.

Introduction

On one hand cough represents a primary defensive mechanism of the airways. It prevents inhalation and aspiration of harmful gasses and particles from the environment and helps the mucous clearance from the lower respiratory tract. On the other hand cough is one of the most frequent reasons for medical consult (1). The classification of cough as symptom is based firstly on its duration. Acute uncomplicated cough is usually self limiting in less than three weeks and in most of the cases it is imputable to upper airways viral infections (2). Although the management of acute cough can require more than one visit, the impact on patient’s quality of life is limited if compared to chronic cough. When cough lasts for more than 8 weeks it is considered chronic cough. The chronic cough represents a larger and more important problem in terms of medical and economical burden because it frequently leads patients to seek medical attentions due to the concern raised by the persistence of the symptom (3). In early 1980s the first cough diagnostic protocols appeared (4). The implementation of a diagnostic protocol showed significant improvements in diagnosis and treatment of cough, but some cases still miss a recognized cause (5). In this way patients with persistent and refractory cough frequently receive a diagnosis of idiopathic cough (6). It’s known that the unresponsive patients may exceed 20% of cases (7) (Table 1). Several authors consider inappropriate to use the term “idiopathic” as long as a deep diagnostic assessment has not been completed (14). The persistence of cough can worsen both clinical and psychological condition of the patient, because a long history of unexplained chronic cough often entails poor quality of life, compromised social life and depression (15).

Assessment of the etiology of chronic cough

The evaluation of chronic cough usually starts with a general practitioner visit. If patients seek only a symptomatic treatment it is up to the physician to remark the importance of an appropriate clinical evaluation. When approaching a patient reporting chronic cough is mandatory to carefully follow a validated diagnostic protocol, as the one proposed in the American College of Chest Physicians (ACCP) guidelines for diagnosis of cough (16). In patients with history of chronic cough of unknown etiology the most common causes (Figure 1) are asthma, gastroesophageal reflux (GER) and upper airways cough syndrome (UACS). When the physical examination and the chest radiography are not significative, efforts should be aimed toward an appropriate and complete evaluation of these conditions (17).
The diagnosis of chronic cough due to asthma can be made only after the resolution with specific therapy for asthma. Although the identification of asthma can be relatively easy when the cough is associated with wheezing and dyspnea, errors can occur both in diagnosis and in the selection of the treatment. Respiratory functional tests with bronchoreversibility could disclose an undiagnosed asthma, especially in cough variant asthma (CVA) and reduce incorrect diagnosis of chronic bronchitis in asthmatic smokers. Provocative tests are recommended whether physical examination and spirometry are not determinant. Although the empiric therapy is suggested even in its absence, the execution of methacoline inhaled challenge can reduce unnecessary treatments. If in the presence of strong suspects of asthma induced cough, the empirical treatment fails, another course with higher doses should be attempted (18). Nonasthmatic eosinophilic bronchitis (NAEB) is a frequent cause of cough. The association with asthma is limited to the presence of eosinophilic pattern in bronchoalveolar lavage or sputum. Indeed normal bronchial responsiveness and absence of airflow limitation are required for the diagnosis of NAEB (19). The treatment is based on inhaled corticosteroids (ICS) and avoidance strategies for allergens and exposures. A 4 weeks course of ICS usually shows improvements in cough and sputum eosinophilia (20, 21).
Gastroesophageal reflux (GER)

GER is one of the most common causes of cough and its incidence is constantly increasing. Changes in lifestyle are the first line in suspect of gastroesophageal reflux, but they are rarely effective on cough caused by reflux disease. The 24-h pH monitoring and impedance measurement are the elective tests to assess the presence of both acid and non-acid reflux diseases (4<pH<7) (22, 23). Chronic cough can be the only sign of acid and non-acid reflux diseases; thus the empiric treatment with proton pump inhibitors (PPI) is recommended even in absence of a clear reflux disease symptomatology (24). However an empiric course of PPI of two weeks is not enough to rule out chronic cough due to GER because of the scarce response of cough (25). Several factors influence the response to PPI treatment as the presence of non-acid reflux, the persistence of neuronal inflammation and disorders of gastroesophageal motility (26). Chronic cough due to non-acid gastroesophageal reflux requires an intensive medical treatment before the symptoms start to improve and cough can last for several months after reflux is suppressed (27, 28).

Upper airways cough syndrome

Upper airways cough syndrome (UACS) is reported as the most common cause of chronic cough (29). In chronic conditions it could be hard to recognize the etiology of the postnasal drip, but chronic sinusitis, recurrent upper airways infections and allergic rhinitis are responsible of most of the cases of UACS. Together with reflux disease, UACS takes advantage of empiric therapy and first generation antihistamines are the recommended agents. Newer compounds have less sedative effects, but their efficacy in UACS is lower. Allergologic tests should be performed to identify cases which could benefit from appropriate antihistaminic treatment or even immunotherapy (30). In silent rhinitis, cough can be present alone in absence of other symptoms (headache, discoloured nasal discharge, pain, throat clearing) but endoscopy would reveal the presence of a chronic condition. A morphologic study of nasal cavity structures with computed tomography scan is important to evaluate complicated rhinosinusitis (31).

Angiotensin converting enzyme (ACE) inhibitors

ACE-inhibitor drugs are a frequent cause of dry persistent cough. Although ACE-inhibitors are considerably easy to be identified and removed, their involvement in pathogenesis of cough can be unclear. Recent studies on transient receptor potential (TRP), a subgroup of receptors expressed by neurons of cough reflex, showed that they might be involved in ACE-inhibitors induced cough (32). The mechanism seems to be intrinsic to the ACE-inhibitor effects. The inhibition of angiotensin converting enzyme increases levels of bradykinin and PGE2, which stimulate TRP receptors and the afferent pathway of cough (33). The cough caused by ACE-inhibitors can occur months after the treatment has started and stopping the drug for less than 1 month is not considered enough to appreciate improvements in symptoms (34). Therefore angiotensin converting enzyme inhibitors should be discontinued (if a valuable therapeutic option is available) in patients with chronic cough.

Additional problems

The patient’s compliance to proposed empiric treatments and to behavioural recommendations is often an unpredictable variable (35-37). Sequential and addictive therapies are often required and long treatment courses can break down the patient compliance, especially when the resolution of cough is not prompt. Patients simultaneously presenting two or more of the above mentioned conditions can be a challenge for physicians. An appropriate diagnostic approach often resolves the problematic, but delay of resolution of chronic cough can favour the overlap of GER, asthma and UACS. In these patients the identification of the underlying causes becomes harder and they often refer to a specialist. Two or more causes are present in more than 20% of consultations (4). There are several mechanisms of interaction between the three most common causes of chronic cough. Chronic rhinosinusitis can predispose to develop asthma (38) and silent gastroesophageal reflux and microaspiration can exacerbate or worsen bronchial hyperreactivity (39). Asthma favours the development of GER through mechanical and neurologic effects (40, 41). The overlap of these conditions requires an accurate evaluation for each episode which frequently leads to correct diagnosis and treatments (4, 6, 10). However, even after a comprehensive and specialistic evaluation, some patients still present cough. Among these patients can be found several rare causes of cough. Birring et al. reported tonsilar enlargement as cause of chronic cough and they observed a reduction in cough sensitivity reflex after tonsillectomy (11). Heightened cough reflex can also be observed in patient with autoimmune hypothyroidism, although the pathogenic stimulus is still a matter of debate (42) and in obstructive sleep apnoea syndrome (43). All of the conditions reported above share as common feature the neuronal inflammation, induced by different stimuli.

Cough hypersensitivity syndrome

Patients with chronic cough presenting vague features of GERD, asthma and UACS frequently receive a diagnosis of idiopathic cough. But if all these conditions share a common pathogenic mechanism, could we re-
Studies on gender prevalence and environmental exposures have highlighted the importance of cough hypersensitivity syndrome as cause of chronic cough.

The exposition both to irritants and common intense physical stimuli in those patients (58). Studies on gender prevalence and environmental exposures have highlighted the importance of cough hypersensitivity syndrome (CHS) as cause of chronic cough. Women with chronic cough show a heightened reflex compared to men, probably due to overexpression of TRPs (59).

The existence both to irritants and common intense odors seem to increase the cough reflex through the afferent pathway activated by TRPs (60, 61). As discussed above, cough hypersensitivity is associated to the most common causes of chronic cough and it helps to understand the pathogenesis of the symptom. But can we still refer to cough as a symptom in patients with isolated cough hypersensitivity? Considering hypersensitivity cough syndrome as a disease with its own phenotypes may help in management and treatment. Patients with hypersensitivity cough may present different degrees of symptoms of UACS, GER and asthma, which may represent different phenotypes (62, 63) with their own therapy. However, even after an appropriate treatment the hypersensitivity cough may last longer than the resolution of the other symptoms. Thus the hypersensitivity cough syndrome may be considered as a neuropathic disease sustained by a secondary dysregulation of the cough reflex (46). Moreover, diagnosis of hypersensitivity syndrome prevents physicians to label patients as idiopathic coughers, which is a negative prognostic factor, because a history of persistent cough is often associated with both psychological and functional deterioration (64). Finally a specific disease may deserve a specific treatment. Recent discoveries on TRP suggest a more prominent role of the neurological regulation of cough reflex in development of chronic cough and new treatments are starting to show beneficial effects (65, 66).

Nowadays an updated approach to chronic cough should consider the role of hypersensitivity as a potential cause of persisting cough, despite the primary trigger may be extinguished. Changing the paradigm from symptom to disease could be a crucial milestone in the management of cough.

References

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