



# Etiological Evaluation of Infants with Wheezing

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## Abstract

**Objective:** Patients with recurrent wheezing should be evaluated for asthma and the differential diagnosis should be posed carefully. The study aimed to evaluate the demographic and etiological characteristics of patients presenting with recurrent wheezing less than 3 years.

**Methods:** Ninety-two children with wheezing were included in this retrospective study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The demographic characteristics, number of wheezing episodes over the last year, the number of hospitalizations, and eosinophil counts were recorded.

**Results:** The mean age of the participants was 19.9+9.4 months and the youngest patient was 6 months old. The sample population included seventy (70) boys. The etiologic evaluation of the study population included 42 patients with atopic wheezing, 28 patients with gastroesophageal reflux (GER), and 23 patients with a viral associated wheezing. Eosinophilia was not statistically significant in patients with a family history of atopy (18 patients) related to those with no family history of atopy.

**Conclusion:** In this study, the most prevalent etiological factor was atopy, followed by GER and viral agents, respectively. The definition of children with wheezing includes diseases with different pathophysiology, course, and prognosis. Children with non-atopic wheezing may develop chronic lung inflammation similar to asthma. It is necessary to identify these disorders early enough via monitoring closely and managing adequately. Obtained from the thesis titled, "Is there a diagnostic value of high-sensitivity C-reactive protein in wheezing infants?"

**Keywords:** Wheezing infant, asthma, eosinophilia, etiology

## INTRODUCTION

Wheezing is a high-frequency polyphonic whistling sound, which is usually caused by irregular airflow in narrowing bronchial lumen caused by bronchospasm, mucosal edema, and inflammation (1). Although it can be heard at any age, it is most common in infancy. The prevalence of wheezing ranges between 4-32% in infancy (2). An infant with wheezing can be defined as the occurrence of at least 3 lower respiratory tract infections with wheezing (first episode before 1 year of age) in the first 2 years of life (3).

Recurrent childhood wheezing is often associated with recurrent upper respiratory tract infection (2). Lower respiratory tract infections (bronchiolitis, pneumonia), gastroesophageal reflux

(GER), aspiration, congenital malformations (vascular ring, tracheoesophageal fistula, esophageal cyst), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, congenital heart diseases, foreign body aspiration are the other origins of wheezing in infancy (4). Wheezing in early childhood can be classified into 3 subgroups namely early transient wheezing, late-onset wheezing, and persistent wheezing (5,6).

The differential diagnosis of asthma should be posed in a patient below 3 years presenting recurrent wheezing after exclusion of other possible etiologies (5). Wheezing attacks in early childhood may be the first sign of asthma, and it is important to determine the patients at risk of asthma by evaluating hereditary and environmental risk factors; thus, initiating treatment early enough for effective disease control (6). Eosinophils, mast cells,



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lymphocyte mediators, and cytokines released from these cells are responsible for chronic inflammation in the pathogenesis of asthma. Eosinophils play an important role in asthmatic chronic inflammation (7). Although there are studies evaluating factors that play a role in the development of childhood asthma, its real cause is still unclear.

This study aimed to evaluate the demographic and etiologic characteristics of patients with recurrent wheezing under the age of 3 years, related to the eosinophil counts and IgE levels, according to the asthma predictive index (API) and the presence of a family history of atopy, respectively.

## METHODS

Ninety-two wheezy children were included in this retrospective study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The inclusion criteria for the group were as follows: (i) Age between 6 and 36 months; and (ii) wheezing episodes during the last 12 months. The exclusion criteria were: (i) any evidence of bacterial infection, body temperature  $>39^{\circ}\text{C}$ , white blood cell count  $>20.000/\mu\text{L}$ , predominantly neutrophilia on a peripheral blood smear, positive throat, urine, or blood cultures; (ii) pleural effusion, lobar consolidation other than lung hyperinflation, interstitial infiltration, and peribronchial thickening on chest X-ray; (iii) inflammatory disease, obesity, heart disease, or diabetes mellitus.

Age, sex, passive smoking exposure, family history of atopy, number of attacks in the last year, the number of hospitalizations, white blood cell count, and eosinophils (evaluated at 4% or more in peripheral smear) were recorded. The patients were grouped according to the modified API criteria (8). Serum total immunoglobulin E (IgE) was evaluated on nephelometry (Siemens Healthcare Diagnostics, Deerfield, Germany), and readings  $>2$  standard deviation (SD) were considered high with respect to age.

In patients with treatment failure, a detailed evaluation was performed for differential diagnosis (sweat test, cardiac evaluation, thorax CT, immunodeficiency tests) and these cases were excluded from the study.

### Statistical Analysis

All results were analyzed using Statistical Package for Social Sciences version 22-SPSS 22 (SPSS, Chicago, IL, USA). Categorical variables are described as percentages and numbers while continuous variables were expressed as minimum, maximum,

and mean  $\pm$  SD. The chi-squared and Mann-Whitney U tests were used for non-normally distributed variables. Student's t-test was used to compare normally distributed parametric data. Statistical significance was set at  $p<0.05$ . The Spearman correlation test was used to evaluate the potential correlations between variables.

## RESULTS

The mean age of the 92 patients included in this study was  $19.9\pm 9.4$  months and the youngest patient was 6 months old. Demographic characteristics of the study participants are reported in Table 1. The presence of a family history of atopy was revealed (maternal asthma in 6 cases, maternal allergic rhinitis in 4 cases, paternal asthma in 3 cases, paternal allergic rhinitis in 2 cases, asthma in the brother in 3 cases) in 18 cases (19.6%).

There was no statistically significant difference between the frequency of wheezing attacks and the number of hospitalizations in patients with smoking exposure compared to non-smokers ( $p=0.5$ ). There was no statistically significant difference between the frequency of wheezing attacks and the number of hospitalizations in preterm cases compared to term cases ( $p=0.8$ ).

The etiological evaluation of the cases is displayed in Table 2. The mean number of wheezing attacks was  $5\pm 1.4$  (4-12), 51 patients (55%) were hospitalized at least once within the last 12 months of the study period. Elevated IgE levels were detected in 39 (42%) and eosinophilia in 20 (21%) cases. Fifty-one (55%) of the patients have been treated in the last 3 months. Treatment

	n (%)
<b>Gender</b>	
Male	70 (76)
<b>Gestational age</b>	
Term	79 (85)
Smoking exposure	47 (51)
Pet feeding	7 (7)
Presence of atopy in family members	18 (19.6)
Asthma predictive index positivity	42 (45)

	n (%)
Patients with atopic wheezing	42 (45)
Patients with gastroesophageal reflux	28 (30)
Patients with viral induced wheezing	23 (25)

options for the positive cases were as follows: 27 (29%) cases were managed with inhaled corticosteroids, 18 (19%) cases with leukotriene antagonists and meanwhile, 6 (6%) patients with combined inhaled corticosteroids and leukotriene antagonists.

Eosinophilia or IgE elevation was not statistically significant in 18 patients with a family history of atopy compared to those without an atopic family history ( $p=0.053$  and  $p=0.844$ ). Mean eosinophil percentages of cases with familial atopy was  $4.08\pm 3.15$ , and mean eosinophil percentages of cases without familial atopy was  $2.41\pm 1.50$ .

Eosinophil percentages of the patients with a family history were statistically significantly higher than those without familial atopy in family members ( $p=0.001$ ). No correlation was found between eosinophilia and IgE elevation. There was a moderate correlation between IgE and Eosinophilia levels in patients with a family history of atopy ( $r=0.579$ ,  $p=0.012$ ).

## DISCUSSION

Ninety-two wheezy children were consequently enrolled in this study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The most common etiological factor was atopy, followed by GER and viral agents, respectively. The mean age of the study subjects was  $19.9\pm 9.3$  months and the youngest patient was 6 months old. The mean number of wheezing attacks was  $5\pm 1.4$ .

Boys constituted the majority of our study participants, which is inconsistent with the literature (2). In a study by İnal et al. (9) 60% of the cases were male. This male/female ratio was similar to our study.

Possible explanations of this male predominance could be relative airway obstruction, delayed immune maturation, low lung capacity, high airway resistance, or hormonal or vascular/bronchial tone differences.

In our study, 14% of the cases were preterm. No statistically significant difference was observed between the preterm and term infants in terms of frequency of attacks and the number of hospitalizations. Although preterm infants may have a more severe risk of developing bronchiolitis, they are more likely to receive Respiratory Syncytial Virus Ig prophylaxis and their families are more conscious.

Because GER is an important disease that increases wheezing, the diagnosis and treatment of GER should not be overlooked in patients with recurrent wheezing. GER is one of the major

concomitant diseases in infants with wheezing; thus, it is important to educate families about GER regarding the importance of treatment (10). In this study, GER was detected in 28 cases (30%). GER should be investigated especially in patients with a history of vomiting, wheezing, and increased cough after feeding and night coughs. In a study evaluating infants between 3 and 48 months with recurrent wheezing episodes in Turkey, the frequency of reflux was revealed to be 21.1% (4).

Differential diagnosis of wheezing is important and will improve the treatment success, and also has an important role in the case follow-ups. In patients resistant to the treatment, tuberculosis, cystic fibrosis, congenital lung malformations, and congenital heart diseases should be considered in the differential diagnosis (11,12). In our study, cases with therapeutic failure were evaluated for possible etiological factors, and patients with underlying disorders were excluded from the study.

Some studies endorse the idea that smoking exposure is an important risk factor for wheezing in the prenatal and postnatal periods. In our study, smoking exposure was disclosed in 47 cases (51.1%). Contrary to other literature, the frequency of wheezing attacks and hospitalization were not increased due to smoking exposure. When smoking at home was investigated in detail, it was disclosed that none of the smokers were the mothers of the cases. Additionally, most of the smokers smoked on the balcony (40 cases) and some of them changed their clothes after smoking (10 cases). These factors may explain the fact that the number of episodes and the frequency of hospitalizations were not different from those of non-smokers. Feeding a pet is known to increase the frequency of wheezing (8). In our study, detailed statistical analysis could not be performed due to the limited number of participants involved in pet feeding.

Eosinophilia or IgE elevation was not statistically significant in 18 cases with a family history of atopy related to those without atopy in family members ( $p=0.053$  and  $p=0.844$ ). But eosinophil percentages of the patients with the presence of atopy in family members were found to be significantly higher than those without a family history of atopy ( $p=0.001$ ). Although higher eosinophilia was detected in peripheral blood in atopic wheezing infants, this difference was not statistically significant compared to their non-atopic counterparts. This finding suggests that the pathological changes in asthma-like remodeling in wheezing infants without atopy inconsistent with the literature.

Bronchial biopsy disclosed a significantly higher basal membrane thickness and eosinophilic inflammation increases with increasing basal membrane thickness in patients with recurrent wheezing (13,14). In the study by Turato et al. (15) it was reported

that basal membrane thickness and eosinophil count were significantly higher in preschool children with wheezing without atopy than in the control group.

## CONCLUSION

In summary, the definition of wheezy children includes diseases with different pathophysiology, course, and prognosis. It is necessary to differentiate these diseases in the early stages and provide adequate follow-up and management approaches. Moreover, it should be noted that children with non-atopic wheezing may develop chronic lung inflammation similar to asthma.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: H.S.Ş., Concept: H.S.Ş., Design: Ö.V., Data Collection or Processing: Ö.V., H.S.Ş., Analysis or Interpretation: H.S.Ş., Literature Search: H.S.Ş., Ö.V., Writing: H.S.Ş., Ö.V.

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