General review • DOI: 10.2478/pneum-2022-0027 • 70 • 2021 • 111-116

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Pneumologia

Diagnosis and management of cough-variant asthma

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Abstract

English:

Cough is a natural defence mechanism of the lungs to prevent aspiration and to keep the airway clean. Cough, wheezing and shortness of breath are common symptoms of asthma. Cough-variant asthma is one of the phenotypes of asthma with the main symptom of cough without shortness of breath and wheezing. Cough-variant asthma is largely observed in patients with bronchial hyperresponsiveness who experience cough due to innocuous stimuli, and it is associated with a family history and seasonal allergy. In the present study, in patients with cough-variant asthma, no abnormalities were found during the lung function test, particularly forced expiratory flow in the first second (FEV1) or peak expiratory flow (PEF), although these values were lower than those in normal individuals. A bronchial provocation test using methacholine is needed to assess airway hyperresponsiveness, and depending on the outcome of the test, an assessment can be made as to the probability of the patient requiring a diagnosis of cough-variant asthma. Administration of inhalation therapy with bronchodilators and corticosteroids is the mainstay of management in patients with cough-variant asthma presenting with the symptom of persistent cough. Until now, there have been no specific guidelines for drug selection, dose and duration of inhaled corticosteroid use in cough-variant asthma. If symptoms do not resolve with inhaled corticosteroid monotherapy, consideration may be given to increase the inhalation dose or to add other drugs such as long-acting B2 agonists, slow-release theophylline or leukotriene receptor antagonist (LTRA).

Keywords

asthma • cough • phenotype • cough-variant • hyperresponsive

Diagnosticul și managementul astmului tusiv

Rezumat

Romanian:

Tusea este mecanismul natural al plămânilor care previne aspirația și menține căile respiratorii curate. Tusea, wheezing-ul și dispneea sunt simptome comune ale astmului bronșic. Astmul tusiv este unul dintre fenotipurile de astm bronșic care are ca simptom principal tusea, fără dispnee sau wheezing. Astmul tusiv se întâlnește la pacienți cu hiperreactivitate bronșică ce reacționează cu tuse la stimuli obișnuiți, asociind istoric familial de astm și alergie sezonieră. În această formă de astm nu sunt decelate anomalii spirometrice, în particular ale volumului expirator maxim pe secundă (FEV1) sau ale debitului expirator de vârf (PEF), cu toate că aceste valori sunt mai reduse în comparație cu ale indivizilor normali. Testul de provocare bronșică cu metacolină este necesar pentru evidențierea hiperreactivității bronșice, sugestivă pentru astmul tusiv. Tratamentul pacientilor cu astm tusiv și tuse persistentă constă în administrarea de bronhodilatatoare și corticosteroizi pe cale inhalatorie. Pentru acest fenotip de astm nu există ghiduri speciale care să recomande anumite preparate medicamentoase, doza și durata tratamentului inhalator. Dacă simptomele nu se remit ca urmare a monoterapiei cu corticoid inhalator, poate fi avută în vedere fie creșterea dozei fie adăugarea altei clase terapeutice, ca beta2-agoniști cu acțiune de lungă durată, teofilină retard sau antagonist de receptor de leucotriene (LTRA).

Cuvinte-cheie

astm • tuse • fenotip • varianta tusivă • hiperreactivitate

Introduction

Cough is a natural defence mechanism of the lungs to keep the airway clean and open. Cough is a vital protective reflex to prevent aspiration and improve airway clearance. Cough, wheezing and shortness of breath are the common symptoms of asthma. However, cough might be the only symptom that can be detected with the aid of normal pulmonary function

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tests. Early studies that examined this type of asthma showed that some patients presented with a cough without wheezing or shortness of breath. There was no reversibility on pulmonary function tests, but bronchial hyperreactivity and a good response to certain asthma therapies were found. Patients with various conditions as aforementioned were classified into specific asthma phenotypes, such as cough-variant asthma (1).

The cough reflex is a complex process consisting of peripheral receptors, afferent nerves, cough control centres in the medulla and efferent nerves. Cough receptors are found in the upper respiratory tract, sinuses, hypopharynx, ear, glottis, trachea, bronchi, pleura, oesophagus, stomach and pericardium. Until now, the exact cause of cough-variant asthma is unknown, although there are few differences between cough-variant asthma and classic asthma. Several theories of cough-variant asthma have been proposed, including regional bronchoconstriction, inflammation, upregulation of cough receptor sensitivity and increased vagal activity (1).

All classic asthma therapies can be applied to cough-variant asthma. Bronchodilators such as B2 agonists or theophylline can be used, particularly in patients with an intermittent cough. Keeping in view the fact that the remodelling and inflammation of the airways that are observed in patients with cough-variant asthma closely resemble those in classic asthma patients, the use of inhaled corticosteroids is suggested for cough-variant asthma patients with persistent cough (2). Approximately 30%–40% of patients with cough-variant asthma can develop classic asthma accompanied by wheezing. Early use of inhaled corticosteroids and bronchodilators can prevent the progression of cough-variant asthma to classic asthma, although this is also influenced by other factors such as the degree of inflammation and the degree of airway hyperresponsiveness (3). Here, we summarise the literature on how to establish the diagnosis of cough-variant asthma and its management.

Cough

Cough is one of the innate primitive reflexes that are part of the immune system to protect the body from foreign objects. Cough is characterised by closure of the glottic apparatus and an increase in intrathoracic pressure to more than 300 mmHg, followed by jerking of the airway contents through the glottis into the pharynx and out of the body. The strength of this process results in the release of mucus attached to the airway wall, resulting in expectoration of the sputum. Most coughs are uncontrollable, and until now, no tool has been available that can measure cough intensity (4).

Coughs caused by upper respiratory tract infections generally last about 1–3 weeks and are self-limited. There are some conditions that can cause coughs to become persistent, lasting for several weeks, and this is a sign of a more serious illness. In adults, chronic cough is defined as a cough that lasts more than 8 weeks, while an acute cough lasts for less than 3 weeks and a subacute cough lasts for 3–8 weeks. However, persistent cough can lead to several undesired events, such as vomiting, muscle pain, fracture of the sternum, fatigue, urinary incontinence and depression (5).

There are four phases of cough, namely, the receptorial phase, the inspiratory phase, the compressive phase and the expiratory phase. The receptorial phase is the phase where the cough receptors are stimulated and activated so that they can send impulses to the cough centre via the vagus nerve. The inspiratory phase begins with the wide opening of the glottis due to contraction of the arytenoid cartilages, followed by rapid inhalation. The compressive phase consists of rapid closure of the glottis, followed by contraction of the adductor muscles of the arytenoid cartilages, causing the vocal cords to retract. At the same time, there is a strong contraction of the abdominal muscles and other respiratory muscles, causing an increase in intrapulmonary pressure and compression of the alveoli and bronchioles. The expiratory phase is the final phase marked by the sudden opening of the epiglottis and vocal cords, causing a rush of air from the lungs to the outside of the body (6).

Asthma

Asthma is one of the most common non-communicable diseases that can occur in children and adults. In 2019, there were about 300 million asthmatic patients worldwide, and this number is projected to increase by 100 million by 2025 (7). Asthma is a respiratory disease that generally affects 1%–18% of the population (8). Asthma can occur in various age groups with prevalence variations from one place to another. A large number of deaths due to asthma occur in many developing countries, although asthma management has made rapid progress over the past few decades (7).

Asthma is a heterogeneous disease characterised by various symptoms, such as wheezing, chest tightness, shortness of breath and/or cough and variable expiratory airflow limitation. Asthma is often associated with hyperresponsiveness and airway inflammation, and for this reason the diagnosis requires several elements of objective evidence. Characteristics of symptoms and airflow limitation in asthma vary in terms of time and intensity and are triggered by various factors, such as weather, physical activity, exposure to allergens or irritants, viral infections and emotions. Asthma can improve spontaneously or with treatment depending on the severity. Nevertheless, between stable periods, there may be mild to life-threatening exacerbations (8,9).

The phenotype is a characteristic that can be observed in organisms as a result of the interaction between the genotype and the environment (10). The concept of phenotype was put forward as an introduction to the endotype, which is a specific biological pathway that forms the basis of observable traits in the phenotype. In the concept of immunity, one of the phenotypes of asthma involves T-helper 2 (Th2) as it is closely related to atopy and allergies, type 1 hypersensitivity reactions, eosinophilic inflammation and responses to corticosteroids. The Th2 pathway begins with antigen recognition by antigen-presenting cells (APC) to Th2, leading to the release of several cytokines, such as Interleukin (IL)-4, IL-5 and IL-13. These cytokines stimulate eosinophilic inflammation and changes in the epithelium and smooth muscle cells, which play a role in the pathobiology of asthma (10).

Asthma diagnosis is made by identifying symptom characteristics, asthma history and risk factors. Asthma symptoms include wheezing, shortness of breath, chest tightness and cough, worsening at night, varying with time and intensity and triggered by certain exposures. Genetic predispositions that influence the development of asthma include genetic asthma, atopy, bronchial hyperresponsiveness, gender and race. Environmental exposures only increase the risk of asthma in individuals with asthma genetics. Both environment and genetics increase the risk of developing asthma (9).

Expiratory wheezing is a common physical examination finding in asthmatic patients, which is usually not found in life-threatening exacerbations (silent chest). Expiratory airflow resistance in asthma can be measured objectively through several parameters in spirometry examination, such as forced expiratory flow in the first second (FEV1) and forced vital capacity (FVC). A decrease in the FEV1/FVC ratio indicates lower airway obstruction, whereas an FEV1 variation with or without a bronchodilator indicates a variation in airflow resistance, which is a component of the variability commonly found in asthma. In asthma, there is reversibility as seen from the improvement of FEV1 after giving a rapid-acting bronchodilator or a few weeks after giving controller therapy (9).

Cough-variant asthma

Cough-variant asthma is one of the phenotypes of asthma with the main symptom of cough without shortness of breath and wheezing (11). Asthma and cough-variant asthma are the most common causes of chronic cough. The incidence is around 14%–41.3%, and it covers up to a quarter of the adult population who do not smoke (12). In China, cough-variant asthma is the most common cause of chronic cough in pulmonologist practice (13). A chronic cough is often associated with other symptoms such as wheezing or shortness of breath, although this symptom can stand alone. Establishing a diagnosis of cough-variant asthma often requires evidence of airway hyperresponsiveness using spirometry and bronchodilator testing to determine the degree of reversibility. Another method is the bronchial provocation test using methacholine inhalation if no abnormalities are found on physical examination and spirometry (12).

According to the Global Initiative for Asthma (GINA) 2021, several diagnoses that can be considered in patients with non-productive cough as the only complaint are cough-variant asthma, eosinophilic bronchitis, upper airway cough syndrome (UACS) or postnasal drip, angiotensin-converting enzyme (ACE) inhibitor-induced cough, gastroesophageal reflux (GERD) and sinobronchial syndrome (classic chronic rhinosinusitis and neutrophilic lower airway inflammation). Patients with cough-variant asthma have a chief complaint of persistent cough associated with airway hyperresponsiveness. These symptoms can be severe, particularly at night (8).

Cough-variant asthma is different from eosinophilic bronchitis, which shows symptoms of chronic cough with the findings of eosinophils in sputum but not accompanied by airway hyperresponsiveness (8). There are many cough receptors in the proximal airway, and their number decreases distally. In cough-variant asthma, inflammation is more pronounced in areas that are often stimulated, such as the proximal airway, while inflammation in the distal airway causes narrowing of the airway lumen, causing wheezing, shortness of breath and other symptoms usually found in classic asthma (4).

In cough-variant asthma, there is an increase in eosinophils found in sputum, bronchoalveolar lavage (BAL) and bronchial mucosal tissue. The severity of eosinophilic inflammation and the degree of basement membrane thickening are similar between classic asthma and cough-variant asthma. In cough-variant asthma, the structural changes are thickening of the subepithelial layer, goblet cell hyperplasia and vascular proliferation caused by airway inflammation. Various pathological changes in cough-variant asthma can also be found in classic asthma; thus, early anti-inflammatory therapy is recommended to prevent the development of wheezing by inhibiting airway responsiveness and airway inflammation (11,13).

Several consequences of mechanical stimulation due to chronic cough may occur, including an increase in various inflammatory mediators (histamine, prostaglandins D2 and E3, and leukotrienes C4, D4 and E4), an increase in the expression of the capsaicin transient receptor potential cation channel subfamily V member 1 (TRPV-1) receptor and a decrease in the pH of the fluid lining the airways (2). A prospective study comparing clinical and inflammatory characteristics of patients with cough-variant asthma and classic asthma found that cough-variant asthma has a significantly lower level of fractional exhaled nitric oxide (FeNO), blood eosinophil count

and sputum eosinophil count. Total serum IgE was lower in cough-variant asthma, even though the proportion of atopy was similar (14).

A study revealed that cough-variant asthma was present in patients with bronchial hyperresponsiveness who experienced cough due to innocuous stimuli such as talking, laughing or respiring cold air and was associated with a family history and seasonal allergy (4). In cough-variant asthma, there is no abnormality in the lung function; therefore, it is important to obtain data regarding variability in lung function in patients whose diagnosis is suspected to be either classic asthma or cough-variant asthma, thus enabling a definitive diagnosis to be made on this basis. Cough-variant asthma must be distinguished from non-asthmatic eosinophilic bronchitis (NAEB), although dry cough, eosinophilic inflammation and chronic airflow obstruction can also present in both diseases. In NAEB, patients have chronic cough without objective evidence of variable airflow obstruction, normal bronchial provocation test and sputum eosinophilia (5). Airway hypersensitivity is a distinctive characteristic that differentiates cough-variant asthma from non-eosinophilic bronchitis (15).

Research conducted by Matsumoto et al. found that 13 out of 42 patients with CVA developed wheezing during the 4 years, thus intervention with inhaled steroids could prevent disease progression (3).

Diagnosis of cough-variant asthma

In cough-variant asthma, no abnormalities were found during the lung function test, particularly FEV1 or peak expiratory flow (PEF), although these values were considered lower than those in normal individuals. Diurnal variation of PEF may occur according to the degree of cough. The reversibility of FEV1 by bronchodilators in patients with cough-variant asthma is less than that of classic asthma because some individuals with cough-variant asthma have a nearly normal baseline of FEV1. Cough-variant asthma presents with the only chronic cough that responds to bronchodilators and inhaled corticosteroids, albeit the addition of leukotriene receptor antagonists to inhaled corticosteroids may further improve the cough symptom (2,16).

Establishing the diagnosis of asthma can be hampered if the only symptom is cough without significant findings on other examinations. In such cases, a bronchial provocation test using methacholine can be incorporated to assess airway hyperresponsiveness, and based on the results of the test, the probability of the patient having asthma can be estimated with increased accuracy, thus contributing towards an accurate diagnosis (12). Airway hyperresponsiveness is defined as increased sensitivity and response to non-allergic stimulation that causes airway narrowing. In addition to asthma, airway hyperresponsiveness can also be found in other diseases associated with inflammation or airway obstruction. The degree of airway hyperresponsiveness may increase during periods of exacerbation or decrease during treatment with anti-inflammatory therapy (17).

The methacholine test is a direct bronchial provocation test recommended by the American Thoracic Society (ATS). Methacholine is a non-specific cholinergic stimulant that can induce bronchoconstriction without causing exacerbations. Methacholine is similar to the neurotransmitter acetylcholine in that it can interact directly with muscarinic receptors on airway smooth muscles, causing airway contraction and narrowing. This may occur at low inhalation doses in individuals with airway hyperresponsiveness. A decrease in lumen diameter results in an increase in airway resistance, which affects expiratory airflow (17). Methacholine can be used up to concentrations >200 mg/mL without any side effects, while histamine with concentrations >32 mg/mL can cause various side effects. The methacholine test is a direct bronchial provocation test that is widely used to date compared to the histamine test (18).

A study has found that during the bronchial provocation test, patients with cough-variant asthma showed symptoms of cough more often than wheezing (11). The bronchial provocation test has a high negative predictive value; thus, if there is no bronchial hyperresponsiveness in this test, the diagnosis of asthma can be ruled out. However, the bronchial provocation test has limited specificity, and thus it is necessary to evaluate a diagnosis other than asthma in patients who show positive results (18). A definitive diagnosis of cough-variant asthma can be made if the cough resolves with specific asthma medication (12).

The steps involved in carrying out a bronchial provocation test are inhalation of a bronchoconstrictor followed by an assessment of the decrease of FEV1. If the decrease reaches 10%–20% of the baseline value, the test will be stopped to measure the provocation concentration (PC20) or the provocation dose (PD20). The term concentration is more appropriate than dose because it is difficult to measure the amount of aerosol that passes through the vocal cords or that is deposited in the airway, and there is a possibility of evaporation of the aerosol mass fraction due to the nebulisation process. PC20 is the concentration that causes a 20% decrease in the FEV1 (18).

Several diagnostic criteria have been framed by the Japanese Cough Research Society to aid the diagnosis of cough-variant asthma, and these include chronic non-productive cough lasting >8 weeks; no history of shortness of breath or wheezing; no additional breath sounds on physical examination; no history of wheezing; postnasal drip that causes cough, lung function within normal limits measured by FEV1, FVC and

FEV1/FVC ratio; bronchial hyperresponsiveness (PC20 <10 mg/mL); cough reflex sensitivity within normal limits (C5 >3.9 mmol/L); no radiological features supporting the aetiology of cough; and cough subsides after bronchodilator therapy (19).

Management of cough-variant asthma

Treatment of cough-variant asthma is no different from that of classic asthma. Administration of inhalation therapy with bronchodilators and corticosteroids is the mainstay of management in patients with cough-variant asthma presenting with the symptom of persistent cough. Until now, there have been no specific guidelines for drug selection, dose and duration of inhaled corticosteroid use in cough-variant asthma. If symptoms do not resolve with inhaled corticosteroid monotherapy, consideration may be given to increase the inhalation dose or to add other drugs such as long-acting B2 agonists, slow-release theophylline or leukotriene receptor antagonist (LTRA) (2).

Leukotriene receptor antagonists can improve symptoms as assessed by a cough score in cough-variant asthma that does not improve with inhaled corticosteroid therapy. Leukotriene receptor antagonists can modulate the inflammatory environment of cough sensory receptors in the airway epithelium by a mechanism that remains unclear. However, the aerosols formed on inhalation therapy can also induce or exacerbate cough symptoms. Partial response to inhalation therapy can be overcome by changing the form of treatment to oral therapy or a combination of oral and inhaled, if needed. The addition of short-term corticosteroids may also be considered in some cases of exacerbations (16).

In cough-variant asthma, there are mast cell infiltration in smooth muscles, thickening of the epithelial lining and airway remodelling associated with impaired airway function. Persistent cough symptoms after the administration of inhalation therapy can be caused by severe inflammation. In this case, it is necessary to assess the degree of airway inflammation through the examination of sputum or BAL fluid to identify patients who would benefit from more aggressive anti-inflammatory therapy (10). Eosinophilic cough-variant asthma with a finding of eosinophils in sputum or BAL has a better response to corticosteroids than the non-eosinophilic type (13).

Liu et al. (20) conducted a study on the effect of long-term inhaled corticosteroids on improving levels of inflammatory mediators and airway hyperresponsiveness in patients with cough-variant asthma. They found that there was a decrease in IL-5 levels and an increase in IL-10 levels in the cough-variant asthma group after several months of therapy. Sputum eosinophil levels in patients with cough-variant asthma were significantly reduced after the use of inhaled corticosteroids for 6 months. The degree of hyperresponsiveness and lung function as measured by PD20 and FEV1 were significantly increased in patients with cough-variant asthma after using inhaled corticosteroids for 3 months, while in the asthmatic group, the increase occurred after 9 months of treatment.

Some patients with cough-variant asthma may progress to classic asthma with additional symptom of wheezing. Patients with cough-variant asthma who do not use inhaled corticosteroids have a progression rate to classic asthma of 30%–40% (3). Several factors that influence the progression of cough-variant asthma to classic asthma include airway hyperresponsiveness, excessive airway response to methacholine, sputum eosinophilia and sensitisation to allergens (21). The early use of inhaled corticosteroid therapy can reduce the risk of progression to classic asthma (3). In another study, it was found that as much as 50% of patients with cough-variant asthma experienced resolution of symptoms after 1 month of therapy using bronchodilators (3). However, cough-variant asthma may reappear if the treatment is discontinued (2).

Summary

1. Asthma is a heterogeneous disease characterised by various symptoms such as wheezing, chest tightness, shortness of breath, cough and variable expiratory airflow limitation.
2. Cough-variant asthma is one of the asthma phenotypes with the main symptom of cough without shortness of breath and wheezing.
3. In cough-variant asthma, there are no abnormalities found during the lung function test. However, there is airway hyperresponsiveness, which can be proven by using the bronchial provocation test.
4. Treatment of cough-variant asthma is not different from that of classic asthma, including inhaled corticosteroids and bronchodilators.

Authors' contributions

We confirmed that the manuscript has been read and approved by all authors.

Conflict of interest statement

The authors have no conflicts of interest associated with this publication and there has been no significant financial

support for this work that could have influenced its outcome or generate conflicts of interest.

Acknowledgements

We would like to thank dr. Hana Khairina PF for the constructive feedback and usefull discussions. We would also like to show our gratitude to Department of Pulmonology and Respiratory Medicine Universitas Indonesia for sharing their pearls of wisdom with us during the course of this paper.

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