

## PAPER DETAILS

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# Characteristics of pediatric patients with chronic cough: data from a pediatric immunology and allergy outpatient clinic

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## ABSTRACT

**Aims:** Chronic cough is a common complaint in childhood. A differential diagnosis is very important in children with a chronic cough. We aimed to investigate the etiology and underlying risk factors of chronic cough in children.

**Methods:** Patients aged 1-18 years who were referred to Sincan Training and Research Hospital Pediatric Immunology and Allergy Outpatient Clinic were included. Demographic, clinical and laboratory features of patients were recorded.

**Results:** The study included 403 children with a median age of 8 years (IQR 6-12) (53% males). 30% of patients had allergic rhinitis (AR), 4.7% of patients had atopic dermatitis (AD), and 2% patients had food allergy (FA) history. 78 (19.3%) patients also complained of dyspnea and 9 (2.2%) patients had a diagnosis of cardiovascular disease. 245 (60.8%) asthma-wheezy infant, 107 (26.6%) post-infectious cough, 36 (9%) postnasal drip syndrome, 9 (2.2%) gastroesophageal reflux and 6 (1.5%) psychogenic cough were detected in the whole group. The number of patients with accompanying dyspnea 76 (28.5%) and familial history of atopy 113 (42.3%) were higher in the asthma-wheezy infant group than others group ( $p<0.001$  vs.  $p<0.001$ ). Skin prick tests were performed in 273 patients and the presence of aeroallergen sensitivity was shown in 122 (30.2%) patients. Immunoglobulin deficiency was detected in 43 (10.7%) patients. Serum IgG, IgA, and IgM levels were low in 26 (6.5%), 18 (4.4%), and 12 (3%) patients, respectively.

**Conclusion:** We found the most common reasons are asthma and post-infectious cough in patients. Chronic cough can be the first symptom of primary immunodeficiency diseases and systemic diseases. A detailed history is necessary to avoid unnecessary procedures, treatments and to avoid delay in diagnosis.

**Keywords:** Asthma, chronic cough, children, immunoglobulin

## INTRODUCTION

Chronic cough is a frequent cause of hospital admission and significantly affects the quality of life of the child and parents.<sup>1,2</sup> Chronic cough is considered as a daily cough lasting four or more weeks in children.<sup>3,4</sup> Estimates for the prevalence of chronic cough in school-aged children range as high as 10.4%.<sup>5</sup> The differential diagnosis is extensive. The most common causes of chronic cough include recurrent respiratory tract infections, postinfectious cough, protracted bacterial bronchitis, gastroesophageal reflux disease (GERD), asthma, and upper airway cough syndrome (UACS). The most common cause of chronic specific cough is asthma.<sup>6</sup> Two studies from the USA and Türkiye reported higher percentages of asthma, GERD and UACS diagnoses in children with chronic cough.<sup>7,8</sup>

It is very important to know the history, symptoms and possible related factors to determine the cause of chronic cough. The character of the cough, triggering factors, accompanying symptoms and findings, conditions that increase cough, comorbid diseases, treatments, and family history of atopy

should be questioned in detail. The main treatment for chronic cough should be based on the underlying cause.<sup>9</sup>

Due to the high prevalence of chronic cough in children and its burden on quality of life, it is important to identify the most common causes of chronic cough so the present study aimed to define the underlying causes of chronic cough in children.

## METHODS

### Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee approval was obtained for this retrospective study (Date: 10.09.2024, Decision No: 2024-BÇEK/150).

### Study Population and Data Collection

The study included children aged 1-18 years with chronic cough who were being followed at Pediatric Immunology

and Allergy Outpatient Clinic at Sincan Training and Research Hospital between December 2023 and September 2024. We evaluated demographic information (age, gender, family history, etc.), clinical features and medical history (cough character, wheezing, rhinitis, respiratory tract infection history, exposure to secondhand tobacco smoke and treatments), presence of atopic comorbidities (AR, AD, FA), total serum IgE, Skin prick test (SPT) and Lung function tests (LFTs) (FEV 1%, FEF 25%-75%) results. LFTs were administered to all asthma patients under the participant's supervision, by American Thoracic Society guidelines.<sup>10</sup> The diagnosis of asthma/recurrent wheezing, allergic rhinitis and atopic dermatitis was made according to international guidelines.<sup>11-13</sup> A cough lasting longer than four weeks was diagnosed as chronic cough and we used the "CHEST guideline and expert panel report" guideline for diagnosis, management and treatment methods in chronic cough.<sup>9,14</sup> Serum IgM, IgA, and IgG levels were assessed for primary immunodeficiency diseases (PID) in patients with frequent and severe infections according to age-related reference intervals.<sup>15,16</sup>

**Skin Prick Tests**

In the routine practice of the pediatric immunology and allergy outpatient clinic, SPT was performed with common aeroallergens [Dermatophagoides pteronyssinus, Dermatophagoides farinea, cat, dog, Alternaria alternata, Cladosporium herbarum, tree pollen mix (Betula pendula, Corylus avellana, Olea europaea, cupressus), weed pollen mix (Artemisia vulgaris, Chenopodium album, Wall pellitory), grass pollen mix (Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis), Cynodon dactylon]. Allergen extracts [Lofarma®, (Italy)] were performed on the volar surface of the forearm with positive and negative controls and measured after 15 minutes. Positive results were defined as a mean wheal diameter 3 mm greater than the negative control.<sup>17,18</sup>

**Statistical Analysis**

Data analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Values are shown as the median and interquartile range for non-normally distributed data. Descriptive analysis was used to characterize the patients. Pearson's Chi-square ( $\chi^2$ ) test was used for between-group comparisons. The Mann-Whitney U test was used to compare values. All statistical tests were two-sided, and the level of statistical significance was set at  $p < 0.05$ .

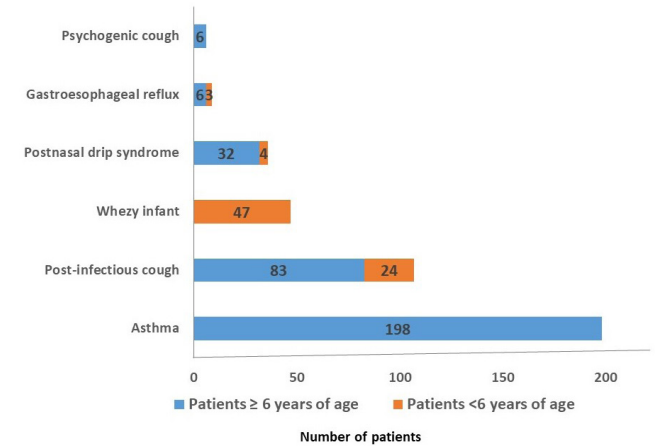
**RESULTS**

**Study population**

The study included 403 children with a median age of 8 years (IQR 6-12) (53% males). 30% of patients had allergic rhinitis, 4.7% of patients had atopic dermatitis history, and 2% of patients had FA. 78(19.3%) patients also complained of dyspnea and 9 (2.2%) patients had a diagnosis of cardiovascular disease. 128 (31.8%) patients had a family history of atopic diseases, and 156 (38.7%) patients had tobacco smoke exposure (Table).

**Etiologies of Chronic Cough**

When the etiologies of chronic cough were examined; 245 (60.8%) asthma-wheezy infants, 107 (26.6%) post-infectious cough, 36 (9%) postnasal drip syndrome (PNDS), 9 (2.2%) gastroesophageal reflux and 6 (1.5%) psychogenic cough were detected in the whole group. We divided the study group according to age by six years. 78 (19.4%) patients were <6 years and 325 (80.6%) patients were  $\geq 6$  years age. In <6 years age group, 47 (60.2%) patients were diagnosed with wheezy infant, 24 (30.8%) patients with post-infectious cough, 4 (5%) patients with postnasal drip syndrome and 3 (3.8%) patients with gastroesophageal reflux. In  $\geq 6$  years age group; 198 (61%) patients were diagnosed with asthma, 83 (26%) patients with post-infectious cough, 32 (9.8%) patients with postnasal drip syndrome, 6 (1.8%) patients with psychogenic cough and 6 (1.8%) patients with gastroesophageal reflux (Figure 1). Four patients were diagnosed with bronchiectasis during follow-up.



**Figure 1.** Diagnosis of patients with chronic cough according to age of six years

**Table.** The characteristics of the study group and its subgroups according to diagnosis of patients

	Whole group (n: 403)	Asthma-wheezy infant (n: 267)	Other diagnoses (n: 136)	p value
Age, year*	8 (6-12)	7 (5-12)	8 (6-11)	NS
Gender-male, n (%)	214 (53)	142 (53.2)	72 (53)	NS
Dispne, n (%)	78 (19.3)	76 (28.5)	2 (1.5)	<0.001
Atopy, n (%)	122 (30.2)	84 (31.5)	38 (28)	NS
AR, n (%)	121 (30)	88 (33)	33 (24.2)	0.072
AD history, n (%)	19 (4.7)	14 (5.2)	5 (3.7)	NS
FA history, n (%)	8 (2)	5 (1.9)	3 (2.2)	NS
Cardiovascular disease, n (%)	9 (2.2)	7 (2.6)	2 (1.5)	NS
Familial history of atopy, n (%)	128 (31.8)	113 (42.3)	15 (11)	<0.001
Tobacco smoke exposure, n (%)	156 (38.7)	104 (39)	52 (38.2)	NS

\*Median, IQR: Inter quartile range, NS: Nonsignificant, AR: Allergic rhinitis, AD: Atopic dermatitis, FA: Food allergy

### Asthma-Wheezy Infant and Other Groups Comparison

When asthma-wheezy infant and other groups were evaluated; 267 (66.3%) patients were followed with asthma-wheezy infant and 136 (33.7%) patients were followed with other diagnoses. The number of patients with accompanying dyspnea 76 (28.5%) and familial history of atopy 113 (42.3%) were higher in the asthma-wheezy infant group than others group ( $p<0.001$  vs.  $p<0.001$ ), respectively. Although, there was no difference in tobacco smoke exposure, age, gender and atopic comorbidities (Table).

### Skin Prick Tests

Skin prick tests were performed in 273 patients and the presence of aeroallergen sensitivity was shown in 122 (30.2%) patients. 18.4% of patients were sensitized to grass pollen, 10.4% to weed pollen, 8.4% to cat, and 7.2% to house dust mite. Aeroallergen sensitivities of the patients are shown in Figure 2.

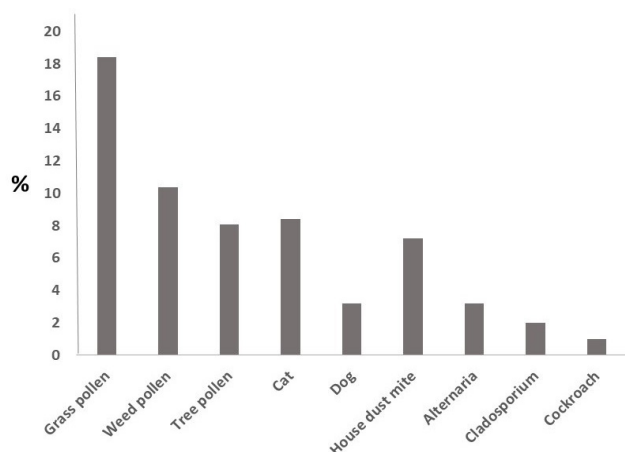


Figure 2. Aeroallergen sensitivities of the study population

### Laboratory Characteristics of Study

Immunoglobulin deficiency was detected in 43 (10.7%) patients. Serum IgG, IgA, and IgM levels were low in 26 (6.5%) patients, 18 (4.4%) patients, and 12 (3%) patients, respectively (Figure 3). The median level of serum IgE was 54 IU/ml (IQR 22-181). When the spirometric values of the patients were examined, the median value of FEV<sub>1</sub> was 104 (IQR 95.5-116) and for FEF<sub>25-75%</sub> was 105 (IQR 87-116). There was no significant difference in IgE levels and LFTs levels according to asthma-wheezy infant and other groups comparison.

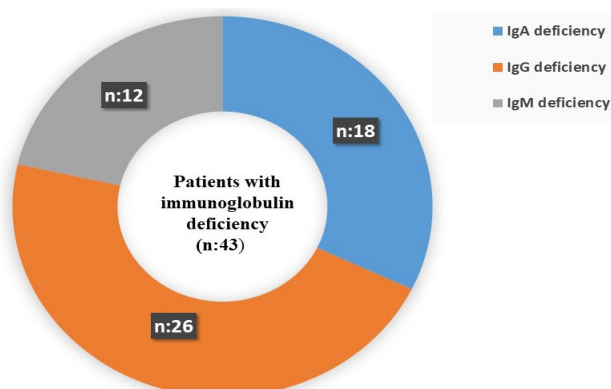


Figure 3. Distribution of patients with immunoglobulin deficiency

### Treatment

Antibiotic treatment was started in 81 (20%) patients and inhaled corticosteroids (ICS) treatment was started in 198 (49%) patients. 70/198 (35.4%) of these ICSs were inhaled corticosteroids-long-acting beta agonist combination. 115 (28.5%) patients received leukotriene receptor antagonist treatment. 103 (25.6%) patients were treated with antihistamines and 83 (20.6%) were treated with nasal steroids. Four patients were treated with anti-GERD treatment. Six patients received trimethoprim-sulfamethoxazole prophylaxis because of primer antibody deficiency and recurrent infection. One patient received omalizumab treatment due to severe asthma diagnosis.

### DISCUSSION

Chronic cough is one of the most common reasons for referral to the pediatrician in childhood. Chronic cough is distressing and burdensome for patients and their families and it increases health expenditures due to frequent hospital admissions. Coughing can be the first symptom of many systemic diseases or may be caused by a simple disease such as upper respiratory tract infection.<sup>19</sup> Therefore, it is important for the physician to know the appropriate definition of chronic cough and its underlying causes. The study encompassed children aged 1-18 years with chronic cough and investigated the causes of chronic cough in these patients.

In our study, the most common cause of chronic cough was asthma 49%, approximately half of the whole patients group. In most studies on chronic cough etiology, asthma has been found the most common underlying cause.<sup>14,20,21</sup> In our report, 19.3% of patients also complained of dyspnea in whole group, 97% of these patients were in the asthma-wheezy infant group. Asthmatic patients often complain of chest tightness, wheezing, dyspnea and cough. These symptoms may occur alone or in different combinations. Sometimes the only symptom is chronic cough, which is called "cough variant asthma".<sup>22,23</sup> Although nearly 40% of all young children worldwide experience at least one episode of asthmatic symptoms such as wheezing, coughing, dyspnea, only 30% of preschoolers with recurrent wheezing are eventually diagnosed with asthma by the age of six years.<sup>24</sup> We diagnosed wheezy infants in 47 (60.2%) patients in the under 6 age group.

The duration and dose of exposure to allergens and irritant factors, genetic predisposition, and allergen sensitivity may be risk factors for the development of asthma in individuals.<sup>25</sup> We show aeroallergen sensitivity in 30.2% of patients, 69% of them in asthma-wheezy infant group. In our study, 38.7% of patients had tobacco smoke exposure. Exposure to tobacco smoke can negatively affect lung development in infants and cause wheezing, and is a risk factor for the development of asthma in the future. The presence of atopy in parents has been shown a risk factor for the development of asthma in children.<sup>25</sup> In accordance with the literature, we found familial history of atopy were significantly higher in the asthma-wheezy infant group than others group.

We found post-infectious cough, the second cause of chronic cough in our study. Postinfectious cough should be



considered when cough persists after an upper respiratory tract infection. It has been shown that up to 40% of school-age children proceed coughing 10 days after a common cold, with 10% of preschool children having a persistent cough after 25 days.<sup>26</sup> Postinfectious cough is self-limited and will resolve spontaneously, but it may persist for three or more weeks. In the etiology of chronic cough, epithelial disruption and inflammation are suggested to play a main role. Inflammation of the mucosa promotes the production of mucus and in this situation stimulating the cough receptors to clearance airways.<sup>27</sup>

In our study, 9% of the patients were diagnosed with postnasal drip syndrome. PNDS is a clinical condition that develops directly with inflammatory nasal secretions or due to mechanical stimulation and irritation of cough receptors belonging to afferent fibers in the upper airways. The leading causes of PNDS are sinusitis, allergic and non-allergic rhinitis, vasomotor rhinitis, postinfectious rhinitis, and environmental irritants. In treatment, first-generation antihistamines and decongestants were recommended.<sup>3,28</sup> In our study, 25.6% of patients were treated with antihistamines and 20.6% of patients were treated with nasal steroid due to PNDS and AR symptoms.

Gastroesophageal reflux disease should be considered with a prolonged cough or unexplained lung disease or recurrent otitis media attacks in children. Respiratory symptoms can be observed in 10-20% of patients with GERD, and cough may be the only symptom of GERD.<sup>22</sup> In the present report, nine patients were diagnosed with GERD and six patients, all of them adolescents were diagnosed with psychogenic cough, after detailed history and examination. Many patients with psychogenic cough do not cough during sleep, are not awakened by cough, and frequently do not cough during pleasant distractions. Psychogenic cough is a diagnosis of exclusion<sup>29</sup> as we diagnosed six patients in this way.

Recurrent lung infections and chronic cough may be the first warning signs of PID in pediatric patients.<sup>30</sup> Antibody deficiencies are the most common PID group. The subgroup of PID that most frequently presents with pulmonary findings is antibody deficiencies.<sup>30,31</sup> In our study, 10.7% of patients were followed up for immunoglobulin deficiency and trimethoprim-sulfamethoxazole prophylaxis treatment was started in six patients. In primary immunodeficiency diseases, it is important to make early diagnosis, monitor respiratory complications, and provide immunoglobulin replacement therapy as the basic treatment approach and to give prophylactic and therapeutic doses of antimicrobial therapy in case of infection.

### Limitations

The main limitation of this retrospective study is that the study was conducted in pediatric immunology and allergy outpatient clinic may not reflect the real population. Although, detection of underlying diseases and determination of risk factors of chronic cough were examined in accordance with the purpose of the study.

## CONCLUSION

We found the most common causes are asthma, post-infectious cough and postnasal drip syndrome in children with chronic cough. Factors that may cause or trigger cough should be carefully questioned, and a diagnosis and treatment algorithm in accordance with current guidelines should be followed. A detailed history is necessary to guide further testing, to avoid unnecessary procedures and to avoid delay in diagnosis. Immunoglobulin deficiency was detected in ten percent of our patients. It should not be forgotten that respiratory system symptoms, especially chronic cough, may often be the first presenting symptom in primary immunodeficiency diseases.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 10.09.2024, Decision No: 2024-BÇEK/150).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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