

It is chronic cough variant asthma a realistic diagnosis in children?

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ABSTRACT

The similarities and, especially, the differences between the chronic cough in children and adults are noticed. The chronic cough in adult usually means the "big three": asthma, upper airway cough syndrome, and gastroesophageal reflux. A different situation concerns the children chronic cough. The most part of the chronic cough in children seems to be "an expected one", due to respiratory infections, followed by nonspecific and specific causes. The cough variant asthma (CVA) is one of these causes and differences comparing CVA with classical asthma are pointed out.

Key words: Chronic cough, children, adult, cough variant asthma

INTRODUCTION

"The child is not a small size adult", said Bousquet looking comparatively at the two of them. The same phrase came into our minds when we compare the mechanism of the chronic cough in children and in adults.

In adult the chronic cough is defined by a cough which duration extends over 8 weeks.

In children for a cough to be considered a chronic cough, it must have duration of more than 4 weeks (1).

As a very special type of chronic cough, **Cough Variant Asthma (CVA)** is an entity that

was described for the first time in adult, in 1975 (2). In children we start discussing about CVA in 1981 (3). For that time, the asthma was considered underdiagnosed and undertreated, so many pediatricians considered a good choice for isolated persistent cough to be treated with a combination of inhaled β agonists and corticosteroids. The absence of a good response to combined therapy, in that light, was probably a problem of inadequate dosage rather than diagnostic failure and was followed by increasing the dosage. Retrospectively, it was notice that this attitude had no benefit and occasionally had even a detrimental outcome (4).

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The CVA is a type of cough with duration of more than 4 weeks without a clear etiology and which is associated with bronchial hyperactivity (5). Other authors consider that only if there is a good response to beta-2 simpatomimetics of a chronic cough with no etiology and bronchial hyperactivity associated, this can be called CVA (6). Usually, CVA is a dry cough if there are no respiratory infections associated (7). The association of a high serum level of IgE is an important diagnostic element (8)

The **criteria for cough variant asthma** proposed by the **Japanese Cough Research Society** are:

1. Isolated chronic non-productive cough lasting more than 8 weeks.
2. Absence of a history of wheeze or dyspnoea, and no adventitious lung sounds on physical examination.
3. Absence of postnasal drip to account for the cough.
4. FEV₁, FVC, and FEV₁/FVC ratio within normal limits.
5. Presence of bronchial hyperresponsiveness.
6. Relief of cough with bronchodilator therapy.
7. No abnormal findings indicative of cough etiology on chest radiograph. (9)

Our proposed diagnostic criteria for cough – variant asthma are: (chronic cough + minim 2 criteria)

- Allergy symptoms or increased serum levels of IgE or Prick test positive.
- Spirometry or Tidal breath analysis performed.

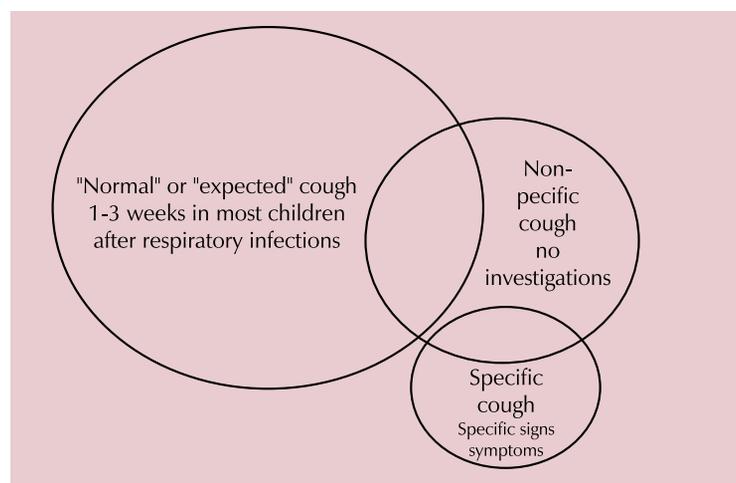


FIGURE 1. Classification of the chronic cough in children (after Chang, modified)

- Hyperresponsiveness evidence and reversibility test positive.
- Good response to inhaled corticosteroids (CSI) (optional).

Causes of chronic cough in adults

Although there are many similarities between the physiology of the respiratory system in children and adults, the question is if there are any important differences between adult and children cough. To answer to this question we have to look comparatively the most important causes of cough both in adult and in children. In adult we can talk about the "big three" when we are referring to the etiology of cough: asthma, upper airway cough syndrome, and gastroesophageal reflux (1, 10). Other authors consider non-asthmatic eosinophilic bronchitis another frequent cause of chronic cough in patients with a normal chest X-ray, non-smoking and not taking ACE inhibitors (11). These represent 72 -90% from all causes of cough in adult and are less common causes of chronic cough in children (12). Tobacco smoke exposure can affect both the adult and child (13, 14).

The CVA seems to be one of the most important causes of cough in adult but in children, there are other more important causes for chronic cough than CVA.

Causes of chronic cough in children

Etiologic classification of the chronic cough in children:

- **expected:** after respiratory tract infections, and do not last more than 1-3 weeks (1, 15).
- **specific:** when there are other symptoms and signs suggestive for a specific disease. In this case, there are necessary supplementary investigations (1).
- **nonspecific:** when there are no clues for a specific respiratory disease and the cough, usually dry cough, is the only symptom present (1).

The McKenzie concept put light into the practice of many physicians. In his paper (18), entitled "A paper that changed my practice: S McKenzie. Cough but is it asthma? Arch Dis Child 1994;70:1-2.", the author made a very good analyze of the influence of CVA in clinical practice.

"What I learned from McKenzie's review was not that cough variant asthma does not exist,

| Adult (16): (Dicpinigaitis PV, Chest, 2006) | Child (1): (Chang A, Chest, 2006) |
|--|--|
| <ul style="list-style-type: none"> - Asthma – the first etiologic option for chronic cough - The CVA suspicion - in normal spirometry it must be determined bronchial hyperactivity - Treatment: CSI si beta 2 ag - In refractory cough it is necessary to demonstrate the presence of the eosinophilic inflammatory process, which can justify a more aggressive therapy - Severe cough – orally corticosteroids | <ul style="list-style-type: none"> - The use of the isolated cough as an asthma marker is controversial. - Some studies have shown that asthma is the most frequent cause, but others did not show the same. - Cellular studies showed that asthma specific inflammation is less cited. - In children with isolated chronic cough there are no significant differences between those treated with salbutamol vs placebo (17). - Although cough is the most frequent symptom is difficult to distinguish between asthma and viral infection. |

TABLE 1. Differences in diagnose interpretation of CVA between children and adults

because the axiom remains that it is unwise to use “never” in medicine and I do have a **very small number of patients who fit this label**. Instead, it has made the **diagnosis of cough variant asthma one of exclusion**. It has led me to always seriously question the diagnosis when a patient presents with **isolated cough, especially in the absence of other evidence of IgE-mediated disease**. My threshold for investigating such patients in detail is lower and has resulted in an alternative diagnosis being reached with increased frequency.”

In children, if there are suggestive signs, like familial allergies, the suspicion of a CVA can be made. The diagnosis of CVA seems to be a diagnosis that easily can be overestimated (19). Looking at this study, on a 1178 children diagnosed first as having CVA, the conclusion was that the diagnosis of CVA was wrong at the most part of them (20).

We compare the situation of CVA in our hospital 10 years ago with the present one. In a study performed 10 years ago in our hospital, the situation of CVA in children looked overdiagnosed (21). Between 1996 and 1997 a prospective study was conducted in Lung Function Department, Institute for Mother and Child Health Bucharest. We observed 100 children (6-16years, mean age 9,8 years) which were divided in two groups: group A – 45 children with chronic cough only (defined as persistent symptom without wheezing for more than 4 weeks, associated with no identifiable cause and non responsive to conventional treatment); group B- 55 children with history of asthma, but clinically asymptomatic at examination. Spirometric lung function was performed in all children. In group A 37 patients

had normal lung function, and 8 patients presented distal obstructive syndrome (mean% value maxim expiratory flow 50% vital capacity, MEF_{50} was 50.85, maxim expiratory flow 25% vital capacity, MEF_{25} was 35.45). All patients with normal lung function received 1‰ inhaled histamine. Airways hyperresponsiveness was present in 17 children (n=17) in group A, with mean % fall forced expiratory volume in 1 second (FEV_1) = 20.16 (SD=12.767, and mean % fall MEF_{50} = 35.94 (SD=19.94), and in group B was present in 27 children (n=27) with mean % fall FEV_1 = 26,69 (SD=14.17), and mean % fall MEF_{50} = 38.88 (SD=17.706). Airway hyperresponsiveness in group A was not significantly different from group B (p>0.05). Our conclusion was that for some patients with chronic cough, asthma needs to be taken into consideration (chronic cough variant asthma).

We strongly believed that only hyperresponsiveness evidence in chronic cough it is sufficiently for chronic cough variant asthma

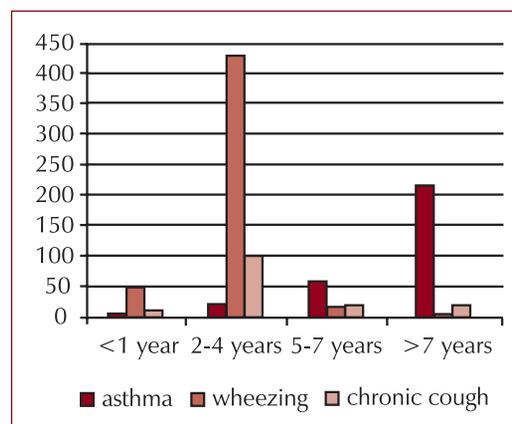


FIGURE 2. The structure of consultations/age. IOMC, Lung Function Department

diagnosis in children. After a 10 years experience, the situation seems to be much different.

In a study performed in our hospital recently (22), on a period of 2 years (2006 – 2007) we observed that chronic cough has the same frequency like in 1997. The main group aged 2-4 years presented recurrent wheezing and chronic cough (fig 2). 267 children were seen. 35.2% (94 cases) of them had the suspicion of CVA but in only 11.6% (31 cases) this was confirmed.

How it can be explained the absence of wheezing in CVA?

There are two theories, which try to explain the absence of wheezing in CVA. On one hand is the theory of a higher wheezing threshold (the minimum level of the obstruction when the sound can be heard) and on the other hand, the milder degree of airway hyperresponsiveness (23 – 25). If wheezing is present in CVA, it is associated with lower oxygen saturation (26).

In order to clarify the mechanism of the absence of the wheezing in CVA in children, a study was performed by Hiroyuki Mochizuki (27). It has as objective to evaluate the physiologic differences in the airways of children with classic asthma and CVA, analyzing the curve dose-response of the methacholine of respiratory resistance.

Regarding the bronchial sensitivity, both CVA and classical asthma has a higher degree comparing with control group. However, differences appear regarding the bronchial reactivity, which is lower in children with CVA

comparing with classical asthma and control group. This means that in CVA there is a lower degree of bronchoconstriction to stimuli, which can **explain the absence of wheezing in chronic cough** (27 – 29). The level of bronchial reactivity is a risk factor for CVA becoming classical asthma (30, 31).

Conclusion

1. The chronic cough must be evaluated and treated according to the guidelines, beginning with evaluating the etiology (character of cough, other signs and symptoms associated, etc).
2. The chronic cough is more probable to be an expected cough after respiratory infections and less probable to be asthma.
3. If the chronic cough is associated with risk factors for asthma, a short-term specific treatment (beclomethasone, 400 µg/d, or the equivalent dosage with budesonide) can be indicated, although the most part of these children do not have asthma and after a period of 2 – 4 weeks reevaluated
4. If the cough does not disappeared in a period after a therapy was initiated, the treatment must be withdrawn and the child reevaluated.
5. CVA, characterized by a lower bronchial responsivity and the absence of wheezing, is less frequent than we thought before (1998).
6. An algorithm based on an adult pathway do no help diagnose of chronic cough in children.

REFERENCES

1. **Chang AB, Glomb WB** – Guidelines for Evaluating Chronic Cough in Pediatrics ACCP Evidence-Based Clinical Practice Guidelines. *Chest*. 2006; 129:260S-283S
2. **McFadden ER Jr** – Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. *N Engl J Med*. 1975; 13-292:555-559
3. **Cloutier MM, Loughlin GM, DeCubellis SD, et al** – Chronic Cough in Children: A Manifestation of Airway Hyperreactivity. *PEDIATRICS*. 1981; 67:6-12
4. **Todd G, Dunlop K, McNaboe J, et al** – Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; 348:27-29
5. **Boulet LP, Milot J, Boutet M, et al** – Airway inflammation in nonasthmatic subjects with chronic cough. *Am. J. Respir. Crit. Care Med*. 1994; 149-2:482-489
6. **Irwin RS, French CT, Smyrniotis NA, et al** – Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. *Arch Intern Med*. 1997;22; 157(17):1981-1987
7. **BTS/SIGN**. British guideline on the management of asthma. *Thorax* 2003; 58(Suppl 1):1-94
8. **Wang MZ, He QN, Yuan HX, et al** – Roles of IL-4, IL-5 and IgE in childhood cough variant asthma. *Zhongguo Dang Dai Er Ke Za Zhi*. 2006; 8:382-384
9. **Fujimura M, Ogawa H, Nishizawa Y et al** – Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax* 2003; 58:14-18
10. **Abouzgheib W, Pratter MR, Bartter T** – Cough and asthma. *Curr Opin Pulm Med*. 2007; 13:44
11. **Irwin RS, Baumann MH, Bolser DC, et al** – Diagnosis and Management of Cough Executive Summary. ACCP Evidence-Based Clinical Practice Guidelines; *Chest*. 2006; 129:1S-23S
12. **Chang AB** – Cough: are children really different to adults? *Cough*. 2005; 1:7
13. **Carter ER, Debley JS, Redding GR** – Chronic productive cough in school children: prevalence and associations with asthma and environmental tobacco smoke exposure. *Cough*. 2006; 27:2-11
14. **Delpisheh A, Kelly Y, Rizwan S, et al** – Salivary cotinine, doctor-diagnosed asthma and respiratory symptoms in primary schoolchildren. *Matern Child Health J*. 2008; 12:188-193
15. **Braman SS** – Chronic Cough Due to Acute Bronchitis. ACCP Evidence-Based Clinical Practice Guidelines. *Chest*. 2006; 129:95S-103S
16. **Dicpinigaitis PV** – Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129(1 Suppl):75S-79S
17. **Tomerak AA, Vyas H, Lakenpaul M, et al** – Inhaled beta2-agonists for treating non-specific chronic cough in children. *Cochrane Database Syst Rev*. 2005; 20(3):CD005373
18. **Spencer D**. A paper that changed my practice: S McKenzie. Cough but is it asthma? *Arch Dis Child* 1994;70:1-2. *Arch Dis Child* 2007; 92:82-83
19. **Antoniou SA, Mihaescu T, Donner CF** – Pharmacotherapy of cough-variant asthma. *Expert Opin Pharmacother*. 2007; 8:3021-3028
20. **Turktas I, Dalgic N, Bostanci I, et al** – Extrathoracic airway responsiveness in children with asthma-like symptoms, including chronic persistent cough *Pediatr Pulmonol*, 2002; 34-3:172-180
21. **Cernatescu I, Soaita Adina** – Chronic cough – variant asthma. European Respiratory Society Annual Congress, P0268, Geneva, Switzerland, 1998
22. **Cernatescu I** – Astmul – varianta tuse! Conferinta Nationala de Medicina a Familiei. 2007, published in abstract volume, pag 25-26, Bucharest, Romania
23. **Koh YY, Chae SA, Min KU** – Cough variant asthma is associated with a higher wheezing threshold than classic asthma. *Clin Exp Allergy*. 1993; 23(8):696-701
24. **Bakirtas A, Turktas I** – Methacholine and adenosine 5'-monophosphate challenges in preschool children with cough-variant and classic asthma. *Pediatr Pulmonol*. 2007; 42:973-979
25. **Ribeiro M, Pereira CA, Nery LE, et al** – Methacholine vs adenosine on intra and extrathoracic airway hyperresponsiveness in patients with cough variant asthma. *Allergy*. 2008; 63:527-532
26. **Koh YY, Kang H, Yoo Y, et al** – Wheeze detection as a measure of bronchial challenge in young children with cough-variant asthma and with classic asthma. *Acta Paediatr*. 2007; 96:1223-1227
27. **Hiroyuki M, Hirokazu A, Kenichi T, et al** – Bronchial Sensitivity and Bronchial Reactivity in Children With Cough Variant Asthma. *Chest*. 2005; 128:2427-2434
28. **Ryan G, Latimer KM, Dolovich J et al** – Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway caliber. *Thorax*. 1982; 37(6): 423-429
29. **Faniran AO, Peat K, Woolcock AJ** – Persistent cough: is it asthma? *Arch Dis Child* 1998; 79:411-414
30. **Kang H, Koh YY, Yoo Y, et al** – Maximal Airway Response to Methacholine in Cough-Variant Asthma. Comparison With Classic Asthma and Its Relationship to Peak Expiratory Flow Variability. *Chest*. 2005; 128:3881-3887
31. **Koh YY, Park Y, Kim CK** – The importance of maximal airway response to methacholine in the prediction of wheezing development in patients with cough – variant asthma. *Allergy* 2002; 57:1165 – 1170
32. **Chang AB, Landau LI, Van Asperen PP, et al** – Cough in children: definitions and clinical evaluation. Position statement of the Thoracic Society of Australia and New Zealand. *MJA* 2006; 184(8):398-403