Evaluation of Chronic Cough Etiologies in Children

Çocuklarda Kronik Öksürük Sebeplerinin Değerlendirilmesi

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ABSTRACT

Objective: Cough is one of the leading causes of hospitalization in children worldwide. It should be considered important because it can be a symptom of various serious diseases and affects the quality of life of the child. A differential diagnosis should be performed on all children with a chronic cough. This study aimed to determine the etiologies in patients evaluated for chronic cough.

Material and Methods: The study included patients admitted to the pediatric immunology and allergy outpatient clinic, with the complaint of chronic cough between the ages of 0–18 years. Clinical and demographic characteristics of patients were recorded.

Results: This study included 323 patients between the ages of 0-18years. The median age of the patients was 7 (interquartile range: 5-9.7) years. One hundred and forty five (45%) of the patients were female. One hundred seventy-nine (55.4%) patients had a family history of atopic diseases such as asthma and/or allergic rhinitis. The presence of aeroallergen sensitivity was demonstrated in 127 patients. One hundred and forty-four (44.6%) patients were diagnosed with asthma, 75 (23.2%) patients with wheezing, 54 (16.7%) patients with post-infectious cough, 43 (13.3%) patients with postnasal drip syndrome, 4 (1.2%) patients with gastroesophageal reflux, 2 (0.6%) patients with foreign body aspiration, and 1 (0.3%) patient with psychogenic cough. Moreover, two patients with asthma, and one patient with wheezing had reflux symptoms in addition to the diagnosis of asthma and wheezing. One patient was found to have a partial IgA deficiency, and 18 patients had hypogammaglobulinemia. Immunoglobulin replacement therapy was initiated for a patient with hypogammaglobulinemia. Of the 219 patients diagnosed with asthma or wheezing, 144 had an atopic disease in the family ($p<0.001$). It was found that one hundred and eighty-five patients (57.3%) had domestic smoke exposure. Furthermore, smoke exposure was observed in 58 (77.3%) of 75 patients under the age of 6 years who were followed up with the diagnosis of wheezing ($p= 0.010$).

Conclusion: In our study, asthma, which is one of the most common causes of chronic cough in the literature, was found to be the most common cause. For a correct approach when making a differential diagnosis in pediatric patients presenting with chronic cough, the patient's history, physical examination, laboratory tests, and risk factors should be evaluated as a whole with systematic evaluation.

Key Words: Chronic Cough, Child, Asthma, Wheezy Infant

ÖZ

Amaç: Öksürük, tüm dünyada çocukluk çağında en sık hastaneye başvuru sebeplerinden biridir. Çeşitli ciddi hastalıkların da belirtisi olabilmesi ve çocuğun hayat kalitesini etkilemesi nedeniyle önemsenmelidir. Tüm kronik öksürüğü olan çocuklar ayırıcı tanı açısından değerlendirilmelidir. Bu çalışmada kronik öksürük sebebiyle değerlendirilen hastalarda etyolojilerin belirlenmesi amaçlanmıştır.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The approval for the study was obtained from the Gaziantep University Clinical Research Ethics Committee (no:2022/372).

Contribution of the Authors / Yazarların katkısı: Yilmaz Topal Ö: 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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Gereç ve Yöntemler: Çalışmaya çocuk immünoloji ve alerji polikliniğine 0-18 yaş aralığında kronik öksürük şikayeti ile başvuran hastalar dahil edildi. Hastaların klinik ve demografik bilgileri retrospektif olarak dosyalarından kayıt edildi.

Bulgular: Bu çalışmada 0-18 yaş aralığında 323 hasta yer almaktaydı.Hastaların yaş ortancası 7 yıl (çeyreklerarası aralık:5-9.7)'di. Hastaların 145'i (%45) kızdı. Yüzyetmişdokuz (%55.4) hastanın ailesinde atopik hastalık öyküsü vardı. Hastaların 127'sinde aeroalerjen duyarlılığının varlığı gösterildi. Yüzkırkdört (%44.6) hastaya astim, 75 (%23.2) hastaya hışıltılı çocuk, 54 (%16.7) hastaya postenfeksiyoz öksürük, 43 (%13.3) hastaya postnazal akıntı sendromu, 4(%1.2) hastaya reflü, 2 (%0.6) hastaya yabanci cisim aspirasyonu, 1 (%0.3) hastaya psikojenik öksürük tanısı konuldu. Ayrıca iki hastada astım, bir hastada ise hışıltılı çocuk tanısına ek olarak reflü semptomlarının olduğu görüldü.Bir hasta parsiyal IgA eksikliği, 18 hasta da hipogamaglobulinemi sebebiyle takibe alındı. Onsekiz hastanin birine ise immunoglobulin replasman tedavisi başlandi. Astım veya hışıltılı çocuk tanısı alan 219 hastanın 144'ünde aile de atopik bir hastalık olduğu öğrenildi (p<0.001). Yüzseksenbeş hastada (%57.3) ev içi sigara maruziyeti olduğu öğrenildi. Ayrıca 6 yaş altında hışıltılı çocuk tanısı ile takibe alınan 75 hastanın 58'inde (%77.3) sigara maruziyeti olduğu görüldü (p= 0.010).

Sonuç: Literatürde kronik öksürüğün en sık nedenleri içinde yer alan astım, bizim çalışmamızda da en sık sebep olarak saptanmıştır. Kronik öksürük ile başvuran çocuk hastalarda ayırıcı tanı yaparken, sistematik değerlendirme ile hastanın öykü, fizik muayene ve laboratuvar tetkikleri ile risk faktörleri bütün olarak değerlendirilmelidir.

Anahtar Sözcükler: Kronik Öksürük, Çocuk, Astım, Hışıltılı Çocuk

INTRODUCTION

Chronic cough is defined as a cough that lasts more than 3–4 weeks and is one of the most common childhood symptoms (1, 2). Furthermore, cough is one of the leading causes of hospitalization in children worldwide (3, 4). It is a major source of concern for parents in the pediatric population. (5)

Chronic cough in children differs from chronic cough in adults in terms of etiology and management, as it may be a symptom of an underlying disease (6). Young children are likely to cough more as they are more likely to have infections. In the light of the data based on the subjective observations of the parents, it has been reported that up to 10% of preschool- and early-school-aged children have a chronic cough without wheezing at any time (7). Another study reported that 35% of preschool children reported coughing in any month (8). A multicenter study of children aged 7 to 11 found that 9% of them had a chronic cough (9).

Chronic cough is often nonspecific and may be accompanied by causes that cannot be easily identified during the initial assessment (10). Congenital airway problems, postnasal drip, rhinitis, rhinosinusitis, asthma, eosinophilic bronchiolitis, and gastroesophageal reflux disease (GERD), foreign body aspirations, and protracted bacterial bronchiolitis are the underlying reasons for this problem (11, 12). Asthma was found to be the most common cause in three studies focusing on the etiology of chronic cough in children in Turkey, while postnasal drip syndromes were found to be the most common cause in another study (13-16).

Chronic cough in children is associated with impaired quality of life, school absences, multiple doctor visits, (17) and inappropriate use of antibiotics (18, 19). A differential diagnosis should be performed on all children with a chronic cough.

This study aimed to determine the etiologies in patients evaluated for chronic cough.

MATERIALS and METHODS

The study included patients admitted to the pediatric immunology and allergy outpatient clinic at Gaziantep Cengiz Gökçek Gynecology and Pediatrics Hospital between 01.02.2022-08.08.2022 with the complaint of chronic cough between the ages of 0–18 years. The approval for the study was obtained from the Gaziantep University Clinical Research Ethics Committee (no:2022/372).

Coughs are classified as acute, prolonged acute, or chronic based on their duration. Acute cough includes coughs lasting up to 14 days. Prolonged acute coughing includes coughs lasting between 2 and 4 weeks. Chronic cough is a cough that lasts longer than 4 weeks (20). In this study, chronic cough was defined as cough lasting more than 4 weeks. The patients were evaluated by taking into account the American College of Chest Physicians (ACCP) guidelines on the approach to chronic cough (21). Accordingly, further examinations were planned for the differential diagnosis of patients with specific disease symptoms based on the initial evaluations. After the evaluation of the lung x-rays of the patients, the patients with no specific findings were followed up, and in the case of their complaints not regressing, the necessary treatment was started based on the nature of the cough.

Demographic characteristics of patients such as gender, age at clinical visit, personal and family history of allergic and chronic diseases, cigarette smoke exposure history of the patient, symptoms and physical examination results, and skin prick test results were recorded. Immunoglobulin (Ig) levels were requested in (22) patients with frequent infections and findings defined as "10 alarm findings" for primary immunodeficiency, and these results were also recorded retrospectively. The patients' Ig values were classified as low or normal according to the relevant age-related reference intervals for each Ig value. For these reference intervals, we used reference systems based on age-related normal Ig ranks determined in Turkish children (23).

A skin prick test was performed on patients with suspected allergen sensitivity in their history.

Skin Prick test:

Skin prick tests with dermatophagoides farinae (Allergopharma), Dermatophagoides pteronyssinus (ALK), Alternaria (ALK), Aspergillus (Lofarma), Canis familiaris (ALK), Cat epithelia (Allergopharma), Cockroach (ALK), Grasses/cereals (Allergopharma), 7-grass polen mix solution (Phleum pratense, Dactylis glomerate, Poa Pratensis, Agrostis capillaris, Festuca pratensis, rye, sweet vernal grass) (ALK), Olive tree (Allergopharma), Composite mix (Mugwort, Golden Rod, Sunflower, Cocklebur) (Lofarma), willow tree (Allergopharma), Birch mix (Grey Alder,White Birch (Betulacea Mix)) (Lofarma), Sheep dander (Inmunotek) were performed in patients with positive (histamine) and negative (saline) controls and were interpreted 15 minutes after the application of the allergens to the skin. A positive SPT result was accepted as a wheal diameter of 3 mm or larger.

Statistical Analysis:

Statistical methods: Statistical analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY). Data were reported as number and percentage for nominal variables and as mean and SD, or median and interquartile range (IQR) for continuous variables. The Chi-square test was used for comparisons of nonparametric data.

RESULTS

This study included 323 patients between the ages of 0-18 years. The median age of the patients was 7 (interquartile range: 5-9.7) years. One hundred and forty five (45%) of the patients were female, and 178 (55%) were male.

One hundred and forty-four (44.6%) patients were diagnosed with asthma, 75 (23.2%) patients as wheezy infant, 54 (16.7%) patients with post-infectious cough, 43 (13.3%) patients with postnasal drip syndrome, 4 (1.2%) patients with gastroesophageal reflux, 2 (0.6%) patients with foreign body aspiration, and 1 (0.3%) patient with psychogenic cough. Moreover, two patients with asthma, and one patient with wheezing had GERD symptoms in addition to the diagnosis of asthma and wheezy infant. Figures 1 and 2 show the etiology of chronic cough according to whether the patients were under or above the age of 6.

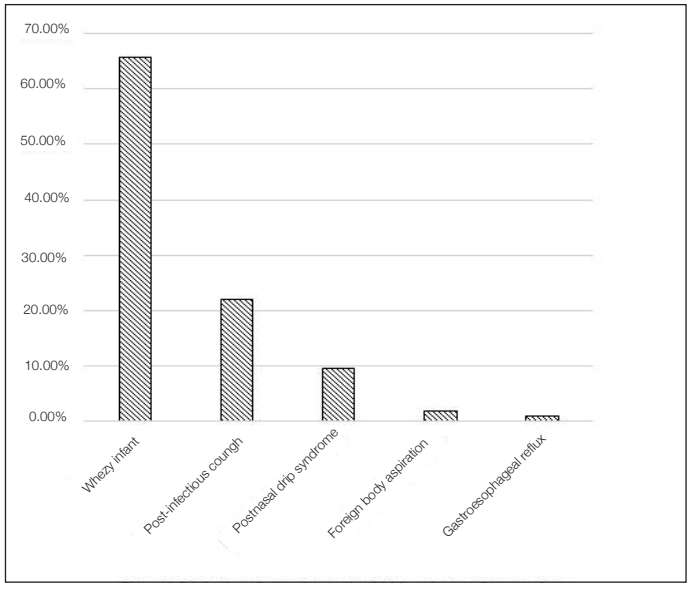

Figure 1: Etiologies of chronic cough of 114 patients < 6 years of age.

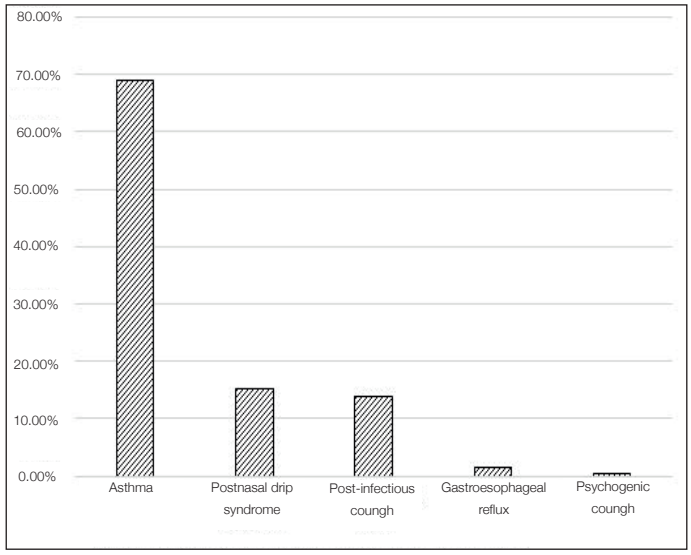

Figure 2: Etiologies of chronic cough of 209 patients ≥ 6 years of age.

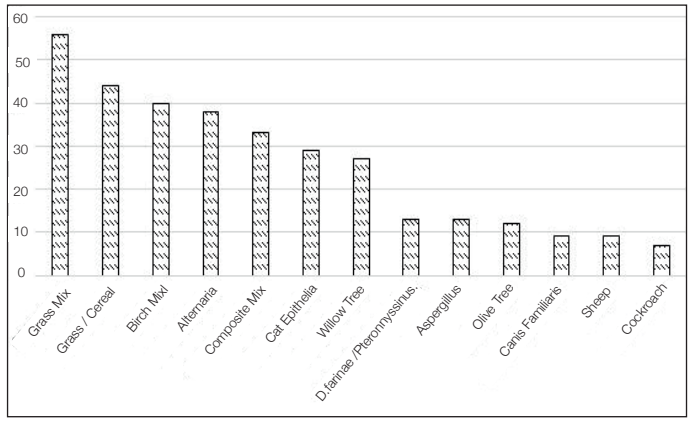

Figure 3: Aeroallergen sensitivites of the patients. (D.farinae / Pteronnyssinus: Dermatophagoides farinea / Pteronyssinus.)

Inhaled corticosteroids (ICS) treatment was started on 216 patients (66.9%). 24 patients were treated with antibiotics, 1 patient with nasal steroid (NS) and leukotriene receptor antagonist (LTRA), 3 patients with antihistamines (AH) and NS, 3 patients with anti-GERD treatment, and 1 patient with LTRA, while 184 patients were started on ICS treatment alone. Antibiotic treatment was started in 87 patients (27%), 51 patients received only antibiotic treatment, while 1 patient received with AH and NS, 1 patient received with anti-GERD treatment, 2 patients received with LTRA, and 8 patients received with NS

Table I: Association of atopic disease history in family and having asthma or wheezy

	Asthma or wheezy infant n (%)	Other etiologies n (%)	p
Having atopic disease history in family	144 (65.75)	35 (33.65)	<0.001

Table II: Association of smoke exposure history and having wheezy in patients under 6 years

	Wheezy infant n (%)	Other etiologies n (%)	p
Having smoke exposure history	58 (77.3)	21 (53.85)	<0.010

treatment. Nasal steroid treatment was started on 45 patients. While 12 patients received only NS treatment, 18 patients received NS and AH, and 2 patients received NS with LTRA. Three patients were treated with anti-GERD treatment alone, and four patients were treated with LTRA only.

One hundred seventy-nine (55.4%) patients had a family history of atopic diseases such as asthma and/or allergic rhinitis. Prick test to show aeroallergen sensitivity was not performed on 101 patients. The presence of aeroallergen sensitivity was demonstrated in 127 (57.2%) of 222 patients who underwent a Prick test. Aeroallergen sensitivities of the patients are shown in Figure 3.

The immunoglobulin levels of 109 patients who described recurrent infections were also examined. Among these patients, one patient was found to have a partial IgA deficiency, and 18 patients had hypogammaglobulinemia. A patient with hypogammaglobulinemia was 11 months old, and immunoglobulin replacement therapy was initiated due to a serum IgG level of <200 mg/dl. The results of a genetic mutation analysis to identify the patient's primary immunodeficiency are awaited.

Of the 219 patients diagnosed with asthma or as wheezy infant, 144 had an atopic disease in the family. This rate was statistically higher in patients followed up with the diagnosis of asthma and/or wheezing compared to other patients (p: <0.001) (Table I). It was found that one hundred and eighty-five patients (57.3%) had domestic smoke exposure. Furthermore, smoke exposure was observed in 58 (77.3%) of 75 patients under the age of 6 years who were followed up with the diagnosis of wheezing. This rate was statistically higher in patients under the age of 6 who were followed up with other diagnoses compared to the rate of smoking exposure (p= 0.010) (Table II.).

DISCUSSIONS

Coughing can be the first symptom of many diseases or conditions that affect the respiratory tract as it is more than a defense mechanism. Almost all respiratory diseases, as well as some extrapulmonary diseases in some cases, can cause chronic cough. It is critical for the physician to detect serious illnesses that require immediate treatment (24). However, an inadequate definition of the disease that causes chronic cough results in patients receiving inappropriate treatments, which can be harmful to both patient health and the national economy by causing unnecessary drug use.

In our study, asthma, which is one of the most common causes of chronic cough in the literature, was found to be the most common cause. Chronic cough in asthma can occur in a variety of clinical settings and is not always associated with airflow obstruction, wheezing, or dyspnea. Asthma can manifest itself mostly as nocturnal cough, and the diagnosis is supported by the presence of bronchial hypersensitivity (11, 25).

Asthma pathogenesis is influenced by both genetic and environmental factors, and the majority of children with asthma have an allergic component of the disease. Allergen sensitivity plays a role as an important risk factor in the development of asthma. Allergen sensitivity in asthma patients has been reported to range between 44% and 60% (26-28). In another allergen evaluation conducted in Gaziantep with patients who applied with the complaint of chronic cough, 57.1% of the patients were observed to have at least one allergen sensation. However, food allergens and aeroallergens were evaluated together in this study (29). An aeroallergen evaluation was performed in our study, and the presence of aeroallergen sensitivity was found in 127 (57.2%) of 222 patients.

In our study, 16.7% of the patients were diagnosed with post-infectious cough. Cough reflex hypersensitivity, which begins with an airway viral or bacterial infection, can last for weeks and is a common cause in people of all ages (30-32). It often causes dry cough and no other symptoms are seen. Recovery takes time in most patients with post-infection cough and is associated with hypersensitivity (6).

Gastro-esophageal reflux disease should be considered in children with prolonged cough and recurrent ear infections. The cough is both long-term and usually non-productive in these patients. Studies have emphasized that 75% of patients may have cough as the only symptom of GERD (33, 34). In our study, 7 patients were diagnosed with GERD.

Immune deficiencies cause frequent recurrent lung infections, diarrhea, aphtha, and other infections. Along with sibling stories, it is a disease that should be kept in mind in Turkey, where consanguineous marriages are common (35). In our study, 19 patients were followed up for immunodeficiency, and immunoglobulin replacement therapy was started in 1 patient. Chronic cough can be a warning sign of many underlying diseases. Therefore, these diseases should also be kept in mind.

Exposure to smoke is an important cause of cough in children. Passive smoking has been shown to increase the risk of lung infection and to weaken pulmonary functions (2, 35). In our study, it was found that 57.3% of the patients had domestic smoke exposure. It was observed that there was a significant difference in smoke exposure between the children under the age of 6 with wheezing and the patients who were followed up due to other chronic coughs, and that smoke exposure could be a facilitating factor for wheezing in children. Moreover, the presence of atopic disease in the family was found to be significantly different in patients diagnosed with asthma or wheezing compared to other patient groups when all age groups were examined.

In conclusion, it is important to provide disease-specific treatment in pediatric patients with chronic cough if the underlying cause is determined. Among the preventable factors, reasons such as avoiding smoke exposure and allergens causing sensitization should be reviewed. For a correct approach when making a differential diagnosis in pediatric patients presenting with chronic cough, the patient's history, physical examination, laboratory tests, and risk factors should be evaluated as a whole with systematic evaluation.

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