



RESEARCH

Early-onset wheezing in preschool children: etiology, risk factors, and implications for asthma prevention

Okul öncesi dönemde erken başlangıçlı hışıltılı solunumun etiyolojisi, risk faktörleri ve astımın önlenmesindeki olası etkileri

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Abstract

Purpose: This study aimed to examine the etiological factors and clinical characteristics of wheezing in preschool children presenting to the emergency department, focusing on environmental, viral, and demographic risk factors.

Materials and Methods: A total of 199 children aged 27 days to 70 months (mean age 19.38 months) were included in this prospective study conducted from November 2017 to January 2019. Demographic, clinical, and environmental data were collected, and respiratory virus detection was performed using PCR tests. The modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, administered to parents, assessed asthma susceptibility and potential wheezing triggers.

Results: Wheezing was present in 97.5% of the patients at presentation. Respiratory viruses were identified in 67.3% of cases, with rhinovirus (33.5%) and RSV (25%) being the most frequent pathogens. Rhinovirus peaked in autumn, while RSV was more prevalent in spring. Early wheezing onset, male gender, and shorter breastfeeding duration (< six months) were associated with higher wheezing recurrence. Allergic comorbidities, including asthma and atopic dermatitis, were present in 8% of children. House dust and pollen were the primary environmental triggers.

Conclusion: The study highlights the significant role of viral infections in preschool wheezing episodes and suggests preventive measures, such as influenza vaccination and reduced daycare attendance for children under three during peak viral seasons, to limit viral exposure.

Keywords: Preschool wheezing, respiratory viruses, risk factors, asthma prevention, environmental triggers

Öz

Amaç: Bu çalışma, acil servise başvuran okul öncesi çocuklarda hışıltının etiyolojik faktörlerini ve klinik özelliklerini incelemeyi; özellikle çevresel, viral ve demografik risk faktörlerini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Kasım 2017 – Ocak 2019 tarihleri arasında yürütülen bu prospektif çalışmaya, 27 gün ile 70 ay arasında değişen yaşlarda toplam 199 çocuk (ortalama yaş: 19,38 ay) dâhil edildi. Demografik, klinik ve çevresel veriler kaydedildi; solunum yolu virüsleri polimeraz zincir reaksiyonu (PCR) yöntemiyle araştırıldı. Astım yatkınlığı ve olası hışıltı tetikleyicileri, ebeveynlere uygulanan modifiye Uluslararası Çocukluk Çağı Astımı ve Alerjisi (ISAAC) anketi kullanılarak değerlendirildi.

Bulgular: Başvuru sırasında hastaların %97,5'inde hışıltı mevcuttu ve özellikle kış aylarında daha sık karşımıza çıktı. Olguların %67,3'ünde solunum yolu virüsü saptandı; en sık görülen etkenler rinovirüs (%33,5) ve Respiratuar Sinsityal Virüsü (RSV) (%25) idi. Rinovirüs enfeksiyonları sonbaharda, RSV ise ilkbaharda zirve yaptı. Erken hışıltı başlangıcı, erkek cinsiyet ve altı aydan kısa emzirme süresi, tekrarlayan hışıltı ile ilişkili bulundu. Astım ve atopik dermatit dâhil olmak üzere alerjik komorbiditeler çocukların %8'inde mevcuttu. Ev tozu ve polen en yaygın çevresel tetikleyiciler olarak belirlendi.

Sonuç: Bu çalışma, okul öncesi çocuklarda hışıltı ataklarında viral enfeksiyonların belirgin rolünü ortaya koymaktadır. Bulgular, viral maruziyeti azaltmak için influenza aşısı gibi önleyici yaklaşımların ve özellikle üç yaş altındaki çocuklarda viral sezonlarda kreş/gündüz bakımı süresinin sınırlandırılmasının önemini vurgulamaktadır.

Anahtar kelimeler: Okul öncesi hışıltı, solunum yolu virüsleri, risk faktörleri, astımın önlenmesi, çevresel tetikleyiciler

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INTRODUCTION

Wheezing is a frequent presenting respiratory symptom in preschool-aged children and holds significant diagnostic importance as it can serve as an early marker for asthma¹. Studies indicate that the prevalence of wheezing ranges between 4-32% within the pediatric population². Although often linked to simple viral respiratory infections, wheezing may also indicate complex, challenging-to-treat conditions³. The high incidence, diverse etiology, and potential role of wheezing as an initial symptom of asthma, a disease known for its considerable morbidity in childhood underscore the necessity for early recognition and targeted intervention.

Wheezing accompanied by at least three lower respiratory tract infections within the first two years of life is typically categorized as “wheezy infant syndrome”⁴. Early-onset wheezing is generally defined as the occurrence of wheezing episodes within the first three years of life and is most commonly triggered by viral respiratory infections^{5,6}. This phenotype is clinically important because it may represent the earliest manifestation of asthma in susceptible children.

The onset, severity, and recurrence of wheezing episodes are influenced by several factors, including viral exposure, genetic predispositions, environmental triggers, and socioeconomic conditions⁵. Viral bronchiolitis ranks as the leading cause of wheezing in early childhood⁶. Given this, identifying specific risk factors for wheezing is crucial for improving prognosis, as early diagnosis and timely treatment can prevent irreversible bronchial damage⁵. Furthermore, implementing preventive measures may positively impact asthma progression in later stages of life.

This study is essential in addressing these clinical needs by investigating the factors that trigger wheezing episodes in preschool-aged children (defined as children younger than 70 months) presenting to our emergency department. Specifically, the study aims to assess associated physical examination findings, relevant laboratory test results when available, and viral agents identified through nasopharyngeal swabs. We hypothesized that wheezing episodes in preschool children presenting to the emergency department are predominantly associated with respiratory viral

infections, and that specific demographic, environmental, and early-life factors contribute to wheezing recurrence and severity, potentially influencing the risk of progression to asthma. Despite the high prevalence of wheezing in early childhood, data integrating viral, environmental, and early-life risk factors in preschool children presenting to the emergency department remain limited. Most previous studies have focused on outpatient populations or specific viral pathogens. The present study aims to comprehensively evaluate the etiological factors, clinical characteristics, and viral profiles of wheezing in preschool children in an emergency care setting, thereby contributing novel insights into early wheezing phenotypes and their potential role in asthma prevention.

MATERIALS AND METHODS

Sample and setting

The study was conducted at the Pediatric Emergency Department of Çukurova University Faculty of Medicine, a tertiary care referral center. The study population included infants and preschool children aged between 27 days and 70 months who presented with wheezing attacks at the pediatric emergency clinic between November 1, 2017, and January 31, 2019. Inclusion criteria included preschool children younger than 70 months who presented to the pediatric emergency department with wheezing and whose parents provided informed consent. During the study period, all eligible children presenting with wheezing to the pediatric emergency department were consecutively included in the study (n = 199). Children attending daycare or nursery school were not excluded from the study. The presence of neuromotor delay, immunodeficiency, chronic lung disease, epilepsy, congenital heart disease, gastroesophageal reflux, or other chronic conditions was recorded for all patients. Exclusion criteria included children with incomplete clinical data or those whose parents did not provide informed consent. All children and their families were informed about the study objectives and procedures, and informed consent was obtained.

Procedure

This single-center, prospective study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee

of Çukurova University Faculty of Medicine (Approval No: 6, 28 December 2017).

Data collection

A comprehensive data form was developed to gather detailed information from each child included in the study. This form collected demographic data (gender, birth date, date of presentation), clinical data (presenting symptoms, perinatal and early childhood risk factors), environmental and socioeconomic factors, family medical history, and a history of previous wheezing episodes. To further characterize wheezing, all children completed the modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire ².

Scoring system for wheezing episodes

At presentation, in addition to recording vital signs and performing a standard physical examination, the severity of each wheezing episode was assessed based on the 2014 guidelines of the Global Initiative for Asthma (GINA) ⁷. Severity scoring included parameters such as the presence of suprasternal, intercostal, and subcostal retractions, air entry into the lungs, auscultation findings, and oxygen saturation levels. A score of 0 was assigned if no symptoms were present, with scores of 1, 2, or 3 assigned depending on severity; these were then summed to obtain a total severity score.

Laboratory analysis and nasopharyngeal swab collection

Upon presentation, blood samples were collected to measure complete blood count and C-reactive protein (CRP) levels, with radiologic imaging performed in select cases. Allergy testing results (if available) for aeroallergens (tree pollen, grass, weed pollen, molds, dust mites) and food allergens (milk, egg, wheat, peanut, soy, fish) were documented.

Allergy testing was performed using the radioallergosorbent test with fluoroenzyme immunoassay (RAST FEIA) method. Values above 0.35 kU/L were considered positive ⁸. Additionally, total IgE and serum vitamin D levels were recorded if available. Nasopharyngeal swabs were collected from all patients and analyzed by PCR in the Virology Laboratory to detect Influenza A and B, human respiratory syncytial virus (RSV), human metapneumovirus (hMPV), human coronavirus (HCoV), human parainfluenza virus (hPIV), and rhinovirus.

Statistical analysis

Categorical variables were summarized as counts and percentages, while continuous variables were presented as means \pm standard deviations. The chi-square test was used to evaluate associations between categorical variables, whereas the independent samples t-test was applied for comparisons of continuous variables between groups. These statistical tests were selected according to the distribution and type of the variables analyzed. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant. Correlation analyses between vitamin D levels, total IgE levels, wheezing severity scores, and viral infection status were not performed, as these associations were not part of the predefined study objectives. No formal sample size calculation was performed because all eligible children presenting with wheezing during the study period were consecutively included.

RESULTS

This study included 199 pediatric patients presenting with wheezing to the emergency department between November 1, 2017, and January 31, 2019. The ages ranged from 27 days to 70 months, with a mean age of 19.38 ± 15.17 months, and 115 (57.8%) were male. For 78 (39.2%) children, this was their first wheezing episode, while 77 (38.7%) had been previously hospitalized due to wheezing. Demographic and clinical characteristics are summarized in Table 1.

According to the modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, 121 (60.8%) children had a history of wheezing in the last 12 months, and 23 (11.6%) had persistent wheezing. The most commonly reported trigger was house dust, affecting 11 (5.5%) patients. Detailed questionnaire findings are presented in Table 2.

Regarding clinical status at presentation, 134 children (67.3%) were classified as good, 47 (23.7%) as moderate, and 18 (9.0%) as poor. Fever above 38°C was observed in 33 patients (16.6%) whereas 166 children (83.4%) were afebrile. Tachycardia (heart rate >140 bpm) was present in 71 children (35.7%), and tachypnea (respiratory rate >30 /min) in 160 children (80.4%). Oxygen saturation below 90% was detected in 14 patients (7.0%). Complete blood count

was available for 127 children (63%). The mean white blood cell count was $13,941 \pm 7,404 \times 10^3/\mu\text{L}$ (range: 2,500–63,440), hemoglobin level was $11.2 \pm 1.8 \text{ g/dL}$ (range: 6.3–15.1), hematocrit was $34.1 \pm 5.2\%$ (range: 19.2–45.4), and platelet count was $361,275 \pm 145,513 \times 10^3/\mu\text{L}$ (range: 30,000–754,000). C-reactive protein levels were measured in 27 patients (13.6%), with a

mean value of $4.6 \pm 7.1 \text{ mg/L}$ (range: 0.1–31.3). Total immunoglobulin E levels were available in 56 children (28.1%), with a mean of $81.6 \pm 263.1 \text{ IU/mL}$ (range: 5–1,780). Vitamin D levels were assessed in 53 patients (26.7%), with a mean value of $34.1 \pm 19.8 \text{ ng/mL}$ (range: 4–102).

Table 1. Demographic, clinical, and environmental characteristics of study participants

Category	Variable	n (%)
Demographics	Gender (Male/Female)	115 (57.8) / 84 (42.2)
	Age (months, Mean \pm SD)	19.38 \pm 15.17
	Most Common Admission Season	Winter, 118 (59.3)
Clinical Characteristics	Wheezing	194 (97.5)
	Cough	178 (89.4)
	Rhinitis	102 (51.3)
	Dyspnea	91 (45.7)
	Gestational Age <37 weeks	38 (19.1)
	Birth Weight <2500g	36 (18.1)
	Duration of Breastfeeding (<3 months, 3-6 months, 6-12 months, >1 year)	63 (31.7), 34 (17.1), 41 (20.6), 61 (30.7)
	Recurrent Wheezing Attacks	121 (60.8)
	First Episode	78 (39.2)
	Hospitalization Due to Wheezing	77 (38.7)
Allergic Comorbidities (Asthma, Atopic Dermatitis, Other)		9 (4.5), 2 (1.0), 5 (2.5)
	Non-Allergic Chronic Disease	98 (49.2)
Environmental and Lifestyle Factors	Number of Siblings (0, 1, 2, 3+)	50 (25.1), 65 (32.7), 43 (21.6), 41 (20.6)
	Presence of Pets	25 (12.6)
	Maternal Smoking (During Pregnancy, Postnatal)	40 (20.1), 42 (21.1)
	Paternal Smoking	110 (55.3)
	Daycare Attendance (Patient, Sibling)	15 (7.5), 100 (50.3)
	Housing Type (Detached House/Apartment)	132 (66.3) / 67 (33.7)
Parental Education Level	Primary, Middle, High, University	55 (27.6), 52 (26.1), 35 (17.6), 34 (17.1)
Family History of Allergies	Rhinitis (Mother/Father)	11 (5.5) / 5 (2.5)
	Asthma (Mother/Father)	14 (7.0) / 1 (0.5)

SD, standard deviation; RSV, respiratory syncytial virus; hMPV, human metapneumovirus; hPIV, human parainfluenza virus; HCoV, human coronavirus.

Table 2. Modified ISAAC questionnaire results

Variable	Period 1 (n=199)
Cold Incidence in Last 12 Months	Mean \pm SD (min-max)
	3.28 \pm 2.9 (0-20)
Cold Incidence n (%)	
≤ 3	102 (51.3)
> 3	97 (48.7)
Cough Without Cold Association n (%)	33 (16.6)
Wheezing History in Last 12 Months n (%)	121 (60.8)
Wheezing Characteristics n (%)	
After Cold	98 (49.2)
Persistent	23 (11.6)
Wheezing Triggers n (%)	
House Dust	11 (5.5)
Pollen	9 (4.5)
Exercise	5 (2.5)
Laughter	4 (2.0)
Food	1 (0.5)
Animal Contact	0 (0)
Wheezing Attack Frequency in Last 12 Months n (%)	
1-3	68 (34.2)
4-12	46 (23.1)
> 12	7 (3.5)
Shortness of Breath During Attacks n (%)	
Never	13 (6.5)
Occasionally	77 (38.7)
Always	31 (15.6)
Attack Waking Patient from Sleep n (%)	
Never	10 (5.0)
< 1 Night Per Week	32 (16.1)
≥ 1 Night Per Week	79 (39.7)
Impact on Daily Activities n (%)	
None	5 (2.5)
Mild	31 (15.6)
Moderate	69 (34.7)
Severe	16 (8.0)

ISAAC, International Study of Asthma and Allergies in Childhood.

Respiratory viruses were detected in 134 of 199 patients (67.3%). Rhinovirus was the most frequently identified virus (67/199, 33.5%), followed by IAV (50/199, 25%). The distribution of detected viruses in the total study population was as follows: rhinovirus in 67 (33.5%), RSV in 50 (25%), influenza A in 22 (11%), human coronavirus (HCoV) in 14 (7%), human parainfluenza virus (hPIV) in 13 (6.5%), human metapneumovirus (hMPV) in 5 (2.5%), and influenza B in 1 (0.5%) patient. Co-infections

involving two or three viruses were identified in 34 of 134 virus-positive patients (25.4%). Among the 100 cases of mono-infection (100/134, 74.6%), rhinovirus was detected in 38 (38%), RSV in 34 (34%), influenza

A in 15 (15%), HCoV in 5 (5%), hPIV in 4 (4%), hMPV in 3 (3%), and influenza B in 1 (1%) patient.

A comparison between children with and without detected respiratory viruses revealed no statistically significant association with gender ($p > 0.05$). Cough was significantly more frequent among virus-positive patients ($p < 0.05$), whereas dyspnea showed no significant association with viral detection ($p > 0.05$). Perinatal and early childhood risk factors, environmental or socioeconomic factors, family history of atopy, breastfeeding duration, and attack severity score were not significantly associated with viral positivity ($p > 0.05$).

No statistically significant association was identified between fever ($>38^{\circ}\text{C}$) and virus detection ($p > 0.05$). Similarly, chest X-ray infiltrates and other physical examination findings were not significantly associated with viral positivity ($p > 0.05$). ISAAC questionnaire responses were not significantly related to respiratory virus detection. Seasonal variation was observed in viral distribution. Rhinovirus and RSV demonstrated statistically significant seasonal differences ($p < 0.05$). Rhinovirus was most

frequently detected in autumn, whereas RSV was most common in spring. Influenza A positivity was significantly higher in December ($p < 0.05$). No significant seasonal association was observed for other viruses ($p > 0.05$). RSV positivity was more frequent in children presenting with a first wheezing episode and in those without a prior history of wheezing ($p < 0.05$). Influenza A positivity was significantly associated with the presence of fever and absence of dyspnea ($p < 0.05$).

Table 3. Comparison of virus-positive and virus-negative groups

Variable	Virus + (n=134)	Virus – (n=65)	p-value
Gender			
Female	56 (66.7)	28 (33.3)	0.86
Male	78 (67.8)	37 (32.2)	
Age (months)			0.31
0-6	28 (68.3)	13 (31.7)	
7-12	33 (75)	11 (25)	
13-24	28 (57.1)	21 (42.9)	
Season			0.88
Spring	12 (66.7)	6 (33.3)	
Autumn	44 (69.8)	19 (30.2)	
Winter	78 (66.1)	40 (33.9)	
Presenting Symptoms (+)			
Cough	124 (69.7)	54 (30.3)	0.04
Wheezing	131 (67.5)	63 (32.5)	0.53
Dyspnea	59 (64.8)	32 (35.2)	0.5
Rhinitis	66 (64.7)	36 (35.3)	0.42
Perinatal and Early Childhood Risk Factors (+)			
Birth Weight <2500 g	20 (55.6)	16 (44.4)	0.1
Gestational Age <37 weeks	21 (55.3)	17 (44.7)	0.08
Breastfeeding Duration <6 months	38 (39)	59 (61)	0.23
Chronic Disease	64 (65.3)	34 (34.7)	0.55
Attack Characteristics			
First Episode	56 (71.8)	22 (28.2)	0.28
Recurrent	78 (64.5)	43 (35.5)	0.07
History of Hospitalization Due to Attack	46 (59.7)	31 (40.3)	0.32
Allergic Disease	9 (56.2)	7 (43.8)	
Environmental Factors			
Pet Ownership	16 (64)	9 (36)	0.70
Maternal Smoking (Pregnancy)	24 (60)	16 (40)	0.27
Maternal Smoking (Postnatal)	27 (64.3)	15 (35.7)	0.63
Paternal Smoking	70 (63.6)	40 (36.4)	0.22
Daycare Attendance	8 (53.3)	7 (46.7)	0.18
Sibling in Daycare	72 (72)	28 (28)	0.16
Severity Score - General Condition			
<6 (Good)	89 (66.4)	45 (33.6)	0.636
6-10 (Moderate)	34 (72.3)	13 (27.7)	
>10 (Poor)	11 (61.1)	7 (38.9)	

CRP, C-reactive protein; IgE, immunoglobulin E; SpO₂, oxygen saturation; SD, standard deviation.

DISCUSSION

The present study provides a comprehensive evaluation of clinical characteristics, viral profiles, and associated risk factors in preschool children presenting with wheezing to an emergency department setting. Our findings reinforce the central role of respiratory viral infections in early childhood wheezing and highlight the multifactorial nature of wheezing phenotypes in this age group.

Wheezing in early life represents a heterogeneous clinical entity with varying trajectories, ranging from transient viral-associated episodes to persistent wheezing that may evolve into asthma. As previously described^{1,3}, preschool wheezing disorders require careful phenotypic characterization. Recent advances further emphasize the heterogeneity of preschool wheezing and the importance of individualized assessment and management strategies⁹. In line with prior epidemiological data reporting high wheezing prevalence in infancy^{10,11}, our cohort demonstrates that wheezing remains a common cause of emergency visits in early childhood.

Respiratory viruses were detected in a substantial proportion of patients, with rhinovirus and respiratory syncytial virus (RSV) being the predominant pathogens. This distribution is consistent with previous reports identifying these viruses as leading etiological agents in wheezing illnesses among young children¹². Recent studies have also confirmed that viral pathogens, particularly rhinovirus and respiratory syncytial virus, remain the most common triggers of wheezing episodes in preschool children and are associated with recurrent wheezing and later asthma development^{13,15}. In recent years, rhinovirus-associated wheezing has gained particular attention due to its potential association with subsequent asthma development¹⁶. The predominance of viral pathogens in our cohort supports the concept of episodic viral wheezing described in preschool children^{6,17}.

Interestingly, RSV showed a peak detection in spring in our study. Although RSV classically demonstrates a late-fall winter predominance in temperate climates, seasonal variation may differ according to geographic location and climatic conditions. Recent global epidemiological analyses have highlighted regional variability and shifting seasonal patterns of RSV circulation¹⁸. The spring predominance observed in our cohort may therefore reflect regional epidemiological variation in the Mediterranean

climate, as well as year-to-year fluctuations in viral activity rather than a deviation from established viral behavior.

Perinatal and environmental factors have been implicated in early wheezing pathogenesis. Previous studies suggest that early-life exposures may modify immune responses and alter wheezing susceptibility¹⁹. While our study explored these associations, no consistent relationship was observed between most evaluated perinatal or socioeconomic variables and viral positivity. This finding underscores the complexity of early wheezing phenotypes and suggests that viral triggers may operate independently of some traditionally recognized risk factors in acute emergency presentations.

Allergic comorbidities and family atopy have been associated with persistent wheezing and later asthma development²⁰. However, ISAAC questionnaire responses were not significantly associated with viral detection in our study. This may indicate that viral-associated wheezing episodes in preschool children frequently occur regardless of atopic background, particularly in acute-care settings where viral triggers predominate.

The association between influenza A positivity and fever observed in our study aligns with the well-established systemic inflammatory profile of influenza infection. In contrast, RSV positivity was more frequently identified in first-time wheezing episodes, consistent with its recognized role in primary lower respiratory tract infections in infancy.

This study has several strengths. It prospectively evaluated a well-defined preschool population, incorporated systematic viral testing using PCR, and assessed clinical and environmental variables in an emergency department setting, providing real-world insight into acute wheezing presentations. However, certain limitations should be acknowledged. The single-center design may limit generalizability. Bacterial pathogens and airway microbiota were not assessed. Additionally, not all laboratory parameters were available for every patient, and the absence of a control group precluded direct risk estimation.

Overall, our findings emphasize the predominant contribution of respiratory viruses, particularly rhinovirus and RSV, to wheezing episodes in preschool children presenting to emergency care. The observed seasonal variation and heterogeneous clinical patterns further support the need for region-

specific epidemiological surveillance and individualized clinical assessment in early childhood wheezing.

In preschool children presenting to the emergency department with wheezing, respiratory viral infections, particularly rhinovirus and RSV, represent the leading etiological factors. Seasonal variability and heterogeneous clinical presentations highlight the multifactorial nature of early childhood wheezing. These findings contribute to a better understanding of viral-associated wheezing phenotypes in acute-care settings and underscore the importance of region-specific epidemiological awareness in guiding clinical management and preventive strategies. Improved surveillance of circulating respiratory viruses and early identification of high-risk children may contribute to better management and prevention strategies. Future multicenter studies with longitudinal follow-up are warranted to better clarify the progression from early viral wheezing to persistent asthma phenotypes.

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