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Update on Pediatric Cough

Ahmad Kantar[1]

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Abstract Despite the high prevalence of cough in children, the topic has been poorly researched. Although pediatricians recognize that chronic cough in children is different from that in adults, this difference seems less recognizable to other health professionals. During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence the cough reflex. Additionally, immunological responses undergo developmental and memorial processes that make infection and congenital abnormalities the overwhelming cause of cough in children. The lack of comprehensive clinical data regarding chronic cough in children has initially required pediatricians to adopt an adult approach to the problem. In the last 10 years, however, research has led to the reconsideration of the etiology of chronic cough in children. Currently, attention has focused on protracted bacterial bronchitis as a major cause of chronic cough in preschool-aged children and as a possible precursor of bronchiectasis. New research horizons are emerging for both the treatment and prevention of particular causes of chronic cough in children.

Keywords Chronic cough · Children · Protracted bacterial bronchitis · Cough etiology

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✉ Ahmad Kantar
kantar@centropediatricotosse.com

[1] Pediatric Asthma and Cough Centre, Istituti Ospedalieri Bergamaschi, University and Research Hospitals, via Forlanini 15, Ponte San Pietro-Bergamo, 24036 Bergamo, Italy

Introduction

Increasing data have confirmed that the etiology of chronic cough in children differs from that in adults [1–3]. Various elements are involved in this distinction. Respiratory airways undergo morphological and physiological developmental changes during childhood. Noxious insults to these airways may be more damaging in children than in adults. The airways and the cough reflex, which are part of the neurological system, are less controlled by the central nervous system in children. The immune system is immature in children, giving rise to increased vulnerability to many infections associated with prolonged or chronic coughing.

Studies in adults with cough can rarely be applied to children because of the above-mentioned differences and other essential factors, such as increased exposure to infection, especially viruses, with a consequently high percentage of spontaneous resolution and increased damage to the developing lungs by environmental agents [2]. Moreover, few cough medications have been investigated in pediatric populations, and the increased placebo effect in children needs to be considered [4].

Cough in pediatrics has recently attracted more research interest because of the increased awareness that many adult respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), have their roots in childhood [5]. Understanding the causes of chronic cough in children is essential for their future respiratory health. Moreover, preventing some causes of pediatric chronic cough, such as infection resulting from inadequate immunization or foreign body inhalation, by increasing family awareness would reduce lung damage and heath care costs.

Because cough is audible and can intensely interfere with the quality of life, it is not surprising that parents are

often anxious about their children's cough and often seek medical advice and remedies [6]. Children have less control over their coughing than adults do; thus, it may interrupt daily activities at school or other social activities. A good example of this difficulty is the recently reported episode where a renowned violinist shocked the audience at London's Royal Festival Hall by publicly berating the parents of a coughing child and scolding the parents from the stage, stating "Maybe bring her back when she's older" [7].

Chronic Cough in Children: Exploring Lung Deep

The lack of available comprehensive clinical data regarding chronic cough in children has caused pediatricians to adopt an adult-oriented approach to the problem. For years, the main causes of chronic cough in children were believed to be the same "big three" that affect adults: asthma, upper airway cough syndrome, and gastroesophageal reflux (GER) [8]. In 2006, the work by Marchant et al. represented a breakthrough in our knowledge about the etiology of chronic cough in children [9]. In that study, the authors prospectively evaluated young children using the protocol of Irwin et al. for chronic cough in adults, but they modified it by performing early bronchoscopy and bronchoalveolar lavage (BAL) [10]. They found that the diagnostic categories for chronic cough in children are heterogeneous and that the most common diagnosis was protracted bacterial bronchitis (PBB); in contrast, the three most common chronic cough-related diagnoses in adults were found in only 9 % of young children. The use of BAL was particularly helpful in this study because it pinpointed the pathogens that are crucial in PBB. The microbiology of PBB was typical respiratory organisms, including *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Moreover, the cytological profile revealed neutrophilic inflammation. These observations regarding PBB were confirmed in studies by other investigators [11–14]. Although PBB was a known pathological condition in children (it was formerly called persistent endobronchial infection, chronic bronchitis, protracted bronchitis or pre-bronchiectasis), it was never adequately characterized and investigated until the study done by Marchant et al. [9]. This study presented a new path for the study of PBB. Further characterization of the disease has uncovered immunological alterations [15–17] and structural anomalies of the airways, particularly malacia [9, 11–13]. A role of viral infection with adenovirus has been suggested [18, 19]. The therapeutic approach to PBB has been empirically prolonged antibiotic therapy, namely with amoxicillin clavulanate, and physiotherapy [20]. These data were recently confirmed in a double-blind, placebo-controlled study [21], which demonstrated that a 2-week course of amoxicillin clavulanate (45 mg/kg/day bid) was significantly more likely to achieve cough resolution (48 % in the treatment group compared with 16 % in the placebo group). We routinely prescribe higher doses (80–90 mg/kg/day divided q8 h) for a period of 2–4 weeks. Children with PBB are typically very young boys with a prolonged wet cough and parent-reported wheezing who have attended childcare (OR, 8.43; 95 % CI, 2.34–30.46) [22]. Children with PBB have significantly elevated percentages of neutrophils in the lower airways compared with control subjects, and adenovirus is more likely to be detected in the BAL specimens of children with PBB (OR, 6.69; 95 % CI, 1.50–29.80) [22].

The cough sound is caused by the vibration of larger airways and laryngeal structures during a turbulent flow in expiration. Mucus in the large airways, as opposed to the small airways, is required for a detectable difference in cough quality. Laminar airflow in the small airways is inaudible. The rheological properties of mucus influence cough sounds, and the shearing of the secretions from the airways contributes to the sounds. In adults, a large amount of airway secretions must be present for the cough to sound wet, and hence, the concept of dry and wet cough is less valid than it is in children. Numerous investigations have underlined the helpfulness of the cough's sound (dry or wet) in guiding the diagnostic approach [13, 23–25]. To diagnose PBB, the ORs for wet cough and abnormal chest radiograph findings are infinite and 23.4 (1.4–391.0), respectively [25]. In contrast, children with a chronic dry cough and no cough pointers can be safely managed using the watchful waiting approach.

Awareness of PBB is currently increasing based on a clinical observation that indicates untreated PBB as a forerunner of bronchiectasis [26, 27]. The first observation that bronchitis predisposes children to bronchiectasis was reported in 1949 by Field [28]. All of these data called for the early recognition and treatment of PBB in children [25, 29], confirming the utility of defining chronic cough in children as a cough that lasts more than 4 weeks rather than the adult definition of 8 weeks.

It has been demonstrated that longer duration of symptoms and greater neutrophilic inflammation in the airways are associated with more severe abnormalities on high-resolution computed tomography (HRCT) scan [26, 30].

Neutrophils have emerged as an important component of effector and regulatory circuits in the innate and adaptive immune systems. In contrast to the traditional view of these cells as short-lived effectors, evidence now indicates that they have diverse functions [31]. There is a prevailing view that bacterial infection provokes an exaggerated and uncontrolled neutrophilic response and that the complex interplay between bacterial infection and airway

inflammation, in addition to the release of tissue-damaging substances, leads to the progressive damage that typifies bronchiectasis [32]. Individual variability in innate responses may help explain why not all individuals exposed to predisposing triggers will develop bronchiectasis.

Chronic cough is common in the pediatric population, but the true prevalence of this condition remains difficult to define. The prevalence of each etiology depends on the population being considered, the epidemiology of infectious diseases, the patient's age, the diagnostic tools used, antibiotics use, immunization, and the local health system [9, 14, 33–35]. A good example of this variation is the increased incidence of GER in settings that employ flexible laryngoscopy for diagnosis rather than gold standard techniques such as pH impedance [35] or in settings that attribute cough to the mere presence of GER [36]. This issue is also confirmed by the inconclusive data regarding the efficacy of GER treatment for addressing chronic cough in children [37].

We retrospectively analyzed the prevalence of various etiologies of chronic cough at our center during the years 2011–2012. The sample included 64 children (36 males) with an age range between 16 months and 16.2 years [mean (SD) = 7.9 (4.2) years] and a cough duration ranging from 5 to 43 weeks [median (IQR) = 12 (6–19.5) weeks] who were referred by community pediatricians for chronic cough. Chronic cough was defined as a cough lasting more than 4 weeks. Thirty-four of the children had a wet cough, and 19 presented wheezing. The diagnostic protocol employed at our center is based on a modified Australian chronic cough protocol [38]. The diagnostic approach was patient centered, and the parents shared in the diagnostic approach and management. The study was approved by Local Ethical Committee and parents gave informed consent.

The approach was based on an initial detailed medical history and physical examination. This step was followed by first-phase investigations that included one or more of the following assessments: chest radiograph, laboratory examination (immunoglobulins; IgE; markers for pertussis, mycoplasma, and chlamydia infections; sweat test; Alpha-1-antitrypsin; Mantoux or Quantiferon tests), skin prick test ($n = 60$), oscillometry ($n = 13$), spirometry ($n = 47$), FeNO ($n = 44$), induced sputum ($n = 32$; children >5 years), nasal brushing for ciliary analysis ($n = 10$), and psychological evaluation ($n = 16$). The first exam performed was selected based on the patient's clinical profile and the nature of cough. In the second phase, CT scanning (Dual Source Flash Spiral; $n = 21$), pH impedance ($n = 16$), and/or flexible bronchoscopy ($n = 10$) were performed. These tests were conducted if the initial investigation did not lead to a diagnosis and the cough persisted. In two patients, esophagogastroscopy was also performed.

A primary diagnosis was obtained for 61 children, who were followed up for 6 months (Fig. 1). Among these children, the primary diagnosis was spontaneous resolution (post-infectious cough) ($n = 12$, of which pertussis $n = 4$ and mycoplasma $n = 3$), asthma ($n = 11$), PBB ($n = 9$), bronchiectasis ($n = 8$), tracheobronchomalacia ($n = 6$; two were primary, 3 were secondary [vascular compression], and one was a complication of tracheoesophageal fistula), RGE ($n = 3$), upper airway cough syndrome ($n = 3$), "psychogenic" somatic cough ($n = 3$), atelectasis ($n = 1$), PCD ($n = 1$), pulmonary tuberculosis ($n = 1$), Alpha-1-antitrypsin deficiency ($n = 1$), aspiration syndrome ($n = 1$), and eosinophilic bronchitis ($n = 1$). A secondary diagnosis was defined as a diagnosis that was made during the investigation but did not contribute to cough resolution. The following secondary diagnoses were found in 16 patients: airway malacia ($n = 6$), GER ($n = 8$) and mycoplasma infection ($n = 2$). One patient remained without a clear diagnosis. Two patients were lost to follow-up and did not complete their investigations at our center. Only two cases of children with wet cough were not associated with a specific disease. During the follow-up period 2 children with PBB had experienced a second recurrent episode.

The retrospective design of the study and the representativeness of the cohort are the major limitations of these data. In comparison with other studies, these results confirm, as mentioned above, that the prevalence of various etiologies of chronic cough depends on numerous factors.

Future Management and Prevention

Respiratory infections and their sequelae appear to be the principal cause of chronic cough in children. This conclusion suggests various possibilities for both treatment and

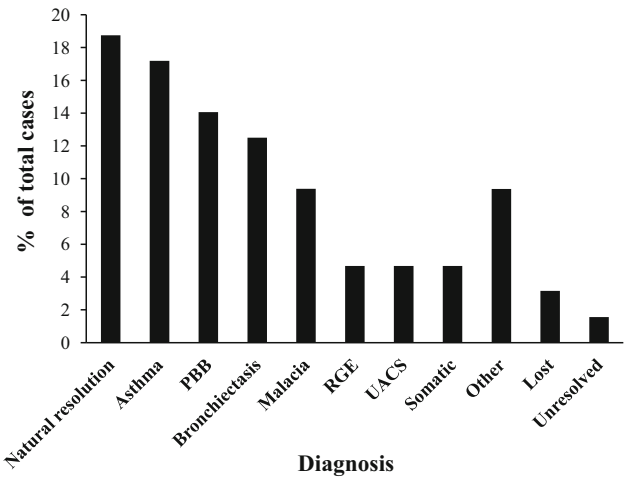

Fig. 1 Frequency (%) of the primary diagnosis in 64 children with chronic cough, defined as cough >4 weeks duration. Protracted bacterial bronchitis (PBB), gastroesophageal reflux (GER), and upper airway cough syndrome (UACS)

prevention. Immunization is a cornerstone of infectious disease prevention. The best strategy for preventing acute respiratory tract infections is primary prophylaxis against diseases that are preventable by vaccination. From the pulmonologist's perspective, vaccinations are important safeguards against diseases of particular relevance in chronic cough, such as pneumococci and *Bordetella pertussis*.

In some countries, pertussis continues to be the most poorly controlled vaccine-preventable bacterial disease. Pertussis epidemics—that is an increase in the number of pertussis cases in children, adolescents, and infants younger than 6 months of age—have been reported in several regions of the world [39–41]. The prevention of pertussis requires an integrated approach and the adoption of different immunization strategies, with the objective of achieving and maintaining high coverage rates. Various immunization strategies have been suggested, including the immunization of newborns, preschool and school children, adolescents, adults, health care workers, childcare workers, and pregnant women [42].

The introduction of the pneumococcal conjugate vaccines (PCV)-7 and subsequently PCV-13 has contributed to a change in the pattern of pneumococcal serotypes contributing to this disease through serotype replacement [43]. Priftis et al. demonstrated that children with PPB who are immunized with PVC are highly unlikely to show isolated vaccine serotypes in their BAL cultures [44]. Although it is not clear whether this result is because of individual immunity or the concurrent change in serotype circulation in immunized populations, these results also indicate that serotype replacement is occurring after the introduction of conjugate pneumococcal vaccines. Nevertheless, whether this process negatively or positively impacts the overall incidence or severity of PBB remains to be explored.

In recent years, interest in the lung microbiome and its role in health and disease have increased substantially. This complex polymicrobial system is composed of bacteria, viruses, and fungi [45]. The rapid development of new technologies has opened up possibilities for better defining the compositions and role of the respiratory microbiome in homeostasis, during infection and in chronic diseases. Commensal microbes that live on and in us are critical for our health. In addition to serving the gatekeeper between our cells and the external environment, the human microbiome is critical to the maturation and function of our immune system and affects the entire spectrum of the immune processes. The infant microbiome shows great interindividual variability and relatively low diversity, but it becomes more diverse and converges into an "adult-like" structure by 3 years of age [46, 47]. Analogous to the gut microbiome, the respiratory microbiome at equilibrium is thought to be beneficial to the host by priming the immune system and providing colonization resistance, whereas an imbalanced ecosystem might predispose humans to bacterial overgrowth and the development of respiratory infections [48, 49]. Asymptomatic transient nasopharyngeal colonization with bacteria is common in infants and children and declines with age and immune maturation. The most common colonizing pathogens are *S. pneumonia*, *Haemophilus influenza,* and *Staphylococcus aureus* [50]. Maternal health, mode of delivery, breast-feeding history, age, geographic region, ethnicity, nutrition, season, day care attendance, environmental factors, overuse of antibiotics, and vaccinations are important determinants of bacterial colonization in healthy children [46, 51–53]. The disruption of the lung microbial ecosystem by infection, inflammation, and/or antibiotic therapy may create a simplified microbial community with downstream consequences for immune function. Falkow and Blaser coined the term 'disappearing microbiota hypothesis' to explain the rising burden of diseases, including diseases of inflammatory pathogenesis [54]. Many disease-associated microbiomes can serve as a type of fingerprint that reflects the underlying disease condition. Our understanding of the dynamics of the human microbiome throughout the human life stages has been driven primarily by sequencing technology developments in recent years. Data sets are starting to emerge of 16-s sequences from the lung microbiota of healthy individuals and those of individuals with PBB, GSLD, and bronchiectasis. Van der Gast et al. recently demonstrated that the core microbiota in PBB is remarkably similar to those in bronchiectasis and cystic fibrosis. These data suggest a unified model of early airway infections in which a defect in the clearance (such as immunological deficit and mucociliary alterations) of otherwise normal airway microbiota contributes to progressive inflammation and damage [55]. Manipulation of the microbiome, if possible, is a favorable way to restore its normal defensive function and prevent diseases. Promising results are now emerging for manipulating the gut microbiome [56, 57]. Further studies in this field would encourage new approaches to the prevention of chronic cough in children and help maintain respiratory health.

Conclusion

Whereas research on asthma consistently continues, research on chronic cough in children remains limited. However, new findings on the etiology of cough continue to play key roles in advancing our understanding of cough. Regardless of the setting, children with chronic cough should be carefully evaluated using pediatrics-specific protocols. Prolonged infections seem to be a major cause of

chronic cough in preschool children. The prevention of respiratory infections and inflammation will help control particular forms of chronic cough.

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Compliance with Ethical Standards

Conflict of interest The author declares no conflict of interest regarding this manuscript.

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