

Evaluation of Patients with Chronic Cough Referred to Pediatric Pulmonology Outpatient Clinic

Kronik Öksürük Şikayeti ile Çocuk Göğüs Hastalıkları Polikliniğine Başvuran Hastaların Değerlendirilmesi

Beste OZSEZEN

Department of Pediatric Chest Diseases, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey



ABSTRACT

Objective: A cough that lasts longer than four weeks in children is called chronic cough. The aim of this study is to determine the underlying causes of chronic cough.

Material and Methods: Patients aged 0-18 years who were referred to Şanlıurfa Training and Research Hospital pediatric pulmonology outpatient clinic between 27 December 2021 and 30 June 2022 due to chronic cough were enrolled. Patients with known cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, asthma, bronchopulmonary dysplasia were excluded from the study. The "CHEST Guideline and Expert Panel Report" guideline was used in the approach to chronic cough.

Results: 153 patients were included in this study. The most common causes of chronic cough were asthma (30.7%), protracted bacterial bronchitis (20.3%), and upper respiratory tract cough syndrome (11.1%). Wet cough was present in 60.8% of the patients with chronic cough and the most common diagnosis in patients with wet cough were protracted bacterial bronchitis (33.3%), pneumonia and other lung infections (17.2%) and bronchiectasis (12.9%). The most common diagnoses were asthma (68.3%), upper airway cough syndrome (6.7%), and natural recovery (6.7%) in patients with dry cough. Failure to thrive was more common in patients with wet cough than patients with dry cough ($p<0.030$) and fever, weight loss and desaturation were only present in patients with wet cough.

Conclusion: The most common reasons are asthma, protracted bacterial bronchitis and upper airway cough syndrome. The differential diagnosis should be made by pediatricians based on specific cough pointers, careful physical examination and tests performed in line with the recommendations of the guidelines.

Key Words: Asthma, Bronchitis, Child, Chronic Cough, Pneumonia

ÖZ

Amaç: Çocuklarda dört haftadan uzun süren öksürük kronik öksürük olarak adlandırılmaktadır. Bu çalışmada kronik öksürüğün altta yatan nedenlerinin saptanması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya kronik öksürük nedeniyle 27 Aralık 2021- 30 Haziran 2022 tarihleri arasında Şanlıurfa Eğitim ve Araştırma Hastanesi Çocuk Göğüs Hastalıkları Polikliniğine başvuran 0-18 yaş arası hastalar dahil edildi. Bilinen kistik fibrozis, primer silyer diskinezi, interstisyel akciğer hastalığı, astım, bronkopulmoner displazi tanısı olan hastalar çalışma dışı bırakıldı. Kronik öksürüğe yaklaşımda "CHEST Guideline and Expert Panel Report" kılavuzu örnek alındı.

Bulgular: Çalışmaya 153 hasta dahil edildi. Bu çalışmada kronik öksürüğün en sık nedenleri astım (%30.7), uzamış bakteriyel bronşit (%20.3), üst solunum yolu öksürük sendromu (%11.1) olarak sıralandı. Kronik öksürük olan hastaların %60.8'inde ıslak öksürüğün mevcut olduğu, ıslak öksürüğü olan hastalarda ise en sık tanılardan uzamış bakteriyel

0000-0002-0052-8361: OZSEZEN B

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Contribution of the Authors / Yazarların katkısı: OZSEZEN B: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Correspondence Address / Yazışma Adresi:

Beste OZSEZEN
Department of Pediatric Chest Diseases,
Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey
E-posta: besteozsezen@gmail.com

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bronşit (%33.3), pnömoni ve diğer akciğer enfeksiyonları (tüberküloz ve kist hidatik) (%17.2) ve bronşektazi (%12.9) olduğu görüldü. Kuru öksürüğü olan hastalarda ise en sık tanılar astım (%68.3), üst solunum yolu öksürük sendromu (%6.7) ve doğal iyileşme (%6.7) olarak sıralandı. Islak öksürük olan hastalarda kilo alamama şikayeti kuru öksürük olan hastalara göre daha belirgin iken ($p<0.030$) ateş, kilo kaybı ve desaturasyon sadece ıslak öksürük olan hastalarda mevcuttu.

Sonuç: Kronik öksürüğün en sık nedenleri astım, uzamış bakteriyel bronşit, üst solunum yolu öksürük sendromudur. Kronik öksürüğü olan hastalarda dikkatli fizik muayene ve rehberlerin önerileri doğrultusunda yapılan tetkikler ile hastalara tanı konulup tedavi kararı verilmelidir.

Anahtar Sözcükler: Astım, Bronşit, Çocuk, Kronik öksürük, Pnömoni

INTRODUCTION

Cough is one of the most common causes of hospital admission during childhood. It negatively affects the quality of life of both the child and the family. A cough that lasts more than four weeks is called chronic cough (1).

A detailed history along with detailed physical examination is necessary to determine the underlying cause of chronic cough. Early detection of the underlying cause of chronic cough can provide early intervention for preventable or progressive lung diseases. The frequency of chronic cough varies among populations and is reported at a rate of 1% in India, 9% in Eastern Europe, and 5-12% in China (2-4). The frequency of chronic cough increases in regions where air pollution is more intense (4).

The most common causes of chronic cough are nonspecific causes such as prolonged bacterial bronchitis, upper airway cough syndrome, natural healing. Apart from this, asthma, gastroesophageal reflux, infections, immune deficiencies, cystic fibrosis, primary ciliary dyskinesia, airway malacia, trachea-esophageal fistula (TEF), congenital heart diseases, foreign body aspiration and psychogenic cough (5).

The aim of this study is to define the underlying causes of chronic cough.

MATERIALS and METHODS

Patients aged between 0-18 years who applied to Şanlıurfa Training and Research Hospital pediatric pulmonology outpatient clinic between 27 December 2021 and 30 June 2022 due to chronic cough were included in this study. Patients with known cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, asthma and bronchopulmonary dysplasia were excluded.

The "CHEST Guideline and Expert Panel Report" guideline was conducted in the approach to chronic cough. (6) Detailed history of the patients (cough duration, cough character, wheezing, snoring, foreign body aspiration, drug use, rhinitis, sinusitis, respiratory tract infection history, presence of concomitant diseases, presence of allergic disease in the family, exposure to secondhand tobacco smoke) was taken and physical examination and additional tests (chest radiography, chest computed tomography (CT) in selected patients, nasal endoscopy in patients with suspected upper

airway cough syndrome, flexible bronchoscopy in cases with suspected malaise and foreign body aspiration, genetics analysis in patients suspicious of cystic fibrosis and primary ciliary dyskinesia) were performed. The physical examination of the patients was performed in two-week intervals until the cough resolved.

A cough with sputum or productive due to airway secretions was defined as wet cough, and cough without sputum or non-productive was defined as dry cough (7). Presence of more than two episodes of wheezing and/or increase in forced expiratory volume in one second (FEV1) of 12% predicted or more by spirometry after administration of bronchodilator therapy (400µg salbutamol or equivalent) was considered as asthma. The modified asthma prediction index or response to treatment was used to diagnose asthma in children who could not perform spirometry (8). Protracted bacterial bronchitis diagnosed was made if the wet cough resolved in two to four weeks of treatment with amoxicillin-clavulanate and there were no alternative causes of cough (1). Upper airway cough syndrome was diagnosed if there were findings such as hyperemia in the pharynx or nasal mucosa, postnasal discharge in the history and physical examination compatible with the diagnosis, and a response to nasal saline solution and oral or nasal decongestant treatment within 2-4 weeks. Recovery of cough under medical supervision without any treatment was defined as natural recovery (9). Mycoplasma pneumonia was diagnosed if there was serological positivity for Mycoplasma pneumonia IgM antibody, findings consistent with atypical pneumonia in physical examination and chest X-ray, and cough responding to clarithromycin treatment (9). Psychogenic cough diagnosis was made in patients when organic causes were excluded (10). The diagnosis of bronchiectasis was confirmed with thorax CT in patients who had persistent wet cough and abnormal chest X-ray findings, who did not respond to antibiotic treatment (11).

Statistical analysis was evaluated in SPSS 23 package program. Data were given as mean \pm standard deviation (SD), median (interquartile range (IQR), number (percent)). Chi-square test was used to compare qualitative data. The Mann Whitney U test was used to compare the median values between the two groups. Significance level was taken as $p<0.050$.

The study was carried out in accordance with the principles of the Declaration of Helsinki. Harran University Ethics Committee approved the study (Decision number: HRU/22.13.09).

RESULTS

153 patients were included in this study. Eighty patients (52.3%) were boys. The median cough interval was 12 weeks (IQR: 7-29). The parental consanguinity rate was 32.7% (50 patients). Mean gestation age and birth weight was 38.2 weeks (SD: 2.7) and 3159.2 kg (SD:0.4) respectively. The symptoms accompanying cough, physical examination findings, tobacco smoke exposure, environmental and personal factors triggering cough such as pet (such as cat, dog, bird), family history, and laboratory findings are summarized in Table I.

Sixty patients (39.2%) had dry; 93 patients (60.8%) had wet cough. Daytime and night cough was present in 149 patients (97.4%). Thirty-two patients (20.9%) had seasonal, 83 patients (54.2%) had exertional cough, and four patients (2.6%) had a cough associated with feeding. Seasonal cough was present in 40% of the patients with dry cough and 8.6% of the patients with wet cough ($p<0.001$). Exercise induced cough was present in 78.3% of the patients with dry cough and 38.7% of the patients with wet cough ($p<0.001$). Thirty percent of the patients with dry cough had secondhand tobacco smoke exposure whereas this ratio was 9.7% in patients with wet cough ($p<0.001$). There

Table I: The symptoms accompanying cough, physical examination findings, environmental factors, and laboratory findings in patients with chronic cough.

Symptoms accompanying cough*	
Wheeze	16 (10.5)
Dyspnea	17 (11.1)
Loud snoring /mouth breathing	21 (13.7)
Failure to thrive*	11 (7.2)
Weight loss*	1 (0.7)
Fever*	1 (0.7)
Allergic rhinitis findings*	29 (19)
Family history- Environmental exposure*	
Asthma/ atopy history in the family	33 (21.6)
Presence of pet at home	10 (6.5)
Secondhand tobacco smoke exposure	27 (17.6)
Physical findings	
Desaturation*	3 (2)
Tachypnea*	6 (3.9)
Oxygen saturation, mean (SD)	97.5 (1.4)
Crackles*	37 (24.2)
Rhonchus*	24 (15.7)
Clubbing*	7 (4.6)
Laboratory, median (IQR)	
Hemoglobin g/dl [†]	12.6 (11.7- 14.0)
White blood cell mm ^{3†}	8.9 (7.5-12.6)
Platelets mm ^{3†}	329 (282-386)
IgA mg/dL [‡]	116 (79-297)
IgG mg/dL [‡]	947 (891-1460)
IgM mg/dL [‡]	83 (63-142)

Ig: immunoglobulin, **IQR:** interquartile range, **SD:** standard deviation, *****: n(%), **†:** Complete blood count was performed in 35 patients. **‡:** Quantitative immunoglobulins were available in 15 patients.

Table II: Thorax CT findings of patients with chronic cough

Thorax computed tomography findings	n (%)
Pectus carinatum	1 (0.7)
Hilar/ mediastinal lymphadenopathy	4 (2.6)
Mosaic attenuation	2 (1.3)
Consolidation	5 (3.3)
Ground glass opacity	3 (2)
Atelectasis	14 (9.2)
Infiltration	3 (2)
Bronchiectasis	14 (9.2)

was no significant difference in findings such as cough related with feeding, mouth breathing, snoring, and accompanying wheezing in patients with dry and wet cough. Shortness of breath was detected in 13.3% of patients with dry cough and 9.7% of patients with wet cough, failure to thrive was present in 1.7% of patients with dry cough and 10.8% of patients with wet cough ($p=0.500$ and $p=0.030$ respectively). Desaturation was present in three patients (3.2%) with wet cough. Fever and weight loss was detected in only one patient (1.1%) with wet cough. None of the patients with dry cough had crackles, clubbing or tachypnea, whereas among patients with wet cough 39.8% had crackles, 7.5% had clubbing and 6.5 % had tachypnea ($p<0.001$, $p=0.030$, $p=0.050$ respectively). Rhonchus rates were similar in patients with dry and wet cough; rhonchus was present in 11.7% of the patients with dry cough and 18.3% of the patients with wet cough ($p=0.300$).

All patients had a chest X-ray and it was normal in 74 patients (48.4%). The frequency of pathological findings were as follows: peribronchial thickening in 27 patients (17.6%), infiltration in 17 patients (11.1%), chronic changes in 10 patients (6.5%), bronchiectasis in nine patients (5.9%), atelectasis in nine patients (5.9%), bilateral hyperinflation in six patients (3.9%), unilateral hyperinflation in one patient (0.7%).

A thorax CT was present in 34 patients (22.2%). Chest CT findings is shown in Table II. A flexible bronchoscopy was performed in 11 patients (7.2%) in which two patients had tracheomalacia, four patients had bronchomalacia and two patients had infection. The final diagnosis of the two patients with infection were protracted bacterial bronchitis and primary ciliary dyskinesia. Two patients were referred to pediatric surgeons because of findings resembling TEF. In one patient macroscopic flexible bronchoscopy findings were normal but Mycobacterium tuberculosis culture was positive in bronchoalveolar lavage sample. This patient was diagnosed with tuberculosis.

The final diagnosis of the patients is shown in Table III. The longest duration of cough was seen in the patients with bronchiectasis (median 48 weeks (IQR: 34-130), whereas shortest duration of cough was seen in patients with pneumonia (median 4 weeks (IQR:4-8) ($p<0.050$).

Table III: The final diagnosis of patients with chronic cough

Diagnosis	n (%)
Asthma	47 (30.7)
Protracted bacterial bronchitis	31 (20.3)
Upper airway cough syndrome	17 (11.1)
Pneumonia	14 (9.2)
Bronchiectasis	12 (7.8)
Malacia	6 (3.9)
Interstitial lung disease	5 (3.3)
Gastroesophageal reflux -Swallow dysfunction	4 (2.6)
Natural healing	4 (2.6)
Post infectious cough	3 (2)
Immunodeficiency	2 (1.3)
Tuberculosis	2 (1.3)
Tracheoesophageal fistula	2 (1.3)
Psychogenic cough	2 (1.3)
Foreign body aspiration	1 (0.7)
Hydatid cyst	1 (0.7)

The most common diagnoses in patients with wet cough were protracted bacterial bronchitis (33.3%), pneumonia and other lung infections (tuberculosis and hydatid cyst) (17.2%), and bronchiectasis (12.9%). The most common diagnoses in patients with dry cough were asthma (68.3%), upper airway cough syndrome (6.7%), and natural recovery (6.7%).

Reversibility test was performed in 17 (36.2%) of 47 patients diagnosed with asthma and reversibility was positive in all of them. Inhaled fluticasone treatment was initiated to these patients. Thorax CT was performed in one patient who did not respond to treatment. In the thorax CT, there was a hyperechoic appearance in the mediastinal window and a localized increase in aeration was present in the right middle lobe in the parenchyma window consistent with a foreign body in the right intermediate bronchus. The foreign body in the right intermediate bronchus was removed by the pediatric surgeons by rigid bronchoscopy. After rigid bronchoscopy the corticosteroid therapy was discontinued.

In 31 patients diagnosed with protracted bacterial bronchitis cough resolved in 22 patients after two weeks of oral antibiotic treatment. Among the remaining eight patients cough resolved in 7 of them after four weeks of oral antibiotic treatment. Infection was detected by flexible bronchoscopy in one patient who did not respond the standard therapy. During follow up four patients had recurrent protracted bacterial bronchitis. None of the patients with recurrent protracted bacterial bronchitis had bronchiectasis on chest CT.

Nasal saline and nasal steroid treatments were started by the otorhinolaryngologists in patients who were diagnosed with upper airway cough syndrome. The details history of the patients diagnosed with pneumonia revealed that seven patients applied

to the hospital within the two days of the onset of complaints, oral antibiotic treatment was initiated for these patients, but none of them received treatment for more than seven days. Mycoplasma IgM/ IgG positive was positive in nine patients. Patients diagnosed with mycoplasma pneumonia received oral macrolide therapy for ten days. Patients diagnosed with non-mycoplasma pneumonia received oral amoxicillin-clavulanate therapy. All patients responded to antibiotic treatment.

Among patients with bronchiectasis two of them were diagnosed with cystic fibrosis based on history, physical examination and cystic fibrosis genetic analysis. Of the remaining ten patients nine of them had a PICADER score above seven. These nine patients were diagnosed with primary ciliary dyskinesia by whole exome sequencing. The remaining one patient was diagnosed with non-cystic fibrosis and non-primary ciliary dyskinesia. This patient had bronchiectasis localized to the right lower lobe, and no anatomical abnormality was detected by flexible bronchoscopy, except for purulent secretion. Staphylococcus aureus growth was detected in the bronchoalveolar lavage sample.

The diagnosis of interstitial lung disease patients were as follows: hypersensitivity pneumonia, bronchiolitis obliterans, Rubinstein Taybi related interstitial lung disease, cutis laxa related interstitial lung disease and immunodeficiency related interstitial lung disease. Chest physiotherapy was initiated for all patients with interstitial lung disease. Patients with hypersensitivity pneumonia and bronchiolitis obliterans responded to clinical treatment. No specific treatment was given for the remaining patients with interstitial lung disease.

Two patients were diagnosed with tuberculosis. Flexible bronchoscopy was performed first patient with prolonged cough and sputum who had hilar after hilar lymphadenopathy, atelectasis, consolidation and bronchiectasis on thorax CT. Tuberculosis acid-resistant bacillus and polymerase chain reaction was positive and Mycobacterium tuberculosis culture growth was detected in the bronchoalveolar lavage.

The second patient had chronic cough with a family history of tuberculosis. She had

hilar lymphadenopathy and atelectasis in the right middle lobe on thorax CT. Mycobacterium tuberculosis culture growth was positive in sputum culture. Both patients recovered at the end of six months.

DISCUSSION

Cough in childhood is one of the most common reasons for referral to the pediatrician. Chronic cough is burdensome for patients and their families. At the same time, it increases health expenditures due to frequent hospital admissions (5). Because of the significant anatomical and physiological differences between children and adults, and existence of different diseases

and treatment approaches, the first pediatric-based guideline the American College of Chest Physicians, was published in 2006 (2). Cough may be caused by a simple disease such as upper respiratory tract infection or it can be an indicator of a systemic illness such as underlying chronic lung disease, immunodeficiency and heart diseases (12). Since cough can sometimes be the only indicator of respiratory disease, it should be carefully evaluated. Otherwise, it may lead to delayed diagnosis and progression of the disease. In this study, the most common causes of chronic cough were asthma, protracted bacterial bronchitis, and upper airway cough syndrome. Wet cough was present in 60% of patients with chronic cough, and the most common diagnoses in patients with wet cough were protracted bacterial bronchitis, pneumonia and other lung infections (tuberculosis and hydatid cyst), and bronchiectasis, respectively. In patients with dry cough, the most common diagnoses were asthma, upper airway cough syndrome, and natural recovery. While failure to thrive was more frequent in patients with wet cough than patients with dry cough, fever, weight loss and desaturation were only present in patients with wet cough. In addition, crackles, clubbing and tachypnea were prominent findings in patients with wet cough. Seasonal and exercise-induced cough was more frequent in patients with dry cough.

The most common cause of chronic cough was asthma in this study. In the first study which examined the etiology of chronic cough in children, the most common cause of chronic cough was asthma (2). In a systematic review evaluating 14 studies, asthma and protracted bacterial bronchitis were stated as the most common causes of chronic cough (6). Different studies from our country evaluated the reasons of chronic cough., Pedük et al. (13) showed that 23.4% of the children with chronic cough were diagnosed with asthma, whereas this ratio was 39% in the study by Asilsoy et al. (9). Both of the studies stated the most common cause of chronic cough was asthma followed by protracted bacterial bronchitis. Similar results, were reported by Çullas İlarıslan et al. (14) where asthma, protracted bacterial bronchitis, pneumonia and obstructive sleep apnea were the most common causes of chronic cough. In studies conducted abroad, both Marchant et al. (7) as well as Chang et al. (15) showed that protracted bacterial bronchitis was the most common cause of chronic cough. Different results between studies can be explained by the different age groups and regional prevalence of diseases. When Turkish studies supporting this idea are compared with American and Australian studies, it is seen that asthma is the most frequent cause of chronic cough in Turkey (7,9,15,16).

In this study, 60% of patients with chronic cough had wet cough. The frequency of wet cough was similar in studies conducted by Çullas İlarıslan et al. (14) and Gedik et al. (17) study. In a patient with chronic wet cough, clinical evaluation and the improvement of cough with antibiotic treatment suggests the diagnosis of protracted bacterial bronchitis.

CHEST guidelines recommend a two-week course of treatment for protracted bacterial bronchitis (6,10). It is recommended to repeat the course of antibiotics in persistent cough and to perform further investigations such as flexible bronchoscopy only in persistent cases after four weeks of treatment in the same guideline. Common bronchoscopy findings of protracted bacterial bronchitis are purulent airway secretions and airway malaise. While the diagnosis of protracted bacterial bronchitis was based on the results of bronchoscopy and bronchoalveolar lavage in the study by Marchant et al. (7), Asilsoy et al. (9) and Chang et al. (15) diagnosed patients based on clinical findings and response to treatment. In this study, similar to the study by Asilsoy et al. (9) the diagnosis of protracted bacterial bronchitis was made clinically and with response to treatment, and flexible bronchoscopy was performed in only one patient because there was no adequate antibiotic response.

In the differential diagnosis of chronic cough, additional diagnostic methods such as thorax CT and or flexible bronchoscopy can be performed in cases where there is no response to standard treatments or when there is a suspicion of an additional disease. Suppurative lung disease, non-healing pneumonic consolidation and vascular anomalies can be detected with thorax CT (6). In this study, thorax CT was performed in 20% of the patients for diagnostic purposes. The diagnosis based on thorax CT were bronchiectasis, interstitial lung disease, and aspiration suggesting swallowing dysfunction. In addition, foreign body aspiration was diagnosed by thorax CT in a patient who was diagnosed with asthma and did not respond to treatment. The patients were diagnosed with malacia and TEF by flexible bronchoscopy. The thorax CT and flexible bronchoscopy was also helpful in diagnosing psychogenic cough by excluding other etiological causes of chronic cough.

In this study, one of the common causes of chronic cough was pneumonia (9%). *M. pneumoniae* IgM or IgG antibodies were positive in nine of 14 patients diagnosed with pneumonia. In studies conducted in our country on chronic cough, Çullas İlarıslan et al.(14) stated the incidence of pneumonia as 7.6%, and Gedik et al. (17) found it to be 3%. In the study by Asilsoy et al. (9) it was stated that one of the common causes of chronic cough was pneumonia and 17 of 41 patients were positive for *M. pneumoniae* IgM or IgG antibodies. The authors stated that although these results suggest acute infection in only some of the patients, such factors may cause chronic cough. The different follow-up periods in the studies may explain pneumonia frequency in patients with chronic cough. In this study, which had a shorter follow-up period, patients were frequently diagnosed with pneumonia, while in the study of Gedik et al. (17) where patients were followed up for a longer period of time the frequency of pneumonia was much lower. In the presence of recurrent pneumonia, the underlying etiological causes are investigated and patients can be diagnosed with different diseases such as chronic suppurative lung disease

and immunodeficiency. These findings suggest that patients with pneumonia in should to be followed up for recurrent pneumonia, and further investigations should be performed in the presence of recurrent pneumonia.

Smoking is one of the leading causes that triggers cough. In this study, while 18% of children with chronic cough had secondhand tobacco smoke exposure, this rate increased to 30% in the group with dry cough. Secondhand tobacco smoke exposure is a modifiable risk factor affecting long-term lung health. By preventing secondhand tobacco smoke exposure, lung infections and progression of chronic lung diseases can be prevented.

This study has some limitations. First, a validated cough questionnaire was not used in this study and patients did not keep a cough diary. In addition, a longer follow-up period may allow a better understanding of the natural history of cough, recurrence rates, and diagnostic changes. Finally, the fact that the study was conducted in the pediatric pulmonology outpatient clinic may not reflect the real population.

In conclusion, chronic cough is an important health problem that patients frequently seek medical consult. The most common reasons are asthma, protracted bacterial bronchitis and upper airway cough syndrome. The differential diagnosis should be made by pediatricians based on specific cough pointers, careful physical examination and tests performed in line with the recommendations of the guidelines.

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