Chapter 12

Cough Variant Asthma as a Phenotype of Classic Asthma

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Abstract

Cough variant asthma (CVA) was first described by Glauser. CVA was described as the isolated chronic cough as the only presenting symptom responsive to bronchodilator therapy. The authors now suggest that CVA is present with airway hyperresponsiveness, eosinophilic inflammation of central and peripheral airways and bronchodilator responsive coughing without typical manifestation of asthma such as wheezing or dyspnea. Pathologically, CVA shares common features such as eosinophilic inflammation and remodeling changes with classic asthma. Because of that, CVA is clinically considered as a variant type of asthma, a phase at the beginning of asthma pathogenesis or as a precursor of classic asthma. Nearly 30% of patients with CVA eventually develop intermittent wheezing, an average of 3–5 years. It is clinically very important to recognize CVA because long-term inhaled corticosteroids can significantly decrease the development of classic asthma in these patients.

Keywords: asthma, cough variant asthma, airway hyperresponsiveness, chronic cough, airway remodeling, airway inflammation

1. Introduction

Asthma could be defined more as a syndrome characterized by several different phenotypes [1–3]. Therefore, one of the possible definitions describing the characteristics of the disease and unifying more different definitions could define asthma as chronic inflammatory disease characterized by acute variable onset of symptoms (coughing, air deficiency, chest tightening) with bronchoconstriction (clinical definition) reversible and passes spontaneously or under

the impact of therapy (pharmacological definition), followed by bronchial hyperactivity on different stimulants (functional definition) and the inflammation of different stage, duration and difficulty (biological definition) [1]. Cough variant asthma (CVA) is defined as a phenotype of asthma, which characterized by cough as the sole symptom and airway hyperreactivity (AHR) [4]. Corrao and colleagues first defined "cough variant asthma" as AHR, chronic cough and absence of wheezing [5].

The authors agree that CVA and classic asthma have the same pathophysiological and immunological mechanisms, so CVA is considered a precursor of classic asthma [6–8].

Case 1 [9]: A 5-year-old boy presented to the clinic because of prolonged dry coughing with no history of wheezing. Because boy could not do spirometry, a forced oscillation technique was made. The total respiratory resistance was decreased by −20.4% after beta-2-agonist inhalation. At the first visit, 2-week therapy of inhaled beta-2-agonist was started. This treatment was clearly effective against his cough. The CVA was diagnosed, and his treatment with leukotriene receptor antagonist (Montelukast) and LABA (tulobuterol patch) was started for next 8 weeks. Eight months later, boy has the same symptoms. The same treatment was restarting. Three years later, boy has another episode of a dry cough with no complaints of wheezing. A physician confirmed a wheeze during expiration by auscultation. The treatment with inhaled steroid (Fluticasone), LABA (Salmeterol) and leukotriene receptor antagonist (Montelukast) was started. Over time, after boy developed recurrent wheezing, the diagnosis of asthma was set.

Case 2 [10]: "A 64-year-old female presented to the clinic as a self-referral complaining of a persistent cough." She said that the symptoms last for almost 17 years. The patient had diagnosed seasonal rhinosinusitis with positive skin prick test. Previous evaluations were all unremarkable. She underwent a methacholine challenge test. Spirometry showed increase in FEV1 with a 13% change from baseline. The patient was diagnosed with CVA and therapy with a combination of medium dose inhaled steroid and long-acting beta-2-agonist (Mometasone/Formoterol) was started.

Case 3 [11]: "A 32-year-old women presented with an intermittent nonproductive hacking cough that had lasted several days." Her medical history was unremarkable, and previous evaluations were normal. Results of a methacholine challenge test showed severe airway hyperreactivity. The patient was diagnosed with CVA, and bronchodilator with ICS treatment was started.

The prevalence of CVA is unknown, and from these cases it can be noticed that patients with chronic cough, as the only symptom, remain unrecognized as asthma for a long-time period.

The isolated cough is less common than other clinical manifestations of classic asthma [11]. Diagnosis of CVA may prove to be a challenge for the physicians. Therefore, evaluation results of patients with CVA are usually normal (spirometry, skin prick test, chest radiography, blood test) [12]. Previous clinical history is also normal in these patients [2, 11, 13].

Clinical feature of CVA is a good response to bronchodilator and ICS therapy [12, 13]. Studies have shown that the ICS therapy in CVA patients prevents the development of classic asthma [3, 7, 12]. Namely, it has been noticed that an average of 30% of patients with CVA without treatment

develop classic asthma with wheezing [3]. A smaller number, about 10% of patients with CVA and with adequate therapy (bronchodilator, ICS or Montelukast) develop classic asthma. A good response of chronic cough to the therapy with ICS cannot be used to distinguish other cough present diseases (atopic cough, non-asthmatic eosinophilic bronchitis) from CVA [2, 8].

It should be emphasized that in patients with chronic cough, a diagnostic evaluation for asthma should be performed.

2. Pathological mechanism underlying CVA

The main underlying pathophysiological mechanism of CVA is airway hyperresponsiveness (AHR) [3]. Airway hyperresponsiveness in CVA patients is milder than in patients with classic asthma. AHR is defined by two basic parameters: bronchial sensitivity and bronchial reactivity.

Airway remodeling is milder in CVA than in classic asthma [14, 15]. The more important is their airway sensitivity (threshold dose of methacholine to increase respiratory resistance) and airway reactivity (slope of respiratory resistance response curves), which are tested by challenge tests [15]. The difference in the challenge test between CVA and classic asthma patients was only in airway reactivity. Since bronchial reactivity is the one that is crucial in patients with CVA, there is a normal baseline result in these patients, but only challenge tests are positive [15, 16]. Airway reactivity is lower in CVA patients mostly because bronchoconstriction is lower and limited in CVA. Niimi et al. suggested that airway remodeling does not protect against bronchial sensitivity but against bronchial reactivity [15]. Bronchial hyperreactivity plays a significant role in the pathophysiology of CVA development. Cough reflex sensitivity does not change in patients with CVA, and it is not essential in pathophysiology in CVA [7, 8].

An important role in the pathophysiology of CVA has eosinophilic inflammation [3]. The results of studies have shown that BAL and sputum in patients with CVA contain an increased percentage of eosinophils [2]. Also, the studies showed that there was no significant difference between CVA and classic asthma in the sputum levels of eosinophilic cationic protein, interleukin 8 (IL-8) and levels of exhaled nitric oxide (FeNO) [2, 7, 12, 17, 18]. Studies have suggested that the basic pathophysiological characteristics of CVA are eosinophilic inflammation and AHR [3].

Bronchoconstriction is milder in CVA than in classic asthma patients, and this can be a possible reason why these patients do not have wheezing as a symptom [16]. The main puzzle in the clinical feature of CVA is the absence of wheezing. One of the possible mechanisms may be slower and limited bronchoconstriction. The possible cause of this slower bronchoconstriction may be airway remodeling [12] and variations in cytokine production [16].

The bronchodilatory test in patients with CVA is often negative because baseline FEV1 values are normal in CVA patients [12]. Corrao and colleagues defined “cough variant asthma” as AHR, chronic cough and absence of wheezing [5]. The peak expiratory flow (PEF) assessment does not show any variability in CVA patients [2]. The spirometric measurements are normal in patients with CVA [2].

Structural changes such as subepithelial thickening, goblet cell hyperplasia and vascular proliferation in the bronchial tree were noticed in patients with CVA [12]. These changes are less expressed than in patients with classic asthma and most commonly associated with airway inflammation. An important role in the development of cough in CVA patients has inflammatory mediators such as histamine, prostaglandins D2 and E2, leukotrienes C4, D4 and E4 [12, 19]. The study by Liu et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum) [3].

Because of this, researchers agree that early anti-inflammatory treatment in patients with CVA can prevent the development of classical asthma in these patients [7, 15].

The pathophysiological aspects of CVA are similar to classical asthma [7, 16]. The study of Fujimura et al. also showed that the use of ICS prevents the development of classical asthma in patients with CVA [7].

It is necessary to emphasize that further investigations in this matter are necessary.

3. Biomarkers and diagnostic criteria

Patients with CVA frequently report that cough is provoked by trivial stimuli (cold air, talking, etc.) and do not respond to the antitussive preparations [3].

Mochizuki and associates in their study showed that children with CVA have slower bronchoconstriction against non-specific airway stimuli, but have significant bronchial sensitivity as well as children with classical asthma [16]. Children with CVA show latent bronchoconstriction without wheezing [16].

Bronchodilatatory test, spirometry and chest radiography are usually normal in patients with CVA. The bronchodilatory test in patients with CVA is often negative because baseline FEV1 values are normal in CVA patients [12]. Methacholine testing has a positive predictive value up to 90, a negative predictive value of 100 for CVA [11, 20].

The more important is their airway sensitivity (threshold dose of methacholine to increase respiratory resistance) and airway reactivity (slope of respiratory resistance response curves), which are tested by challenge tests [15]. The difference in the challenge test between CVA and classic asthma patients was only in airway reactivity. Airway reactivity is lower in CVA patients mostly because bronchoconstriction is lower and limited in CVA [12].

Positive challenge test and good response on bronchodilator or ICS therapy can be criteria for diagnosis of CVA [11]. Improvement of chronic cough with bronchodilators is the essential diagnostic feature of CVA [12, 13, 21].

The study by Liu and et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum) [3]. The improvement of these criteria was lower in the classic asthma group with the ICS therapy. The IL-5 level in the CVA group decreased after 3 months of treatment, while in the classic asthma group decreased after 6 months of treatment. The percentage of eosinophils in the sputum decreased after 6 months of ICS treatment in the CVA group and after 12 months in the classic asthma group.

Biomarkers that can be used in diagnosis of CVA do not differ from biomarkers in classic asthma. Studies have shown that there are elevated sputum markers (eosinophils, IL-5, IL-10, prostaglandins D2 and E2, leukotrienes C4, D4 and E4) in patients with CVA [12]. Patients with CVA have structural changes in the bronchial epithelium such as subepithelial thickening, goblet cell hyperplasia and vascular proliferation [12]. These changes are less expressed than in patients with classic asthma.

Fractional exhaled nitric oxide (FeNO) is a biomarker that is related to allergic cough [1]. FeNo levels were significantly higher in patients with CVA or classic asthma than in healthy controls in the study by Shimoda et al. [22]. Patients with CVA have significantly lower FeNO than patients with classic asthma. In this study, FeNO values correlated with the severity of asthma symptoms [22]. Asano et al. had the same results in their study [23].

Another significant marker that is listed in the literature as a useful marker of inflammation in classic asthma is serum high sensitivity C-reactive protein (hs-CRP). Serum hs-CRP levels were significantly higher in patients with CVA and classic asthma. However, no significant difference was detected between CVA and classic asthma patients. Studies have shown that the levels of FeNO rise in patients with CVA and classic asthma. Serum hs-CRP is considered inappropriate as a marker of airway inflammation. Namely, this marker is higher in men than in women, also its values are elevated in other various systemic inflammations, arterial hypertension, diabetes and cardiovascular disease. The values of hsCRP are also elevated in smokers [22].

The authors of CVA studies agree that the criteria proposed by the Japanese Cough Research Society are adequate for diagnosing CVA [6, 8, 13]. The above criteria are as follows [13]:

- isolated chronic non-productive cough lasting more than 8 weeks;
- absence of a history of wheeze or dyspnea, and no adventitious lung sounds on physical examination;
- absence of postnasal drip to account for the cough;
- FEV1, FVC, and FEV1/FVC ratio within normal limits;
- presence of bronchial hyperresponsiveness (PC20 < 10 mg/mL);
- cough reflex sensitivity within normal limits (C5 > 3.9 mmol/L);
- no abnormal findings indicative of cough etiology on chest radiograph and
- relief of cough with bronchodilator therapy.

If all the criteria are fulfilled, a diagnosis of CVA can be made. However, if some of the criteria are not presented, the diagnosis of CVA can be set if the following criteria are fulfilled [13]:

- cough without wheezing lasting 8 weeks or more and no wheezing on auscultation
- no upper respiratory tract infection and
- relief of cough with bronchodilator therapy.

The most important criterion is the response to bronchodilator therapy that can be excellent when cough was totally resolved, good when sleep and daytime quality of life were improved, fairly good when severity and frequency of cough were somewhat decreased and poor when cough was unchanged [6].

4. Therapy

Therapeutic approach for CVA is similar to the treatment for classic asthma [10, 12]. Therapy with short-acting bronchodilators can be useful in patients with intermittent cough. Most of researchers agree that eosinophilic inflammation and remodeling require ICS therapy especially in patients with persistent cough [12].

The choice of ICS, its dose and duration of therapy should be as in patients with classic asthma. The results of the studies show that early application of ICS therapy reduces the risk of progression of CVA to classical asthma [8, 12, 21]. Namely, an average of 30% of patients with CVA without treatment develop classic asthma with wheezing in the future [3, 7]. A smaller number, about 10% of patients with CVA and adequate therapy (bronchodilator, ICS or Montelukast) develop classic asthma [12].

The study by Liu and et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum). The IL-5 level in the CVA group decreased after 3 months of ICS treatment, while in the classic asthma group decreased after 6 months of treatment. The percentage of eosinophils in the sputum decreased after 6 months of ICS treatment in the CVA group and after 12 months in the classic asthma group [3].

A fact that significantly influences the therapeutic response in children is described by Hutton et al. The fact is that "the parents who wanted medicine at the initial visit reported more improvement at follow-up regardless of whether the child received a drug, placebo or no treatment" [24, 25].

5. Differentiation of the reactive airway diseases

Whether CVA represents a self-standing airway disease is still the object of debate. CVA is pathophysiologically similar to asthma, but with mild bronchial hyperreaction and eosinophilic inflammation [6, 7]. CVA has been considered a precursor of classic asthma [6, 7].

Reaction to bronchodilator therapy could be a pathognomic feature in the differential diagnosis of CVA [7]. Namely, in conditions such as postnasal drip induced cough, gastroesophageal reflux associated cough and atopic cough bronchodilators have no antitussive effect [7, 26].

The presence of eosinophilia in the sputum, bronchial hyperactivity and a positive bronchodilator test is a sign of a stronger immune response of the respiratory tract. In essence, the differences between CVA and classical asthma are in the immune system's response to different stimuli [27].

6. Evaluation of chronic cough in children

A cough is a natural and universal occurrence, and it is a part of the body's defense mechanism of the respiratory system. Chronic cough is defined as lasting more than 4 weeks in children and more than 8 weeks for adults [26, 28–30]. Diagnosis and management of patients with chronic cough are challenging for clinicians. Chronic cough can be a primary symptom of a variety of underlying conditions [25, 31]. The most common conditions that cause chronic

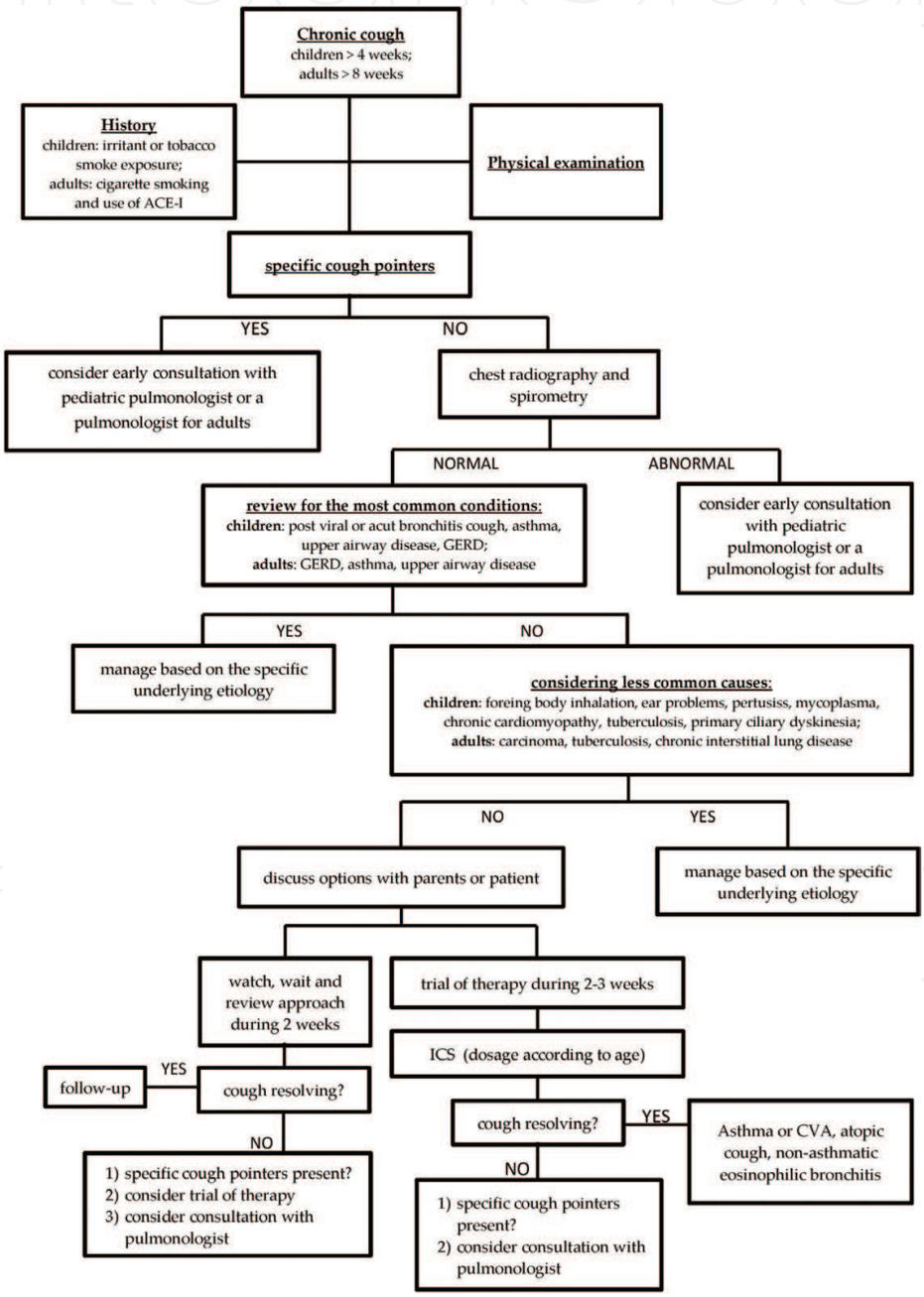

Figure 1. Algorithm for evaluation of chronic cough in children and adults for primary level doctors (general practitioner, pediatrician, family doctor, etc.).

cough in children under 14 are CVA, atopic cough, gastroesophageal reflux disease (GERD) and upper airway cough syndrome (formerly postnasal drip cough) [28–30]. CVA should be considered when chronic cough is exacerbated by cold or exercise [30]. Besides asthma and CVA in adult patients with chronic cough in the differential diagnosis, smoking and ACE-I induced a cough should always be considered [30]. Less common conditions include heart failure, interstitial lung disease, tuberculosis and primary lung cancer [26, 29, 31].

A few algorithms of the evaluation of chronic cough in adults and children are available in the literature [25, 30–32]. The use of these protocols or algorithms can improve clinical outcomes [28]. Most appropriated algorithm for adults can be found in a review article by Terasaki et al. [31]. In adults, the clinicians need to be attentive to two high-yield elements of the history patients: the use of an angiotensin-converting enzyme inhibitor (ACE-I) and cigarette smoking. Of equal importance is to inquire about exposure to second-hand smoke in children [25, 26, 31]. Most appropriated algorithm for children can be found in a review article by Chang et al. [25]. We have designed one of the algorithms that can be used as a guide for the primary level physicians (**Figure 1**).

Initial diagnostic evaluation should include the chest radiograph and pulmonary function testing in patients with chronic cough [25, 29–31]. It is not recommended to routinely performing additional tests (skin prick test, bronchoscopy, chest CT) for all children with chronic cough. Additional tests should be individualized and undertaken in accordance with the clinical symptoms and signs [29]. Chronic cough suggestive of serious underlying lung disease includes neonatal onset of cough [30].

It is recommended that in case of inadequate response to inhalation therapy, it should try with the inhalation therapy through an aerochamber which can help to maximize drug delivery to the lungs [31].

In a clinical evaluation of patients with chronic cough, it can be tried with the diagnosis *ex juvantibus*. There are no agreement about recommendations how long to use a particular therapy and wait for a therapeutic response to confirm the diagnosis *ex juvantibus* [25, 29, 31].

7. Conclusion

The CVA has the same pathophysiological features as classical asthma but in a mild form. The main pathophysiology of CVA is bronchial hyperreactivity.

Since a large percentage of patients with CVA develop classical asthma and wheezing over time, ICS treatment in these patients is very important because of the prevention of classical asthma development. One very important diagnostic criterion in CVA patients is an improvement of the symptoms after bronchodilator therapy. The positive therapeutic effect of ICS on cough in children with CVA should not be considered as a diagnostic criterion because the positive therapeutic effect also has patients with atopic cough [8].

"In children with chronic cough parental expectations should be determined, and the specific concerns of the parents should be sought and addressed" [25].

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