The Asthma Risk Is Increased in Children with Severe Allergic Rhinitis

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ABSTRACT

Objective: The aim of the study was to evaluate the allergic rhinitis severity, to identify risk factors associated with asthma, and to determine the frequency of comorbid conditions in allergic rhinitis patients with positive skin prick test.

Materials and Methods: Clinical characteristics of pediatric patients with allergic rhinitis were investigated. The frequency of comorbidities and risk factors for asthma development were investigated.

Results: A total of 120 patients with a mean age of 13.05 ± 3.20 years were included in the study. Dermatophagoides pteronyssinus was the most common source of allergic sensitization (n = 78, 61.0%), whereas mild-persistent disease was the most common type of allergic rhinitis severity (n = 44, 36.6%). Sensitization to Dermatophagoides farinea, Dermatophagoides pteronyssinus, and Alternaria was more common in patients with a moderate–severe course of allergic rhinitis than in the mild group (P = .006, P = .008, and P = .005, respectively). The most frequent comorbidity in children with allergic rhinitis was allergic conjunctivitis (71.7%). The incidence of asthma in those with moderate–severe allergic rhinitis was found to be significantly higher compared to those with mild disease severity (P = .009). Also, the multivariate analysis disclosed moderate–severe allergic rhinitis severity and persistent allergic rhinitis symptoms (OR: 3.822; 95% CI: 1.587–9.200; P = .003 and OR: 0.333; 95% CI: 0.150–0.737; P = .007, respectively) as risk factors for asthma development.

Conclusion: Sensitization to Dermatophagoides farinea, Dermatophagoides pteronyssinus, and Alternaria was more frequent in patients with moderate–severe allergic rhinitis course. Also, having moderate–severe allergic rhinitis severity and persistent allergic rhinitis symptoms are associated with the development of asthma. Awareness of the risk factors could prevent the progression and complications of allergic rhinitis in children.

Keywords: allergic rhinitis, allergen sensitization, disease severity, children

INTRODUCTION

Allergic rhinitis (AR) is one of the most common chronic disease in childhood.1 The prevalence of AR ranges from 20% to 40% in the pediatric population worldwide.2 AR impairs the quality of life and requires multiple drug use. It was also reported to cause about 3.5 million lost workdays and 2 million lost school days per year.3 Although it is not a life-threatening disease, it is closely associated with the development and progression of multiple comorbid diseases, including asthma, allergic conjunctivitis, acute and chronic sinusitis, otitis media, nasal polyposis development, aggravation of adenoid hypertrophy, and sleep disorders.4–6 Early diagnosis and treatment of AR and the identification of risk factors for the development of comorbid disorders have an important role in preventing comorbidities.

Allergens such as airborne pollens, molds, dust mites, and animals may be triggers for AR.7 Skin prick tests (SPT) are screening tools used to identify sensitizing allergens in
patients with suspected AR. SPT positivity was reported in 46.4% of pediatric AR patients. The relationship between the type of allergen sensitization and AR disease severity, asthma, and other comorbidities has been investigated so far. For example, the severity of asthma and AR was reported to be associated with house dust mite and pollen sensitization, respectively. However, this link between the type of allergen and the severity of asthma and AR has not been demonstrated in other studies. AR and asthma also share similar immunopathological characteristics. AR has been reported to be associated with house dust mite and pollen sensitization, respectively. However, this link between the type of allergen and the severity of asthma and AR has not been demonstrated in other studies. AR and asthma also share similar immunopathological characteristics. AR has been reported in 78% of patients with asthma. It is not only a risk factor for the development of asthma, but it also compromises asthma control and increases the rate of attacks and hospital admissions. On the other hand, there are few literature data regarding whether there is an association between the sensitization profile of allergens and the incidence of asthma in pediatric AR patients with positive skin prick test.

In this study, we aimed to evaluate the characteristics and comorbidities of AR patients with positive skin prick test, to assess the severity of the disease, and to determine risk factors for the development of asthma in pediatric AR patients.

**MATERIALS AND METHODS**

**Study Design**

A total of 120 patients with positive SPT among 450 pediatric AR patients who were admitted to pediatric allergy-immunology clinics between January 2016 and January 2017 were included in the study. Those with negative skin test results and a diagnosis of non-AR were excluded. Differential diagnosis was made for cystic fibrosis, ciliary dyskinesia, foreign bodies, choanal atresia, and immunodeficiency. The diagnosis of AR is based on the concordance between the presence of characteristic symptoms (rhinorrhea, nasal pruritis, sneezing, and nasal obstruction) and diagnostic tests (SPT or the blood-specific immunoglobulin (Ig) E) according to the ARIA (Allergic Rhinitis and its Impact on Asthma) guideline. The medical records of body mass index (BMI) values, place of residence (urban or rural areas), family history of atopy, exposure to cigarette smoke, pet ownership, presence of sleep apnea syndrome, whether alternative methods were used in AR treatment, the previous diagnosis of otitis, sinusitis, tonsillitis, adenoid hypertrophy, and atopic dermatitis were also evaluated. AR severity was classified according to ARIA classification (Figure 1). The patients were classified as mild or moderate–severe according to the severity of AR and as intermittent or persistent according to the duration of symptoms. Total eosinophil counts, serum total Ig E levels, skin prick test, and respiratory function test results were assessed. Eosinophilia is defined as an increased number of peripheral blood eosinophil counts (>500/mcL (>0.5 × 10^9/L)). Serum total Ig E concentrations higher than 100 IU/mL indicate increased total Ig E level. We also divided into three groups according to age (6–9, 10–14, and 15–18 years) and investigated whether there is any difference in the frequency of allergen sensitizations between age groups. BMI values of patients were calculated, and the presence of obesity was determined based on reference ranges according to age. Asthma diagnoses were based on the GINA (Global Initiative for Asthma) guideline.

**Method and Interpretation of Skin Prick Tests**

Standard solutions of Dermatophagoides farinae (Der f), Dermatophagoides pteronyssinus (Der p), pollens (grass, weed, and tree pollens), Aspergillus, Alternaria, cat, and dog dander were used in the skin tests (Allergopharma Reinberk, Germany). Histamine dihydrochloride (10 mg/mL) was used as positive control, and normal saline was used as a negative control. Histamine was evaluated at 10 minutes (min) and the allergens were evaluated at 15 minutes. The widest diameter of induration (wheat) and perpendicular diameter were measured. Indurations that were larger than 3 mm compared to the negative control were considered positive results. Patients were also classified as mono or poly sensitized according to the number of allergen sensitization in the skin prick test. Respiratory function tests were performed using the “Zan GPI 3.0 Spirometer” (nSpire Health, Longmont, Colo, USA).

**Statistical Analysis**

Descriptive statistics such as frequency distribution, mean, and standard deviation were used for description. Kolmogorov–Smirnov/Shapiro Wilk test and visual methods (histograms and probability graphs) were used to determine whether the variables were normally distributed. Categorical data

| Intermittent | Persistent |
|--------------|------------|
| • <4 days per week | • >4 days/week |
| • or <4 consecutive weeks | • and >4 consecutive weeks |

| Mild | Moderate-severe |
|------|-----------------|
| All of the following | One of more items |
| • Normal sleep | • Sleep disturbance |
| • No impairment of daily activities, sport, leisure | • Impairment of daily activities, sport, leisure |
| • No impairment of work and school | • Troublesome symptoms |
| • Symptoms present but not troublesome |

Figure 1. ARIA classification of severity of allergic rhinitis. ARIA, Allergic Rhinitis and its Impact on Asthma.
were examined using the chi-square significance test or Fisher’s exact test (when chi-square test assumptions do not hold due to low expected cell counts). For the comparison of continuous variables, the Mann-Whitney U-test was used since the parameters were not normally distributed. Univariate and multivariate logistic regression analyses were applied to identify risk factors for asthma development in AR patients and to determine the independent risk factors. The “Enter” method of regression was used. The Hosmer-Lemeshow test goodness of fit statistics was used to assess model fit. The explanatory power of the model was evaluated by Nagelkerke $R^2$ values. It was accepted that the closer the $R^2$ values are to 1, the better is the fit of the model. Odds ratios (ORs) were calculated with 95% CI. The data were analyzed using SPSS software. A significance level of 95% (or $\alpha = 0.05$ margin of error) was used to determine the presence of significant differences.

Ethics Statement
This study was approved by the ethics committee of Akdeniz University (approval number: 2012 KAEK-20) and was conducted according to the guidelines of the Declaration of Helsinki.

RESULTS

Characteristics of Patients
A total of 120 patients, 72 boys (60%), with a mean age of 13.05 ± 3.20 years were included in the study. Half of the patients had a family history of atopic disease (n = 60). BMI results revealed that 11 (9.2%) patients were obese. While 86 (71.7%) of the patients lived in urban areas, 34 (28.3%) lived in rural areas. Eosinophilia was present in 41 (34.2%) of the patients whereas total IgE values were higher than age-adjusted reference values in 100 of the patients (86.2%). The characteristics of the patients are summarized in Table 1. Der p was the most common source of allergic sensitization (n = 78, 61.0%). On the other hand, sensitization to aspergillus was less common in patients with a moderate–severe course of AR, sensitization to Der f, Der p, and Alternaria was more common than in the mild group ($P = .006$, $P = .008$, and $P = .005$, respectively). Furthermore, asthma was more common in patients with moderate–severe AR group (65.7% vs. 38.8%, $P = .007$).

Comorbidities of AR
Allergic conjunctivitis was the most common comorbidity accompanying AR (71.7%). The frequency of other comorbidities was as follows: adenotonsillar hypertrophy in 54.1%, sinusitis in 49.2%, asthma in 46.7%, otitis media in 40.8%, atopic dermatitis in 20%, chronic tonsillitis in 9%, and obstructive sleep apnea syndrome in 4.5% of the patients (Table 3).

Evaluation of AR Disease Severity
Mild forms of AR were observed in eighty-five patients (70.7%) whereas thirty-five patients (29.1%) had moderate–severe symptoms. Regarding the duration of AR symptoms, the persistent disease was present in 55.7% of patients (n = 67). Mild-persistent AR was the most common disease severity group in all study population (n = 44, 36.6%). Disease severity did not differ according to age, gender, presence of obesity, location of dwelling, family history of atopic disease, history of passive smoking, pet ownership, presence of eosinophilia, polyps, and characteristic features of patients such as age, gender, and living in urban areas were not the risk factors. Two risk factors that were significant in the univariate analysis were re-evaluated with multivariate analysis (Nagelkerke’s $R^2$ value $= 0.157$). Having moderate–severe AR severity and persistent AR symptoms were also the independent risk factors for asthma development ($OR: 3.822$; 95% CI: 1.587–9.200; $P = .003$ and OR: 0.333; 95% CI: 0.150–0.737; $P = .007$) (Table 5).

DISCUSSION
The present study assessed the characteristics of AR patients, risk factors for disease severity and asthma development,
was found that 271 of 509 (53.2%) patients had accompanying asthma. In a pediatric study with AR, it was reported that 20.3% of those with AR developed asthma, and AR occurred in 85.7% of those with asthma. In a pediatric study with AR, it was found that 271 of 509 (53.2%) patients had accompanying asthma.38

Having moderate–severe AR severity and persistent AR symptoms were risk factors for developing asthma in our study. Bousquet et al19 also reported that patients with moderate–severe persistent rhinitis were more prone to developing asthma. Similarly, previous studies demonstrated that asthma significantly correlated with the severity of AR.11,12,30 However, there are also studies reporting that there is no correlation between AR severity and the prevalence of asthma.31 Nevertheless, it seems to be beneficial to closely monitor moderate–severe AR patients for the development of asthma.

The skin test is the most frequently used method to confirm sensitization in allergic disease.23 Although the type of allergen sensitization can be affected by many factors such as environment and genetics, in general, house dust mites were reported to be the most frequent sensitizing allergen consistent with our findings.24,25 Patients sensitized to Der f, Der p, and Alternaria had a more severe course of AR in our study. Sensitization to Der p and Der f was also associated with moderate to severe allergic rhinitis in previous studies.26,27 Likewise, in a study consisting of 100 children, a relationship between the severity of AR and the Der p and Der f sensitization was observed.28 As for Alternaria, it is one of the most common fungal allergens associated not only with the development of asthma but also with the severity of asthma.29 Alternaria sensitization has also been linked to AR.30 However, few data exist regarding its impact on AR severity. One study reported that 77% of children sensitized to Alternaria had moderate/severe AR, while another study involving adult and pediatric AR patients reported no association between AR severity and allergen type.31,32 With these differences kept in mind, our study indicates that AR patients sensitized to Alternaria, Der f, and Der p tend to have a more severe course of the disease. In addition, we have demonstrated the increasing frequency of sensitivity to pollen, cats, and dogs with the increasing age. Along the same lines, assessment of specific Ig E levels of the children at four and eight years of age in a birth cohort study consisting of a sample of 5362 individuals revealed an increased sensitization to nondomestic allergens such as furred animals and pollens at the age of eight.33

There are conflicting results in the literature regarding the relationship between the type of allergen and the incidence of asthma in patients with AR. The sensitization to house dust mites was reported to be an independent variable that increased the risk of asthma development around eightfold.34 On the other hand, no statistically significant association was found between allergen type and incidence of asthma.35 Our results also indicated that the development of asthma was independent of the allergen type.

Since the coexistence of allergic conjunctivitis and AR is common, the Nomenclature Review Committee of the World Allergy Organization has proposed to term allergic rhinoconjunctivitis.36 Allergic conjunctivitis was also the most common comorbidity accompanying AR in our study which was consistent with the results of previous studies.37,38

Its retrospective nature is the main limitation of our study. We did not assess the long-term follow-up of patients for the development of comorbidities. Accompanying asthma was more frequent in severe AR patients, but we do not know whether patients with mild disease will develop asthma in long-term follow-up. However, we believe that it will contribute to the literature on the factors affecting the severity of AR and the evaluation of asthma development risk factors in children with AR. This study has also provided some evidence of the relationship between sensitization to three common allergens, Der f, Der p, and Alternaria, and the severity of AR. Further multicenter studies with larger numbers of participants might provide an additional perspective on the general population.

In conclusion, our study highlights the presence of common comorbidities such as conjunctivitis and asthma in AR patients with positive SPT. Since having moderate–severe AR severity and persistent AR symptoms were the independent predictors of asthma development, effective treatment and maintaining disease control are needed to minimize the risk of persistence. Furthermore, the symptoms and clinical findings of AR

Table 2. Comparison of the Frequency of Sensitivity to Allergens Between Age Groups

| Allergen Sensitization | Age (Year) | P value |
|------------------------|-----------|---------|
|                        | 6–9 (n,%) | 10–14 (n,%) | 15–18 (n,%) |
| Der p                  | 13 (16.7) | 36 (46.2) | 29 (37.2) | 0.986* |
| Der f                  | 14 (18.2) | 38 (49.4) | 25 (32.5) | 0.436* |
| Pollens                | 6 (8.0)   | 33 (44.0) | 36 (48.0) | 0.000* |
| Cats                   | 3 (5.4)   | 26 (46.4) | 27 (48.2) | 0.003* |
| Dogs                   | 2 (3.9)   | 24 (47.1) | 25 (49.0) | 0.000* |
| Alternaria             | 6 (15.4)  | 17 (43.6) | 16 (41.0) | 0.789* |
| Aspergillus            | 5 (18.5)  | 11 (40.7) | 11 (40.7) | 0.782* |

Table 3. The Frequency of Comorbidities Accompanying Allergic Rhinitis

| Disease                  | n (%)  |
|--------------------------|--------|
| Allergic conjunctivitis  | 86 (71.7) |
| Adenotonsillar hypertrophy | 65 (54.1%)  |
| Sinusitis                | 59 (49.2%) |
| Acute                    | 39 (32.5%)  |
| Chronic                  | 20 (16.7%) |
| Asthma                   | 56 (46.7%) |
| Otitis media             | 49 (40.8%)  |
| Atopic dermatitis        | 24 (20%)  |
| Chronic tonsillitis      | 10 (9%)  |
| OSAS                     | 5 (4.5%)  |

OSAS: obstructive sleep apnea syndrome.
Table 4. Evaluation of Disease Severity According to Allergen Type and Patient Characteristics

| Severity of AR | Mild (n = 85) | Moderate–Severe (n = 35) | P  |
|----------------|--------------|-------------------------|----|
| Age, years (mean ± SD) | 13.0 ± 3.3  | 13.0 ± 3.2               | .979a |
| Male, n (%) | 55 (64.7)  | 17 (48.6)               | .101b |
| Living in urban areas, n (%) | 58 (68.2)  | 28 (80.0)               | .194b |
| Obesity, n (%) | 9 (10.6)  | 2 (5.7)                 | .400c |
| Family history of atopic disease, n (%) | 42 (49.4)  | 18 (51.4)               | .841b |
| History of passive smoking, n (%) | 33 (38.8)  | 12 (34.3)               | .641b |
| Pet ownership, n (%) | 16 (18.8)  | 5 (14.3)                | .552b |
| Duration of AR symptoms, n (%) | 41 (48.2)  | 12 (34.3)               | .162b |
| Allergen sensitization, n(%) | Der f  | 29 (82.9)              | .008b |
| Pollens | 38 (44.7)  | 18 (51.4)               | .502b |
| Cats | 37 (43.5)  | 14 (40.0)               | .722b |
| Dogs | 21 (24.7)  | 18 (51.4)               | .005b |
| Alternaria | 17 (20.0)  | 10 (28.6)               | .307b |
| Aspergillus | 0.010  | 0.382                   | 0.001 |
| Presence of eosinophilia, n (%) | 71 (86.6)  | 29 (85.3)               | .854b |
| Asthma, n (%) | 33 (38.8)  | 23 (65.7)               | .007b |

AR, allergic rhinitis; Der f, Dermatophagoides farinae; Der p, Dermatophagoides pteronyssinus; Ig, immunoglobulin; SD, standard deviation.

a Mann-Whitney U-test.

b Chi-square test.

c Fisher's exact test.

Bold values indicate statistical significance (p-value less than 0.05).

Table 5. Evaluation of Risk Factors for Asthma Development in Children with Allergic Rhinitis by Univariate and Multivariate Logistic Regression Analysis

| B   | SE  | Wald | P     | OR   | 95% CI       |
|-----|-----|------|-------|------|--------------|
| Age | 0.065 | 0.056 | 1.338 | .247 | 1.067       | 0.956–1.192 |
| Male gender | −0.056 | 0.374 | 0.022 | .881 | 0.946       | 0.455–1.967 |
| Obesity | 0.926 | 0.704 | 1.731 | .118 | 2.524       | 0.636–10.022 |
| Living in urban areas | −0.143 | 0.407 | 0.124 | .725 | 0.866       | 0.390–1.925 |
| Having moderate–severe AR severity | 1.105 | 0.420 | 6.928 | .008 | 3.020       | 1.326–6.878 |
| Persistent AR symptoms | 0.862 | 0.376 | 5.247 | .022 | 2.367       | 1.132–4.948 |
| Family history of atopic disease | 0.134 | 0.366 | 0.134 | .714 | 1.143       | 0.558–2.344 |
| History of passive smoking | −0.286 | 0.378 | 0.570 | .450 | 0.752       | 0.358–1.577 |
| Pet ownership | −0.278 | 0.481 | 0.333 | .564 | 0.758       | 0.295–1.946 |
| Allergen sensitization | Der f  | 0.010 | 0.382 | 0.001 | .980 | 1.010       | 0.478–2.133 |
| Pollens | −0.143 | 0.378 | 0.143 | .706 | 0.867       | 0.413–1.818 |
| Aspergillus | −0.116 | 0.439 | 0.069 | .793 | 1.122       | 0.474–2.656 |
| Alternaria | 0.582 | 0.394 | 2.183 | .140 | 1.789       | 0.827–3.870 |
| Cats | −0.288 | 0.368 | 0.611 | .434 | 0.750       | 0.365–1.543 |
| Dogs | −0.110 | 0.371 | 0.088 | .767 | 0.896       | 0.433–1.852 |
| Sensitization to multiple allergens | 0.151 | 0.569 | 0.071 | .790 | 1.163       | 0.381–3.548 |
| Elevated levels of immunoglobulin E | −0.131 | 0.542 | 0.059 | .809 | 0.877       | 0.303–2.539 |
| Presence of eosinophilia | 0.577 | 0.389 | 2.206 | .138 | 1.781       | 0.831–3.815 |

Asthma Development Risk Factors (Multivariate Logistic Regression Analysis)

| B   | SE  | Wald | P     | OR   | 95% CI       |
|-----|-----|------|-------|------|--------------|
| Having moderate–severe AR severity | 1.341 | 0.448 | 8.944 | .003 | 3.822       | 1.587–9.200 |
| Persistent AR symptoms | 1.100 | 0.406 | 7.354 | .007 | 3.033       | 1.050–9.737 |

AR, allergic rhinitis; OR, odds ratio; Der f, Dermatophagoides farinae; Der p, Dermatophagoides pteronyssinus.

Bold values indicate statistical significance (p-value less than 0.05).
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were more severe in patients sensitized to Der f, Der p, and Alternaria, which requires close follow-up of these patients.

Ethics Committee Approval: This study was approved by Ethics committee of Akdeniz University (Approval No: 2012 KAEG-20).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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