ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Investigation of Allergen Sensitization in Asthmatic Children Aged 3-6 and Their Relationship with Other Allergic Diseases

3-6 Yaş Grubu Astımlı Çocuklarda Alerjen Duyarlılıklarının Araştırılması ve Diğer Alerjik Hastalıklarla İlişkisi

*Emre Karaağaç[1] (0009-0002-3710-8800), **Yakup Canıtez[1] (0000-0001-8929-679X), *Burcu Eryılmaz (0009-0002-7344-8642), *Tuğba Altunkaynak Topu (0009-0008-8785-8857)

[1]These authors contributed equally to this work as the first author (Pediatrics residency training, graduation thesis study, Y. Canıtez is thesis advisor)

*Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Türkiye

**Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy, Bursa, Türkiye

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Abstract

Introduction: Sensitivity to inhalant allergens in asthmatic children is closely related to asthma symptoms and exacerbations. This study aimed to investigate various characteristics of allergen sensitivities and their association with other comorbid allergic diseases in children aged 3-6 years diagnosed with asthma.

Materials and Methods: A total of 239 children (3-6 years old) diagnosed with asthma were included in the study. Other allergic disease diagnoses accompanying asthma, allergen sensitivities (using skin prick and serum allergen-specific IgE tests), total IgE test results, and the age distribution of allergen sensitivities were analyzed retrospectively.

Findings: Sensitivity to at least one allergen was detected in 46.4% of asthmatic children and they were defined as atopic. In children with asthma, the prevalence of atopy was determined to be 38.4% in the 36-47 month age group, 47.3% in the 48-59 month age group, and 50% in the 60-72 month age group (p=0.39). In the entire study population, allergen sensitivities were most frequently detected against mites at 29.7% and pollens at 23%. In asthmatic children, inhalant allergen sensitivities tended to increase with age. Mites sensitivity rates were determined as 17.3% in the 36-47 month group, 31.2% in the 48-59 month group, and 35.1% in the 60-72 month group (p=0.073). The sensitivity rates to pollen were found to be 1.9% in the 36-47 month group, 13% in the 48-59 month group, and 44.6% in the 60-72 month group (p=0.001). It has been determined that sensitivity rates to food allergens tend to decrease with increasing age. In all three age groups, total IgE levels were found to be higher in children with atopic asthma compared to children without atopic asthma (p=0.000-0.002). The most common comorbid allergic diseases in asthmatic children were allergic rhinitis (44.4%), atopic dermatitis (25.1%), and allergic conjunctivitis (8.8%). In asthmatic children, sensitivity to dust mites (56.3% vs. 43.7%) and pollens (72.7% vs. 27.3%) was found to be higher in cases with comorbid allergic rhinitis compared to cases without allergic rhinitis.

Conclusion: In children with asthma, inhalant allergen sensitivities tend to increase with age, while food allergen sensitivities tend to decrease with age. Identifying allergen sensitivities and comorbid allergic diseases in children diagnosed with asthma is necessary; this should be considered during the diagnosis and treatment processes of these patients and should be re-evaluated during follow-up.

Keywords
Asthma, child, allergen, sensitivity, atopy, allergic rhinitis

Anahtar kelimeler
Astım, çocuk, alerjen, duyarlılık, atopi, alerjik rinit

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Address for Correspondence/Yazışma Adresi: Emre Karaağaç, Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Türkiye
E-mail: dremrekaraagac@gmail.com

Öz

Giriş: Astımlı çocuklarda çeşitli inhalan alerjen duyarlılıkları, astım semptomları ve alevlenmeleri ile yakından ilişkilidir. Bu çalışmada, astım tanısı almış 3-6 yaş grubu çocuklarda alerjen duyarlılıklarının çeşitli özelliklerinin ve eşlik eden diğer alerjik hastalıklarla ilişkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Astım tanısı alan toplam 239 çocuk (3-6 yaş) hasta çalışmaya dahil edilmiştir. Astıma eşlik eden diğer alerjik hastalık tanıları, alerjen duyarlılıkları (alerjenlerle deri prick ve serum alerjen spesifik IgE testleri ile), total IgE test sonuçları, alerjen duyarlılıklarının yaşlara göre dağılımı, retrospektif olarak analiz edilmiştir.

Bulgular: Astımlı çocukların %46,4'ünde en az bir alerjene karşı duyarlılık saptandı ve atopik olarak tanımlandı. Astımlı çocuklarda yaş gruplarına göre atopi saptanma oranları sırasıyla; 36-47 ay grubunda %38,4, 48-59 ay grubunda %47,3 ve 60-72 ay grubunda %50 olarak tespit edilmiştir (p=0,39). Tüm çalışma populasyonunda alerjen duyarlılıkları en sık %29,7 oranında akarlara ve %23 oranında polenlere karşı saptandı. Astımlı çocuklarda inhalan alerjen duyarlılıkları yaş ile birlikte artış eğilimi göstermiştir. Akarlar için duyarlılık oranları; 36-47 ay grubunda %17,3, 48-59 ay grubunda %31,2 ve 60-72 ay grubunda %35,1 olarak tespit edilmiştir (p=0,073). Polenlere duyarlılıkları oranları; 36-47 ay grubunda %1,9, 48-59 ay grubunda %13 ve 60-72 ay grubunda %44,6 bulundu (p=0,001). Besin alerjenlerine duyarlılık oranlarının yaşla birlikte azalma eğiliminde olduğu tespit edilmiştir. Atopik astımlılarda her 3 yaş grubunda da, total IgE değerlerinin atopik bulunmayan çocuklara göre, daha yüksek olduğu görülmüştür (p=0,000-0,002). Astımlı çocuklarda en sık eşlik eden alerjik hastalıklar; alerjik rinit (%44,4), atopik dermatit (%25,1) ve alerjik konjonktivit %8,8 olarak belirlendi. Astımlı çocuklarda ek olarak alerjik rinitin birlikte bulunduğu olgularda, alerjik rinitin bulunmadığı olgulara kıyasla akarlara (%56,3'e karşı %43,7) ve polenlere (%72,7'ye karşı %27,3) duyarlılık oranlarının daha yüksek olduğu tespit edilmiştir.

Sonuç: Astımlı çocuklarda inhalan alerjen duyarlılıkları yaş ile birlikte artış eğilimi gösterirken, besin alerjen duyarlılıklarının yaş ile azalma eğiliminde olduğu görülmektedir. Astım tanılı çocuklarda alerjen duyarlılıklarının saptanması ve komorbid alerjik hastalıkların belirlenmesi gereklidir, bu hastaların tanı ve tedavi süreçlerinde göz önünde tutulması ve ek olarak izlemlerinde tekrar değerlendirilmesi gereken bir konu olduğu düşünülmüştür.

Introduction

Asthma is characterized by chronic inflammation of the airways in susceptible individuals; symptoms include shortness of breath, wheezing, chest tightness, and coughing, and are often exacerbated in relation to triggers (1,2). Major environmental factors that trigger asthma attacks include inhalant allergens, viral respiratory infections, and exercise-induced bronchoconstriction. Additionally, environmental pollutants such as air pollution, irritants, and cigarette smoke can worsen symptoms by increasing airway sensitivity (2). Current guidelines emphasize that reducing trigger exposure is important in asthma control (3).

Childhood asthma is a heterogeneous disease, and a significant portion of its phenotypes are associated with immunoglobulin E (IgE)-mediated sensitization to inhalant allergens (1,2). It is known that approximately 40-80% of childhood asthma cases are generally defined as allergic (atopic) asthma (4,5). Atopy is defined as the presence of sensitivity to at least one allergen in an individual and is closely associated with many allergic diseases, primarily asthma (6,7). A significant proportion of asthmatic children also have other allergic diseases such as allergic rhinitis, atopic dermatitis, and/or food allergies concurrently (6,7).

In the allergic (atopic) asthma phenotype, airway inflammation is associated with inhalant allergen sensitivity, which often begins in early childhood and can persist throughout life. Large epidemiological studies such as ISAAC have shown that the increase in the prevalence of childhood asthma, allergic rhinitis, and atopic dermatitis parallels the western lifestyle, changes in indoor allergen exposure, and global climate dynamics (8). Inhalant allergen (aeroallergen) sensitivity refers to the development of specific IgE against indoor mites, fungal spores, pollens, pet allergens, cockroaches, and other environmental allergens, and is closely related to both asthma development and disease severity (2,9,10). Inhalant allergen sensitivity develops as a result of the interaction of multiple factors such as environmental exposure level, genetic predisposition, epithelial barrier integrity, and early life infections (1,2).

Inhalant allergens are the most important environmental factors that trigger symptoms in childhood allergic asthma, allergic rhinitis, and allergic conjunctivitis (8). Inhalant allergen sensitivities frequently detected in cases of allergic asthma in childhood are reported to be house dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*), pollens (grass, tree, and weed pollens), fungal spores (*Alternaria, Cladosporium,* etc.), cockroaches, and domestic animals (cats, dogs, horses, etc.) (9, 11-14). Determining allergen sensitivities is of great importance in identifying the allergic phenotype of asthma and planning appropriate treatment strategies (15). Skin prick tests with allergens and evaluation of serum allergen-specific IgE levels are commonly used diagnostic methods (16).

It has been reported that inhalant allergen sensitivities in asthmatic children show significant differences between regions and countries, depending on many factors such as genetics, living conditions, regional and geographical characteristics, climate and vegetation, urban/rural settlement, air pollution, lifestyle, and environmental features (9,12,13,17-22). Additionally, the prevalence of atopy and sensitivity to inhalant allergens in asthmatic children shows significant changes with age, generally tending to increase with age (10,23-25).

Current data on allergen sensitivities in asthmatic children aged 3-6 years in our region are limited. Therefore, this study aimed to investigate the frequency of general atopy, the prevalence of various inhalant allergen sensitivities, the age-related changes in these sensitivities, and the relationship between allergen sensitivities and other allergic diseases in children aged 3-6 years diagnosed with asthma.

Materials and Methods

In this study, data from 3-6 year old children diagnosed with asthma at the Department of Pediatric Allergy, Faculty of Medicine, Bursa Uludağ University, between May 1, 2020 and October 1, 2022 were examined. Asthma diagnosis in the patients included in the study was evaluated according to the 2020 GINA criteria (26). The diagnosis of other accompanying allergic diseases was made based on the patients' history, physical examination findings and laboratory test results. The case files were retrospectively reviewed; allergic disease diagnoses, skin prick test with allergens, serum allergen-specific IgE and total IgE test results were analyzed.

Skin prick tests with allergens were performed and evaluated in accordance with the EAACI skin prick test application recommendations, as required by the clinic's routine practice (27). Skin prick tests with allergens were performed on the volar surface of both forearms using standardized allergen extract solutions from Lofarma SpA (Milan, Italy). Skin prick tests were performed after discontinuing any medications that could affect the skin test results for the appropriate time. Each allergen was applied to the skin with separate sterile lancets; evaluation was made by comparing it with positive (histamine) and negative (saline) controls. The test result was considered positive if edema of ≥3 mm was detected 15-20 minutes after allergen application compared to the negative control (27). The allergens used in skin prick testing (as part of the clinic's routine standard practice for children aged 3-6 years) included house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*); grass pollens (grass mix, *Phleum pratense*, *Dactylis glomerata*, *Lolium perenne*, *Cynodon dactylon*, *Poa pratensis*); cereal pollens (*Secale cereale*, *Triticum sativum*, *Avena sativa*); tree pollens (tree mix, *Alnus glutinosa*, *Betula verrucosa*, *Olea europaea*); weed pollens (weed mix, *Artemisia vulgaris*, *Plantago lanceolata*, *Parietaria officinalis*, *Chenopodium album*); fungal spores (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*); cat, dog, cow's milk, egg white, egg yolk, peanut, hazelnut, and walnut.

Serum allergen-specific IgE and total IgE levels were measured using the IMMULITE 2000 XPi immunoassay system (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). In allergen-specific IgE testing, values ≥0.35 kU/L (Class I) were considered positive. The allergens included in the serum allergen-specific IgE assays were as follows: mite panel (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, *Blattella germanica*), grass pollen panel (*Phleum pratense*, *Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Poa pratensis*), *Olea europaea*, *Alternaria alternata*, cat, dog, cow's milk, egg white, egg yolk, peanut, hazelnut, and walnut.

When determining allergen sensitivity results, sensitivity to each allergen was considered present if at least one of the skin prick tests and/or serum allergen-specific IgE tests with the allergen was found to be positive. Additionally, when analyzing allergen sensitivity results, the presence of sensitivity to at least one allergen in a group (such as mites, pollen, grass pollen, etc.) was defined as the presence of general sensitivity for that group (e.g.,"mites general", "pollens general", "grass pollens general", etc.).

In statistical analyses, data were analyzed using SPSS (Statistical Package for the Social Sciences) 28.0 program. The normality of the data distribution was checked using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables, and as number and percentage (%) for categorical variables. Pearson chi-square, Fisher-Freeman-Halton, or Fisher's exact chi-square tests were used to compare categorical data; Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric data. The statistical significance level was accepted as $p<0.05$.

Results

A total of 239 asthmatic children aged 3-6 years (36-72 months) were included in this study; 60.7% (n=145) were boys and 39.3% (n=94) were girls. The median age of the cases was calculated as 57 months (minimum: 36 - maximum: 72). No statistically significant difference was found between age groups in terms of gender distribution (p=0.688).

The distribution of other allergic diseases accompanying asthma in asthmatic children is given in Table 1. In 34.7% of the cases, only asthma was present as an allergic disease. Among the allergic diseases accompanying asthma, allergic rhinitis was the most common with 44.4%, followed by atopic dermatitis with 25.1%.

In 46.4% (n=111) of all children diagnosed with asthma, sensitivity to at least one allergen (inhalan or food) was detected, and these patients were defined as atopic. 53.6% (n=128) of asthmatic children were defined as non-atopic. The distribution of atopic and non-atopic cases among asthmatic children by age group (n=239) is given in Table 2. The rates of atopy detection by age group were 38.4% in the 36-47 month group, 47.3% in the 48-59 month group, and 50% in the 60-72 month group. The lowest rate of atopy detection was observed in the 36-47 month age group among asthmatic children; an increasing trend in the rate of atopy detection was observed with age, but the differences between age groups were not statistically significant (Table 2).

The results of allergen sensitivities detected in asthmatic children, and their comparisons across the entire study population and by age groups, are detailed in Table 3. The lowest rate of atopy ("any allergen" sensitivity: presence of sensitivity to at least one inhalant or food allergen) was observed in the 36-47 month age group of asthmatic children, with an increasing trend with age (p=0.39). In the entire study population of asthmatic children, allergen sensitivities were most frequently detected as mite general sensitivity (sensitivity to at least one of the allergens *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) at 29.7% and pollens general (sensitivity to at least one of the pollens of grass, tree, cereal, and weeds) at 23%. Within the pollen group general, grass pollen general sensitivity was the most frequently detected (8.8%). Sensitivities were found to pet allergens (cat and/or dog) (7.5%) and food allergens (sensitivity to at least one of the following allergens: cow's milk, egg white, egg yolk, peanuts, hazelnuts, walnuts) (5.9%). Among food allergens, egg white sensitivity was the most common (3.8%) (Table 3).

As a general trend in asthmatic children, sensitivity rates to inhalant allergens were found to increase with age (Table 3). For inhalant allergens, sensitivity rates for pollens general (p=0.001), grass pollens general (p=0.018), cereal pollens general (p=0.002), tree pollens general (p=0.006), and fungal spores general (p=0.014) increased significantly with age. A similar trend was observed for pets (cats and/or dogs) with increasing age, but the differences were not statistically significant (p=0.454). Sensitivity rates to food allergens, however, tended to decrease with age (p=0.405) (Table 3).

The rates of atopy detection in cases where any additional allergic disease is present alongside asthma are given separately for each disease in Table 4. In the presence of allergic rhinitis, atopic dermatitis, and allergic conjunctivitis accompanying asthma, the overall rates of atopy were found to be higher (although not statistically significant). In cases with accompanying angioedema, anaphylaxis, and food allergy, the rates of atopy were found to be statistically significantly higher (p=0.001-0.021) (Table 4).

Table 1. Distribution of other allergic diseases accompanying asthma in children with asthma

Diagnoses	n	%
Allergic rhinitis	106	44,4
Atopic dermatitis	60	25,1
Allergic conjunctivitis	21	8,8
Urticaria	18	7,5
Angioedema	6	2,5
Anaphylaxis	3	1,3
Food allergy	21	8,8
Only asthma	83	34,7

Data are given as n (%)

Table 2. Distribution of atopic and non-atopic cases by age group in children with asthma (n=239)

Characteristics	36-47 Months (n=52)		48-59 Months (n=93)		60-72 Months (n=94)		p[1]
	n	%	n	%	n	%	0,39[2] 0,37[3] 0,18[4] 0,71[5]
Atopic (n=111)	20	38,4	44	47,3	47	50	
Non-atopic (n=128)	32	61,6	49	52,7	47	50	

1: Pearson chi-square test
2: Age groups of 36-47 months, 48-59 months, and 60-72 months were compared.
3: Age groups of 36-47 months and 48-59 months were compared.
4: Age groups of 36-47 months and 60-72 months were compared.
5: Age groups of 48-59 months and 60-72 months were compared.
Data are given as n (%)

Table 3. Allergen sensitivities detected in all asthmatic children, their distribution and comparison by age group (n=239)

Allergens	**Total** (n=239)		**36-47 months** (n=52)		**48-59 months** (n=93)		**60-72 months** (n=94)		p
	n	%	n	%	n	%	n	%	
Any allergen[1]	111	**46,4**	20	38,4	44	47,3	47	50	0,39[3]
Mites general[2]	71	**29,7**	9	17,3	29	31,2	33	35,1	**0,073[3]**
D. pteronyssinus	70	29,2	9	17,3	29	31,2	32	34	0,091[3]
D. farinae	67	28	8	15,3	28	30,1	31	32,9	0,065[3]
Pollens general[2]	55	**23**	1	1,9	12	13	42	44,6	**0,001[3]**
Grass pollens general[2]	21	**8,8**	1	1,9	6	6,5	14	14,9	**0,018[3]**
Grasses miks	21	8,8	1	1,9	6	6,5	14	14,9	**0,018[3]**
Dactylis glomerata	13	5,4	1	1,9	4	4,3	8	8,5	0,360[4]
Lolium perenne	14	5,9	1	1,9	5	5,4	8	8,5	0,306[3]
Phleum pratense	10	4,2	1	1,9	4	4,3	5	5,3	0,839[4]
Cynodon dactylon	9	3,8	0	0	3	3,2	6	6,4	1,000[4]
Poa Pratensis	16	6,7	1	1,9	5	5,4	10	10,6	0,228[3]
Cereal pollens general[2]	13	**5,4**	0	0	2	2,2	11	11,7	**0,002[3]**
Secale cereale	12	5	0	0	2	2,2	10	10,6	**0,008[4]**
Triticum sativum	11	4,6	0	0	1	1,1	10	10,6	**0,008[4]**
Avena sativa	4	1,7	0	0	0	0	4	4,3	0,102[4]
Tree pollens general[2]	16	**6,7**	0	0	4	4,3	12	12,8	**0,006[4]**
Trees mix	16	6,7	0	0	4	4,3	12	12,8	**0,006[4]**
Alnus glutinosa	1	0,4	0	0	0	0	1	1,1	1,000[4]
Betula verrucosa	2	0,8	0	0	0	0	2	2,1	0,678[4]
Corylus avellana	1	0,4	0	0	0	0	1	1,1	1,000[4]
Olea europae	16	6,7	0	0	4	4,3	12	12,8	**0,006[4]**
Weed pollens general[2]	5	**2,1**	0	0	0	0	5	5,3	**0,026[4]**
Weeds mix	5	2,1	0	0	0	0	5	5,3	0,078[4]
Artemisia vulgaris	4	1,7	0	0	0	0	4	4,3	0,138[4]
Chenopodium album	1	0,4	0	0	0	0	1	1,1	1,000[4]
Plantago lanceolata	2	0,8	0	0	0	0	2	2,1	0,671[4]
Pets general[2]	18	**7,5**	2	3,8	7	7,6	9	9,6	0,454[3]
Cat	16	6,7	2	3,8	7	7,6	7	7,4	0,649[3]
Dog	3	1,3	0	0	0	0	3	3,2	0,238[4]
Foods general[2]	14	**5,9**	5	9,6	5	5,4	4	4,3	0,405[3]
Cow's milk	2	0,8	2	3,8	0	0	0	0	0,351[4]
Egg white	9	3,8	4	7,6	3	3,2	2	2,1	0,415[4]
Egg yolk	2	0,8	1	1,9	1	1,1	0	0	0,521[4]
Peanuts	5	2,1	2	3,8	1	1,1	2	2,1	0,455[4]
Hazelnuts	1	0,4	1	1,9	0	0	0	0	0,236[4]
Walnuts	3	1,3	2	3,8	1	1,1	0	0	0,414[4]

Table 3. Continued

Allergens	**Total** (n=239)		**36-47 months** (n=52)		**48-59 months** (n=93)		**60-72 months** (n=94)		p
	n	%	n	%	n	%	n	%	
Fungal spores general[2]	20	**8,3**	0	0	7	7,6	13	13,8	**0,014**[3]
Alternaria alternata	20	8,37	0	0	7	7,6	13	13,8	**0,014**[3]
Cladosporidium herbarum	1	0,4	0	0	0	0	1	1,1	1,000[4]
Aspergillus fumigatus	4	1,7	0	0	3	3,2	1	1,1	0,450[4]

1: Sensitivity to at least one inhalant or food allergen (presence of atopy)
2: Sensitivity to any of the allergens in this group
3: Pearson chi-square test.
4: Fisher's exact chi-square test.
Data are given as n (%).
Grasses mix*; Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, Festuca pratensis*
Trees mix; *Alnus glutinosa, Corylus avellana, Betula verrucosa*
Weeds mix; *Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Parieteria officinalis*

Table 4. Rates of atopy detection in the presence of various allergic diseases accompanying asthma

	Total	Atopic		Non-atopic		p[1]
Diagnoses	n	n	%	n	%	
Allergic rhinitis	106	61	57,5	45	42,5	0,256
Atopic dermatitis	60	38	63,3	22	36,7	0,063
Allergic conjunctivitis	21	13	61,9	8	38,1	0,087
Urticaria	18	8	44,4	10	55,6	0,395
Angioedema	6	5	83,3	1	16,7	**0,001**
Anaphylaxis	3	2	66,6	1	33,4	**0,021**
Food allergy	21	15	71,4	6	28,6	**0,002**

1: Pearson chi-square test.
Data are given as n (%)

Allergic rhinitis was found to be the most common allergic disease accompanying asthma in children with asthma (Table 1). Table 5 shows the rates of allergen sensitivities in cases of asthma accompanied by allergic rhinitis. In pediatric patients with allergic rhinitis in addition to asthma, the sensitivities to allergen groups such as dust mites general, pollens general, grass pollens general, cereal pollens general, and tree pollens general were found to be statistically significantly higher (p=0.003-0.042). Sensitivities to fungal spores general and pet allergens general tended to be lower in the presence of allergic rhinitis (Table 5).

In the study population, serum total IgE levels of all asthmatic children aged 3-6 years were found to be in the range of 1-3057 IU/mL, with a median value of 65 IU/mL. The distribution of serum total IgE levels in patients according to age groups, with and without atopy, is shown in Table 6. In atopic patients, total IgE levels were found to be statistically significantly higher in all 3 age groups (p=0.000-0.002) (Table 6).

Discussion

This study evaluated the frequency of various allergen sensitivities in asthmatic children aged 3-6 years and the relationship of these sensitivities with age groups and related conditions such as concomitant allergic diseases, using current data. In the study population, it was observed that boys were more prevalent (male/female ratio=1.54) among asthmatic children aged 3-6 years. Studies on asthma epidemiology show that symptoms tend to start earlier in boys with asthma in childhood, that the incidence and prevalence of asthma in early childhood are higher in boys than in girls, and that the age of onset of asthma symptoms is generally earlier (28-31). A study conducted in the Bursa region in 2021 reported a male/female gender ratio of 1.4 in asthmatic children aged 5-18 years (32). A review of asthma prevalence in children in Middle Eastern countries showed that the male/female ratio was around 1.5 on average (33). A study conducted in Van, Manisa, Ankara, Antalya, and Trabzon found no statistically significant difference between genders (34). It has also been

Table 5. Allergen sensitivity rates when allergic rhinitis accompanies asthma (n=239)							
	Total (n=239)		**Allergic rhinitis (+)** (n=106)		**Allergic rhinitis (-)** (n=133)		**p**
Allergens	n	%	n	%	n	%	
Mites general[1]	71	29,7	40	56,3	31	43,7	**0,015**[2]
Pollens general[1]	55	23	40	72,7	15	27,3	**0,008**[2]
Grass pollens general[1]	21	8,8	15	71,6	6	28,4	**0,009**[2]
Tree pollens general[1]	16	6,7	11	68,7	5	31,3	**0,042**[2]
Cereal pollens general[1]	13	5,4	11	84,6	2	15,4	**0,003**[3]
Weed pollens general[1]	5	2,1	3	60	2	40	0,658[2]
Fungal spores general[1]	20	8,3	12	40	8	60	0,141[3]
Pets general[1]	18	7,5	7	38,9	11	61,1	0,628[2]
Foods general[1]	14	5,9	8	57,1	6	42,9	0,321[2]

1: Sensitivity to any of the allergens in this group
2: Pearson chi-square test.
3: Fisher's exact chi-square test.
Data are given as n (%) and % values are calculated according to allergens

Table 6. Comparison of serum total IgE levels in children with atopic and non-atopic asthma			
Age groups	**Total IgE** (IU/mL)		**p**[1]
36-48 months (n=52)	Atopic 115 (2:3057)	Non-atopic 16,5 (2:446)	0,002
48-60 months (n=93)	Atopic 159,5(2:1685)	Non-atopic 34 (2:1087)	0,000
60-72 months (n=94)	Atopic 166 (9:2642)	Non-atopic 37 (1:948)	0,000

1: Mann-Whitney U test.
Data are presented as median (minimum:maximum)

reported that asthma prevalence and atopy rates are higher in boys until school age, while an increase in asthma prevalence and atopy rates is observed in girls after puberty (30,31,33). In the literature, it is reported that many genetic, epigenetic, immunological, and environmental mechanisms, as well as changes in airway diameter and sex hormones, play a role in explaining this gender difference (35-37). It is thought that the relatively narrower airway diameters, higher viral infection load, and earlier and stronger Th2 response in boys in the early years may be related to this situation (29,37). In addition, environmental risk factors such as prematurity, low birth weight, prenatal exposure to cigarette smoke, obesity, and early childhood infections are reported to increase the risk of asthma in boys, combined with their already narrower airways and reduced expiratory flow (30,31,35,38). In adolescence and adulthood, it is suggested that factors such as obesity, physical activity level, air pollution, and occupational/household exposures may interact with sex hormones in girls, increasing the prevalence and severity of asthma (33,35,38).

In childhood, two or more of the following diseases can occur together and in significant proportions: allergic asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis. When the additional allergic diseases detected in children aged 3-6 years diagnosed with asthma in our study were examined, the presence of comorbid allergic diseases such as allergic rhinitis (44.4%), atopic dermatitis (25.1%), and allergic conjunctivitis (8.8%) was observed, respectively. Childhood asthma frequently occurs together with other allergic diseases due to "atopic burden" (39-43). Allergic rhinitis, in particular, is the most common comorbid condition affecting asthma control through the common Th2-inflammatory pathway of the upper and lower airways. A meta-analysis conducted on Chinese children reported the prevalence of allergic rhinitis in asthmatic children as 54.9% (39). Another multicenter study conducted in China reported the comorbidity of asthma and allergic rhinitis as 56.3% (40). In a pediatric study based on an allergy clinic, allergic rhinitis (AR) was detected in 70.5% of asthmatic children, suggesting that the rate may be higher in selected populations (41). In a study conducted in Japan on children aged 2-10 years, allergic rhinitis was detected in 83.8% of children diagnosed with asthma (42). The literature supports the strong co-occurrence of asthma and allergic rhinitis with numerous studies. Similarly, a systematic review conducted in Iran showed that the co-occurrence rates of allergic rhinitis in asthmatic children varied between 30-80% in

different studies (33). Additionally, allergic conjunctivitis, in the context of ocular allergy, can occur in significant proportions alongside allergic rhinitis. In a study of children diagnosed with asthma and/or allergic rhinitis, the frequency of allergic conjunctivitis was reported as 33.3% in the asthma group and 61.7% in the asthma+allergic rhinitis co-occurrence group (43). This finding is consistent with the information that allergic conjunctivitis is more common, especially in the presence of allergic rhinitis. In terms of skin involvement, atopic dermatitis is an early link in the "atopic march" and is bidirectional with asthma. The prevalence of atopic dermatitis in a pediatric asthma cohort was found to be 11.1% (41). In addition, another study reported the cumulative prevalence of asthma in patients with atopic dermatitis as 25.7% (44). In a study conducted in Bursa, asthma was observed in 20.2% and allergic rhinitis in 15.8% of pediatric cases with atopic dermatitis, and the co-occurrence of asthma and allergic rhinitis was reported in 19.3% (45). Careful evaluation of these allergic comorbidities is critically important in clinical practice for trigger control, treatment adherence, and symptom burden reduction. The incidence rates of childhood asthma, allergic rhinitis and allergic conjunctivitis, and atopic dermatitis may vary in different countries and societies depending on different factors (age, genetic factors, environmental factors, diagnostic methods used in studies, characteristics of the selected population, etc.) (18).

The presence of allergen sensitivity (atopy) is one of the important risk factors for the development of asthma (6,7). In our study, patients with asthma who tested positive in allergen skin prick tests and/or serum allergen-specific IgE tests were considered atopic, and the rate of atopic patients was found to be 46.4%, while the rate of non-atopic patients was 53.6%. Various studies investigating allergen sensitivity in asthmatic children in Turkey have reported sensitivity to at least one allergen in varying rates between 42-61% (23,46,47). Studies outside of Turkey have reported this rate to be approximately between 28-83% (48-50). Many studies in the literature have reported that inhalant allergen sensitivity increases significantly with age in childhood (10,23-25,49,51). Regarding the highly variable data reported in the literature, it is considered possible that different rates were obtained as a result of various characteristics of the populations selected in the studies, age group, study methods, regional, environmental and other possible factors. The rates of atopic cases detected in our study are generally consistent with the literature; however, it is thought that they may have been found to be slightly lower due to the age group being 3-6 years. The increasing trend in the incidence of atopy and inhalant allergen sensitivities with increasing age in the 48-59 month and 60-72 month age groups in our study group is considered as data supporting this possibility.

In our study, when allergen sensitivities of asthmatic children were examined, the highest rate of sensitivity to mites was observed (29.7%), followed by sensitivities to pollens (grass, cereal, weed, tree pollens) (23%), fungal spores (8.3%), and pet allergens (7.5%) (Table 3). In the literature, most studies investigating allergen sensitivity in children with asthma report that mites are the most frequently detected allergens in asthmatic children (10,52,53). In a study conducted in the Mediterranean region of Turkey, the distribution of allergen sensitivities in children diagnosed with asthma was reported as follows: mite sensitivity was most frequent (66%), followed by grass/cereal pollen mixture (51.2%), and then tree pollen mixture (50.9%) (53). In Ankara, it was reported that the most common allergen sensitivity in asthmatic children was pollen sensitivity (32%), followed by mite sensitivity (15.9%) (54). In Malatya, sensitivity to grass-cereal pollen mixture was found to be 48.9%, sensitivity to weed-pollen mixture was 48.5%, and sensitivity to mites was 40.2% in children diagnosed with asthma and allergic rhinitis (55). In a study of asthmatic children in Korea, sensitivity to mites was reported at a rate of 47.9% (10). A large cohort study in South China, based on real-life data and including 39,831 patients, reported that the most frequently detected aeroallergen in children was the mite (52). While sensitivity to mites was 28.1% in the entire cohort, this rate increased to 29.7% in children and to 55.3% in asthmatic children (52). Inhalant allergen sensitivities in asthmatic children; it is reported that there are significant differences between regions and countries depending on many factors such as genetics, age, living conditions, regional and geographical features, climate and vegetation, urban/rural settlement, air pollution, lifestyle, and environmental characteristics (17-20).

In this study, we observed that sensitivity to inhalant allergens (mite, grass, cereal and weed pollens, and fungal spores) increased significantly with age in asthmatic children, while sensitivity to food allergens gradually decreased. Similar age-dependent sensitization patterns have been reported in the literature. In an 18-year birth cohort study conducted on the Isle of Wight, the rate of atopy increased to 2% at age 1, 3% at age 2, 10% at age 4, 18-20% at age 10, and approximately 40% at age 18; it was shown that inhalant allergen sensitivity showed a regular increase with age (51). Similarly, according to the results of a child asthma cohort

in China, inhalant allergen sensitivity increased from 28% in the 3-5 age group to 55% in the 6-11 age group and to 62% in the 12-17 age group (49). In children, while inhalant allergen sensitivities increase with age, the decrease in food allergies over time is described as a natural part of the "atopic march". For example, in a multicenter study involving 5276 children, it was reported that cow's milk allergy decreased from 2.7% at age 1 to 0.5% at age 5; egg allergy decreased from 4.3% at age 1 to 0.8% at age 6 (7). Similarly, in a prospective cohort study, wheat allergy decreased from 1.8% at age 3 to 0.2% at age 6 (56). These data show that while food allergen sensitivities, which are dominant in early childhood, decrease significantly in later years, the increase in inhalant sensitivities with age reflects the expected course of immunological maturation, changes in environmental exposures, and the atopic march, which is similar to the data obtained in our study.

The sensitization rates to allergen groups such as mites general, pollens general, grass pollens general, cereal pollens general, and tree pollens general were found to be statistically significantly higher in children with asthma who also had allergic rhinitis. Additionally, while 46.4% of the general study population was diagnosed with asthma had sensitization to at least one allergen (inhalant or food) and were defined as atopic, this rate was found to be higher (57.5%) in those who also had allergic rhinitis (Table 4). Epidemiological studies show that sensitization rates to house dust mites, pollens, and animal dander are significantly higher in cases with both asthma and allergic rhinitis compared to children with asthma alone. In a multicenter study, inhalant allergen sensitization was found to be over 70% in children with both asthma and allergic rhinitis, while it was approximately 40-45% in those with asthma alone (57). In a comprehensive cohort study of 39,831 patients in southern China, house dust mite sensitivity was found to be 55.3% and grass pollen sensitivity 39.2% in children with asthma-allergic rhinitis comorbidity (52). For these reasons, it was considered that the significantly higher overall sensitivity to dust mites, grass pollen, tree pollen, and cereal pollen in asthmatic patients with concomitant allergic rhinitis in our study was consistent with current literature.

In this study, it was additionally found that children with atopic asthma had significantly higher total IgE levels than children without atopic asthma in all three age groups. Atopic asthma is characterized by a Th2-dominant immune system response in early childhood, during which a significant increase in total IgE levels is observed (58). Although not a general rule, total IgE is considered to be an indirect indicator of atopic sensitization in many cases and is found to be significantly higher in children with atopic asthma compared to their non-atopic or healthy peers. Similarly, data from the Tucson Children's Respiratory Study revealed that total IgE was higher in children with atopic asthma than in children with non-atopic wheezing (59). European-based studies have also shown that total IgE levels are statistically significantly higher in asthmatic children aged 3-6 years who have been sensitized to inhalant allergens compared to asthmatic children who have not been sensitized (58). In addition, it is emphasized that high total IgE levels in asthma are more frequently seen with accompanying atopic diseases such as allergic rhinitis and atopic dermatitis, and that these children have a higher risk of developing persistent asthma in later life (60). However, it is known that total IgE alone is not diagnostic; IgE levels can vary with age, parasitic infections, exposure to cigarette smoke, environmental factors, and comorbid conditions (61).

Study Limitations

The limitations of this study include its retrospective nature and the fact that it was conducted in only one healthcare facility. However, given that our institution specializes in allergic diseases, possesses standardized clinical and laboratory facilities, and is a tertiary healthcare center serving all relevant patients in the Bursa region, it can be considered that it contains sufficient data regarding the research results on allergen sensitizations in childhood asthma.

Conclusion

In this study, sensitivity to at least one allergen was detected in 46.4% of asthmatic children aged 3-6 years and was defined as atopic, with sensitivities most frequently found to be to mites (29.7%), pollens (23%), and fungal spores(8.3%). In asthmatic children, an increasing trend in the rate of atopy detection with age was observed (p=0.39). Inhalant allergen sensitivities in asthmatic children showed an increasing trend with age. Food allergen sensitivities, on the other hand, showed a decreasing trend with age. In asthmatic children, allergic diseases such as allergic rhinitis, atopic dermatitis, and allergic conjunctivitis were frequently observed to accompany asthma. In pediatric patients with both asthma and allergic rhinitis, significantly higher sensitivities to allergen groups such as dust mites, pollens, grass pollens, cereal pollens, and tree pollens have been found. In atopic asthmatics, total IgE levels were significantly higher in all three age groups compared to non-atopic children. Since inhalant allergen sensitivities in asthmatic children tend to increase with age, it was considered

necessary to re-evaluate these patients, especially in terms of the presence of inhalant allergen sensitivities (particularly in cases of additional allergic diseases), in parallel with increasing age. It is thought that the data obtained from this study will be useful in considering in the evaluation and follow-up of asthmatic pediatric patients.

Ethics

Ethics Committee Approval: The study received approval from the institution's ethics committee (Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision no. 2023-16/39 dated 01.08.2023).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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