

Cough, wheezing and asthma in children: lesson from the past

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Recurrent cough is an important medical and sometimes frustrating problem encountered by pediatricians, especially if it is not associated with wheeze or other evidence of systemic disease. In the past, many children with chronic cough have been diagnosed as asthmatic. However, epidemiological, clinical and laboratory studies conducted over the last ten years elucidated many aspects of the relationship between cough and bronchoconstriction. It is difficult to make a diagnosis of asthma on cough alone, but the setting in which the patient is seen (i.e., in a primary care setting or in a specialized clinic) may address doctors to the right diagnosis. A prudent “wait and see” approach may be useful in many occasions.

Fernando Maria de Benedictis¹, David Selvaggio¹ and Diletta de Benedictis²

¹Department of Pediatric Medicine, 'Salesi' Children's Hospital, Ancona, Italy, ²Pediatric Clinic, University of Perugia, Perugia, Italy

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Fernando Maria de Benedictis, Department of Pediatric Medicine, 'Salesi' Children's Hospital, 11, via Corridoni, I-60123 Ancona, Italy
Tel.: +39 071 5962351
Fax: +39 071 5962234
E-mail: debenedictis@ao-salesi.marche.it

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The diagnosis of asthma is relatively easy when wheezing, cough and breathlessness are associated. It is more difficult to sustain a diagnosis of asthma in children who present only one of the clinical symptoms of the disease.

Epidemiological studies indicate that the prevalence of wheezing is very high in early childhood (1). However, parents and clinicians frequently use the term ‘wheeze’ for a range of audible respiratory noises, which may be leading to overdiagnosis of asthma (2).

The characteristics and the natural history of wheezing have been evaluated in several studies. In a population-based sample, nearly half of children who presented wheezing during the preschool years became symptom-free at follow-up, 38% continue to wheeze, and 15% reported recurrent cough (3). Children with persistent wheeze displayed clinical findings consistent with a diagnosis of asthma, such as airway hyper-responsiveness and atopy.

Powell et al. (4) assessed the natural history of respiratory symptoms in a population of primary school children by repeating a questionnaire survey after 2 yr. Of children who initially wheezed, about half had stopped wheezing and 18% had been labelled as having asthma. Those with more frequent wheezing episodes and a

personal history of hay fever were more likely to retain their wheezing symptoms.

By far the most important data on the natural history of wheezing in childhood come from the longitudinal Tucson Children's Respiratory Study (5). Early wheeze resulted to be a transient symptom in about half of children, and an Asthma Predictive Index has been proposed to recognize children who are likely to develop asthma later (6).

Cough is a very common symptom in childhood and accounts for 30% of children under the age of 11 yr (7). Chronic or recurrent cough in childhood is responsible of a large number of visits to general practitioners and of 2.5% of outpatient consultations in the USA (8). Furthermore, children with cough can have frequent episodes (9) leading to repeated school absence (10). In the Tucson Children's Respiratory Study, the prevalence of recurrent cough without a cold progressively increased from 13% at age 2 to 27% at age 6 (11). However, the cough had resolved by age 6 for more than half of children with recurrent cough at age 2.

Cough is frequent in asthma. The prevalence of nocturnal cough in asthmatic children has been reported as 14.5% at the age of 7 yr and

9.5% at the age of 12 yr (12). Interestingly, in a population-based sample of children, nocturnal cough was more frequent in current wheezers (39%) than in asymptomatic children (19%) (13).

The problem of isolated cough

Children with a history of recurrent or persistent cough that is not associated with wheeze or other evidence of systemic disease are commonly seen in general practice. Historically, these children have represented a confusing and uncertain area of paediatric medicine.

In 1976, Corrao et al. (14) described six patients with chronic cough without history of dyspnea or wheezing, who had normal baseline spirometry but airway hyper-reactivity, as demonstrated by methacholine challenge. On the basis of their persistently hyper-reactive airways, inducible diffuse bronchoconstriction and excellent response to bronchodilator therapy, these patients were classified to have a variant form of asthma in which the only presenting symptom is cough.

Since then, several authors faced with the problem of isolated chronic cough. Cough variant asthma (15), cough type asthma (16), cough asthma equivalent (17) and hidden asthma (18) were common labels used to define a clinical picture characterized by a non-productive, often nocturnal cough, frequently exacerbated by respiratory infections and cold air. In different studies, a positive personal and family history of allergy was found in about half of the patients, spirometry was usually normal, and bronchial challenges were positive in the majority of cases (19). From 10 (20) to 80% (18) of patients responded to asthma treatment or developed wheezing at the follow-up.

Over the years, doctors became progressively aware – often *acritically* – that cough may be the sole manifestation of asthma ('you don't have to wheeze to have asthma'). The inevitable consequence of this ideological approach was the increased tendency to diagnose asthma, as well as prescribing asthma medications, in patients with unexplained chronic cough (21).

Two cross-sectional community surveys of primary school children were performed in 1991 and 1993 to determine the prevalence of cough, wheeze and breathlessness, both as single symptom and in combination, and their relation to doctor diagnosed asthma (22). The percentage of children with different respiratory symptom patterns was similar in the two surveys. However, the prevalence of doctor diagnosed asthma increased from 17 to 22% over the study period. In 1991, of children with cough alone, one in

eight was diagnosed asthmatic, while twice as many doctors made the diagnosis of asthma on this basis in 1993.

Recently published Australian data list salbutamol as the most commonly prescribed drug (23). While the use of asthma medications is probably appropriate in most situations, it is possible that some of the increase is related to the overuse of asthma medications in children and adults with chronic unexplained cough.

Early studies in children with isolated chronic cough have been conducted in outpatients, which are unlikely to be representative of children in the community. Indeed, in recent epidemiological studies children with chronic cough were found to differ in important aspects from children with asthma, and it became progressively evident that cough alone is unlikely to be a manifestation of asthma in most children (24).

The role of epidemiological studies

Cross-sectional studies

In a large population survey in schoolchildren, Clifford et al. (25) found no association between cough and airway hyper-responsiveness or atopy after controlling for wheeze, and suggested that, in absence of wheeze, the significance of cough and dyspnea for the diagnosis of asthma in an epidemiological setting should be questioned.

Approximately 10% of 8–11-yr-old Australian children had 'troublesome night cough' but did not wheeze (26). They had a similar rate of allergic sensitization and airway hyper-responsiveness to asymptomatic children. Because allergic sensitization and airway hyper-responsiveness have been reported to be strongly associated with asthma (27), it was suggested that persistent night cough may have different origins from asthma.

In a cross-sectional study in Scotland, prevalence of hay fever and history of parental eczema in schoolchildren with persistent nocturnal cough was less than in children with multiple respiratory symptoms, and similar to the asymptomatic group (28). The authors conclude that persistent cough in absence of wheeze, breathlessness or chest tightness is likely to be a manifestation of hidden asthma only in a minority of cases.

Characteristics of children with chronic respiratory symptoms and doctor-diagnosed asthma were investigated in eastern Finland by using a questionnaire (29). Skin prick test (SPT), spirometry and serum total immunoglobulin E (IgE) measurements were also performed. Children with isolated cough had a history of less frequent

parental asthma, self-reported allergies, SPT and daily respiratory medications than asthmatic patients. There were no differences between children with asthma and those with chronic cough in serum total IgE levels and lung function, except for maximal mid-expiratory flow values which were lower among asthmatic children.

Faniran et al. (30) applied a screening questionnaire to the parents of 1245 children aged 6–12 yr. Children with persistent cough had less respiratory morbidity and less atopy compared with those with wheeze. Notably, a significant number of children with persistent cough had been diagnosed as having asthma and were treated with asthma medications.

Recently, repeated IgE inhalant antibody testing in coughing toddlers has been found useful to indicate the subsequent risk of asthma. Children who had become IgE-positive were more frequently diagnosed by their general practitioners as having asthma. A visit for shortness of breath and two or more visits for wheeze were indicators of becoming IgE-positive (OR: 6.9 and 6.0, respectively) (31).

Prospective studies

Risk factors for recurrent cough in childhood and its relation to asthma were investigated as part of the longitudinal Tucson Children's Respiratory Study (11). At age 6, children were classified as having recurrent cough without wheeze, recurrent cough with wheeze, wheeze alone, and no respiratory symptoms. Children with recurrent cough without wheeze did not differ from asymptomatic children in serum total IgE levels, skin test results, lung function, and response to cold air challenge. Recurrent cough alone was associated with an increased risk (12.6%) of developing asthma later in childhood compared with children with no symptoms (5.5%). However, the risk was much lower than children reporting both cough and wheeze (33.3%) or wheezing alone (21.1%). The Authors argue that lumping chronic cough and recurrent wheezing under the same 'asthma' label may obscure important differences, which may be critical to understanding of pathophysiology of these distinct conditions, as well as to the development of appropriate therapy.

In a 2-yr follow-up study in schoolchildren in the United Kingdom, about 20% of children with nocturnal cough had developed wheezing, 43% had a reduced frequency of nocturnal coughing, and 14% had stopped coughing. Children with nocturnal cough were more likely

to develop wheezing if they had a family history of atopy (4).

A cohort of children with recurrent cough in the preschool period was reassessed during the early school years by Brooke et al. (32). Over half of children became symptom-free at follow-up, about one-third continued to have recurrent cough in the absence of colds, and 7.2% reported recent attacks of wheeze. Children who were still coughing at the follow-up showed greater bronchial reactivity than children who outgrew their cough. Interestingly, although the atopic status and lung function were similar to controls, children with recurrent cough were more likely to be diagnosed as asthmatic.

Nishimura et al. (33) evaluated the relationship between bronchial hyper-responsiveness and asthma development in children with chronic cough. After 10 yr follow-up, 45% of the children with a history of chronic cough in early life developed asthma. Bronchial hyper-responsiveness was found to be a strong risk factor for the development of subsequent wheezing.

The role of antiasthmatic drugs

Reported benefits of asthma medications in patients with chronic cough were largely based on anecdotal evidence (15, 18, 34–36). Many of these studies were not controlled and have used subjective reporting of cough, which is known to be an unreliable method compared with objective measurements (37–39).

Evald et al. (40) first evaluated the effect of antiasthmatic treatment in a controlled study in patients with chronic cough. After 2 wk treatment with budesonide (200 mcg b.i.d.) or placebo, no significant treatment effect was found for any of the measured variables. In a double-blind randomized trial, 43 children with unexplained chronic cough received inhaled salbutamol or placebo for a week, and then beclomethasone or placebo for 4–5 wk (41). The children used an ambulatory cough meter, kept cough diaries, measured the capsaicin cough sensitivity, and performed hypertonic saline challenge and SPT. Salbutamol or beclomethasone had no effect on cough severity, irrespective of the presence of airway hyper-reactivity. Davies et al. (42) evaluated 50 consecutively referred children with persistent nocturnal cough. Placebo or fluticasone propionate (1 mg b.i.d. for three nights, and then 500 mcg b.i.d. for 11 nights) were administered by a metered dose inhaler plus spacer. Compared with baseline, cough improved consistently in both groups (17 of 24 subjects on inhaled steroids and 8 of 23 on placebo), but a

significant difference was found in favour of fluticasone at the end of treatment. The authors conclude that a 2-wk, high dose course of inhaled steroids may benefit some children with chronic unexplained cough.

The effect of a 14-day course of zafirlukast against placebo was recently evaluated in a small number of subjects with cough variant asthma refractory to inhaled β -agonists and inhaled corticosteroids (43). The majority of subjects experienced significant improvement in cough and cough sensitivity to capsaicin after treatment with zafirlukast. Antileukotriene drugs may therefore represent a promising tool for the treatment of cough variant asthma, but studies in a larger number of patients are necessary.

The results of reported studies progressively alerted clinicians that cough variant asthma is likely to be a misnomer for most children in the community who have persistent cough, and that more attention should be paid to the indiscriminate use of asthma drugs in this clinical setting. Over the years, the enthusiasm in diagnosing cough variant asthma has been probably reduced, but the results in terms of reduction of antiasthmatic drug prescription are much awaited.

Chronic cough and airway inflammation

Several studies have investigated the role of inflammation in children with chronic cough. Marguet et al. (44) evaluated the bronchoalveolar lavage (BAL) cell profile in primary school children with asthma, infantile wheeze, cystic fibrosis, chronic cough, and in a control group. While asthma and infantile wheeze were characterized by a high ratio of eosinophils and neutrophils respectively, children with chronic cough were indistinguishable from controls in relation to differential cell count. Fitch et al. (45) performed a non-bronchoscopic BAL in different groups of children who received elective surgery. In children with a history of chronic unexplained cough, the percentage of eosinophils and neutrophils in BAL was higher than controls, but lower than asthmatics. Eosinophilic cationic protein (ECP) was detectable in BAL fluid in 14% of children with chronic cough, 7% of normal children and 28% of asthmatics.

In a community-based survey, the role of eosinophilic airway inflammation, as detected in induced sputum analysis, was investigated in children with wheeze, chronic cough, recurrent chest colds, and no symptoms (46). Sputum eosinophils were significantly higher in children with wheeze compared with the other groups.

Children with cough reported greater exposure to environmental tobacco smoke and did not show bronchial hyper-responsiveness to hypertonic saline. Zimmerman et al. (47) evaluated inflammatory markers in children with persistent post-infectious cough and in children with treated and untreated atopic asthma. The percentage of eosinophils in the sputum, in the peripheral blood and in the nasal mucosa, and the serum ECP levels were significantly lower in patients with cough than those of patients with untreated asthma.

Airway inflammation markers have been evaluated in children with cough and gastro-oesophageal reflux (GER), in asthmatic patients with or without GER and in healthy subjects (48). The sputum eosinophil percentage, ECP levels and exhaled nitric oxide value were normal in patients with cough and GER, but were significantly increased in asthmatic patients irrespective of GER.

In a recent prospective study, cough severity score, cough receptor sensitivity (CRS) and inflammatory markers (sputum interleukin 8, ECP, myeloperoxidase, and serum ECP) were evaluated in children with asthma during a non-acute, acute, and resolution phase (49). In asthmatic children who coughed as a dominant symptom, cough heralded the onset of an exacerbation, but neither cough scores nor CRS were related to any inflammatory marker.

'Atopic cough' is a new clinical entity that has been recently proposed as a cause of isolated cough in adults. These patients manifest chronic, non-productive, bronchodilator-resistant cough, atopic constitution, eosinophilic tracheobronchitis, and cough receptor hypersensitivity without bronchial hyper-responsiveness. The evolution to classical asthma is rare, thus this entity should be separated from cough variant asthma (50).

Taken together, the results of previous studies indicate that children with chronic, unexplained cough do not have the same pattern of airway inflammation as children who wheeze. Therefore, persistent cough should not be considered a variant of asthma, and antiasthmatic drugs are not indicated as initial therapy for the majority of children with chronic cough.

Cough and bronchial tone

Cough severity and bronchoconstriction

For a long time it has been accepted that cough and bronchoconstriction share the same mechanisms. This 'traditional model' was based on anecdotal observation that bronchodilators such

as ephedrine and isoprenaline were, in addition, effective antitussive agents (51). Moreover, histamine- and methacholine-induced cough was found to be related to the degree of induced bronchoconstriction (52).

Over the years, increasing evidence has accumulated, either in the laboratory or in clinical setting that cough occurs independently of bronchoconstriction. Inhalation of lignocaine blocks cough but not bronchoconstriction (53), while cromoglycate or atropine block bronchoconstriction, but not cough, induced by distilled water aerosol (54). Similarly, lignocaine was effective in inhibiting capsaicin-induced cough but not bronchoconstriction (55). Finally, mechanisms that initiate exercise and cold air-induced cough or bronchoconstriction in asthmatics appear to be different (56).

The results of clinical studies supported laboratory data of a lack of relationship between cough severity and airway calibre. Indeed, in adults with persistent cough or stable asthma, no correlation was found between 24 h-recorded cough frequency and lung function parameters (57). Furthermore, no relationship was documented between night cough severity and diurnal peak expiratory flow variability, either in children with stable asthma (58) or in those with current wheeze (8).

Cough receptors sensitivity and airway calibre

Several studies have investigated the relationship between airway calibre changes and CRS in different group of patients. Fuijmura et al. (59, 60) measured cough response to capsaicin and tartaric acid before and after methacholine-induced bronchoconstriction or procaterol-induced bronchodilatation. Cough response did not differ after methacoline challenge or bronchodilator treatment, neither in normal subjects nor in asthmatics. Similarly, Shimuzu et al. (61) evaluated the acetic acid cough threshold before and after histamine-induced bronchoconstriction and salbutamol-induced bronchodilatation in children with stable asthma. No relationship was found between cough threshold and airway calibre.

The CRS has been also evaluated in several respiratory diseases. A transient increase of CRS was found in patients with dry cough associated with upper respiratory tract infection, but not in those who did not cough or who had a productive cough (62). Some children with recurrent cough had increased CRS and others had airway hyper-responsiveness during the coughing period, which returned to values of controls when

cough-free (63). In children with asthma who coughed as a major symptom during their acute episodes, a transient increase in CRS during exacerbations occurred (64). In contrast, children who did not usually cough during their asthma exacerbations had no change in CRS, either in acute or non-acute asthma periods (62). CRS of children with asthma was similar to controls during the non-acute phase (65).

The reason why increased CRS develops in some but not in other subjects with chronic cough is not known. Potential factors like persistent inflammation, qualitative or quantitative surfactant abnormalities, increased calcitonin gene-related peptide nerve density, or release of tachykinins could be involved in that phenomenon, but their role needs to be properly studied (66).

Reconciling the problem

An 'alternative model' of cough, CRS, and airway hyper-responsiveness in children with and without asthma has been proposed by Chang et al. (67, 68) In asthmatic children, a trigger factor may lead to airway inflammation which, in presence of airway hyper-responsiveness, is expressed by wheeze and dyspnea. If cough receptor hypersensitivity is present, patients also manifest cough. In non-asthmatic subjects, increased CRS could be responsible of isolated cough. Some of these children do have airway hyper-responsiveness during the coughing episodes. Whether or not some of them will develop classical asthma with cough as dominant symptom is unknown.

It has also been suggested that children with cough variant asthma may represent a subset of asthmatic subjects with a higher wheezing threshold (69, 70). Indeed, an increase of airway hyper-responsiveness may have a pathogenetic role in the development of wheezing during the course of this clinical entity (71).

Isolated chronic cough: to be or not to be asthma?

There is no doubt that children with asthma can present with isolated cough, as wheeze can be under-recognized by parents or may not be evident when children visit their doctor. However, there is a large body of evidence that cough alone is a poor marker of asthma, and most children with persistent cough do not have asthma but rather cough receptor hypersensitivity.

Children with persistent, isolated cough seem to occupy an intermediate clinical position

between children with no cough and those with wheeze, with respect to atopy, family history of asthma, response to antiasthmatic drugs, and prognosis for asthma.

The setting in which the patient is seen may govern positioning cough in a specific frame. Isolated cough is unlikely due to asthma in a community or in a primary care setting, but in a specialist clinic, where a highly selected group of patients are seen, some children who cough in response to asthma triggers may improve when treated with asthma medication (72).

Does a patient with unexplained chronic cough have asthma? This doubt is still justified. However, the following diagnostic criteria may help to better classify the patient as asthmatic: (i) abnormally increased cough, with no evidence of any non-asthma diagnosis; (ii) clear-cut response to a therapeutic trial of asthma medications; (iii) relapse on stopping medications, with second response to recommencing them; (iv) the presence of atopic eczema, positive egg or inhalant prick tests, a parental and particularly maternal history of atopic asthma (73, 74).

In alternative, chronic non-specific cough in childhood frequently improves with time and without treatment. In such clinical setting, a 'wait and see' diagnosis may be more appropriate for many children.

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