

Short-term follow-up of episodic wheeze and predictive factors for persistent wheeze

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ABSTRACT

Wheezing phenotypes may not be stable, and phenotype transitions may occur over time. This study investigates the natural course of episodic viral wheezing (EVW) and identifies the risk factors that predict persistence of wheezing through short-term follow-up. The medical records of children <3 years of age at hospital admission and classified as having EVW were retrospectively screened by two pediatric allergists. A total of 236 children were classified as having EVW between January 2010 and February 2011. The median follow-up period was 19.5 months. At the end of follow-up, wheezing persisted in 145 patients (61.4%) and changed to multiple-trigger wheeze in 37 patients (15.7%). Factors associated with persistent wheeze were age at initial wheezing <24 months, anti-inflammatory treatment at the time of diagnosis, history of severe episodic wheeze in the previous year, wheezing requiring systemic steroids in the previous year, frequent episodic wheeze, parental asthma, and a positive modified asthma predictive index (mAPI) for major criteria (each, $p < 0.05$). The logistic regression analysis revealed three independent risk factors: anti-inflammatory treatment at the time of diagnosis ($p = 0.03$), history of severe episodic wheeze in the previous year ($p = 0.02$), and a positive mAPI for major criteria ($p = 0.02$). The initial wheezing phenotype may vary over time. History of severe episodic wheeze in the previous year, anti-inflammatory treatment at the time of diagnosis, and a positive mAPI for major criteria predicts persistent wheeze at short-term follow-up.

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Recurrent wheezing episodes frequently occur in children <3 years of age.¹ Wheeze is defined as a continuous high-pitched sound with a musical quality emitted from the chest during expiration. It is one of several types of noisy breathing in preschool children.² Wheeze was previously classified as transient, late-onset, and persistent wheeze according to population-based cohort studies. However, these categories can only be identified retrospectively^{1,3,4}; hence, although they are useful in epidemiological studies, they have no value in clinical practice. In 2008, the European Respiratory Society (ERS) preschool study group divided wheezing phenotypes into episodic (viral) wheeze (EVW) and multiple-trigger wheeze (MTW).⁵ However, wheezing phenotype may change over time.^{6,7} Most previous investigations have been long-term studies,^{1,8,9} and few short-term follow-up studies have been conducted.^{6,7,10} The present study investigated short-term changes in phenotype and the risk factors predicting persistence of wheeze.

METHODS

Study Population

The medical records of patients <3 years of age who experienced recurrent wheezing on hospital admission between January 2010 and February 2011 were retrospectively screened by two pediatric allergists. Each investigator reviewed all charts consecutively to ensure consistency. Patients who did not attend a follow-up visit and those whose follow-up duration was <1 year were excluded from the study. Furthermore, patients diagnosed with MTW, those suffering from chronic lung disease or congenital cardiac disease, and children born prematurely were excluded from the study. The age of the patients at the initial wheezing episode, the number of wheezing episodes, attacks requiring systemic corticosteroid treatment and/or hospitalization in the previous year, parental atopic disease, prenatal smoke exposure, duration of breastfeeding, comorbid atopic diseases, anti-inflammatory treatment at the time of diagnosis, triggers of wheezing other than viral respiratory infections, peripheral eosinophil count, and sensitization to food and aeroallergens were documented. Furthermore, skin tests were performed using standardized allergen extracts against the following 10 most common aeroallergens: house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass mix (*Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Anthoxanthum odoratum*, *Festuca elatior*, *Agrostis vulgaris*, *Holcus lanatus*, and *Bro-*

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mus), weed mix (*Artemisia vulgaris*, *Plantago lanceolata*, and *Chenopodium album*), cereal mix (*Hordeum vulgare*, *Triticum vulgare*, *Avena sativa*, and *Zea mays*), tree mix (*Acer pseudoplatanus*, *Aesculus hippocastanum*, *Platanus vulgaris*, *Robinia pseudoacacia*, and *Tilia platyphyllos*), mold mix (*Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium*), animal dander, cow's milk, and hen's egg (Stallergenes, Antony Cedex, France). The data from the follow-up visits were obtained subsequently.

Definitions

Wheeze was defined as a continuous high-pitched sound with a musical quality emitted from the chest during expiration. It is one of a several types of noisy breathing that occurs in preschool children.² The patients who had ≥ 2 wheeze episodes were defined as having recurrent wheeze. Wheezing phenotypes were categorized according to the ERS Task Force classification system.⁵ In this system, wheezing attacks triggered only by viral respiratory tract infections with no complaints between attacks were classified as EVW. Wheezing attacks triggered by allergens, exercise, cold weather conditions, or smoke, in addition to viral respiratory tract infections, with complaints between attacks, were classified as MTW. Four or more episodic wheezing attacks in the previous year was classified as "frequent episodic (viral) wheeze"; the attack was classified as "severe episodic (viral) wheeze" if it complied with the criteria for a severe attack. Patients who had experienced no wheeze episodes in the previous year were classified as "no wheeze." Patients who had had a wheezing attack in the previous year were classified as "persistent wheeze." A positive modified asthma predictive index (mAPI) reflects the presence of one major (physician-diagnosed parental asthma, aeroallergen sensitivity, or physician-diagnosed eczema in children) or two minor (wheezing without a cold, peripheral eosinophilia, or sensitivity to food allergens) criteria.¹¹ Peripheral eosinophilia was defined as a peripheral eosinophil count of $>4\%$ of the total number of white blood cells. A positive skin-prick test was defined as a mean wheal diameter ≥ 3 mm compared with the negative control. Peripheral eosinophilia and the skin-prick test results were obtained from the patients' medical records. Patients diagnosed with severe or frequent EVW were administered anti-inflammatory treatment (inhaled corticosteroids at a daily dose of up to 400 μg of beclomethasone equivalent and/or montelukast) via a spacer (pressurized metered-dose inhaler) according to the recommendations of the ERS Task Force.⁵

Informed consent was obtained for all participants, and the study was approved by the Ethics Committee of Gazi University (approval number 250/06.13.2012).

Statistical Analysis

The Statistical Package for the Social Sciences for Windows Version 15 (SPSS, Inc., Chicago, IL) was used to conduct the statistical tests. Descriptive statistics are expressed as frequency and percentage for categorical variables, and quantitative data are expressed as median (interquartile range [IQR] or minimum–maximum) for nonnormally distributed data. The normality of the quantitative variable was verified using the Kolmogorov–Smirnov test. Differences between the two groups (persistent wheeze and no wheeze) were assessed using univariate and multivariate analyses. The Mann–Whitney *U* test, Pearson chi-square, and Fisher's exact tests were conducted, and values of $p < 0.05$ were deemed statistically significant. Variables that had clinical importance or were statistically significant were included in a regression analysis to determine the independent risk factors associated with the persistence of wheeze.

RESULTS

Demographic Features

A total of 345 patients <3 years of age were diagnosed with recurrent wheezing in our department between January 2010 and February 2011. Twenty-four patients were excluded because of incomplete medical records. Of the remaining 321 children, 236 (73.5%) were classified as having the EVW phenotype, and 85 (26.5%) were classified as the MTW phenotype. Only patients with EVW were included in the analysis (Fig. 1). Of the 236 patients included in the study, 167 (70.8%) were male subjects. The median age of the patients at admission was 24 months (IQR, 22), and the median follow-up period was 19.5 months (IQR, 6). The median number of wheezing episodes in the previous years was 3 (range, 1–6). Skin-prick tests were performed on 166 (70.3%) patients, and serum eosinophil count was performed in 181 (76.7%) patients.

Treatment and Follow-Up

Anti-inflammatory treatment was initiated in 156 of the 236 patients (severe episodes in 61 patients, frequent episodes in 95 patients, and both frequent and severe episodes in 44 patients). Inhaled corticosteroids were prescribed for 62 (39.8%) patients, 50 (32%) patients received montelukast, and 44 (28.2%) patients were treated with inhaled corticosteroids and montelukast. At the end of the follow-up period, the wheezing phenotype was persistent in 145 of 236 patients, and the phenotype classification changed from EVW to MTW in 37 patients (Fig. 1). Anti-inflammatory treatment was continued in 84 (35.6%) patients; 38 (45.2%) patients received inhaled corticosteroids, 26 (30.9%)

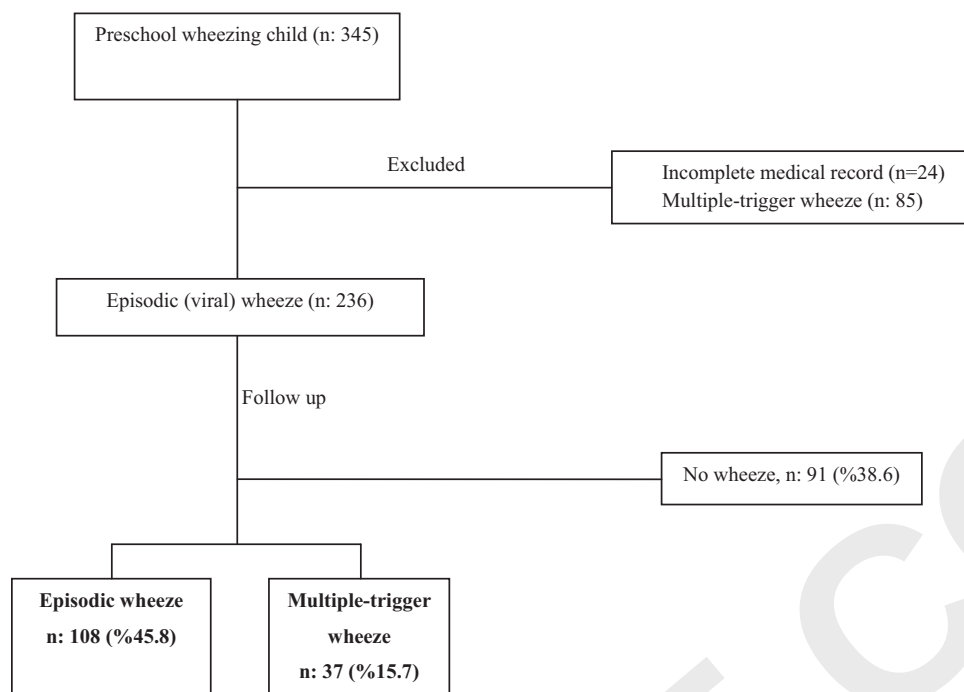


Figure 1. The clinical course of children diagnosed with wheeze in the first 3 years of life

Table 1 A comparison of persistent wheeze and no wheeze (differences of two groups)

	Total n (%)	Persistent Wheeze n (%)	No Wheeze n (%)	p Value
Male gender	167 (70.8)	99 (59.3)	68 (40.7)	0.36
Severe episodic wheeze in previous year	76 (32.2)	59 (77.6)	17 (22.4)	0.001
Frequent episodic wheeze in previous year	168 (71.2)	96 (57.1)	72 (42.9)	0.033
Wheezing requiring steroids in previous year	138 (58.5)	100 (72.5)	38 (27.5)	<0.001
Breast-feeding <6 mo	24 (10.9)	16 (66.7)	8 (33.3)	0.64
Maternal smoking during pregnancy	25 (10.6)	16 (64)	9 (36)	0.95
Age at first wheezing episode ≤24 mo	198 (83.9)	128 (64.6)	70 (35.4)	0.033
Anti-inflammatory treatment at the diagnosis	156 (66.1)	112 (71.8)	44 (28.2)	<0.001
mAPI: positive major criteria	56/176 (31.8)	41 (73.2)	15 (26.8)	0.041
Parental asthma	27 (11.6)	22 (81.5)	5 (18.5)	0.039
Atopic eczema	12 (5.1)	8 (66.7)	4 (33.3)	0.77
Sensitivity to aeroallergen	23/166 (13.9)	15 (65.2)	8 (34.8)	0.86
Peripheral eosinophilia	48/181 (26.5)	31 (64.6)	17 (35.4)	0.85
Sensitivity to food allergen	11/166 (6.6)	6 (54.5)	5 (45.5)	0.75

mAPI = modified asthma predictive index.

patients received montelukast, and 20 (23.9%) patients received inhaled corticosteroids and montelukast.

Risk Factors Associated with Persistent Wheezing

The univariate analysis revealed that persistent wheezing was related to frequent recurrent wheezing in the previous year ($p = 0.033$), severe EVW in the previous year ($p = 0.001$), wheeze requiring systemic corticosteroid treatment in the previous year ($p < 0.001$), initial wheezing at <24 months of age ($p = 0.033$), anti-inflammatory treatment at the time of diagnosis ($p <$

0.001), parental asthma ($p = 0.039$), and a positive mAPI for major criteria ($p = 0.041$). No significant correlations were found between persistence of wheeze and gender, atopic eczema, prenatal exposure to smoke, breast-feeding <6 months, peripheral blood eosinophilia, and sensitivity to food or aeroallergens ($p < 0.05$; Table 1).

A regression analysis was performed on the factors that independently affected persistence of wheeze (Table 2). A severe wheezing episode in the previous year increased the odds of persistent wheeze 2.7 times,

Table 2 Potential predictors for persistence of wheeze

Variable	β	Odds Ratio	95% CI	<i>p</i> Value
Severe episodic wheeze in previous year	1	2.7	1.129–6.565	0.02
mAPI: major criteria positivity	0.9	2.5	0.161–5.796	0.02
Anti-inflammatory treatment at the time of diagnosis	0.7	2.2	1.049–4.647	0.03

Variables in the logistic regression model: severe episodic wheeze in previous year, frequent episodic wheeze in previous year, wheeze requiring systemic steroid in the previous year, age at first wheezing episode ≤ 24 mo, anti-inflammatory treatment at the time of diagnosis, parental asthma, atopic eczema, and sensitivity to aeroallergen.

mAPI = modified asthma predictive index.

and anti-inflammatory treatment at the time of diagnosis and a positive mAPI for major criteria increased the odds of persistent wheeze 2.2 and 2.5 times, respectively ($p < 0.05$).

DISCUSSION

The present study identified three risk factors for persistence of wheeze in preschool children with episodic wheeze at short-term follow-up: a severe wheezing episode in the previous year, anti-inflammatory treatment at the time of diagnosis, and positive mAPI for major criteria. Furthermore, we confirmed that wheezing phenotypes are not stable and may change in the short term.

Birth cohort studies have revealed much about the natural history of wheezing disorders in preschool children.^{8,9,12} In 2008, the reclassification of preschool wheezing disorders as EVW and MTW was recommended.⁵ However, few short-term follow-up studies have assessed the prognosis for these wheezing phenotypes.^{6,7} Schultz *et al.*⁶ followed 38 cases of EVW for a year. They found that the phenotype classification remained as EVW in nearly one-third of the cases, one-third changed to MTW, and the remaining patients recovered. Similarly, Kappelle *et al.*,⁷ who followed 78 preschool children with severe EVW for 3.9 years, reported that one-third of their patients recovered; in one-half of those who remained symptomatic, the phenotype changed to MTW and the other half remained EVW. Our findings are consistent with those of Schultz *et al.*⁶ and Kappelle *et al.*⁷ We found that more than one-third of the children initially classified as having the EVW phenotype recovered. The EVW phenotype was stable in nearly one-half of the remaining children and changed to MTW in $\sim 16\%$ of the patients during the median 20-month follow-up period. The available evidence suggests that the EVW phenotype is not stable and may change during a short-term follow-up period.

The risk factors for persistent wheeze/asthma have been the focus of several investigations in young children with wheezing disorders. Cohort studies in children have documented several early life predictors of

asthma in school-aged children and adults.^{12–15} The severity of wheezing episodes has been shown to be an important predictor of current persistent wheeze in long-term cohort and short-term follow-up studies.^{7,16} Kappelle *et al.*⁷ reported that more than one-half of the patients diagnosed as severe EVW before the age of 4 years continued to wheeze 3.9 years later. Our results showed that wheezing persisted in 77.6% of children with severe episodic wheeze (Table 1) and that severe EVW in the previous year increased the odds of persistent wheeze 2.7 times (Table 2). These findings clearly show that severe EVW is an important short- and the long-term risk factor for persistent wheezing.

A positive mAPI during the first 3 years of life predicted persistent wheeze in school-age children.¹⁷ Castro-Rodriguez *et al.*¹² showed that asthma developed in 77% of school children who were API⁺ by the age of 3 years. Wheezing persisted in $\sim 75\%$ of our cases who were positive for a major mAPI, which was associated with a 2.5 times greater likelihood of persistent wheeze in the short term.

We found that anti-inflammatory treatment for severe or frequent episodic wheeze at the time of diagnosis was a predictive factor for persistent wheeze. This factor increased the risk of persistent wheeze 2.2 times and may be an indirect measure of wheezing severity, although we found it to be an independent risk factor.

In a recent short-term follow-up of patients with wheeze, Sahiner *et al.*¹⁰ found that mothers' smoking during pregnancy and the number of emergency room visits were independent risk factors for persistence of wheeze. Although smoking during pregnancy and frequency of wheeze were included in our logistic regression analysis, neither factor was significantly associated with persistent wheeze. We identified three independent factors that predicted persistence of wheeze at short-term follow-up: severe episodic wheeze in the previous year, a positive mAPI for major criteria, and anti-inflammatory treatment at the time of diagnosis.

Our study has some limitations. First, the retrospective design may have affected our results owing to missing data for variables such as peripheral eosino-

philia count (missing in one-fourth of the cases) and skin-prick tests (missing in less than one-third of the cases). Second, the duration of the follow-up period may have been too short. Third, our data were obtained from a single center, and thus the results may not be applicable to the general population.

In conclusion, the EVW phenotype is not stable and may change over the short term. Severe episodic wheezing, a positive mAPI for major criteria, and anti-inflammatory treatment at the time of diagnosis are predictors of persistence of wheeze in preschool children with EVW.

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