



Prognosis of Childhood Atopic Asthma: A 6-year Follow-up Study

Çocukluk Çağı Alerjik Astım Prognozu: 6 Yıllık Bir Klinik İzlem Çalışması

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ABSTRACT

Objective: There have been few studies on prognosis and factors influencing the prognosis in children with atopic asthma. We intended to evaluate the prognosis, clinical remission rate, and influencing factors of childhood atopic asthma.

Methods: In 72 pediatric patients with atopic asthma who were followed up between 2016 and 2022 with a mean follow-up period of 6.03±2.19 years, demographic characteristics, family history, clinical symptoms, pulmonary function test results, and asthma control test scores were evaluated. Totally controlled patients who had not received any asthma treatment for ≥1 year were considered to be in "clinical remission."

Results: The study group included 72 children with atopic asthma (female/male: 28/44), with a mean age of 13.36±1.98 (8-18) years. 12.5% (n=9) of the patients had uncontrolled asthma, 45.8% (n=33) were partially controlled asthma, 41.7% (n=30) were complete controlled asthma. Clinical remission was seen in 23.6% (n=17) patients with total control. Patients who were symptomatic before the age of three and had a persistent course had a lower clinical remission rate (p=0.05).

Conclusion: In our study, the clinical remission rate in atopic asthma in early adulthood was 23.6%. Our results reveal that the clinical remission rate was lower in patients who developed symptoms and had persistent wheezing before the age of three.

Keywords: Pediatric asthma, allergic asthma, asthma remission, prognostic factors, natural history

ÖZ

Amaç: Alerjik astımı olan çocuklarda prognoz ve prognozu etkileyen faktörler üzerine az sayıda çalışma yapılmıştır. Biz çalışmamızda çocukluk çağı alerjik astımının prognozunu, klinik remisyon oranını ve katkıda bulunan faktörleri değerlendirmeyi amaçladık.

Gereç ve Yöntem: 2016-2022 yılları arasında ortalama takip süresi 6,03±2,19 yıl olan alerjik astım tanılı 72 pediatrik hastada demografik özellikler, aile öyküsü, klinik semptomlar, solunum fonksiyon testi sonuçları ve astım kontrol testi skorları değerlendirildi. Bir yıldan fazla herhangi bir astım tedavisi almayan kontrollü hastalar "klinik remisyonunda" kabul edildi.

Bulgular: Çalışma grubuna yaş ortalaması 13,36±1,98 olan 72 alerjik astımlı çocuk (kız/erkek: 28/44) dahil edildi. Astım kontrol durumuna göre hastaların %12,5'i (n=9) kontrolsüz, %45,8'i (n=33) kısmi kontrollü, %41,7'si (n=30) tam kontrollü idi. Tamamen kontrol altına alınan olguların %23,6'sında (n=17) klinik remisyon gözlemlendi. Üç yaşından önce semptomatik olan ve persistan seyirli hastalarda klinik remisyon oranı daha düşüktü (p=0,05).

Sonuç: Çalışmamızda erken çocukluk döneminde alerjik astımda klinik remisyon oranı %23,6 idi. Üç yaşından önce semptomları başlayan ve persistan seyirli olgularda klinik remisyon oranının daha düşük olduğunu saptadık.

Anahtar Kelimeler: Pediatrik astım, alerjik astım, astım remisyonu, prognostik faktörler, doğal seyir

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INTRODUCTION

Asthma is the most common chronic lung disease in children and a major cause of morbidity and mortality (1,2). Despite advances in treatment, it is still an incurable disease. The aim of asthma treatment is to control the disease (2,3).

While some children with asthma experience remission in their early childhood, the disease persists in some children throughout their lives (1,3). Parents ask many questions, such as, "Will my child's asthma get better?" "When will my child's asthma get better?" The answer and, however, is not so clear and may depend on many factors. It may also differ among populations based on genetic and environmental factors (3-5).

Remission in childhood asthma is most common between the ages of 14 and 21. Studies have reported variable remission rates ranging from 14 to 75%. (6,7). This variation is largely due to the lack of a standardized definition of asthma remission and the heterogeneity of the patient populations (3-5).

There is still no consensus on the definition of asthma remission. There are different definitions of what "remission" in asthma means. Remission can be either complete or clinical. "Complete remission" can be defined as occurring in patients who have received no pharmacologic treatment for ≥ 1 year, have no symptoms, no airway obstruction, objective evidence of the absence of asthma-related inflammation (such as reduced blood or sputum eosinophil counts, exhaled nitric oxide, and/or other relevant measures), and no bronchial hyperresponsiveness. "Clinical remission" can be defined as a patient who has not received any pharmacologic treatment for ≥ 1 year, has no asthma symptoms and the patient and physician agree on disease remission (2). Some patients in clinical remission with persistent bronchial hyperresponsiveness may experience recurrence of symptoms for the rest of their lives, while others do not.

The purpose of this study was to assess the prognosis, clinical remission rate, and risk factors in children with atopic asthma.

METHODS

We selected 120 patients who were diagnosed with atopic asthma according to the Global Initiative for Asthma guidelines (8), who had regular follow-up between 2016 and 2022, and who had not received allergen immunotherapy before. We tried to contact 120 patients, and 96 patients who could be reached were invited to the outpatient clinic control for re-evaluation. Seventy two of the 96

patients were re-evaluated within the specified time frame. Demographic characteristics, time of disease onset, family history, comorbidities, symptom frequency, smoking exposure (passive smoking), serum total IgE, blood eosinophil count, skin-prick test (SPT) results, body mass index (BMI), and asthma medications were recorded. The pulmonary function test and asthma control test (ACT) were repeated. Patients with an ACT score of 25 were regarded to have "total control," those with a score between 20 and 24 were regarded to have "partial control," and those with a score less than 20 were regarded to have "uncontrolled asthma" (9). Patients who were regarded to have completely controlled asthma were evaluated for remission status. Patients without asthma symptoms who had not received asthma treatment for at least a year were classified as being in "clinical remission" (2). Patients with a BMI ≥ 95 p were classified as obese (10).

Specific respiratory diseases (such as cystic fibrosis or tuberculosis) or other seriously interfering diseases were not included in the study. Patients who had previously received allergen immunotherapy for atopic asthma were excluded from the study (due to the effects of allergen immunotherapy on the natural course of the disease).

Skin-prick Tests

SPTs were performed by trained physicians on the volar surface of the forearm of each patient using a commercial extract (ALK Abelló, Horsholm, Denmark) with common allergens [house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), pollens (grass, weed, and tree), molds (*Alternaria*, *Cladosporium*), animal dander (cat and dog), and food (cow's milk, egg, wheat, peanut, fish, and soy)]. The tests were always performed using a histamine-positive control and a saline-negative control. A positive result was defined as a mean wheal diameter greater than 3 mm after 15 minutes of testing the allergen extracts.

Blood Eosinophil Counts and Serum Total IgE Levels

Complete blood count was performed on the Mindray BC-6000 device with peripheral blood samples collected in EDTA tubes. Serum IgE levels were determined by the nephelometric method (Dade Behring Marburg GmbH, Germany).

Spirometry

Forced expiratory maneuvers were measured using a spirometer (ZAN 100 USB Betterflow Spirometer, Germany). Data are presented as a percentage of the predicted values, with race, gender, body weight, and height considered. The best result after at least 3 evaluations was considered. If a patient's spirometry was not satisfactory on the first visit, the

first appropriate spirometry test result and the spirometry test results of all subjects at the last follow-up visit were evaluated.

Asthma Control Test

The control of asthma was assessed using the ACT questionnaire, which consisted of five questions regarding daytime and nighttime asthma symptoms, rescue medication use, and level of impairment in daily activities due to asthma. An ACT score of 25 points was considered total control, 20-24 points as partial control, and <20 points as uncontrolled (9).

Approval for the study was obtained from İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (decision no: 796, date: 30.11.2022).

Statistical Analysis

IBM SPSS version 24.0 (Armonk, New York, United States) was used for all statistical analyzes parametric methods were used for the analysis of variables with a normal distribution, whereas non-parametric methods were used for the analysis of variables that were not normally distributed. Comparisons of continuous variables were made with independent-sample t-test and Mann-Whitney U test as appropriate. Pearson's chi-square and linear-by-linear association tests were used with an exact test for the comparison of categorical data. The categorical data are expressed as a percentage of the number (n) of children evaluated. The level of significance for the analyses was $p < 0.05$.

RESULTS

The study group consisted of 72 patients, 38.9% (n=28) female, 61.1% (n=44) male, mean age 13.36 ± 1.98 years, age at diagnosis 7.54 ± 2.51 years. In the family, atopy was present in 25% (n=18), parental asthma in 6.9% (n=5), allergic rhinitis at diagnosis in 70.8% (n=51), and multiallergen sensitization in 60% (n=36) of cases. 4.2% (n=3) of the patients were obese. Passive smoking was found in 54% (n=34) of patients at the time of diagnosis. The proportion of patients whose symptoms started before the age of 3 years and persisted was 22.5% (n=16).

According to asthma control status at follow-up, 12.5% (n=9) of the patients had uncontrolled asthma, 45.8% (n=33) had partially controlled asthma, and 41.7% (n=30) had totally controlled asthma. Clinical remission was seen in 23.6% (n=17) patients with complete control.

Patients with clinical remission were compared with those without. The clinical remission rate tended to be lower in

patients who were symptomatic before the age of three years and had a persistent course ($p=0.05$). No significant difference was found when atopic asthma patients with and without clinical remission were compared in terms of baseline allergen sensitization, comorbid atopic disease, asthma severity, pulmonary function tests, serum total IgE levels, and eosinophil counts (Table 1).

DISCUSSION

In our study, the clinical remission rate was 23.6% (n=17) at a mean follow-up of 6 years. Patients with symptom onset and persistent wheezing before the age of three years had a lower clinical remission rate.

Remission rates in childhood asthma are different in studies. The fact that atopic and nonatopic asthma patients were chosen together and that the remission criteria used were different may explain some of the differences in remission rates between the studies.

In a 4-year follow-up, Covar et al. (3) reported that only 6% of 909 pediatric patients with atopic asthma developed clinical remission during adolescence. In the 12-year follow-up study of Wang et al. (4) in children with asthma, the clinical remission rate was reported as 26% in early adulthood.

In a 10-year follow-up study conducted by Sekerel et al. (5) in Türkiye, the clinical remission rate in 115 pediatric patients with asthma (both atopic and non-atopic) was 26%. Aydoğan et al. (11) reported that in a 10-year follow-up of asthmatic children from Türkiye, the atopy status of the patients determined the persistence of asthma and that most of the nonatopic patients recovered before the age of 10 years and by the age of 18 years. They also discovered that two-thirds of asthma cases with atopy persisted. In all these studies, children with atopic and non-atopic asthma were evaluated together (3-5,11).

Only a few studies have looked at atopic factors as predictors of asthma remission. When 119 children with atopic asthma were evaluated after 30 years of follow-up at the ages of 32-42 years, the remission rate was 52% (22% complete remission, 30% clinical remission). In this study, high FEV1 values at first admission and in remission were found to be important predictors of clinical remission in children with asthma (12). In our study, the follow-up period was shorter. In terms of pulmonary function, we found no difference between the two groups. However, clinical remission was lower in patients whose respiratory symptoms began before the age of three years and persisted, despite no difference in pulmonary function tests. Lower serum IgE levels, fewer positive skin tests, and less need for medication were found

Table 1. Baseline characteristics for all participants in the study were stratified by clinical asthma remission status (n=72)

	No asthma remission (n=55)	Asthma remission (n=17)	p-value
Age (y), mean ± SD	13.29±2.09	13.58±1.62	0.593
Age at asthma diagnosis (y), mean ± SD	7.56±2.65	7.47±2.06	0.895
The duration of follow-up, year	6.03±2.19	6.11±1.86	0.891
Sex			0.825
Male	47.2% (34)	13.9% (10)	
Female	29.2% (21)	9.7% (7)	
Parental history of asthma (yes)	6.9 (5)	0.0 (0)	0.249
Familial atopic disease (yes)	16.7 (12)	8.3 (6)	0.209
Aeroallergen sensitization on skin testing			0.245
Mite	13.9 (10)	2.8 (2)	
Mold	19.4 (14)	1.4 (1)	
Pollens	6.9 (5)	4.2 (3)	
Cockroaches	1.4 (1)	0.0 (0)	
Multiallergen	34.7 (25)	25.3 (11)	
Pet at diagnosis (yes)	13.9 (10)	2.8 (2)	0.420
Hospitalization with respiratory tract infection in <3-years-old	26.8 (19)	2.8 (2)	0.057
With persistent symptoms from the first age of three years	21.1 (15)	1.4 (1)	0.050
Obesity at diagnosis	4.2 (3)	0.0 (0)	0.440
Allergic rhinitis at diagnosis	52.8 (38)	18.1 (13)	0.399
Additional chronic disease at diagnosis	5.6 (4)	0.0 (0)	0.332
Asthma control at diagnosis			0.668
Uncontrolled, % (n)	72.2 (52)	22.2 (16)	
Partial control, % (n)	4.2 (3)	1.4 (1)	
Passive smoking	39.7 (25)	14.3 (9)	0.591
Asthma severity at diagnosis			0.098
Mild	64.8	23.9	
Moderate	11.4	0.0	
FEV1 at diagnosis (% predicted)*	87.85±14.68	89.92±11.91	0.631
FEV1/FVC ratio at diagnosis (%)*	109.70±7.02	110.14±7.71	0.843
FEF 25-75 at diagnosis	113.95±26.16	123.07±27.73	0.435
Serum IgE level (IU/mL) at diagnosis*	277.04±297.12	223.16 ±115.10	0.147
Eosinophils (%) at diagnosis*	5.72±4.19	4.41±6.07	0.336
Eosinophil count (cells/μL) at diagnosis*	424.58±336.67	400.00±575.69	0.838

*Mean ± SD; FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, FEF 25-75: Forced expiratory flow between 25% and 75% of vital capacity, SD: Standard deviation

Statistical significance was set at 0.05. All statistically significant values are reported in bold

to be predictive for remission in a study in which patients with moderate-to-severe atopic asthma in childhood who received allergen immunotherapy between the ages of

5 and 12 years were evaluated in young adulthood (17-30 years) (13). In our study, there were no patients who had received allergen immunotherapy before.

There are more studies on children with both atopic and non-atopic asthma. In these studies, it has been shown that better pulmonary function is associated with a better prognosis in adulthood (5,12,14). It has been reported that asthmatic adolescents with remission activity represent a distinct phenotype with milder, less atopic, and less hyperresponsive asthma during school years (3). Wang et al. (4) found in a 12-year follow-up study that the most important determinant of asthma remission was the severity of airway obstruction. According to Sekerel et al. (5), decreased airflow, female gender, and eosinophilia appears to predict the "adverse outcome" of childhood asthma. According to some studies, asthma remission rates differ significantly among populations. In these studies, remission was associated with less-allergic sensitivity, milder asthma severity at diagnosis, and male gender (7,15,16). In our study, no difference was found in terms of allergen sensitization, baseline asthma severity, or gender. Stern et al. (16) reported in a birth cohort study that persistent wheezing early in life was one of the factors associated with asthma at the age of 22 years. In our study, we came to a similar conclusion.

According to Aydogan et al. (11), asthma persists in the presence of bronchial hyperresponsiveness and rhinitis. In our study, 70.8% (n=51) of the patients were accompanied by allergic rhinitis, and there was no difference between the group with and without clinical remission in terms of the association of allergic rhinitis.

Our study had several limitations, including the fact that it was retrospective, the number of cases was small (Participants were included in the study provided that they had been receiving regular follow-up since 2016. This is a factor limiting the number of cases) and the patients could not be evaluated for complete remission. Our study included only patients with mild to moderate persistent childhood atopic asthma. Another limitation of our study is that it does not include mild intermittent or severe atopic asthma cases.

CONCLUSION

Childhood asthma usually has a high remission rate. However, there are few studies evaluating remission, especially in atopic asthma. Our study, which was conducted in children with atopic asthma who were symptomatic before the age of three years and had a persistent course, found that the rate of clinical remission was lower. More research is required to determine which factors play a role in predicting remission in children with atopic asthma. The data will help

doctors and parents make decisions about the prognosis of childhood atopic asthma.

ETHICS

Ethics Committee Approval: Approval for the study was obtained from İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (decision no: 796, date: 30.11.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.B.E., H.T.N., Ö.A., Concept: S.B.E., Ö.A., Design: S.B.E., H.T.N., Ö.A., Data Collection or Processing: S.B.E., H.T.N., Analysis or Interpretation: S.B.E., Ö.A., Literature Search: S.B.E., H.T.N., Ö.A., Writing: S.B.E., H.T.N., Ö.A.

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